CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019766/ S026/S028

Trade Name: ZOCOR TABLETS

Generic Name: SIMVASTATIN

Sponsor: MERCK AND COMPANY, INC.

Approval Date: 07/10/98

Indication(s): LIPID-ALTERING AGENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 019766/S026/S028

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019766/ S026/S028

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-026
NDA 19-766/S-028

JUL 10 1998

Merck & Co., Inc.
Attention: Charles Hyman, M.D.
P.O.Box 4
West Point, PA 19486

Dear Dr. Hyman:

Please refer to your supplemental new drug applications dated August 4, 1997, received August 5, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your submissions for supplement S-026 dated August 4, 15, November 13, December 4, 16, 18, 26, 1997, and January 16, 23, March 26, April 1, 24, May 27, June 12 (2), 15, 23, 25, 26(3), and July 2, 6, 7, and 8 (fax), 1998.

We acknowledge receipt of your submissions for supplement S-028 dated August 4, November 13, 19, 1997, and April 6, and June 15, 1998. The user fee goal date for both supplemental applications is August 5, 1998.

These supplemental new drug applications provide for the use of a new dosage strength and dosing regimen (80 mg per day) of Zocor (simvastatin) Tablets, (S-028) and for a new indication for the treatment of patients with homozygous familial hypercholesterolemia (S-026).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert dated July 2, 1998, and immediate container label dated August 4, 1997). Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper

or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-766/S-026, S-028." Approval of these submissions by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated July 8, 1998. These biopharmaceutical commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019766/ S026/S028

MEDICAL REVIEW(S)

NDA # 19-766/S-026
ZOCOR (simvastatin)
Merck
Class: HMG-CoA reductase inhibitor (lipid altering)
Purpose of supplement: 1) initial marketing of 80 mg dosage form, 2) new indication for the treatment of patients with homozygous familial hypercholesterolemia
Date of submission: 8-4-97

Background

Epidemiological data suggest a graded and continuous relationship between plasma cholesterol level and risk for coronary heart disease. The preponderance of evidence from clinical trials of diet, surgery, and drugs in the treatment of hypercholesterolemia suggests that reduction in risk of CHD is likewise graded as a function of degree of cholesterol lowering from baseline. While the question of a threshold of benefit from cholesterol lowering remains and requires testing in prospective trials, nevertheless, it would appear that at least some patients do benefit from further cholesterol lowering even within the low-normal range. Suffice it to say that in patients at relatively low risk based on cholesterol level alone, it is more difficult to detect a benefit of drug treatment in the short term, which in the case of the statin trials, is a median treatment duration of about 5 years.

The place for more potent doses of simvastatin, as well as other members of this class of drugs is, then, to lower cholesterol levels sufficient to accomplish optimal CHD risk reduction. In light of the decade of experience with these treatments, the established overall safety of this approach to lipid altering, and the accumulating evidence that "lower is better" with regard to LDL-C, the risk-benefit assessment of these agents has changed somewhat. Notwithstanding arguments as to the risks and benefits of extreme cholesterol lowering, one obvious place for high-dose statins is the large group of patients with heterozygous familial hypercholesterolemia. The gene frequency for defects affecting the expression and function of the LDL receptor is approximately 1 in 500, and these patients often require much more than 50% lowering from baseline in LDL-C to meet treatment goals. This is rarely if ever achieved with monotherapy, and only occasionally achieved with aggressive combination therapy.

Finally, in patients with homozygous familial hypercholesterolemia, there appears to be a place for drug therapy with high-dose statins as an adjunct to LDL apheresis is reducing LDL-C levels. No clinical outcome data are available or forthcoming in this small population, but a safe pharmacological adjunct both to reduce the frequency of apheresis and to slow the rise in LDL-C between apheresis treatments seems a worthy addition to the limited therapeutic armamentarium in this disease.

The current application includes the data from 3 Phase 2-3 clinical trials, with up to 1.5 years' exposure, exploring the efficacy and safety of ZOCOR 80 mg. These trials have all been actively controlled, with the comparator arm receiving ZOCOR 40 mg daily. In addition, a small, placebo-controlled male adrenal/gonadal study was conducted, of 12 weeks' duration. The sponsor proposes initial marketing of ZOCOR 80 mg, a new

indication for ZOCOR in the treatment of homozygous FH, changes to labeling in the section on skeletal muscle complications of simvastatin use within PRECAUTIONS, and changes in the Dosage and Administration section of the label regarding the recommended initial starting dose.

Controlled trials

A total of 1146 patients received ZOCOR 80 mg in controlled trials presented in this application. The following table summarizes the data regarding the numbers of patients and the actual duration of treatment. Note the total in the table is 1159. This is due to the fact that 13 patients took the wrong dose of drug during the course of treatment.

Table 1. Number of patients on ZOCOR 80 mg daily and duration of treatment

Duration (mos)	≤ 1	> 1 to 3	>3 to 6	>6 to 12	>12 to 18	>18 to 21	total
N	28	213	252	586	89	0	1159

The range of exposure was 1 to 417 days, with a mean of 233.5 days.

Study Designs of the Phase 3 Trials

There were two nominal Phase 3 studies, one in the U.S. and one internationally outside the U.S. These were multicenter, double-blind, randomized, and active controlled. Each was of 6 months' duration with a 6-month extension period. Patients were males and females, aged 21 to 70, generally in good health, though ASCVD was not an exclusion criterion. Of note, among the exclusion criteria were: transaminases more the 10% above the ULN or CK more than 50% above the ULN. In the U.S. study, patients were enrolled if they were eligible for drug treatment to lower cholesterol according to NCEP guidelines, and in the International study, an LDL-C > 160 mg/dL was the lipid entry criterion.

Patient populations

Across the Phase 3 studies, patients were 60% male, with a mean age of 52, and 90% were white. All patients had one or more secondary diagnoses, and most were taking one or more concomitant therapies. The treatment groups were well-matched at baseline for all the variables examined, including lipids and lipoproteins. The mean LDL-C in the U.S. study was 207 mg/dL; mean HDL-C was 48 mg/dL, and mean TG was 163 mg/dL. In the international study, mean LDL-C was 243 mg/dL; mean HDL-C was 49 mg/dL, and mean TG was 148 mg/dL. The U.S. study randomized 521 patients, and the International study randomized 584 patients.

Results

The sponsor prespecified an analysis after pooling the data from the Phase 3 trials. This was not required to achieve sufficient statistical power to detect differences in any of the prespecified efficacy parameters. Rather, it permits exploratory subgroup

analyses (see below) as well as providing precision with regard to the estimates of the effects of the different doses of ZOCOR. The results of the pooled analyses are presented in the table below, from the application.

Table 2. Percent Change in Lipid and Lipoproteins at Weeks 18 and 24 in Combined Phase III Studies
Intention-to-Treat Approach

Parameter	Simvastatin Treatment	n	Mean		Change (%)		p-Value	
			Baseline	Weeks 18 and 24	Mean	SD	95% CI Mean	Between Group
LDL-C (mg/dL)	40 mg	432	228.6	135.3	-40.5	12.9	(-41.7, -39.2)	<0.001
	80 mg	663	223.9	118.1	-47.2	12.4	(-48.2, -46.3)	
Total-C (mg/dL)	40 mg	433	310.6	214.8	-30.5	9.9	(-31.4, -29.5)	<0.001
	80 mg	664	305.9	194.8	-36.0	10.1	(-36.8, -35.3)	
HDL-C (mg/dL)	40 mg	433	48.6	52.2	8.5	13.7	(7.2, 9.8)	0.463
	80 mg	664	48.2	51.7	8.1	12.6	(7.1, 9.0)	
LDL-C/HDL-C	40 mg	432	5.0	2.8	-44.2	14.9	(-45.6, -42.8)	<0.001
	80 mg	663	4.9	2.4	-50.4	13.2	(-51.4, -49.4)	
Total C/HDL-C	40 mg	433	6.8	4.3	-34.8	12.8	(-36.0, -33.6)	<0.001
	80 mg	664	6.7	3.9	-40.0	11.5	(-40.9, -39.1)	
TG* (mg/dL)	40 mg	433	155.0	124.5	-17.8	28.6	(-20.5, -15.1)	<0.001
	80 mg	664	156.8	115.3	-24.4	25.8	(-26.4, -22.5)	
VLDL-C (mg/dL)*,^	40 mg	66	36.5	24.0	-30.6	41.4	(-40.8, -20.5)	0.676
	80 mg	103	36.0	22.0	-35.7	35.8	(-42.7, -28.7)	
Apolipoprotein B, ^ (mg/dL)	40 mg	72	201.3	136.7	-31.4	11.2	(-34.0, -28.7)	<0.001
	80 mg	112	193.8	120.0	-37.9	12.1	(-40.2, -35.6)	
Apolipoprotein A-I, ^ (mg/dL)	40 mg	72	144.1	155.2	8.6	14.0	(5.5, 11.8)	0.009
	80 mg	112	151.2	155.4	3.5	12.2	(1.2, 5.7)	

* ANOVA based upon the normalized ranks of the data. Median (SD of median) and 95% CI for the median reported.
^ Performed in a subset of patients.

[16; 17]

Note that the lipid data cited are the means of the results after 18 and 24 weeks of treatment. Not shown here are data demonstrating that the mean LDL-C for the study population is stable across those two time points.

The 80 mg dose effects an additional ~7% mean lowering of LDL-C relative to baseline and an additional ~5% mean lowering of total-C. No additional effect on mean HDL-C increase was seen at 80 mg. These outcomes translate into an incremental reduction in the ratio of total-C and LDL-C to HDL-C. The reduced effect of the 80 mg dose relative to 40 mg to raise apo A-I, the principal apoprotein of HDL is unlikely to be of clinical significance, particularly in light of the HDL-C results.

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Finally, as expected for this class of drugs, there was observed an additional effect on TG lowering at the 80 mg dose.

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Subgroup analyses performed by the sponsor

When the effects of simvastatin 40 and 80 mg were examined across subgroups of baseline LDL-C the effect of treatment was consistent for the two subgroups. The difference between dosage groups, however, was slightly greater for the groups with lower baseline LDL-C.

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The effects of baseline TG on the effect to lower TG was, however, much more dramatic. As seen in the table below, reproduced from the application, in the group with normal TG, not only are the absolute reductions in TG significantly lower than in the group with elevated TG, but, in addition, the difference across the dosage groups is likewise greater in the subgroup with elevated TG at baseline. Though not included in this application, the group with elevated baseline TG (and lower baseline HDL-C) likewise show a proportionately greater increase in HDL-C with simvastatin therapy

Table 3. Percent Change in Triglycerides at Weeks 18 and 24 by Baseline Triglyceride
Nonparametric Summary Statistics
Intention-to-Treat Approach

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Parameter	Simvastatin Treatment	n	Median		Change (%)		p-Value	
			Baseline	Weeks 18 and 24	Median	SD	95% CI Median	Between Group
TG (mg/dL) ≤200 mg/dL	40 mg	323	136.0	110.0	-16.2	27.1	(-19.2, -13.3)	0.004
	80 mg	475	135.0	104.0	-20.9	25.7	(-23.2, -18.6)	
TG (mg/dL) >200 mg/dL	40 mg	110	252.3	191.0	-27.8	29.5	(-33.4, -22.2)	0.012
	80 mg	189	251.5	162.5	-36.0	23.8	(-39.4, -32.5)	

[16; 17]

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Homozygous FH

Homozygous FH is a rare condition, occurring in approximately 1 per million people in the U.S., which is the result of homozygous (or compound heterozygous) defects in the LDL receptor gene that affect the expression and function of the LDL receptor. Because of the resultant poor uptake of LDL-C by the hepatocyte, and because of continued hepatic cholesterol biosynthesis and secretion of VLDL, these patients have marked elevation in serum total and LDL-C. As a consequence, patients often have atherosclerotic vascular disease symptoms in the first decade of life, and if untreated, will die from CHD in the second or third decades of life. Current therapy involved periodic (every two weeks) LDL apheresis, bile acid sequestrants, and probucol

which appears to cause regression of tendon xanthomas. Ileal bypass surgery was performed in the past, and hepatic transplantation has been utilized in a limited number of patients. In recent years, atorvastatin at high doses has been shown to reduce LDL-C in patients with hFH beyond that accomplished with LDL apheresis alone. While lower-dose statins have little to no effect in this condition, particularly in patients who are receptor negative, at higher doses, perhaps because of significant inhibition of hepatic VLDL production, reductions in LDL-C on the order have been reported. It is important to note, that results in patients with hFH are variable, with some showing no response at all.

The current application includes the results of a small study from South Africa of simvastatin in patients with hFH. These data support a role for high-dose simvastatin in these patients, as tolerated.

Study design

This was an open-label, dose-escalation study in 12 patients with homozygous familial hypercholesterolemia not undergoing LDL apheresis. After a 4-week diet/placebo run-in period, patients were randomized to receive simvastatin 40 mg in the evening (4 patients) or 80 mg in 3 divided doses (20, 20, 40 mg, 8 patients). After 9 weeks, patients in the second group were switched to simvastatin 160 mg/day in 3 divided doses (40, 40, 80) and those in the first group simply had their dose divided (10, 10, 20) for an additional 9 weeks.

Patient population

There were 7 males and 5 females enrolled in the trial. Age ranged
Homozygous familial hypercholesterolemia was defined by an LDL-C of > 500 mg/dL and the presence of at least 2 of the following: tendon xanthomas, both parents with FH, or an LDL receptor genotype showing the presence of mutations in both LDL receptor genes. Mean baseline LDL-C was approximately 550 mg/dL across the two treatment groups. Eleven patients were considered receptor-defective, and one was homozygous for a null mutation and thus was receptor-negative (< 2% normal LDL-receptor activity).

Results

The following table from the application summarizes the response to treatment by dose and treatment period.

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Table 4. Results of simvastatin treatment in homozygous FH

Week	Simvastatin Dosage	N	Mean (mg/dL)		Change (%) From Baseline				
			Baseline	Treatment	Mean	SD	90% CI	p-Value*	Posterior Probability*
6	40 mg (1 dose)	4	519.0	445.5	-14.1	5.4	(-20.5, -7.7)	0.007	0.059
	80 mg/day (3 doses)	8	570.0	421.2	-25.9	7.5	(-30.9, -20.8)	<0.001	0.969
9	40 mg (1 dose)	4	519.0	450.1	-13.7	7.5	(-22.5, -4.9)	0.018	0.096
	80 mg/day (3 doses)	8	570.0	420.6	-24.6	18.9	(-37.3, -11.9)	0.004	0.743
15	40 mg/day (3 doses)	4	519.0	422.1	-17.6	14.6	(-34.8, -0.4)	0.047	0.384
	160 mg/day (3 doses)	8	570.0	387.8	-30.9	15.5	(-41.3, -20.6)	<0.001	0.957
18	40 mg/day (3 doses)	4	519.0	444.6	-13.2	10.3	(-25.4, -1.1)	0.041	0.140
	160 mg/day (3 doses)	8	570.0	388.9	-30.6	20.0	(-44.0, -17.2)	0.002	0.911

* Within-group p-value from one-sided t-test.
* Posterior probability of true mean reduction ≥20%.

Data Source: [4.6]

In the 80/160 mg group, 7 of 8 patients showed reductions in LDL-C from __% to __%. The remaining patient had an increase in LDL-C of __%. The patient who was receptor negative was in the 80 mg group and had a change in LDL-C of 41%.

Safety considerations in the hFH cohort

All patients completed the study, and there were no serious adverse events reported. Reductions in mean morning serum cortisol were observed. These changes were not dose dependent. The range of changes in cortisol across periods and treatment groups was

Morning serum cortisol levels remained near or above 20 ug/dL in all patients. Characterization of the effect of simvastatin on stimulated cortisol production in this patient group may be a better way to assess the clinical significance of this treatment. It should be noted that patients homozygous for defects in the LDL-receptor have been shown in previous studies to have abnormal adrenal responsiveness to Cortrosyn.

Other than the above, however, there appear to be no unique safety concerns regarding the use of high-dose simvastatin in patients with homozygous FH.

Safety assessment in the Phase 3 trials of simvastatin 80 mg

This review will be restricted to the discussion of adverse hepatic and skeletal muscular effects. Overall, simvastatin 80 mg is very well tolerated, and there is no evidence from the trials presented here of any novel side effects of simvastatin emerging uniquely at the 80 or 160 mg doses.

Hepatic effects

One patient in the Phase 3 studies developed non-viral hepatitis attributed to nitrofurantoin. The following table summarizes the data for marked elevations in ALT or AST during the Phase 3 studies, including the safety update report period.

Table 4
Patients With Marked Elevations in Transaminases—Patient Count (%)
Phase III Studies
Intention-to-Treat Approach

	Simvastatin 40 mg	Simvastatin 80 mg*
Number (%) of patients with:		
≥1 elevations ≥3 X ULN in ALT	6/433 (1.4%)	36/860 (4.2%)
≥1 elevations ≥3x ULN in AST	4/433 (0.9%)	23/860 (2.7%)
≥1 elevations ≥3 x ULN in ALT or AST	6/433 (1.4%)	37/860 (4.3%)

*Note that the rate in the original application period (out to 6 months) was 3.9%, and the rate in the safety update report period (N= 760, out to 48 weeks was 1.6%)

Thus, there does appear to be an increase in the incidence of significant LFT abnormalities with simvastatin 80 mg. This is consistent with the findings with atorvastatin at higher doses. It is important to point out that the table above includes all patients with marked LFT abnormalities. Approximately 50% of these patients had persistent marked elevations on repeat testing and were thus discontinued from study. It is the incidence of persistent elevations that is relevant to labeling as these are the events that have been deemed serious an necessitating intervention. The crude incidence rates at 40 and 80 mg for consecutive LFT elevations, excluding 4 patients with myopathy associated transaminase elevations are, respectively, 0.9% and 2.1%.

With regard to the timing of the elevations in transaminases, the following table summarizes the timing of first elevation for the 23 patients treated with 80 mg with ALT or AST elevations ≥3 x ULN without other causes.

Table 5
Marked LFT elevations by week of
treatment with simvastatin 80 mg

week of treatment	6	12	18	24	36	48
n with AST or ALT elevation ≥3 x ULN	1	4	7	5	5	1

It would thus appear that LFT monitoring should continue out at least to the end of the first year of treatment. The sponsor has suggested an additional LFT check at 18 weeks for patients on 80 mg daily. This reviewer agrees with this approach.

With regard to labeling, the sponsor has cited six-month incidence rates for persistent LFT elevations >3 x ULN at the 40 and 80 mg doses based on those cases considered drug-related. Overall rates of persistent elevations are more appropriate for labeling and consistent with the labeling for other members of the class. Furthermore, unless there is clear evidence of another cause for the LFT elevation, all cases should be included, regardless of causality assessment. Thus, all cases of ALT and/or ALT elevations >3 x ULN, persisting on re-check at least one week later, as a fraction of the total number of patients exposed in the Phase 3 trials at a given dose, should be included in the analysis. This has been communicated to the sponsor.

Skeletal muscle effects

Myopathy related to statin therapy is a rare event, thought to be related to increased systemic exposure to HMG-CoA reductase inhibitor activity. It is most frequently reported in the setting of a drug-drug interaction that 1) results in increased systemic levels of inhibitor and/or 2) synergizes at the level of the muscle to induce myopathy. Myopathy has been traditionally defined as unexplained muscle pain or weakness accompanied by marked elevations (> 10 x ULN) in creatine kinase. However, symptoms in the setting of lesser elevations in CK or asymptomatic elevations in CK may also be attributed to drug. The clinical course of any of these manifestations of statin toxicity is not known. Suffice it to say that in rare cases, myopathy does progress to frank rhabdomyolysis with acute renal failure.

In the Phase 3 trials of simvastatin 80 mg, the overall rate of myopathy defined as symptoms and CK > 10 x ULN was 0.7% over the 6-month period reported in the original application. There were no cases of myopathy in the extension period. However, 4 patients were discontinued in the extension period for myalgia and CK elevation between 5 and 10 x ULN (3 patients) and for asymptomatic marked CK elevation (one patient).

Of the five patients developing myopathy in the original 6-month studies, one was taking concomitant nefazodone (an inhibitor of CYP 3A4) and another was taking verapamil (a weak inhibitor of p-glycoprotein).

In sum, with regard to muscle effects, simvastatin 80 mg appears well-tolerated. No marked increase in risk for myopathy is apparent at this dose.

Male adrenal/gonadal study results

Of note, a male adrenal-gonadal study was performed as part of the 80 mg development program, with adrenal stimulation using the 6-hour Cortrosyn infusion protocol. In the non-FH homozygotes in this study, the plasma cortisol versus time curves for simvastatin 80 mg and placebo were identical.

The mean changes in serum testosterone (men only), LH, and FSH (all patients) were not significant. The range of changes in LH and FSH is somewhat broad, but are of unclear significance in light of the absence of an effect on plasma testosterone.

Labeling review
Editorial or other small changes proposed for purposes of clarity will not be commented upon unless they are to be rejected. Comments will be restricted to proposed major changes in labeling for which support has been offered in the submission or major changes that are incidental to this NDA supplement.

Clinical Pharmacology
second paragraph, 5th sentence, change to:
Since each LDL particle contains one molecule of apolipoprotein B, and since, in patients with predominant elevations in LDL-C (without accompanying elevation in VLDL), little apoB is found in other lipoproteins, this strongly suggests...

Clinical Pharmacology, Pharmacokinetics
see Dr. Shore's review

Clinical Pharmacology, Clinical Studies
Table 1
The sponsor has replaced the original table 1 which summarized the results of a dose-response study. The new table combines data from several different studies with lipid and lipoprotein data from different time points. Essentially, the new table is three separate tables. While this may be somewhat unorthodox, as the data for the doses up to 40 mg are not substantially different than those included in the original table, the new table is not misleading. It is acceptable with the addition of the time points at which ~~lab~~ samples were drawn for each of the three individual studies summarized.

Text following table 1
A statement of the response in the highest-response tertile is misleading. If this information is to be included in labeling, also included should be a summary of the data from the other two tertiles. Means or ranges of LDL-C responses by tertile by dose of simvastatin is suggested.

The statement that "percent reduction in LDL-C was essentially independent of the baseline level" is misleading. The analysis cited did not include baseline LDL-C as a continuous variable. It was based on a cut of the data at LDL-C of 200 mg/dL.

The TG lowering effect of simvastatin 80 mg as a function of baseline TG is described appropriately.

Summary of the results in homozygous familial hypercholesterolemia

The data for the patient who did not respond to simvastatin therapy should be stated. The range of responses among the responders should be stated, as well as the mean or median response. Otherwise, this is acceptable.

Endocrine function
These changes are acceptable.

Indications and Usage
Changes are acceptable.

Warnings, Skeletal Muscle
first paragraph, last sentence:
...which were excluded by the designs of these studies *(see below).*

Myopathy caused by drug interactions
second paragraph, second sentence
Simvastatin is metabolized...

third sentence
Certain drugs share .... plasma levels of simvastatin and *thus*...

Reducing the risk of myopathy, third paragraph
Measures to reduce the risk of myopathy caused by drug interactions (see above and Precautions/Drug Interactions).

Liver dysfunction
third paragraph
The summary information on the incidence of consecutive LFT elevations to >3 x ULN has been discussed with the sponsor. In a submission of June 12, 1998, tables were presented summarizing the incidence for the first 6 months and the second 6 months (during which 193 patients had their dose increased from 40 to 80 mg daily) of the Phase 3 trials by dose. Four patients were legitimately excluded from the 80 mg group. These four developed myopathy with elevations in transaminases that occurred and resolved in close temporal relation to elevations in CK. In these patients, the marked transaminase elevations were of muscle origin. The crude rates of consecutive LFT elevations are thus 18/862 (2.1%) and 4/436 (0.9%) for the 40 and 80 mg dosage groups, respectively.

Fourth paragraph
The recommended 3-month LFT check is reasonable in light of the incidence-by-time data for the 80 mg dose.

Precautions, CNS Toxicity
see Dr. Barbehenn's review

Precautions, Carcinogenesis, Mutagenesis, Impairment of Fertility

see Dr. Barbehenn's review

Precautions, Pregnancy
see Dr. Barbehenn's review

Dosage and administration
Second paragraph, change to:
The recommended usual starting dose is 20 mg once a day in the evening. Patients who require only a moderate reduction of LDL cholesterol may be started at 10 mg. See below for dosage recommendation for patients receiving concomitant therapy with cyclosporine, fibrates, or niacin, and for those with severe renal insufficiency.

The recommended dose range is 5-80 mg daily as a single dose in the evening. Doses should be individualized according to baseline LDL cholesterol levels, the recommended goal of therapy (see NCEP Guidelines), and the patient's response. Adjustments of dosage should be made at intervals of 4 weeks or more.

All other changes are acceptable.

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Recommendation:
Pending agreement on labeling, this NDA supplement should be approved. The comments above have been communicated to the sponsor by telephone and fax, and labeling discussions are ongoing as of the time of completion of this review.

APPEARS THIS WAY
ON ORIGINAL

David G. Orloff, M.D.
Medical Officer/Team Leader
DMEDP/CDER/FDA

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Recommendation code: AP

cc:
NDA Arch 19-766
HFD-510
HFD-510: Simoneau/Shen

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MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT

NDA : 19-766/S26
SPONSOR: MERCK RESEARCH LAB.
SAFETY UPDATE
DRUG: ZOCOR 80 MG TAB.

SUBMITTED:08/04/1997
RECEIVED: 08/05/1997
RECEIVED: 12/05/1997
REVIEWED: 3/10/1998

1.Title and General Information

1.1. Title/Heading:

MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT

1.1.1. NDA : 19-766/S26

1.1.2. M.O. Review # 1

1.1.3. Submission Dates:08/5/97
12/5/97

1.1.4. Review completed date:

1.2. Drug name

1.2.1. Generic name: Simvastatin

1.2.2. Proposed trade name: Zocor

1.3. Sponsor: Merck Research Laboratories.

1.4. Pharmacological Category: Inhibitor of 3-HMG-CoA reductase.

1.5. Proposed Indications:

15.1. "as an adjunct to diet to reduce TOTAL-C and LDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb)".

1.5.2. "to reduce TOTAL-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable".

1.6. **Dosage Form and Route of Administration:** 80 mg/day orally.

1.7. **NDA Drug Classification:**

1.8. **Important Related Drugs:** Other 3-HMG-CoA-reductase-inhibitors.

1.9. **Other Related Reviews:** Statistics, Biopharm and chemistry reviews.

2. **Materials Reviewed:**

NDA: 19-766/S026, Vols. 1-32.
NDA:19-766/SE2-026,Vols. 1-3.

3. **Clinical Background**

3.1. **Relevant human experience:**

ZOCOR 5, 10, 20, and 40 mg was approved on 12/23/ 1991 as an adjunct to diet in the treatment of elevated total cholesterol and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb.).

3.1.1. **Dose-response in patients with primary hypercholesterolemia:**

The current Package Insert lists the following dose-responses in patients with primary hypercholesterolemia:

- @ 05 mg qPM, resulted in 24% decrease in LDL-C ; 10% decrease in TG, and 7% increase in HDL-C after 8 weeks of Rx.;
- @ 10 mg qPM, resulted in 33% decrease in LDL-C; 10% decrease in TG, and 9% increase in HDL-C after 8 weeks of Rx.;
- @ 20 mg qPM, resulted in 33 % decrease in LDL-C; 19% decrease in TG, and

11% increase in HDL-C after 8 weeks of Rx.
-@ 40 mg qPM, resulted in 40% decrease in LDL-C; 19% decrease in TG, and 12% increase in HDL-C after 8 weeks of Rx.

3.1.2. The Multicenter Anti-Atheroma Study (MAAS):

The clinical benefit of LDL-C lowering was demonstrated in the Multicenter Anti-Atheroma Study (MAAS) in which 347 patients were treated with either placebo or 20 mg Zocor. The two clinical endpoints were mean lumen diameters and mean changes per-patient in minimum lumen diameters. Simvastatin significantly slowed the progression of the atherosclerotic lesions as measured by these two parameters. In addition, simvastatin significantly decreased the number of patients with new lesions.

3.1.3. The Scandinavian Simvastatin Survival Study (4S):

In some of the clinical intervention studies such as the Helsinki Heart Study, the total mortality rate was unchanged although the cardiovascular mortality rate was significantly decreased. Concerns were therefore raised regarding possible adverse effects of cholesterol lowering on non-cardiovascular mortality rates. However, these fears were laid to rest by the Scandinavian Simvastatin Survival Study (4S). The effect on total mortality was assessed in 4444 patients with coronary heart disease. In this multicenter, randomized, double-blind, placebo-controlled study, the risk of mortality was significantly reduced by 30%, the risk of CHD mortality was significantly reduced by 42% in subjects treated with Zocor 20-40 mg/day. And there was no statistically significant difference in non-cardiovascular mortality.

3.1.4. Rationale for marketing 80 mg Zocor:

The sponsor stated that there are several reasons to believe that even greater benefit could be achieved by further lowering LDL-C.

3.2. Human Pharmacology and Pharmacokinetics:

3.2.1. Pharmacokinetic Procedures:

A pharmacokinetic sub-study to evaluate the plasma concentrations of HMG-CoA reductase inhibitory activity was performed in 18 patients. This was a part of a multicenter, randomized, double-blind, 3-period crossover study to evaluate the safety and tolerability of 40-, 80-, and 160-mg doses of simvastatin in 156 hypercholesterolemic patients. Patients received each dose once daily in the evening for 6 weeks with 2-week washout intervals between successive doses. Timed blood samples were collected after a dose at about the midpoint of each treatment period. Plasma samples were assayed for HMG-CoA reductase inhibitory activity by an enzyme method: " the in vitro inhibition of the enzyme HMG-CoA reductase by L-654,969 (the hydroxy acid form of simvastatin) and other active metabolites of simvastatin".

3.2.2. Pharmacokinetic Results:

Mean plasma concentration profiles for active and total HMG-CoA reductase inhibitors are summarized in sponsor's Table 1 and reproduced as Table 3.2.2.1:

Table 3.2.2.1.

Mean (±SD) Pharmacokinetic Parameters for Active and Total HMG-CoA Reductase Inhibitors in Hypercholesterolemic Patients Receiving Daily Tablet Doses of Simvastatin 40, 80, or 160 mg

Dose mg/day	Active Inhibitors			Total Inhibitors		
	C_{max} (ng•eq/mL)	T_{max} (hr)	AUC (ng•eq•hr/mL)	C_{max} (ng•eq/mL)	T_{max} (hr)	AUC (ng•eq•hr/mL)
40[a]	21 (7)	1.8 (0.7)	120 (59)	75 (26)	1.5 (0.5)	316 (92)
80[b]	50 (28)	1.8 (0.9)	263 (180)	165 (55)	1.4 (0.5)	636 (371)
160[b]	138 (75)	1.8 (1.0)	668 (302)	404 (141)	1.6 (0.8)	1533 (483)

Not unexpectedly, the AUC and C_{max} for active and total inhibitors roughly doubled as the dose of simvastatin increased from 40 to 80 mg. However, from 80 mg to 160 mg dose, it increased disproportionally by more than 2.5 times.. As the sponsor pointed out, "both simvastatin and L-654,969 are >94% bound to plasma proteins", the plasma levels of active and total inhibitors do not necessarily reflect the pharmacodynamic activities. Furthermore because of the high first pass uptake into the liver, measurement of blood levels of HMG-CoA-reductase inhibitors is unlikely to predict the inhibition in liver. And it may result in greater adverse effects.

3.2.3 Pharmacokinetic Evaluation:

For in-depth pharmacokinetic evaluation, please see Biopharm evaluation.

4. Description of Clinical data Sources:

4.1. Study Type, and Design/Patient Enumeration, Demographics, Extent of Exposure:

Summary of the Simvastatin 80-mg clinical program is depicted in sponsor's Table 5, and reproduced below as Table 4.1.1:

Table 4.1.1.

Summary of Clinical Study Designs in the Simvastatin 80-mg Clinical Program

Study	U.S. Phase III [16]	International Phase III [17]	Phase IIb [15]	Phase IIb Extension [19]	Male Adrenal/Gonadal [20]
Design	Parallel	Parallel	Crossover	Parallel	Parallel
Duration	24 weeks	24 weeks	22 weeks	48 weeks	12 weeks
Randomized (N)	521	584	156	126	83@
Treatment (n per group)*	S 40 (207) S 80 (314)	S 40 (229) S 80 (355)	S 40 (148) S 80 (149) S 160 (148)	S 40 (24) S 80 (102)	Placebo (41) S 80 (42)
Age (years)					
LDL-C entry criteria	NCEP criteria#	>160 mg/dL	>160 mg/dL	>160 mg/dL	>145 mg/dL
Primary efficacy parameter (change from baseline)	LDL-C	LDL-C	LDL-C	LDL-C	LDL-C
Secondary efficacy parameters (change from baseline)	Total-C, TG, HDL-C, LDL-C/HDL-C, apo B, A-I, VLDL-C	Total-C, TG, HDL-C, LDL-C/ HDL-C	Total-C, TG, HDL-C, apo B, A-I, VLDL-C	Total-C, TG, HDL-C, apo B, A-I	Total-C, TG, HDL-C

* The abbreviation "S" for simvastatin applies to Table 5 and all subsequent tables where space does not allow to write simvastatin. S 40 mg=simvastatin 40 mg; S 80 mg=simvastatin 80 mg; S 160 mg=simvastatin 160 mg.
# NCEP ATP II criteria for pharmacologic therapy (Section 3.3.2.2).
@ Males only.

The number of patients and the treatment duration are adequate for efficacy evaluation. For safety evaluation, longer duration of drug exposure and more patients are desirable. On 12/4/97, the Sponsor submitted a Safety Update Report which included clinical and laboratory safety data for a total of 765 patients who participated in the 6-month, double-blind, placebo-controlled, Phase III extension studies. The number of patients on simvasatatin 80 mg/day and the actual duration of treatment can be seen from Sponsor's Table 2 of the Safety Update Report and reproduced below as Table 5.1.2.

Table 4.1.2
Summary of Clinical Study Designs in the Simvastatin 80-mg Clinical Program

Original Application Period						Safety Update Report Period	
Study	U.S. Phase III [4]	International Phase III [7]	Phase IIb [3]	Phase IIb Extension [43]	Male Adrenal /Gonadal [6]	U.S. Phase III Extension [4]	International Phase III Extension [8]
Design	Parallel	Parallel	Crossover	Parallel	Parallel	Parallel	Parallel
Duration	24 weeks	24 weeks	24 weeks	48 weeks	12 weeks	24 weeks	24 weeks
Randomized (N)	521	584	156	126	83[1]	448	505
Treatment (n per group)[1]	S 40 (207) S 80 (314)	S 40 (229) S 80 (355)	S 40 (148) S 80 (149) S 160 (148)	S 40 (24) S 80 (102)	Placebo (41) S 80 (42)	S 40 (86) S 80 (362)	S 40 (102) S 80 (403)
Age (years)							

[1] In this table simvastatin is abbreviated to "S."
[1] Males only.

Both the number of patients and duration of treatment are now adequate for the evaluation of the efficacy and safety of simvastatin 80 mg/day.

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4.2. Literature :

The most pertinent report is by Davidson and other PI's in the U.S. Phase III Study (Protocol 117-US), (Davidson et al :The Efficacy and Six-Week Tolerability of Simvastatin 80 and 160 mg/Day, The American Journal of Cardiology, 79:38-42, 1997). The authors conclude, "that simvastatin at doses of 80 mg and 160 mg/day provides additional efficacy with a low short-term incidence of adverse effects."

5. Clinical Studies

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5.1. Trial # 16/Protocol 117-US and 117-Non-US.

5.1.1. Objectives:

To evaluate and compare the efficacy and safety of simvastatin 80 mg/day vs. 40 mg/day in patients with hypercholesterolemia.

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5.1.2. Design

A multicenter, double-blind, two-arm parallel study of 24-weeks duration.

5.1.3. Protocol:

5.1.3.1. Patient Population:

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5.1.3.1.1 Inclusion criteria:

For the U.S. Study , patients were eligible for enrollment in the study if they met all of the following at Week -1: While on diet, patients met the National Cholesterol Education Program (NCEP) Adult Treatment Guidelines (ATP) II LDL-C criteria for pharmacologic therapy: Patients with CHD required an LDL-C >130 mg/dL; those with >2 CHD risk factors and without CHD, LDL-C >160 mg/dL; and those without CHD and <2 risk factors, LDL-C >190 mg/dL. In addition, had to have triglycerides (TG) <350 mg/dL at Week -1.

For the Non-US Study, patients had a plasma LDL-C greater than 160 mg/dL and

For the Non-US Study, patients had a plasma LDL-C greater than 160 mg/dL and triglycerides (TG) <350 mg/dL while on a diet

5.1.3.1.2 **Exclusion Criteria:(As listed by the Sponsor)**

1) Premenopausal women, unless surgically sterilized or highly unlikely to conceive.
2) Age greater than 70 or less than 21.
3) Alcohol consumption greater than 10 drinks per week.
4) LDL-C < (130 mg/dL) or TG >350 mg/dL.
5) A diagnosis of Types I, III, IV, V hyperlipidemias or homozygous familial hypercholesterolemia.
6) Lipid-lowering agents including bile acid sequestrants, hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors and nicotinic acid taken within 6 weeks and fibrates taken within 8 weeks prior to the randomization (Week 1).
7) Patients treated with probucol within 1 year prior to entering the placebo period.
8) Patients on immunosuppressive drugs or receiving systemic antifungal agents of the azole class including itraconazole.
9) Patients taking anticoagulants.
10) Renal insufficiency as measured by serum creatinine 1.8 mg/dL (>179 µmol/L).
11) Elevations of liver transaminases 10% above the upper limit of normal (ULN) or active liver disease or creatine kinase (CK) >50% of the ULN without obvious etiology.
12) Acute coronary insufficiency (i.e., unstable angina or the intermediate syndrome); vasospastic (Prinzmetal) angina.
13) Myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary bypass surgery within the previous 3 months.
14) Uncontrolled hypertension (treated or untreated) with systolic blood pressure >160 mm Hg or diastolic >100 mm Hg.
15) Secondary hypercholesterolemia due to hypothyroidism, the nephrotic syndrome, or any other cause. (Patients with a history of hypothyroidism, who were on a stable dose of thyroxine (T_4) with normalized plasma thyroxine and thyroid-stimulating hormone (TSH) may have been included.)
16) Patients with known Type I (insulin-dependent diabetes mellitus, IDDM) or Type II (non-insulin-dependent diabetes mellitus, NIDDM) with HbA1c >10%.
17) Partial ileal bypass.
18) Patients whose weight was >50% above ideal body weight according to the 1983 Metropolitan Height and Weight Tables .
19) Hypersensitivity to HMG-CoA reductase inhibitors.
20) Any other condition or therapy that in the opinion of the investigator might have posed a risk to the patient or confounded the results of the study.
21) Poor mental function or any other reason to expect patient difficulty in complying with the requirements of the study.
22) Treatment with any other investigational drug within 30 days before baseline.

5.1.3.2. **Procedures:**

Diet:

At Week -4, patients were seen by a dietitian for instruction on following the American Heart Association Step 1 Diet or similar diet Dietary compliance was assessed at Weeks -1, 1, 6, 12, 18, and 24.

Treatment protocol:

After the 4-week run-in period, patients were randomized to treatment with simvastatin 40 or 80 mg/day at a ratio of 2:3, respectively for 24 weeks. Each eligible patient was assigned an allocation number which was stratified by LDL-C levels. There were seven clinic visits Patients had vital signs (pulse rate, systolic and diastolic blood pressure, weight) measured at each visit. Serum chemistry was performed at each visit and hematology/urinalysis at alternating visits. A physical examination and electrocardiogram (ECG) were performed at Week 1 and at the conclusion of the study. An ophthalmologic examination was performed at baseline and included lens evaluation by the methods of Lanties .

Dosing and Lipid Measurements:

The patient took a total of 2 tablets each day in the evening (combination of 1 simvastatin 40-mg and 1 placebo 40-mg tablet or 2 simvastatin 40-mg tablets for the first 12 weeks, and 1 simvastatin 40-mg and 1 placebo 80-mg tablet or 1 simvastatin 80-mg and 1 placebo 40-mg tablet during the last 12 weeks).

Lipids were evaluated at Weeks -4 and -1 for screening purposes and at Weeks 1, 6, 12, 18, and 24 for efficacy.

Efficacy parameters and statistical methods

Lipid Values

Primary parameter of efficacy was the mean percent reduction from baseline in LDL-C. The secondary efficacy parameters included the change from baseline of Total-C, TG, HDL-C, LDL-C/HDL-C, in both U.S. and Non-U.S. studies and apo B, A-I, VLDL-C additionally in the U.S. study only.

Statistical Analyses

Two approaches to the analysis of efficacy data were used in the Phase III studies; intention-to-treat and per-protocol. These approaches differed in handling of protocol deviations and dropouts For detailed analysis, please see Statistics Review.

5.1.4. **Results**

5.1.4.1. **Patient Disposition, comparability**

The baseline demographics and lipid and lipoprotein levels from the Phase III studies are shown in Sponsor's Table 6. There were statistically significant differences e.g .the baseline LDL-C in the International study was approximately 36 mg/dL higher and the Total-C was 35 mg/dL higher than the U.S. study.

Table 5.1

Baseline Comparability of Patients in the Efficacy Studies:
All of the lipid and lipoprotein means and SDs are based on the intention-to-treat population which is defined as all patients with at least one posttreatment value.

	U.S. Phase III	International Phase III
Randomized (N)	521	584
Age (mean±SD)	54.8 (9.9)	51.0 (11.8)
Gender (percent male)	60.3	55.8
LDL-C (mean +SD) (mg/dL)	206.7 (44.8)	242.7 (64.5)
Total-C (mean +SD) (mg/dL)	289.8 (47.4)	323.8 (64.1)
HDL-C (mean +SD) (mg/dL)	47.5 (10.9)	49.1 (12.7)
TG (median and range)	163.5 (49.0, 506.0)	148.0 (51.0, 391.5)

5.1.4.2. **Efficacy endpoint outcomes:**

Except for the differences already noted above, both the U.S. and International Studies share similar design and produced similar results, they are combined for efficacy evaluation. Sponsor's Table 3.2 is reproduced as Table 5.2

Table 5.2

Percent Change in Lipid and Lipoproteins at Weeks 18 and 24 in Combined Phase III Studies Intention-to-Treat Approach

Parameter	Simvastatin Treatment	n	Mean		Change (%)		p-Value	
			Base-line	Weeks 18 and 24	Mean	SD	95% CI Mean	Between Group
LDL-C (mg/dL)	40 mg	432	228.6	135.3	-40.5	12.9	(-41.7, -39.2)	<0.001
	80 mg	663	223.9	118.1	-47.2	12.4	(-48.2, -46.3)	
Total-C (mg/dL)	40 mg	433	310.6	214.8	-30.5	9.9	(-31.4, -29.5)	<0.001
	80 mg	664	305.9	194.8	-36.0	10.1	(-36.8, -35.3)	
HDL-C (mg/dL)	40 mg	433	48.6	52.2	8.5	13.7	(7.2, 9.8)	0.463
	80 mg	664	48.2	51.7	8.1	12.6	(7.1, 9.0)	
LDL-C/HDL-C	40 mg	432	5.0	2.8	-44.2	14.9	(-45.6, -42.8)	<0.001
	80 mg	663	4.9	2.4	-50.4	13.2	(-51.4, -49.4)	
Total C/HDL-C	40 mg	433	6.8	4.3	-34.8	12.8	(-36.0, -33.6)	<0.001
	80 mg	664	6.7	3.9	-40.0	11.5	(-40.9, -39.1)	
TG* (mg/dL)	40 mg	433	155.0	124.5	-17.8	28.6	(-20.5, -15.1)	<0.001
	80 mg	664	156.8	115.3	-24.4	25.8	(-26.4, -22.5)	
VLDL-C (mg/dL)*,^	40 mg	66	36.5	24.0	-30.6	41.4	(-40.8, -20.5)	0.676
	80 mg	103	36.0	22.0	-35.7	35.8	(-42.7, -28.7)	
Apolipoprotein B,^ (mg/dL)	40 mg	72	201.3	136.7	-31.4	11.2	(-34.0, -28.7)	<0.001
	80 mg	112	193.8	120.0	-37.9	12.1	(-40.2, -35.6)	
Apolipoprotein A-I,^ (mg/dL)	40 mg	72	144.1	155.2	8.6	14.0	(5.3, 11.8)	0.009
	80 mg	112	151.2	155.4	3.5	12.2	(1.2, 5.7)	

5.1.4.2.1. **Primary End Point: Change in Low-Density Lipoprotein Cholesterol (LDL-C)**

The mean decrease of LDL-C averaged 47% for the 80 mg dose compared to 41% for the 40 mg dose at weeks 18 and 24. The difference was statistically significant as shown.

The time-course of LDL-C decline (not shown) was identical for both the 40 and 80 mg doses, i.e., reaching maximum by 6 weeks

5.1.4.2.2. **Secondary End Points:**

The following secondary endpoints reached statistical significance at $p<0.001$:

Total-C : 36% for 80 mg dose vs. 31% for 40 mg dose.
Apo B: 38% for 80 mg dose vs 31% for 40 mg dose.
TG: 24 % for 80 mg dose vs. 18% for 40 mg dose.

There was no statistically significant difference in the HDL-C increases between the 40 mg and 80 mg doses groups from baseline , although they increased by 8.5% and 8.1% respectively.

5.1.4.3. **Safety comparisons:**

This will be evaluated under Safety Review for the entire 80 mg Clinical Program.

5.1.5 **Reviewer's Comments/Conclusions of Efficacy Results:**

As noted above, compared to simvastatin 40 mg/day, the 80 mg/day dose significantly decreased the LDL-C from 41% to 47%, total-C from 31% to 36% and TG from 18% to 24%. However, statistical significance does not necessarily denote clinical significance. The sponsor stated that there are several reasons to believe that even greater benefit could be achieved by further lowering LDL-C:

" Coronary angiographic studies with maximal or near-maximal doses of inhibitors of HMG-CoA reductase have consistently shown that the progression of atherosclerotic lesions is slowed but not arrested As long as some lesions are progressing in some patients, coronary events must be expected. More aggressive reduction of LDL-C offers the hope of further slowing or even producing lesion regression. Treatment guidelines are becoming increasingly aggressive. For example, the United States National Cholesterol Education Program (NCEP) goal in CHD patients is LDL-C of 100 mg/dL or less , which often requires reductions of more than 40%. Thus, there is a strong therapeutic rationale for developing treatments that can safely provide further reduction of LDL-C".

However, in the 12/29/97 communication from the Sponsor, it was stated, "The primary purpose of the efficacy studies (Protocol #117, US and Non-US) supporting this submission is to demonstrate the enhanced lipid lowering of 80 mg simvastatin by comparison with 40 mg simvastatin. The relationship of lipid. lowering to pathological process as reflected by clinical, or angiographic endpoints is beyond the scope of this submission ". Therefore, the expected clinical/angiographic data relating the increased LDL-C reduction to improved clinical efficacy/benefit have yet to be established/presented.

The secondary endpoint, TG, decreased 24 % for 80 mg dose vs. 18% for 40 mg dose. In contrast to LDL-C which is monotonously stable throughout the day and from day-to-day, TG fluctuates greatly in relation to food intake, types of diet , exercise....etc. A single fasting TG measurement may not accurately reflect the total TG exposure throughout the day. Furthermore, elevated TG level has not

been established as independent risk factor for atherosclerosis in the general population. This was demonstrated by the Helsinki Heart Study, (Manninen V et al: Lipid Alterations and Decline in the Incidence of Coronary Heart Diseases in the Helsinki Heart Study, JAMA, 2605:641-645, 1988). Significant correlations with reduced CHD events were associated with increased HDL-C ($p<0.01$) and decreased LDL-C ($p<0.04$) during 5-years treatment with genfibrozil. A large decrease in TG of 35% did not have a significant independent relationship to the observed decrease in cardiac endpoints. Therefore, clinical benefit of the observed 24% decrease in TG in these two studies remains to be established.

5.2. Trial #15/Protocol #111 and #111-10: Controlled Phase IIb and the Phase II b extension studies:

5.2.1. Objective:

To evaluate and compare the efficacy and safety of simvastatin 80 mg/day vs. 40 mg/day in patients with hypercholesterolemia.

5.2.2: Study Design:

Protocol 111 was a multicenter, randomized, double-blind, complete block, 3-period crossover study of 22 weeks duration: 4-week placebo/diet run-in period, three consecutive 6-week treatment periods, and two 2-week washout periods between active treatments.

5.2.3. Protocol:

Each patient was randomized to one of the 6 treatment sequences with three treatments periods (simvastatin 40, 80, and 160 mg/day).

Patients took a total of 6 tablets per day. During the active-treatment phase, patients took 40 mg as 2 x 20-mg tablets, 80 mg as 2 x 40-mg tablets, and 160 mg as 4 x 40-mg tablets or matching placebo tablets. Protocol 111-10 provided 1-year data on the safety and efficacy of the 80-mg dose in 124 patients

5.2.3.1.Population, procedures:

Patient selection criteria, diet and treatment procedures are similar to the Phase III studies (Protocol 117-US and 117-Non-US).

Demographic characteristics of the patients were also similar to the Phase III studies patients as shown in Sponsor' Table 6, reproduced as Table 5.3

Table 5.3

Baseline Comparability of Patients in the Efficacy Studies

	U.S. Phase III	International Phase III	Phase IIb	Phase IIb Extension	Male Adrenal Gonadal Study
Randomized (N)	521	584	156	126	83
Age (mean±SD)	54.8 (9.9)	51.0 (11.8)	52.4 (10.9)	52.5 (10.4)	45.4 (11.6)
Gender (percent male)	60.3	55.8	60.3	63.5	100
LDL-C (mean +SD) (mg/dL)	206.7 (44.8)	242.7 (64.5)	199.7 (32.3)	200.5 (31.5)	189.9 (52.2)
Total-C (mean+SD) (mg/dL)	289.8 (47.4)	323.8 (64.1)	282.2 (32.3)	282.6 (34.0)	268.0 (53.2)
HDL-C (mean+SD) (mg/dL)	47.5 (10.9)	49.1 (12.7)	47.3 (11.5)	47.5 (12.0)	46.1 (10.6)
TG (median and range)	163.5 (49.0, 506.0)	148.0 (51.0, 391.5)	173.5 (58.0, 432.5)	168.5 (58.0, 432.5)	141.0 (42.0, 620.0)

Note: All of the lipid and lipoprotein means and SDs are based on the intention-to-treat population which is defined as all patients with at least one posttreatment value.

The treatment groups were well-matched with respect to age and gender. There were non-statistically significant differences in baseline lipid levels in Phase IIb/IIb-extension studies . (Male adrenal-gonadal study will be evaluated under **Section 7: Safety**).

5.2.3.2.Studies Results:

The efficacy end-points, (primary and secondary), and the statistical methods used are similar to the Phase III studies as shown in Sponsor's Table 8 and reproduced as Table 5.4:

Table 5.4

Change(%) in lipid, lipoproteins, and apolipoproteins in Phase II and III Studies Intention-to-Treat Approach.

	U.S. Phase III		International Phase III		Phase IIb			Phase IIb Extension		Male Adrenal Gonadal Study	
Dose (mg)	40	80	40	80	40	80	160^	40	80	Placebo	80
n^^	207	314	229	355	156	156	156	24	102	41	42
LDL-C	-38.1	-45.9**	-42.6	-48.4**	-38.3	-42.9*	-50.3**	-42.2	-43.2^^^	-0.4	-42.9**
Total-C	-28.7	-35.1**	-32.0	-36.8**	-28.7	-32.7**	-38.8**	-27.0	-31.5	0.9	-32.8**
HDL-C	6.0	6.1	10.7	9.8	7.7	7.6	9.4	5.4	7.8	2.1	7.9
LDL-C/HDL-C	-41.1	-48.2**	-47.0	-52.4**	N/A	N/A	N/A	N/A	N/A	-0.8	-46.0**
TG#	-17.0	-24.7**	-18.7	-24.1**	-20.8	-22.8	-32.9**	-26.9	-17.7	-13.8	-25.4**
VLDL-C#	-30.6	-35.7	N/A	N/A	-32.0	-32.6	-41.5*	N/A	N/A	N/A	N/A
Apo B	-31.4	-37.9**	N/A	N/A	-31.8	-36.2**	-43.4**	-29.5	-33.5	N/A	N/A
Apo A-I	8.6	3.5	N/A	N/A	8.1	8.3	7.2	7.0	10.8	N/A	N/A

^ Comparisons for 160-mg dose are versus 80-mg dose in Phase IIb study.
^^ n represents number of patients randomized to treatment.
^^^ Per-protocol LDL-C analysis, N=20 (40 mg), N=89 (80 mg).
* p<0.050 ** p<0.010 between group comparison.
# Median percent change.
N/A = not applicable because parameter was not measured.

The Phase IIb study corroborated the Phase III studies that the 80-mg dose was more effective in reducing LDL-C than the 40-mg dose (42.9% vs. 38.3%) The statistical significance was at the P<0.050 rather than the p<0.010 level. In the IIb-extension study, the difference did not reach statistical significance due to the small number of patients involved, N=20 at 40-mg and N=80 at 80-mg dose. Of the secondary endpoints, both total-C and Apo B were statistically significantly different at p<0.010 (32.7% vs. 28.7% and 36.2% vs. 31.8% respectively). Again, Phase IIb-extension study did not show statistical difference between the two dose groups. Phase IIb-extension study is more useful for the safety evaluation and will be presented under Section 7: Safety Evaluation.

5.3. Summary of Efficacy of Phase III and Phase IIb/IIb-extension Studies: