5.3.1. Exposure: The total number of patients exposed to 80 mg simvastatin is shown in Sponsor's Table 12 and reproduced as Table 5.5

Table 5.5
Total Number of Patients on Simvastatin 80 mg/day Evaluable for Efficacy Studies

Total number of patients on product evaluable for safety	962
Total number of patients on product evaluable for efficacy*	950

	>65 Years	<12 Years	Special Groups
Number of subjects evaluable for safety	112	0	0
Number of subjects evaluable for efficacy*	112	0	0

	Duration of Observations					
	Study Weeks					
	6	12	24	36	48	60
Number of patients for safety (#)	955	927	771	124	116	114
Number of patients for efficacy*	907	910	764	40	113	110

There were sufficient number of patients exposed to 80 mg/day: 950, of which 62.9% were males. Duration of exposure was adequate: 764 patients had exposure of 24 weeks and 110 had exposure of 60 weeks.

The racial breakdown showed: 87% White, 2.7 % Black, 1.5% Asian, 7.0% Hispanic and 1.8% Multiracial.

5.3.1.1.Primary Endpoint:

The primary endpoint was the change in LDL-C from baseline. The data presented above indicate that reduction achieved with 80 mg dose was statistically significantly different from the 40 mg dose. Subgroup analysis (not shown) with regard to age, gender, race and baseline LDL-C similarly showed that the 80 mg treatment was more effective than the 40 mg dose treatment in each subgroup. The maximum reduction was reached within 6 weeks of treatment.

5.3.1.2.Secondary Endpoints:

The secondary endpoints, total-C and TG also showed statistically significant differences from the 40 mg dose. In contrast, there was no difference between the 80-mg and 40-mg treatment-groups in HDL-C increases.

5.4. High-Dose Simvastatin Study in Homozygous Familial Hypercholesterolemia Patients

5.4.1. Trial # 22/Protocol 114.

5.4.1.1.Objectives/Rationale:

To evaluate the LDL-C lowering of high doses of simvastatin in patients with

homozygous FH, and to determine the short-term safety profile of high doses of simvastatin in these patients.

Homozygous FH is a rare condition characterized by very low LDL-receptors with total cholesterol . Clinical presentation includes early CHD with M.I. before age 20. Current available treatments include ileal-by pass, LDL-apheresis and liver transplantation.

5.4.1.2.Design:

This was a single-center, randomized, double-blind, parallel, 2-period, dose-escalation study of 22 weeks duration.

5.4.1.3.Protocol

Study Population:

Inclusion Criteria:

Patients were eligible for enrollment if they had LDL-C >500 mg/dL and two of the following while on diet: (1) The presence of tendinous xanthoma; (2) Both parents with heterozygous familial hypercholesterolemia; or (3) The presence of known mutations in both copies of the patient's LDL-receptor genes.

Exclusion Criteria

1) Premenopausal women, unless surgically sterilized or highly unlikely to conceive.
2) Age less than 13 years or weight less than 88 lbs (40 kg).
3) Alcohol consumption greater than 5 drinks per week.
4) TG level >400 mg/dL (4.5 mmol/L).
5) Lipid-lowering agents taken within 2 weeks prior to the placebo/diet run-in period, except for probucol, that may be taken during the study. Patients receiving probucol must be on a stable dose for at least 3 months and remain on that dose throughout the study.
6) Patients having undergone portacaval shunting, liver transplantation, or currently undergoing LDL apheresis.
7) Patients on immunosuppressive drugs.
8) Patients taking anticoagulants other than aspirin or cimetidine.
9) Renal insufficiency as measured by serum creatinine >1.8 mg/dL (159 mmol/L).
10) Elevations of liver transaminases above the upper limit of normal (ULN) or active liver disease or creatine kinase (CK) >50% of ULN without obvious etiology.
11) Acute coronary insufficiency (i.e., unstable angina or the intermediate syndrome).
12) Myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary bypass surgery within the previous 3 months.
13) Uncontrolled hypertension (treated or untreated) with systolic blood pressure >160 mm Hg or diastolic >100 mm Hg.
14) Secondary hypercholesterolemia due to hypothyroidism, the nephrotic syndrome, or any other cause. (Patients with a history of hypothyroidism, who are on a stable dose of thyroxine with normalized plasma thyroxine and thyroid-stimulating hormone [TSH] may be included.)
15) Patients with known diabetes mellitus or fasting blood glucose >140 mg/dL (7.8 mmol/L) or random blood glucose >200 mg/dL (11.1 mmol/L).
16) Partial ileal bypass.
17) Patients whose weight is >50% above ideal body weight according to the 1983 Metropolitan Height and Weight Tables .

18) Hypersensitivity to HMG-CoA reductase inhibitors.
19) Any other condition or therapy that, in the opinion of the investigator, might pose a risk to the patient or confound the results of the study.
20) Poor mental function or any other reason to expect difficulty with the requirements of the study.
21) Treatment with any other investigational drug within 30 days before baseline

12 patents men and 5 women were enrolled into the study. Table 5.4.1 (Sponsor's Table 4) shows the patient age, gender and receptor genotype.

Table 5.4.1.
Patient Charecteristics and FH Genotype

AN	Age	Sex	FH Genotype Receptor Alleles
1	22	M	Afrik 1/3
2	16	M	Exon 16/16
3	20	F	Afrik 1/1
4	19	M	Afrik 1/2
5	26	F	Afrik 1/2
6	38	F	Afrik 1/Exon 9
7	15	M	Afrik 1/1
8	39	M	Afrik 1/1
9	27	F	Afrik 1/1
10	29	M	Promoter mutation
11	26	F	Afrik 1/2
12	33	M	Afrik 1/3

According to the Sponsor, "Nine patients were homozygous or compound heterozygotes for LDL-receptor genotype FH Afrikaner-1, -2, or -3. The FH Afrikaner-1 and -3 mutations are functional mutations that have 10 to 20% of residual LDL-receptor activity The FH Afrikaner-2 mutation is considered null with <2% of LDL receptor activity (receptor negative) One patient was heterozygous for Afrikaner-1 mutation with an exon-9 mutation. The remaining 2 patients were true homozygotes for exon-16 mutation and a promoter mutation, respectively"

Procedure:

After a 4-week placebo/diet run-in period, 2 consecutive 9-week treatment periods followed.

Period I: 8 patients were randomized to receive 80 mg in 3 divided doses (20 mg in the morning, 20 mg in the afternoon, and 40 mg in the evening). 4 patients received 40 mg in the evening. (2/8 of these patients were on Probucol throughout the study)..

Period II: the eight 80-mg dose patients were increased to 160 mg in divided doses (40; 40; and 80). The four 40-mg dose patients were changed to 40 mg in divided doses. (3/4 of these patients were on Probucol throughout the study).

A physical examination was done at Week 1 and at the conclusion of each treatment period (Weeks 9 and 18). An EKG was done at screening and Week 18. At each clinic visit, vital signs (blood pressure, pulse, weight) were recorded and blood samples obtained for chemistry and hematology. U/A was also done. Lipids, lipoproteins, and apolipoproteins were performed at Weeks 1, 6, 9, 15, and 18.
Patients who developed persistent 3X ULN elevations in transaminases or 5X increases in CK with or without symptoms were discontinued from the study. According to the Sponsor," Continuous evaluations of patients with serious adverse experiences (AEs) and clinical and laboratory discontinuations were provided by the investigator; and those sustaining two times the ULN elevations in hepatic transaminases and threefold elevations in CK were provided by the central laboratory".
Endpoints/Statistical Analyses: A within group comparison of percent change from baseline in LDL-C was used as the primary endpoint Secondary endpoints comparisons of percent change from baseline in total-C, HDL-C, LDL-C/HDL-C, TGs, and apolipoprotein B were similarly made For Lp(a) and lipoprotein E, absolute change from baseline were used.

5.4.1.4. Results:

5.4.1.4.1 Patient Disposition

All 12 patients finished the study with no dropouts.

5.4.1.4.2 Efficacy of Primary Endpoint outcomes:

The results are shown in Table 5.4.2 (Sponsor's Table 10).

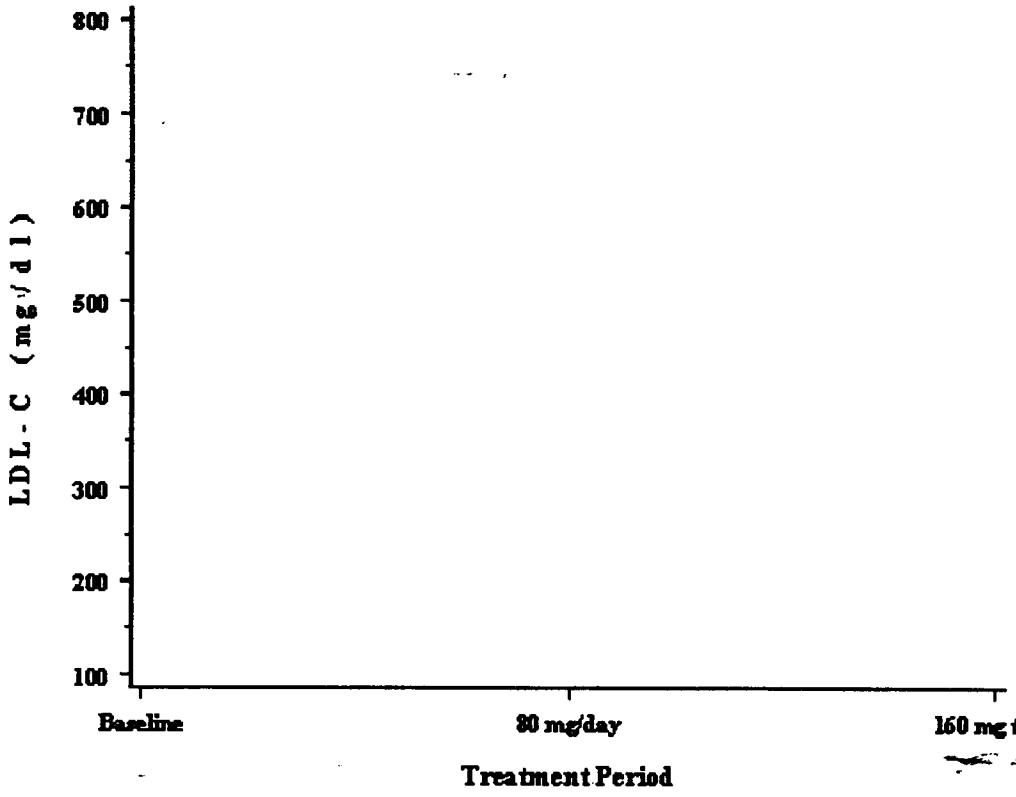
Table 5.4.2
Summary Statistics for Mean Percent Change From Baseline at Each Time Point: LDL-C

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%.

Both the 80-mg- and 160-mg- in divided doses group showed statistically significant decreases of LDL-C from baseline ($p<0.001$).. This included Pt. #10, who was receptor negative due to promotor mutation. His LDL-C decreased by 41% and 45% on 80-and 160-mg respectively. The explanation of his response is not readily apparent. As impressive as these percent decreases are, a closer look at the individual LDL-C plots are shown in Sponsor's Figures 3 and 4.and reproduced as Figure 5.4.1.

Figure 5.4.1.
Individual Plots of LDL-Cholesterol (mg/dL) 80-/160-mg Group



At the 80 mg/day dose period, 7/8 patients had LDL-C greater than 330 mg/dL

At 160 mg/day dose period, 7/8 patients had LDL-C greater than 320 mg/dL

All these LDL-C levels are unacceptably high, especially considering the natural history of homozygous FH. One of the Sponsor's proposed indication for 80 mg simvastatin was, "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". In this study (Protocol #114), 40 mg simvastatin dose (either as a single dose or in divided doses) was used as the "active control". Patients were not exposed to LDL-apheresis. Therefore comparison with LDL-apheresis induced LDL-C decreases could not be made. It is obvious that high dose simvastatin (either 80 mg or 160 mg in divided doses) cannot be stand-alone therapy for patients with homozygous FH.

5.4.1.4.3 Safety evaluations:

The safety data submitted on the adverse effects on the body as a whole, on different body systems are consistent with previously reported safety data. No new unlabeled adverse effects were seen. This review will focus on the followings: the effects on the liver, on the muscle and on adrenal-gonadal steroids.

5.4.1.4.3.1 Effects on liver and muscle:

Clinically important elevations in AST, ALT, and CK , defined as consecutive elevation three times the ULN in ALT or AST or 5 or 10 times the ULN in CK. are summarized in Sponsor's Table 29 and reproduced as Table 5.4.3..

Table 5.4.3.

Number (%) of Patients With Elevations in Liver Functions and Creatine Kinase

	40 mg/day	High Dose
Consecutive elevations >3 x ULN in AST	0/4 (0.0)	0/8 (0.0)
Consecutive elevations >3 x ULN in ALT	0/4 (0.0)	0/8 (0.0)
One or more elevations >5 x ULN in CK	0/4 (0.0)	0/8 (0.0)
One or more elevations >10 x ULN in CK	0/4 (0.0)	0/8 (0.0)

As can be seen from the above, no patient developed consecutive elevations of >3X ULN in ALT or AST or 5 or 10 times the ULN in CK.

5.4.1.4.3.2 Effects on Adrenal/Gonadal Steroids:

There were no significant changes from baseline ($p>0.100$) of testosterone, FSH, and LH in the treatment groups.

Serum cortisol changes were shown in Sponsor's Table 32 and reproduced as Table 5.4.4.

Table 5.4.4.

Summary Statistics for Mean Change From Baseline at Weeks 9 and 18 Serum Cortisol (mcg/dL)

Week	Simvastatin Dosage	N	Pre Mean	Post Mean	Change From Baseline				
					Min	Max	Mean	SD	Median
9	40 mg (1 dose)	4	23.6	19.5	-6.8	1.7	-4.1	3.9	-5.7
	80 mg/day (3 doses)	8	24.7	20.7	-8.3	-1.7	-4.0**	2.7	-2.7
18	40 mg/day (3 doses)	4	23.6	19.4	-6.6	1.0	-4.2*	3.6	-5.6
	160 mg/day (3 doses)	8	24.7	20.7	-9.6	4.8	-4.0*	4.6	-4.5
*, *, ** Significant change from baseline at the $p<0.100$, $p<0.050$, and $p<0.010$ level, respectively.									

First of all, cortisol was given as **mcg/dL** instead of **ug/dL**. This represents a typographic error as was in the text, "Only 1 patient in the 40-mg group had a cortisol level less than 10 **mg/dL** on treatment" There was mean change of -4.0 at Week 9 from baseline serum cortisol at the 80 mg/day (3 doses). This difference was statically significant ($p<0.01$). There were mean changes of -4.2 and -4.0 from baseline at Week 18 for the 40 mg/day(3 doses) and 160 mg/day(3 doses). These differences were statistically significant ($p<0.05$). However, the mean post-treatment cortisol levels of 20.7, 19.4 and even the 10 ug/dL are within the normal range. The observed statistically significant changes are therefore of questionable clinical significance.

5.4.1.5 Reviewer's Comment/Conclusion of study Results:

In this small, (12 patents), and short duration, (18 weeks), study of homozygous FH patients, no safety concerns emerged.

As shown in Figure 5.4.1. and discussed under Efficacy of Primary endpoint outcome evaluation, high dose simvastatin (either 80 mg or 160 mg in divided doses) cannot be stand-alone therapy for patients with homozygous FH. And since patients were not exposed to LDL-apheresis, meaningful comparison with LDL-apheresis induced LDL-C decreases could not be made.

6. Overview of Safety:

Since simvastatin's approval in 1991, there had been extensive experience both in U.S. and world-wide. The adverse effects on the body as a whole, on different body systems and the drug-drug interactions have been reported and evaluated by the Agency. The safety data submitted are consistent with the previously reported data. Therefore, this review will only focus on those safety concerns possibly due to the increased 80 mg dosage: the effects on adrenal-gonadal steroids, the effects on the muscle, and on the liver.

6.1. Effects on adrenal/gonadal Steroids:

There had been several clinical studies, one in the original marketing application and 5 in this marketing application which showed small mean reductions of total testosterone from baseline. There was also an uncontrolled study on 24 hypercholesterolemic patients treated with simvastatin 40 mg/day for 8 weeks. There was a small reduction in peak cortisol response to ACTH . The male gonadal and adrenal study was therefore undertaken to further evaluate these findings.

6.1.1. Objectives:

The primary objective was to evaluate the effects of simvastatin 80 mg/day on the Cortrosyn stimulated cortisol response in men. The secondary objective was to evaluate the effects of simvastatin 80 mg/day on T levels in men.

6.1.2. Design:

A double-blind, randomized, placebo-controlled, parallel, multicenter study of 16 weeks duration.

6.1.3. Protocol #123:

6.1.3.1 Population/procedures:

Patients were eligible for enrollment in the study if they met all of the following criteria: 1) At randomization, while on diet, all patients had a plasma LDL-C >145 mg/dL. and TG <350 mg/dL.2) Normal screening hormone profiles: cortisol, total-T, prolactin, thyroid-stimulating hormone.

Patients were excluded if their ages were greater than 65 or less than 21 and a diagnosis of Types 1, III, IV, V hyperlipidemia. Other exclusion criteria were similar to those in the Phase III studies (protocol 117).

There were two protocol formats:

"Format 1 (F1), patients received baseline and Week 12 Cortrosyn stimulated and basal cortisol testing, and ACTH -stimulated T testing". 33 patients were in this Format.

"Format 2 (F2), only basal and hCG-stimulated T testing". 76 patients were in this Format.

After a 4-week placebo run-in period, patients were equally randomized to receive 12

weeks of therapy with simvastatin 80 mg (once daily in the evening) or placebo. As in Phase III study (protocol 117), 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. The patient Charecteristics are shown in Table 6.1 (Sponsor's Table 9).

Table 6.1

Summary of Baseline Demographic Characteristics—Patient Count (%)

	Simvastatin 80 mg (N=42)		Placebo (N=41)		Total (N=83)	
	n	%	n	%	n	%
Gender						
Men	42	(100.0)	41	(100.0)	83	(100.0)
Women	0	(0.0)	0	(0.0)	0	(0.0)
Age						
20 and under	1	(2.4)	0	(0.0)	1	(1.2)
21 to 30	5	(11.9)	4	(9.8)	9	(10.8)
31 to 40	8	(19.0)	11	(26.8)	19	(22.9)
41 to 50	11	(26.2)	14	(34.1)	25	(30.1)
51 to 60	10	(23.8)	9	(22.0)	19	(22.9)
61 to 70	7	(16.7)	3	(7.3)	10	(12.0)
71 and over	0	(0.0)	0	(0.0)	0	(0.0)
Mean		46.2		44.7		45.4
SD		12.28		10.65		11.46
Median		46.5		43.0		44.0
Range		20 to 65		22 to 65		20 to 65
Race						
Asian	0	(0.0)	1	(2.4)	1	(1.2)
Hispanic American	1	(2.4)	0	0	1	(1.2)
Black	1	(2.4)	3	(7.3)	4	(4.8)
White	40	(95.2)	37	(90.2)	77	(92.8)

The patients were well-matched in terms of number, and age (age distribution). Over 90% of the patients were white for both groups.

6.1.3.2 Endpoints:

The adrenal function endpoints were: basal cortisol and peak cortisol response to the 6-hour Cortrosynâ stimulation test. The gonadal function endpoints were T, LH, FSH and

SHBG parameters.

The primary analyses are based on the per-protocol approach at Week 12. The Sponsor offered the following justification, " This is essentially a safety study and the per-protocol approach was considered a more conservative strategy toward identifying safety concerns since protocol violators (e.g., off drug) may not be indicative of the patient population being targeted for evaluation. A supplementary intention-to-treat analysis was also performed at Week 12 for cortisol and hormones. The intention-to-treat population included all randomized patients with valid baseline and at least one on-therapy measurement". Please see Statistical Review for evaluation of this approach.

6.1.4. Results:

Cortisol-Basal: The results from the analysis of percent change from baseline in basal cortisol for F1 patients are provided in Table 6.2 (Sponsor's Table 17)

Table 6.2
Analysis of Basal Cortisol at Week 12 Per-Protocol Approach

Treatment Group	N	Mean (µg/dL)		Percent Change From Baseline			
		Baseline	Week 12	Mean	SD	LS Mean	95% CI for Mean
Placebo	17	15.9	15.0	4.9	47.8	4.9	(-15.2, 24.9)
Simvastatin 80 mg	16	15.2	14.1	-5.2	26.8	-5.7	(-26.5, 15.2)

Between-Group Comparison	p-Value	LS Mean	95% CI for Difference
Simvastatin vs. Placebo	0.461	-10.5	(-39.3, 18.3)

p-Value for Effect	
Treatment	0.461
Study Center	0.900

Root MSE of Percent Change = 40.3

The mean of percent changes from baseline were -5.2 and 4.9 for simvastatin 80 mg and placebo groups. The differences were not statistically significant. More importantly, the difference between the groups was not significant (p=0.461). Similar analysis for patients in the F2 Format (not shown) also demonstrated no significant differences between the placebo and simvasatatin 80 mg groups (p=0.342).

Cortisol-Stimulated Peak:

The simvastatin and placebo groups had non-significant (p>0.100) mean changes from baseline of -1.7 and -1.2 ug/dL respectively. The between-group comparison was also not significant (p=0.743).

Testosterone-Basal: Nonparametric analysis of total basal pooled T at Week 12 is shown in Table 6.3 (Sponsor's Table 19).

Table 6.3.
Nonparametric Analysis of Total Basal Pooled Testosterone at Week 12 Per-Protocol Approach

Parameter	Treatment	N	Median		% Change		p-Value	
			Baseline	Week 12	Median	SD	Between Group	Center
Total Basal Pooled T (ng/dL)	Placebo	39	541.0	536.0	-1.5	20.5	0.091	0.244
	Simvastatin	37	513.0	474.0	-13.6	30.4		
Note: No significant change from baseline (p>0.050) was observed.								

No significant change from baseline was observed (p>0.050). However, the Sponsor stated,"the difference between the treatment groups approached significance (p=0.091). In the intention-to treat population, the difference between the groups was significant (p=0.049)". To evaluate the clinical implication of this statistically significant difference, it is useful to consider Free T since Free T is biologically active and physiologically more relevant. Table 6.4 (Sponsor's Table 21) shows the nonparametric analysis of free basal pooled testosterone at Week 12

Table 6.4.
Nonparametric Analysis of Free Basal Pooled Testosterone at Week 12 Per-Protocol Approach

Parameter	Treatment	N	Median		% Change		p-Value	
			Baseline	Week 12	Median	SD	Between Group	Center
Free Basal Pooled T (pg/mL)	Placebo	39	131.0	118.0	4.9	44.4	0.588	0.718
	Simvastatin	37	122.0	101.0	-6.3	43.5		
Note: No significant percent change from baseline (p≥0.100) was observed.								

No statistically significant differences were observed in either the percent change from baseline within the group or between the placebo and simvastatin groups.
Sponsor further presented nonparametric analysis in hCG-induced changes in testosterone, hCG-induced changes in bioavailable pooled T at Week 12, LH/FSH at Week 12 as well as Sex Binding Globulin at Week 12. None of these parameters showed statistically significant either within- or between group changes.

6.1.5. Reviewer's Comment/Conclusion:

For more detailed review of Sponsor's statistical approaches of nonparametric vs parametric analysis , per-protocol vs. Intention-to-treat , please see Statistical Review. This reviewer is satisfied that no significant differences were detected in the adrenal/gonadal functions in between the placebo and the 80 mg dose groups.

6.2. Safety Update:

On 12/4/97, the Sponsor submitted a Safety Update Report which provides new clinical and laboratory safety data for a total of 765 patients that participated in the 6-month,

double-blind, placebo-controlled, Phase III (Protocol 117) extension studies . Table 6.5 shows the total number of patients of simvastatin 80 mg clinical program (Sponsor's Table 1 of Safety Update).

Table 6.5
Patient Accounting Summary of Simvastatin 80 mg Clinical Program

Protocol	Number of Patients Who Received Simvastatin 80 mg/day in the Original Application	Number of Patients Who Received Simvastatin 80 mg/day During the Safety Update Report Period	Number of Patients Who Received Simvastatin 80 mg/day in the Original Application and/or the Safety Update Report Period
111	149	NA	149
117	669	765	862[†]
121	93	NA	93
123	42	NA	42
Total	953	765	1146

NA = Not applicable.
[†] One hundred ninety-three patients rerandomized from simvastatin 40 to 80 mg/day in the extension.

The Phase III extension study adds significant number of patients and 6-month longer duration of exposure to the 80 mg simvasatatin program. The study design, diet and protocol procedures are similar to the Phase III studies as shown in Table 6.6.

Table 6.6
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[‡]	448	505
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)	S 40 (86) S 80 (362)	S 40 (102) S 80 (403)
Age (years)	21 to 70	21 to 70	21 to 70	21 to 70	21 to 65	21 to 71	21 to 71

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

6.2.1. Population:

The demographic and other Charecteristics of the study population can be seen in Table 6.7 (Sponsor's Table 5)

Table 6.7

Baseline Patient Characteristics for Patients Who Received Simvastatin 80 mg/day

	Original Application Period	Safety Update Report Period
	(N=962)	(N=765)
	n (%)	n (%)
Gender		
Female	366 (38.0)	301 (39.3)
Male	596 (62.0)	464 (60.7)
Age[†]		
20 and under	2 (0.2)	1 (0.1)
21 to 30	34 (3.5)	27 (3.5)
31 to 40	107 (11.1)	84 (11.0)
41 to 50	239 (24.8)	185 (24.2)
51 to 60	315 (32.7)	250 (32.7)
61 to 70	261 (27.1)	216 (28.2)
71 and over	4 (0.4)	2 (0.3)
Mean	52.5	52.8
SD	10.86	10.97
Median	54.0	54.0
Range		
Race		
Asian	10 (1.0)	12 (1.6)
Black	27 (2.8)	19 (2.5)
Hispanic	52 (5.4)	52 (6.8)
Multi-racial	12 (1.2)	10 (1.3)
Other	3 (0.3)	2 (0.2)
White	858 (89.2)	670 (87.6)

The patients were well-matched in terms of gender, age and race distributions.

6.2.4. Results:

The incidence of clinical and laboratory adverse experiences (AEs) in this extension study are similar to the original submission. As before, this evaluation will focus on the special safety concerns of the effects on adrenal/gonadal functions, on muscle and liver.

6.2.4.1 Effects on Adrenal/Gonadal functions:

The results obtained on Cortisol, Testosterone LH and FSH were consistent with the findings in the original Phase III studies. The male Adrenal/Gonadal Study (see 6.1.) had already evaluated these findings. This reviewer agrees with the Sponsor's conclusion, "there is no evidence that they are of clinical relevance".

6.2.4.2 Effects on Muscle

The most feared adverse effect of simvastatin and other inhibitors of HMG-CoA reductase is myopathy. The mechanism is unknown since fibrates and niacin with different pharmacological properties can also cause myopathy. The clinical manifestation includes unexplained muscle pain or weakness with elevated CK (up to 10X ULN). The most serious form of myopathy, rhabdomyolysis , with or without acute renal failure, can also occur.

The number of patients with myopathy in the Phase III studies are shown in Table 6.8 (Sponsor's Table 23).

Table 6.8
Patients with Myopathy in the Phase III Studies

Study Number	AN	Age/Gender/Race	Concomitant Medication	Relative Onset Day	Peak Creatine Kinase Level (mIU/mL)	Plasma Level# ng•eq/mL
Simvastatin 40 mg (N=436*)						
117042	1615	29/M/ White	None	39	1341	--
Simvastatin 80 mg (N=669*)						
117012	263	68/M/White	Lisinopril, timolol optic	40	1910	102
117014	323	52/F/White	Nefazodone, metronidazole, clarithromycin, cisapride	76	8750	51
117028	1292	61/F/Hispanic	None	36	9590	30.9
117024	1338	63/F/Multiracial	Nifedipine, captopril	17	10,110	--
117001	1379	65/M/Hispanic American	Verapamil, omeprazole	23	1624	39.4

‡ Unexplained muscle pain or weakness accompanied by elevations of CK to 10x the upper limit of normal.
# Total HMG-CoA reductase inhibitory activity in sample drawn approximately 12 hours after the last dose. Expected level ~10 ng•eq/mL [4].
* All patients treated, regardless of whether a CK value was available (see Table 24).

As shown above, 1 patient in the 40-group and 5 patients in the 80-mg group developed myopathy (most of the cases were reported within the first 3 months of therapy). Consistent with the general observation that patients who develop myopathy frequently have high concentrations of HMG-CoA reductase inhibitory activity in plasma, 4 patients on 80 mg-dose (who had total HMG-CoA reductase inhibitory activity measured) all showed 3-10 X the expected normal level of ~10 NG eq/ml None of patients had myoglobinuria or was hospitalized, and the muscle symptoms and elevated CKs resolved upon discontinuation of simvastatin.

The risk of myopathy during therapy with simvastatin is approximately 0.1% at doses up to 40 mg/day according to the Drug Labeling. In the Phase III base studies, 5 of 669 patients receiving the 80-mg dose developed myopathy, for a 6-month incidence of 0.7%. In the 6-month extension of these studies, none of the 765 patients receiving the 80-mg

dose had myopathy as defined above. In the Phase IIb studies (149 patients) and Phase IIb-extension study (126 patients), myopathy did not develop in any of the 240 patients on 80 mg/day of simvastatin.

The incidence of elevated CK are somewhat higher as can be seen in Table 6.9 (Sponsor's Table 19 in Safety Update).

Table 6.9

Number (%) of Patients With Elevations in Creatine Kinase Intention-to-Treat Approach

	Original Application Period	Safety Update Report Period	Cumulative Data
Number (%) of patients with:[1]			
One or more elevations (2 x ULN to 3 x ULN) in CK	32/664 (4.8%)	32/759 (4.2%)	54/860 (6.3%)
One or more elevations (>3 x ULN to 5 x ULN) in CK	13/664 (2.0%)	11/759 (1.4%)	25/860 (2.9%)
One or more elevations >5 x ULN in CK	13/664 (2.0%)	8/759 (1.1%)	21/860 (2.4%)
One or more elevations >10 x ULN in CK	7/664 (1.1%)	3/759 (0.4%)	10/860 (1.2%)

[1] Number of patients with elevated test/patients tested.

Three of the 759 patients in the 6-month extension study had 10X ULN of CK elevations. 2/3 only had single elevation which were not considered to be drug-related by the investigator. The one remaining patient had multiple elevations and were not associated with muscle symptoms. He completed the study without any clinical adverse effect.

It is useful to compare the degrees pf CP elevations in terms of the simvastatin dosage. This is shown in Table 6.10 (Sponsor's Table 24)

Table 6.10

Patients With Marked Elevations in Creatine Kinase—Patient Count (%) #
Phase III Studies Intention-to-Treat Approach

Number (%) of Patients With One or More CK Elevations:	S 40 mg	S 80 mg	p-Values
(2 x ULN to 3 x ULN)	12/433 (2.8%)	32/664 (4.8%)	0.090
(3 x ULN to 5 x ULN)	6/433 (1.4%)	13/664 (2.0%)	0.480
>5x ULN	2/433 (0.5%)	13/664 (2.0%)	0.038
>10x ULN	1/433 (0.2%)	7/664 (1.1%)	0.118

#Number of patients with elevated test/patients tested.

As indicated in the above Table, patients on the 80 mg dose developed higher percentages of elevated CKs. The > 5X ULN reached statistical significance (p=0.038). And the incidence of myopathy increased from 0.1% in the 40 mg- to 0.7% in the 80 mg- dose groups. Clinically, elevated CK serves as an "early warning marker" for possible development of myopathy.

6.2.4.3 Effects on Liver

The liver is the target organ for simvastatin and all drugs in this class tend to increase transaminase levels with ALT increases more than AST. The molecular basis for this effect is unknown. Persistently elevated transaminase levels > 3 x ULN have been used as markers for possible hepatic toxicity. Clinically this "early warning signal" has withstood the test of time for all the HMG-CoA reductase inhibitors.

In the Phase III studies there were more patients with marked elevations of transaminases in the 80-mg group, as shown in Table 6.11 (Sponsor's Table 25)

Table 6.11

Patients With Marked Elevations in Transaminases—Patient Count (%) #

Phase III Studies Intention-to-Treat Approach

	S 40 mg	S 80 mg	p-Values
Number (%) of patients with one or more elevations >3 x ULN:			
ALT	6/433 (1.4%)	26/664 (3.9%)	0.015
AST	4/433 (0.9%)	18/664 (2.7%)	0.039
ALT or AST	6/433 (1.4%)	26/664 (3.9%)	0.015

Number of patients with elevated test/patients tested.

The differences between the 40-mg and the 80 mg dose groups are statistically significant as shown. This can be further confirmed by Sponsor's Table 26, reproduced below as Table 6.12

Table 6.12

Change From Baseline in Transaminases at Week 24 Phase III Studies Intention-to-Treat Approach

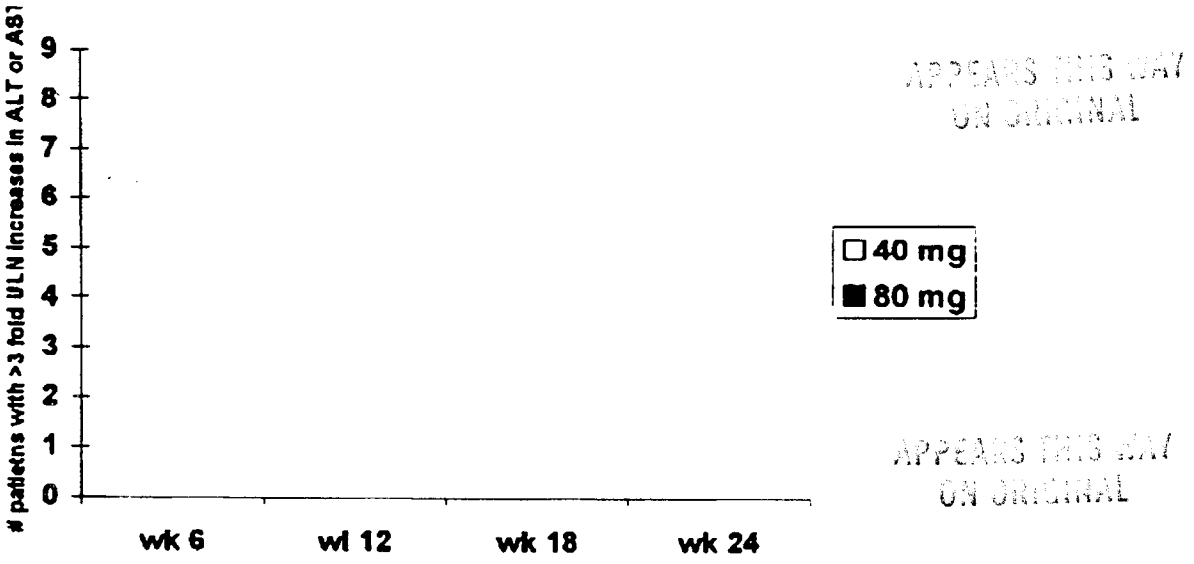
Parameter	Simvastatin Treatment	N	Median		Change		p-Value	
			Baseline	Week 24	Median	SD	Within Group	Between Group
ALT (mIU/mL)	40 mg	433	13.00	16.00	3.00	5.58	<0.001	<0.001
	80 mg	664	14.00	18.00	4.00	8.37	<0.001	
AST (mIU/mL)	40 mg	433	15.00	17.00	1.00	4.65	<0.001	<0.001
	80 mg	664	15.00	18.00	2.00	4.65	<0.001	

As can be seen , the 80 mg-group also had larger median increases in ALT and AST. All these differences are highly significant ($p<0.001$).

The time to the first elevation in ALT/AST for the two dose groups can be appreciated from Figure 6.1 (Sponsor's Fig. 1 of the 12/26/97 letter).

Figure 6.1

Time to First Increase in ALT or AST in Patients with >3X Increases in LFTs.



The majority of initial increases occurred between 12 and 24 weeks in the 80 mg dose group. However, this Figure is misleading since the original Phase III studies only lasted 24 weeks. In the extension study, the time of first elevation can be seen in Table 6.14 (Sponsor's Table 22)

Table 6.14

Patients With ALT and/or AST Elevations >3 x ULN Without Other Cause Phase III Extension Studies Intention-to-Treat Approach

AN	Age /Gender/Race	Week of First Elevation	Consecutive Elevation	Peak ALT/AST mIU/mL	Discontinued
Patients Receiving Simvastatin 80 mg During Base Study and 80 mg During Extension					
67[r]	57/F/W	24	Yes	134/107	Yes
223	53/M/W	40	No	80/35	No
413	53/M/W	40	No	42/105	No
552[r]	38/F/W	24	No	80/53	No
1522[r]	37/M/W	24	No	61/78	No
1526[r]	33/M/W	24	Yes	375/168	Yes

Two patients had initial non-consecutive elevations on week 40.

Since there are other causes for the elevated ALT/AST, it is important to examine only those patients without other causes This is shown in Table 6.13 (Sponsor's Table 27)

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Table 6.13: Patients With ALT and/or AST Elevations >3 x ULN Without Other Cause

AN	Age/ Gender/Race	Week of First Elevation	Consecutive Elevation	Peak ALT/AST mIU/mL	Discontinued
Simvastatin 40 mg N=433*					
157	F/White	6	Yes		Yes
449	F/White	24	Assumed [1]		Effectively[3]
624	F/White	12	Yes		Yes
1272	F/White	18	No		No
1314	F/Multiracial	12	No		No
Simvastatin 80 mg N=664*					
67	F/White	24	Yes		Effectively[3]
395	F/Hispanic	18	Yes		Yes
454	M/White	18	Yes		Yes
552	F/White	24	Yes		No
602	M/White	12	Yes		Yes
628	M/White	18	Yes		Yes
631	M/White	12	No		No
643	F/White	18	No		No
1150	M/White	24	Assumed [1]		Effectively[3]
1255	F/White	18	No		No
1406	M/White	6	Yes		Yes
1435	F/White	12	Assumed[2]		Yes
1458	F/White	12	Assumed[2]		Yes
1475	F/White	18	Assumed[2]		Yes
1522	M/White	24	No		No
1526	M/White	24	Assumed[1]		No
1591	F/White	18	No		No

*Number of patients with at least one transaminase measurement.
[1] Elevations at Week 24 with no available follow-up data within 1 week.
[2] Discontinued without a repeat test.
[3] Patient with elevation at final visit (Week 24) who did not enter extension.

There were 22 patients with >3X ULN increases: 5 on 40 mg and 17 on 80 mg doses .In the 12/26/97 communication from Dr. C. Hyman, Director, Regulatory Affairs, stated that 14, rather than 13 patients were discontinued and only 8 remained on the trial. (AN#1526 was discontinued). Of the 8 patients, 2 were on 40 mg and 6 were on 80 mg. The Sponsor stated," The 40 mg patients; AN 1272, and 1314, remained on drug and had partial or full resolution of the increase after 8 and 13 days, respectively. Of the 6 patients on 80 mg who continued in the trial, 5 (AN 552, 631, 643, 1522, 1591) completed the six-month extension and remained on drug throughout. The time course for resolution or near resolution of enzyme elevations spanned 17 to 98 days.The remaining patient (AN 1255) had an elevation during the base study and drug was discontinued for one week with partial resolution. The patient was subsequently discontinued from the base study due to a clinical adverse experience."
Of the 14 patients discontinued from the trial, all the three 40-mg patients' elevations resolved 20-25 days after drug discontinuation. Of the 80 mg group, 3 patients were lost for follow-up, one patient resolved after 41 days and 7 patients had resolution or partial;

resolution 7 to 23 days after drug discontinuation

6.2.5. Reviewer's Comment/Evaluation of study results

As the simvastatin dose is increased from 40 mg- to 80 mg/day, the following were observed:

(1). No change in adrenal/gonadal functions.

(2). More patients developed elevated Cks, particularly in the higher multiples of ULN.

(3). Elevated ALT/AST (either single or multiple elevations) occurred in more patients and the median increases were larger. The time of initial elevation is variable i.e. from 6 to 40 weeks Therefore, frequent monitoring of ALT/AST is needed throughout the therapy. These elevations had either partial or complete resolutions after discontinuation of simvastatin . Time to resolution varied from 17 to 98 days. Again, frequent monitoring is indicated.

6.3. Clinical Pharmacology of Cytochrome P450 3A4

Simvastatin and other HMG-CoA reductase inhibitors are substrates for CYP3A4. Drugs that inhibit CYP3A4 can potentially raise blood levels of HMG-CoA reductase inhibitors and increase the risk of AEs. A study was conducted to determine whether simvastatin at higher doses in vivo become an inhibitor of CYP3A3. For in-depth evaluations, please see Chemistry/Pharmacology reviews.

7. Overall Evaluation

7.1. Safety Evaluation

7.1.1 Deaths

A total of two deaths were reported in the cumulative data on simvastatin 80 mg/day. These deaths occurred in the original Phase III studies, no new deaths were reported for the Safety Update Report. The pertinent data are shown in Table 7.1(Sponsor's Table 12)

Table 7.1
Listing of Patients Who Died Cumulative Total

Study Number	AN[1]	Gender	Race		Phase	Relative Day of Onset	AE	Duration of AE	Severity	Serious	Action Taken	Drug Relationship
Simvastatin 80 mg												
117004	10	M	White		Treatment	98	Myocardial infarction	1 day	Severe	Y	Therapy discontinued	Definitely not
117036	1098	M	White		Treatment	103	Myocardial infarction	1 day		Y	Therapy discontinued	Definitely not

[1]AN = Allocation Number.
"Onset day relative to study" indicates the number of days since start of treatment.

This reviewer agrees with the Sponsor's interpretation that these two death due to myocardial infarction are unlikely to be drug-related.

7.1.2 Ophthalmologic Findings

Cataracts were noted in two patients (pts 1564 and 181). Although there were theoretical concerns about cataracts with HMG-CoA reductase inhibitors, several large well-controlled studies have not found any adverse effects of simvastatin on the human lens.

This reviewer agrees with the Sponsor's view that , "In these two elderly men, this finding, more likely represented natural disease progression than a drug-related effect".

7.1.3. Other Safety Concerns

The incidence of clinical and laboratory adverse experiences (AEs) in patients with hypercholesterolemia in the Phase III studies (original and the extension studies) and the cumulative safety profile of long-term use of simvastatin up to 40 mg/day are similar. Special safety evaluations of the effects of simvastatin 80 mg/day on muscle, adrenal/gonadal functions were performed. No new or unexpected safety concerns were observed.

With the 80 mg/day dose, >3X ULN elevations of ALT/AST (either single or multiple elevations) occurred in more patients and the median increases were larger. The incidence was 6/433 or 1.4% for the 40 mg dose and 26/664 or 3.9% for the 80 mg dose (See Table 6.11). After subtracting out other causes of elevated ALT/AST, the incidence was 5/436 or 1.1% for the 40 mg dose and 17/669 or 2.5% for the 80 mg dose. (See Table 6.13). As was discussed in 6.2.5. the time to initial elevation and time to resolution (partial resolution) were quite variable, frequent monitoring of ALT/AST is indicated throughout simvastatin therapy.

7.2 Efficacy

7.2.1 Simvastatin 80 mg/day for the treatment of hypercholesterolemia of Types IIa and IIb

7.2.1.1 Primary Endpoint: LDL-C Reduction

The combined Phase III studies and the 6-month extension study demonstrated that 80 mg- was more effective than the 40 mg/day in LDL-C reduction (47% vs. 40.5%, $p<0.001$). The controlled Phase II and Phase IIb extension studies provided similar corroborative data. As was discussed in 5.1.5, the clinical or angiographic data relating the increased LDL-C reduction to improved clinical benefit have not been collected /presented. Therefore, claim of additional clinical benefit cannot be made.

7.2.1.2 Secondary Endpoints: TG-reduction

For TG, the median percent reduction was 18% versus 24% ($p<0.001$) for the 40- and 80-mg doses respectively. Since elevated TG has not been shown to be an independent risk factor for CHD, the clinical significance/benefit of TG reduction is unknown as was discussed in 5.1.5.

7.2.2. Simvastatin 80 mg/day for treatment of homozygous familial hypercholesterolemia

In the submitted study (Protocol #114), 40 mg simvastatin was used as "active control". Patients on 80-and 160-mg in divided doses achieved 25% and 31% LDL-C reductions compared to 14% in the 40 mg dose.($p<0.001$). However, at the 80 mg/day dose period, 7/8 patients had LDL-C greater than 330 mg/dL. At 160 mg/day dose period, 7/8 patients had LDL-C greater than 320 mg/dL. All these LDL-C levels are unacceptably high, especially considering the natural history of homozygous FH. High dose simvastatin (either 80 mg or 160 mg in divided doses) cannot be stand-alone therapy for patients with homozygous FH. Simvastatin cannot replace LDL-apheresis therapy. Simvastatin can be a component of a comprehensive treatment regimen which includes diet, bile-acid

sequestrans, and LDL-apheresis. The addition of simvastatin may serve the useful purpose of decreasing the need/frequency of LDL-apheresis. In such a comprehensive regimen, it is preferable to use as a low dose as possible to minimize the adverse effects.

8. **Proposed Labeling**

Only the proposed changes in this submission will be reviewed and commented.

8.1: **Clinical Pharmacology**

"One third of patients obtained a reduction in LDL-cholesterol of 53% or more at the 80 mg dose. The percent reduction in LDL-cholesterol was essentially independent of the baseline level."

The following should be added:

Although the 80 mg dose was more effective than 40 mg/day in LDL-C reduction (47.2% vs. 40.5%). The clinical or angiographic data relating the increased LDL-C reduction to improved clinical efficacy have not been collected/presented.

At the end of the first paragraph, "....patients with triglycerides > 350 mg/dL were excluded." the following statement should be added:

Elevated TG levels has not been established as an independent risk factor for coronary heart disease (CHD) in the general population Furthermore, the independent beneficial effects of lowering TG on cardiovascular endpoints are yet to be established.

At the end of the second paragraph,".....LDL-cholesterol reduction of 41% with the 80 mg dose.", the following should be added:

At the 80 mg/day dose , 7/8 patients had LDL-C greater than 330 mg/dL. At 160 mg/day dose , 7/8 patients had LDL-C greater than 320 mg/dL.

8.2. **Clinical Pharmacology, Endocrine Function**

The following paragraph should be added:

A small, (12 patents), and short duration, (18 weeks), study of homozygous FH patients, revealed no adrenal/gonadal abnormalities. However, the study population's age were 15-39 years of age. Patients with homozygous familial hypercholesterolemia can be diagnosed and therapy should be started in childhood. The effects of simvastatin on the adrenal/gonadal functions in this age--group are unknown. The relevant clinical parameters that should be monitored are growth and development rather than spermatogenesis and sexual dysfunction.

8.3. **Indications and Usage**

The paragraph, "Zocor is also indicated ti 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 ." should be replaced with the following paragraph :

High dose simvastatin (either 80 mg or 160 mg in divided doses) cannot be stand-alone therapy for patients with homozygous FH. Simvastatin cannot replace LDL-apheresis therapy. Simvastatin can be a component of a comprehensive treatment

regimen which includes diet, bile-acid sequestrans, and LDL- apheresis. The addition of simvastatin may serve the useful purpose of decreasing the need/frequency of LDL-apheresis. In such a comprehensive regimen, it is preferable to use as a low dose as possible to minimize the adverse effects. Patients with homozygous familial hypercholesterolemia can be diagnosed and therapy should be started in childhood. The optimal dosage and safety in these pediatric patients are yet to be established.

8.4: Indications and Usage, General Recommendations
Add the same paragraph as was suggested for the **Clinical Pharmacology, 6.1.).**

8.5: Warning, Liver Dysfunction
"In 2 controlled clinical studies in 1105 patients, the 6 month incidence of persistent hepatic transaminases elevations considered drug -related was 0.7% and 1.8% at the 40 and 80 mg dose, respectively".
The correct percentage should be :
the incidence was 5/436 or 1.1% for the 40 mg dose and 17/669 or 2.5% for the 80 mg dose.

8.6: DOSAGE AND ADMINISTRATION ,Dosage in Patients with Homozygous Familial Hypercholesterolemia
See Comment in **5.4** and **8.3**

9: Recommendations
Zocor 80 mg/day should be approved for the indications specified in the revised Labeling..

/S/

S.W.Shen,~~M.D.~~
Medical Officer, HFD-510

CC:
Original NDA-Supplement
HFD-510-File
HFD-510-SWSHEN
HFD-510-PSIMONEAU.

/S/
3/20/98
See team leader review
/S/

NDA 19-766/S-026
Zocor (simvastatin) tablets
Merck

Memo to the file: 6-30-98

No 90-day safety update is included in this application, as the complete safety data for the completed clinical trials were submitted in the 6-month safety-update.

In addition, the integrated summaries of safety and effectiveness are included in the medical reviews (medical officer and/or team leader).

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

/S/
6-30-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019766/S026/S028

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**2. NDA #** 19-766 Original NDA approved: 23-DEC-1991
3. NAME AND ADDRESS OF APPLICANT Merck & Co., Inc. P.O. Box 4 West Point PA 19486 (Phone): 610-397-2944	**4. SUPPLEMENT** SE2-026 & SCF-028 04-AUG-1997 (Rec. 05-AUG-1997)
	5. Name of the Drug ZOCOR™
	6. Nonproprietary Name Simvastatin
7. SUPPLEMENT PROVIDES for a new higher strength of Simvastatin tablets, 80 mg.	**8. AMENDMENT** -- SCF-028, 13-NOV-1997, 19-NOV-1997, and 06-APR-1998

9. PHARMACOLOGICAL CATEGORY HMG-CoA inhibitor used to treat hyper-lipidemia	**10. HOW DISPENSED** Oral	**11. RELATED** -N. A. -
12. DOSAGE FORM Tablet	**13. POTENCY** 80 mg	

14. CHEMICAL NAME AND STRUCTURE

Butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8α-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),-8αβ]]; $C_{25}H_{38}O_5$, F.W. = 418.57, CAS 56180-94-0 (For the structure, see Chemistry Review #1, dated 16-MAR-1988 in Vol. 3.1 of NDA 19-766).

15. COMMENTS

16. CONCLUSIONS AND RECOMMENDATIONS Satisfactory CMC information has been provided for the drug product. From the Chemistry point of view, this supplement can be approved.

17. REVIEWER NAME (AND SIGNATURE) **DATE**
COMPLETED 10-JUNE-1998
Sharon Kelly, PhD /S/ 25-JUN-98
R/D INITIATED BY

filename: 19766NDASup

DISTRIBUTION: Original: sNDA 19-766 cc: HFD-510 Division File CSO Reviewer

/S/
6/25/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019766/S026/S028

PHARMACOLOGY REVIEW(S)

Merck pp 2-5

NDA 19-766

April 16, 1998

Merck & Co.
West Point, PA

Submission: August 4, 1997 (S-26)

PHARMACOLOGY REVIEW OF SUPPLEMENTAL NDA

DRUG: Zocor (Simvastatin)

CATEGORY: Lipid Altering

SUBMITTED: New dosage formulation (80 mg) which requires new labeling

/S/

Elizabeth Barbehenn, Ph.D.

4/16/98

/S/

cc: NDA Arch
HFD-510
HFD-510/Steigerwalt/Barbehenn/Orloff/Simoneau
zocor label (S-26).doc

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DRAFT LABELING