

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020740/S002

MEDICAL REVIEW(S)

APR 5 1999
S. M. C. C. J. S.

NDA 20-740/S-002

Baycol (cerivastatin sodium) tablets

Bayer

Date of submission: 8-16-98

Date of review: 4-5-99

Proposal to market 0.4 mg dosage strength of cerivastatin

Team leader's note on supplemental NDA

Cerivastatin is marketed in the U.S. at dosage strengths of 0.2 and 0.3 mg to be taken once daily. Approved labeling cites a mean LDL-C reduction of 28.2% from baseline for the 0.3 mg dose in patients with primary hypercholesterolemia. Cerivastatin is indicated for use in patients with primary hypercholesterolemia and mixed dyslipidemia for the reduction of TC, LDL-C, apo B, and TG in conjunction with diet and exercise. Like other statins, cerivastatin use is associated with persistent hepatic transaminase elevations ($> \times$ ULN) in a small percentage ($<1\%$) of patients and has also been implicated in rare cases of myopathy and rhabdomyolysis, again like other statins. The mechanisms of these toxicities are not known, though for myopathy, the risk appears increased when statins are used in conjunction with other drugs themselves independently associated with myopathy (gemfibrozil, niacin). Furthermore, for those statins whose metabolism depends upon CYP 3A4, coadministration with inhibitors of that P-450 isozyme also increases the risk of myopathy, presumably by causing increases in systemic levels of active HMGRI, which may cause muscle damage through perturbation of muscle mevalonate metabolism. Monitoring of LFTs is recommended over the course of therapy with cerivastatin and labeling contains warnings about the risk of myopathy and the premonitory symptoms of same.

The current application presents data from controlled clinical trials in support of the safety and lipid lowering efficacy of cerivastatin 0.4 mg. The issues addressed below will include the patient exposure at this dose, the efficacy of the 0.4 mg dose in comparison to 0.2 and 0.3 mg, and the relative safety with regard to transaminase elevations and CK elevations.

It should be noted that cerivastatin is unique in the class of statins not only in its great potency in lipid altering (on a per-weight basis), but also in the fact that the two marketed doses do not differ by the usual factor of two in weight of active drug. The original development of cerivastatin included 0.05 and 0.1 mg doses, both of which were approved for marketing. The sponsor, however, chose to market only the 0.2 and 0.3 mg doses. The 0.2 mg dose is recommended for use in patients with moderate to severe renal insufficiency instead of the usual recommended dose of 0.3 mg. In the past, the Division has considered an incremental 4-6% lowering of LDL-C with increasing dose of statin to be "clinically significant." This is the equivalent of doubling the dose of statins, a phenomenon that holds across the class. This general guideline provides a framework for the assessment of risk versus benefit, though the 4-6% increment is not based on any clinical efficacy data; rather it merely falls out of the pharmacodynamics of the statin drug class. In the case of cerivastatin, the Division agreed to consider the 0.4 mg dose

even though it was not expected to (and did not turn out to) result in an mean incremental LDL-C lowering of 4-6% as compared to the 0.3 mg dose. This was done in part with the realization that the sponsor had intentions to study the 0.8 mg dose and also with the understanding that lipid altering drugs are titrated to effect and that in individual patients, across the class, increasing doses do result in incremental lipid lowering. Furthermore, a graded and continuous relationship between LDL-C lowering and cardiovascular disease risk reduction is assumed based on both epidemiologic and clinical interventional trial data. Finally, if 0.8 mg becomes available, the dosage range for cerivastatin will allow for titration across a range of lipid altering similar to that of pravastatin (currently available as 10, 20, and 40 mg). In sum, then, the approval of the 0.4 mg dose does not depend on LDL-C lowering 4-6% beyond that of the 0.3 mg and certainly does not require that in all studies the difference be statistically significant. Rather we will rely on the consistent finding of superior lipid lowering compared to 0.3 mg (and compared to 0.2 mg in one study) and an adequate exposure to assure both the relative and absolute safety of the new dosage strength.

Efficacy of cerivastatin 0.4 mg

The table that follows summarizes the exposure to cerivastatin 0.4 mg in US and non-US clinical trials submitted with the sNDA, including the 4-month safety update.

Patients exposed to cerivastatin 0.4 mg by duration of dosing					
	4 weeks	12 weeks	24 weeks	52 weeks	78 weeks
U.S. studies	443		412	385	100
Non-U.S.	463	323	316		
Total	906	323	728	385	100

The results of 5 studies were submitted with this application:

0149 was an 8-week study comparing cerivastatin 0.3 mg, 0.4 mg, and placebo (140, 138, 71 patients randomized, respectively).

D96-008 was a 2-week randomized, double-blind study comparing cerivastatin 0.3 mg, 0.4 mg, and placebo (225, 448, 220 patients randomized, respectively). This study had two extensions, one to 52 weeks (-008B) and a second to 78 weeks (-008C). After 8 weeks, the original placebo group was switched to fluvastatin 40 mg.

D97-001 was a small pilot study comparing cerivastatin 0.8 mg to placebo in 41 patients treated for 28 days.

0161 was a 24-week study comparing cerivastatin 0.2 mg and 0.4 mg (162, 332 patients randomized, respectively).

Z91-031 was a study, with follow up of some patients out to 18 months, of cerivastatin 0.3 mg, 0.4 mg, and lovastatin 40 mg (398, 82 patients randomized, respectively to cerivastatin 0.3/0.4 mg and lovastatin 40 mg).

For the most part, the above studies enrolled patients with primary hypercholesterolemia with LDL-C > 190, > 160, or >130 with < 2 risk factors, 2 or more risk factors, or with CHD, respectively. The cutoff for TG was 350 mg/dL. Thus, patients had either Fredrickson Type IIa or IIb lipoprotein phenotypes. The primary efficacy parameter for all studies was the mean percent change from baseline in LDL-C. In all the studies, the treatment groups were well matched at baseline for variables including age, sex, BMI, and plasma lipids.

The table below summarizes the lipid response data across the trials in this sNDA.

Lipid parameters	Study # (endpoint in wks)	Baseline mean (mg/dL)	Mean % change from baseline (N)					
			Ceriva 0.2	Ceriva 0.3	Ceriva 0.4	Ceriva 0.8	Fluva 40	Lova 40
LDL-C	0149 (8) D96-008 (52) D97-001 (4) 0161 (24) Z91-031 (29)*	~225 ~190 ~175	-30 (162)	-33 (140) -30 (148)	-36 (138) -31 (300) -38 (330) -33 (380)	-44 (27)	-23 (148)	-34 (82)
TG	0149 D96-008 D97-001 0161 Z91-031	~140 ~180	-10 (162)	-17 (132) -3 (148)	-14 (132) -4 (300) -10 (330) -16 (380)	-11 (27)	+5 (148)	-10 (82)
HDL-C	0149 D96-008 D97-001 0161 Z91-031	~54 ~49	+7 (162)	+6 (132) +9 (148)	+4.4 (132) +8 (300) +8 (330) +12 (380)	+3 (27)	+7 (148)	+10 (82)
TC	0149 D96-008 D97-001 0161 Z91-031	~305 ~275	-21 (162)	-25 (132) -20 (148)	-27 (132) -21 (148) -26 (330) -23 (380)	-31 (27)	-15 (148)	-23 (82)

The clinical efficacy results demonstrate that for LDL-C and TC, while the absolute change from baseline varies somewhat across studies, in those trials in which two doses of cerivastatin were compared, there is a clear dose-response in the mean changes from

baseline to endpoint. This is a consistent finding across the statin class. For HDL-C and TG, again consistent with the rest of the class, the effect of drug treatment on the mean change from baseline is much more variable across studies, and while the mean changes may be significantly different from placebo depending upon the size of a particular study, the individual responses are so highly variable that there is no reliable dose response.

The effect of cerivastatin was further examined as a function of baseline TG. In essence, for cerivastatin as well as for other statins so examined, the TG-lowering effect depends upon baseline TG (Stein, et al). The sponsor presents data pooled from seven studies of cerivastatin at various doses and analyzed examining the TG-lowering effect as a function of baseline TG. The table below from the submission summarizes these data.

Mean % change in TG from baseline as a function of baseline TG level			
Treatment group	TG baseline	N	Mean % change
Placebo	< 150 mg/dL	316	+6
	> 150- <250	288	+2.3
	> 250	115	+4.3
Ceriva 0.2 mg	< 150 mg/dL	246	-10
	> 150- <250	278	-15
	> 250	129	-19
Ceriva 0.3 mg	< 150 mg/dL	228	-9
	> 150- < 250	313	-17
	> 250	157	-22
Ceriva 0.4 mg	< 150 mg/dL	430	-9
	> 150- < 250	354	-16
	> 250	105	-25

Labeling with regard to TG lowering will need to be modified. The sponsor has proposed to pool data from several clinical trials in order to generate a tabular summary of overall lipid altering effects of cerivastatin. While this may be acceptable for effects on TC and LDL-C, it conveys misleading information with regard to HDL-C and TG effects, which, as mentioned above, are highly variable across patients with mean changes from baseline thus variable across different trials. While negotiations continue at this time, this reviewer recommends that data from representative studies be presented along with baseline lipid data for the study population or that the pooled data be presented as a function of baseline TG. Furthermore, for TG effects, because of the great variability in individual response, tabular presentation of data should include median, min, and max change from baseline. Another alternative is to present data for individual lipid responses from baseline as "cumulative incidence" curves, in other words showing, as a function of

absolute response from baseline, the percent of patients achieving at least that degree of response. This approach applies to both the HDL-C and TG response data.

Safety of cerivastatin up to 0.4 mg.

Liver function abnormalities and CK elevations

The mechanism by which statins cause elevations in transaminases is unknown. Across the class, the incidence of persistent elevations > 3 X ULN appears dose related. This review of cerivastatin safety will focus on study D96-008 which includes patients treated out to 78 weeks. This was a study comparing efficacy and safety of cerivastatin 0.3 mg, 0.4 mg, and fluvastatin 40 mg (this group switched from placebo after 8 weeks). The findings in this trial are representative of the safety findings in the other studies submitted to this sNDA.

The overall incidence of any ALT or AST elevations (not necessarily persistent) up to 3 X ULN was similar across the three treatment groups and between 35 and 40%. The incidence of elevations > 3 X ULN was between 0 and 2% across the three groups. The overall incidence of CK elevations up to 3 X ULN was 31-35% across the three treatment groups. The incidence of elevations > 3X ULN was between 3 and 6% across the treatment groups. There were no cases of rhabdomyolysis in this or any other trial of cerivastatin 0.4 mg.

The following cerivastatin-treated patients were discontinued due to elevations in transaminases or CK.

Pt. No.	Treatment	Day of tx	SGOT	SGPT	CK	
366	Ceriva 0.3	99	44	77		Returned to normal
729	0.3				912	CK elevated at baseline and off drug
893	0.4			78		
914	0.4	15	42	59		
922	0.4	17		81		Persistent with peak of 215 on day 21
261	0.4	173			211	Muscle cramps. CK normal after discontinu

						ation
52	0.4	14			409	Peak 546 at week 8; returned to normal after discontinu ation

In D96-008A and -008B, two of 448 patients treated with cerivastatin 0.4 mg had 2 or more (not necessarily sequential) elevations in SGOT and/or SGPT to > 3X ULN. This occurred in none of 225 patients treated with cerivastatin 0.3 mg and in 4 of 220 patients treated with placebo/fluvastatin 40 mg. One patient of the cerivastatin 0.4 mg patients did have nausea, vomiting, fever, GI distress, and fatigue, all of which resolved on discontinuation of the medication. The other patient was without symptoms.

Across all US completed studies (not all included in this submission), 1880 patients were treated with cerivastatin for a mean duration of 14 months. The table below, reproduced from the submission shows summary information for the 0.4% of patients experiencing two or more (not necessarily sequential) elevations in LFTs.

Tx group	Patient #	Lab	Tx day	Value	Multiple of ULN	Subsequent value WNL	symptoms	
Cer 0.05	17034	SGOT	208	201	9.1	No	depression	
			211	258	11.7			
			218	277	12.6			
			225	111	5.0			
		SGPT	208	393	15.7			No
			211	574	23			
			218	630	25			
			225	328	13			
			232	163	6.5			
			238	77	3.1			
Cer 0.2	19026	SGOT	15	81	3.7	Yes	Muscle soreness	
			17	279	12.7			
			18	219	10			
			19	131	6			
			20	77	3.5			
		SGPT	17	149	6	Yes		
			18	145	5.8			
			19	131	5.2			
			20	108	4.3			
Cer 0.3	4006	SGPT	29	169	6.8	Yes	None	
			34	107	4.3			
Cer 0.3	1012	SGPT	5	144	3.2	Yes	None	
			6	161	3.6			

			7	162	3.6		
			25	138	3.1		
Cer 0.4	3072	SGOT	230 ¹	98	4.5	No	None
			232	74	3.4		
		SGPT	230	183	7.3		
			232	140	5.6		
Cer 0.4	610	SGPT	171	79	3.2	No ²	Cough
			176	80	3.2		
Cer 0.4	922	SGPT	17	81	3.2	Yes	Nausea, vomiting, fever, fatigue
			21	215	8.6		
			23	110	4.4		
¹ This patient had received cerivastatin 0.2 mg and 0.3 mg for 700 and 198 days, resp. ² SGPT returned to normal in subsequent ongoing treatment period.							

There were no cases of jaundice or biochemical evidence of cholestasis.

From the table above, 5 of 7 cases occurred in the first 24 weeks of therapy and the same 5 of 7 returned to normal either after discontinuation of treatment or during ongoing therapy. The patient distribution by length of exposure in this database is not presented, and the numbers of events are too small to permit conclusions as to risk as a function of time on therapy. Suffice it to say that significant transaminase elevations were observed beyond 6 months of treatment. Finally, the incidence of transaminase elevations to > 3 X ULN on two or more (not necessarily consecutive) occasions across completed cerivastatin trials was 0.2, 0.3, and 0.4% for the 0.2, 0.3, and 0.4 mg doses, respectively.

In a small substudy of D96-008, cortrosyn stimulation testing was performed in males and females at baseline and after 24 weeks of therapy with either cerivastatin 0.3, mg, 0.4 mg, or fluvastatin 40 mg (for 16 weeks). There were no clinically significant changes (arbitrarily defined as a 50% change from baseline) from baseline in peak cortisol or cortisol AUC. Likewise, there were no significant abnormalities among patients undergoing HCG stimulation testing.

Review of the serious adverse events in D96-008 does not reveal any pattern suggestive of unexpected toxicity of cerivastatin. Eighty to 83% of patients completed this study across all three original randomized groups and the spectrum and distribution of reasons for discontinuation were similar across treatment groups.

In summary, the safety of cerivastatin 0.4 mg with regard to clinical adverse events, transaminase elevations and hepatic disease as well as CK elevations and muscle disease was not different than for placebo or lower doses of cerivastatin. In addition, the rates of these events did not exceed those in groups treated with either lovastatin or fluvastatin at comparable LDL-C-lowering doses. With regard to efficacy, while it is clear that 0.4 mg does not necessarily effect clinically significant greater reductions in LDL-C and TC than 0.3 mg, nevertheless, the existence of a reliable dose-response is evident. The impact on

HDL-C and TG, is much more variable and will need to be conveyed in labeling and promotion in order to make this clear.

Recommendation

Pending final agreement on labeling, this supplement should be approved.

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

Recommendation code: AP

Cc:

NDA 20-740 Arch

HFD-510

HFD-510: Shen/Simonea APPEARS THIS WAY ON ORIGINAL

/S/

4-5-99

NDA 20-740/S002
Baycol (cerivastatin sodium) tablets
Bayer

Memo to the file: 5-11-99

**MEDICAL OFFICER'S COMMENTS ON REVISED LABELING
FOR BAYCOL 0.4 MG SUBMITTED 5-11-99**

Clinical Studies: Tables 1 and 2 are acceptable.
The following sentence is to be inserted after Tables 1 & 2:

The clinical benefit(s) of altering these parameters are yet to be demonstrated. (See Clinical Pharmacology).

The paragraph, "In a large clinical study, the number of patients meeting their NCEP-ATP II target....." should be omitted for the following reasons:

- 1). It is promotional rather than informative/instructional.
- 2). Table 3 is misleading in that the results are individual and population dependent:
 - a). Whether or not an individual reaches the target goal depends on that individual's mean baseline LDL-C level;
 - b). The actual percentage of patients reaching the target goal depends on the number of patients in a given trial and the distribution characteristics of the that particular study population.
 - c). The NCEP-ATP II goals are not based on actual data. Therefore, the clinical benefit of having reached the target goal is yet to be demonstrated.
- 3). The Agency is re-considering similar statements/tables from the package inserts of other lipid-lowering agents.

The paragraph, "In a separate dose-scheduling study....." should be omitted since it is no longer needed. In **DOSAGE AND ADMINISTRATION**, it is stated, "The recommended dose is 0.4 mg once daily in the evening."

INDICATIONS AND USAGE: No comments.

CONTRAINDICATIONS: No comments.

WARNINGS: No comments.

PRECAUTIONS: No comments.

CNS and other toxicities: Please see Pharmacology/ Biopharmaceutic Reviews re Cmax/free statements and clinical implication of this ratio.

Pregnancy: Pregnancy Category X: Please see Pharmacology Review.

ADVERSE REACTIONS: No comments.

OVERDOSAGE: No comments.

DOSAGE AND ADMINISTRATION:

To the sentence, "The recommended dose is 0.4 mg once daily in the evening...."
The following should be added:

[REDACTED]

/S/ [REDACTED]

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

5/11/99

CC:
Original NDA
HFD-510-Files
HFD-510-SWSHEN.
HFD-510-MSIMONEAU.

Comments conveyed to sponsor in
e-con 5/11/99. Also, disclaimer on
HDL-card TG to be added in
clin Pharm consistent with labeling
for Provera/3000/Atova.

/S/ [REDACTED]

5/12/99

APPEARS THIS WAY ON ORIGINAL [REDACTED]

Simoneau

APR 5 1999

MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT 20-740/S002

TABLE OF CONTENTS:

	PAGES
I. Introduction and Background	1
II. Clinical Studies	
Study 0149	2
Study D96-008A	10
Study D96-008B	22
III. Supportive Studies	
Study D97-001	27
Study 0161	29
Study Z91-031	31
IV. Safety Update	32
V. Overall Evaluation	36
VI. Conclusion/Recommendation	37
VII. Labeling	38

APPEARS THIS WAY ON ORIGINAL

MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT

- 1.1. Title : NDA:20-740/S002.
- 1.1.2. M.O. Review. 7
- 1.1.3. Submission Date: 08/16/98.
- 1.1.4. Assigned Date: 09/15/98.
- 1.2.1. Generic Name: Cerivastatin sodium tablets.
- 1.2.2. Proposed trade name: Baycol.
- 1.3. Sponsor: Bayer Pharmaceutical Division.
- 1.4. Pharmacological Category: Inhibitor of 3-HMG-CoA Reductase.
- 1.5. Proposed Revisions: This supplement is to add 0.4 mg dose to the presently marketed dose of 0.2 and 0.3 mg tablets.
- 1.6. Dosage Form and Route of Administration: 0.4 mg /day orally.
- 1.7. Important Related Drugs: Other 3-HMG-CoA-Reductase inhibitors:

NDA #	Approval Date	Drug	Sponsor
19643	8/31/1987	Mevacor (Lovastatin)	Merck
19766	12/23/1991	Zocor (Simvastatin)	Merck
19898	10/31/1991	Pravachol (Pravastatin)	Bristol Myers Squibb
20261	12/31/1993	Lescol (Fluvastatin)	Novartis
20702	12/17/1996	Lipitor (Atorvastatin)	Parke Davis
20740	6/26/1997	Baycol (Cerivastatin)	Bayer

2. Materials Reviewed: Paper submission NDA-20-740/S002.
3. Clinical Background:
 - 3.1. Relevant Human Experience: Cerivastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo-B, and TG in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb).
4. Clinical Studies: For this Supplemental NDA, the following studies of the 0.4 mg-treatment were submitted:

Table 4.1: Study List:

Pivotal Studies					
Protocol #	Starting date; n	Design	Treatment/ Doses	# of Pts. Entered	Duration of Drug Rx.
0149	1/1/95; 349	Safety/Effi. Rand,DB,Pa- rallel Group	Cer. 0.3mg	140	8 weeks
			0.4mg	138	
			Placebo.	71	
D96-008A	7/22/96; 893	Safety/Effi.	Cer. 0.3mg	225	24 weeks

		Rand.,DB,Pa -rallel Group	0.4mg Pla/Fluva.40 mg	448 220	
Supportive Short-Term Studies					
0161	4/12/96; 494	Safety/Effic. Rand.,DB, Para. Group	Cer. 0.2mg 0.4mg	162 332	24 weeks
Supportive Long-Term Studies					
Z91-031	8/29/95; 480	Safety/Effic. Rand., DB. Para. Group	Cer. 0.3/ 0.4 Lova. 40mg	398 82	6-18 mos.
D96-008B	7/22/96; 640	Safety/Effic. Rand., DB., Para. Group	Cer. 0.3 mg 0.4 mg Fluva 40 mg. 40mg	160 320 160	52 weeks

4.1. Clinical Protocol: Study 0149 (non-US-Study):

4.1.1. Objectives:

To compare the safety and efficacy of cerivastatin 0.3 mg, 0.4 mg and placebo daily for the first 8 weeks of treatment.

4.1.2. Design: A prospective randomized, double-blind, multicenter study with 3 parallel groups.

4.1.3.1. Study Population:

a). Inclusion Criteria:

- 1). Ages 18 to 75.
- 2). Documented primary hypercholesterolemia.
- 3). Ambulatory men or women (not of childbearing potential).

b). Exclusion Criteria:

- 1). Weight >140% of ideal body weight.
- 2). Homozygous familial hypercholesterolemia.
- 3). History of malignancy (except squamous or basal cell skin cancer) or psychosis.
- 4). Women who were pregnant or breast-feeding.
- 5). Night shift workers that result in reversal of normal sleep/awake cycles.
- 6). Concomitant treatment with other hypolipidemic drugs within 10 weeks of randomization. Probucol must not have been used within 6 months of trial entry.
- 7). Drug or alcohol abuse or current intake of more than 14 standard drinks per week.
- 8). Myocardial infarction, unstable angina, cerebral vascular

accident, Transient ischemic attack or uncontrolled hypertension within 3 months of entry; coronary artery bypass (CABG) or PTCA within 6 months of entry.

- 9). Patients with hypertension who had a change in diuretics or beta-blocker therapy within 3 months of entry.
- 10). Diabetes mellitus (fasting glucose >140 mg/dL or treatment for diabetes) or other diseases of the endocrine system.
- 11). Patients with unstable ophthalmic abnormalities that were expected to require medical or surgical intervention within 18 months. Patients whose best corrected visual acuity was less than 20/50 in either eye secondary to cataracts.
- 12). Active liver disease or unexplained persistent elevation of SGOT or SGPT (SGOT or SGPT >150 % of the upper limit of normal at entry)
- 13). History of GI disorders that could have resulted in impaired absorption of trial investigational products.
- 14). History of hypersensitivity to cerivastatin, fluvastatin or other HMG-C0A reductase inhibitors.
- 15) Other significant lab. abnormalities as defined by: serum creatinine >2 mg/dL, serum creatine kinase (CK) >3 times ULN, serum amylase >150% of ULN, and other lab. abnormalities of clinical significance in the opinion of the investigators.
- 16). Current use of corticosteroids, erythromycin (all macrolide antibiotics including azithromycin and clarithromycin), rifampin, androgens, immunosuppressants, ketoconazole and itraconazole. Post-menopausal women on stable doses of replacement therapy for at least 75 days were eligible to enter the trial.
- 17). Treatment with cerivastatin within 6 months of entry; therapy with another investigational product within 30 days.

4.1.4. Procedures: The study comprised of two assessment periods:

1). Period A: The diet/run-in Period (10 weeks):

- (1). Visit 1: A complete PE and a resting EKG were performed; a complete medical hx. including demography and previous medications, weight, seated blood pressure, pulse rate were also recorded. The following lab. tests were performed: hematology, blood chemistry, plasma lipid profile, TSH, serum beta-HCG for all women <55 years of age; and routine U/A.
- (2). Patients were seen by a dietitian and counseled in the AHA Step 1 diet at Visits 1, 2, 3, and 4 (Weeks -10, -6, -4 and -2)
- (3). Plasma lipid profiles were obtained at Visits 2, 3, and 4; safety lab. testing was repeated at Visit 3 (Weeks -6, -4 and -2).
- (4). At Visit 5 (Week 0), randomization took place in which patients were randomized to the 3 parallel groups (0.3 mg, 0.4 mg and placebo).

- 2). **Period B: The Double-Blind Treatment Phase (8 weeks):**
- (1). Consisted of 6 visits performed at Weeks 1, 2,3, 4, 6, and final visit at Week 8. At each visit, a brief PE, lipid profile, enzymes (ALP, ALT, AST, LDH, CK and amylase) were performed. Compliance and adverse events were also assessed.
 - (2). At final visit, special lipid fraction [ApoA1, ApoB, LpA1:AII, Lp(a)], platelets, RBC, TSH, T-4 were additionally obtained. A complete PE was performed including weight, vital signs, 12-lead EKG.
 - (3). A complete ophthalmologic examination was to be performed by the same ophthalmologist who performed the initial evaluation.
 - (4). The food diary was collected by the dietitian. Activity level and alcohol consumption were also recorded.

4.1.5. Endpoints: The primary efficacy parameter was the relative change (expressed as a percentage) in the calculated plasma LDL-C levels from baseline to the end of the 8-week Active Treatment Period.

4.1.6. Statistical Considerations: Analysis of variance (ANOVA) was used to calculate the least-square mean percentage changes from baseline of the calculated LDL-C and other lipid parameters. Please see Biostatistical Review for complete evaluation.

4.1.7. Results:

4.1.7.1. Baseline characteristics of all patients randomized to treatment are showing in Table 4.4.1:

Table 4.1.7.1:

Safety population: Demographic Data:				
	Placebo	Cerivastatin 0.3 mg	Cerivastatin 0.4 mg	
mean+/-sd	n=71	n=140	n=138	p-value
age (years)	55+/-11	55 +/-11	56 +/-10	0.6
sex(m/f)	47/24	85/55	77/61	0.8
BMI(kg/m²)	27+/-4	27+/-4	27+/-4	0.2
smoker(no/yes)	51/20	112/28	105/33	0.8
alcohol (<7/7-14/>14)	60/9/2	116/21/3	113/20/5	0.6

HLP (no/yes/unknown)	8/30/33	20/55/65	20/54/64	0.9
CAD (no/yes/unknown)	16/34/21	37/67/36	38/63/37	0.5
HLP duration (months)	63+/-2.7	67+/-2.5	59+/-2.6	0.5
prior-treatment	61/10	125/15	131/7	0.6
Efficacy population : Lipid Profiles:				
L.S.-mean +/-se	n=65	n=132	n=132	p-value
LDL-C	233.6+/-6.0	224.1+/-4.2	218.9+/-4.2	0.13
Apo-B	185.2+/-4.7	179.0+/-3.3	175.9+/-3.2	0.24
TG	141.5+/-6.2	138.6+/-4.4	141.9+/-4.4	0.84
Apo-AI	155.7+/-3.3	155.0+/-2.3	152.7+/-2.3	0.67
Total-C	316.0+/-6.1	306.9+/-4.3	301.3+/-4.3	0.14
Lp(a)	62.4+/-9.4	60.2+/-6.4	53.6+/-6.6	0.67
Lipoprot AI	54.0+/-2.3	55.6+/-1.7	56.1+/-1.6	0.75
Lipoprot AI:AI	101.9+/-2.3	99.3+/-1.6	96.3+/-1.6	0.12
HDL-C	54.0+/-1.6	55.1+/-1.1	54.1+/-1.1	0.76
Atherog.Index	6.2+/-0.2	5.8+/-0.1	5.9+/-0.1	0.28

Comments:

- 1). The baseline demographics and lipid profiles of the study groups were not significant different. Thus the randomization process was successful.
- 2). At the end of Period B, 329 patients were valid for evaluation of the primary study objective: 65 patients (20%) received placebo, 132 (40%) received 0.3 mg and 132 (40%) received 0.4 mg cerivastatin. 22 patients were excluded from the analysis due to failure to meet qualifying lipid values, non-compliance and disqualifying concomitant medications.

4.1.7.2. Efficacy Endpoint Outcomes:

4.1.7.2.1. Primary Efficacy Analysis: The percentage change from baseline in LDL-C during treatment are shown below:

Table 4.1.7.2: Change in calculated LDL-C (% reduction from baseline to endpoint):

Valid for Efficacy Analysis			
	Placebo n=65	Cerivastatin 0.3mg n=132	Cerivastatin 0.4 mg n=132
Baseline (mg/dL)	233.6	224.1	218.9
Change (%) (+/-S.E.)	-0.5 (+/-1.4)	-33.5* (+/-1.0)	-35.9* (+/-1.0)
Intent-to-Treat Analysis			
	Placebo n=71	Cerivastatin 0.3mg n=140	Cerivastatin 0.4mg n=138
Baseline (mg/dL)	231.5	223.0	218.2
Change (%) (+/-S.E.)	+0.2 (+/-1.4)	-32.5* (+/-1.0)	-35.8* (+/-1.0)

Comments:

- 1). The results of the Valid for Efficacy analysis and the Intent-to-Treat analysis were similar.
- 2). * denoted statistically significant differences compared to placebo treatment.
- 3). The difference between 0.3 mg and 0.4 mg groups were not statistically significant.

4.1.7.2.2. Secondary Efficacy Parameters: The secondary efficacy parameters were Total-C, HDL-C, TG, ApoA1, ApoB, Lp(a), Lipoprotein AI, LipoproteinAI:AI and atherogenic index (total-C/HDL-C) are shown below:

Table 4.1.7.3: Change in Secondary efficacy parameters (% reduction from Baseline to endpoint): Valid for Efficacy Analysis:

Placebo n=65	Cerivastatin 0.3 mg n=132	Cerivastatin 0.4 mg n=132
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Total-Cholesterol			
Baseline (mg/dL)	316.0	306.9	301.3
Change (%)	+0.5	-24.9*	-26.6*
(+/-S.E.)	(+/-1.1)	(+/-0.8)	(+/-0.8)
HDL-Cholesterol			
Baseline (mg/dL)	54.0	55.1	54.1
Change(%)	+0.5	+5.9*	+4.4*
(+/-S.E.)	(+/-1.5)	(+/-1.1)	(+/-1.1)
Triglycerides			
Baseline(mg/dL)	141.5	138.6	141.9
Change(%)	+9.5	-16.7*	-14.2*
(+/-S.E.)	(+/-3.3)	(+/-2.4)	(+/-2.4)
Apolipoprotein A1			
Baseline(mg/dL)	155.7 (n=59)	155.0 (n=119)	152.7 (n=123)
Change(%)	+0.1	+5.3*	+5.0*
(+/-S.E.)	(+/-1.6)	(+/-1.1)	(+/-1.1)
Apolipoprotein B			
Baseline(mg/dL)	185.2 (n=59)	177.9 (n=118)	175.9 (n=123)
Change(%)	+6.1	-24.2*	-26.1*
(+/-S.E.)	(+/-1.6)	(+/-1.1)	(+/-1.1)
Lipoprotein (a)			
Baseline(mg/dL)	62.4 (n=43)	60.2 (n=95)	53.6 (n=90)
Change(%)	+6.0	+6.5	+6.4
(+/-S.E.)	(+/-3.7)	(+/-2.5)	(+/-2.6)

Lipoprotein AI			
Baseline(mg/dL)	54.0 (n=59)	55.6 (n=118)	56.1 (n=123)
Change(%) (+/-S.E)	+6.0 (+/-3.4)	+16.6* (+/-2.4)	+12.0 (+/-2.4)
LipoproteinAI:AII			
Baseline(mg/dL)	101.9 (n=58)	99.3 (n=118)	96.3 (n=122)
Change(%) (+/-S.E)	-0.5 (+/-2.9)	+1.4 (+/-2.0)	+4.9 (+/-2.0)
Atherogenic Index (Total-C/HDL-C)			
Baseline(mg/dL)	6.2 (n=65)	5.8 (n=132)	5.9 (n=132)
Change(%) (+/-S.E)	+1.0 (+/-1.2)	-28.4* (+/-0.9)	-29.0* (+/-0.9)

Comments:

- 1). * denoted statistically significant difference compared to placebo treatment.
- 2). The difference between 0.3 mg and 0.4 mg groups were not statistically significant in any of the Secondary Efficacy Parameters..

4.1.8. Safety Outcome:

- 1). There was one death in a patient randomized to 0.3 mg group who had a sudden death at home 2 days after the end of treatment period.
- 2). Three patients discontinued the study during Period A (diet-placebo running period) due to diagnosis of prostate cancer, chronic stomach wound infection, and hospitalization for heart pain respectively.
- 3). There was one serious event during Period A: A 45-year female was hospitalized for hysterectomy for hysteromyoma. The event was not drug-related and she completed the study as planned.
- 4). Two serious adverse events, besides the one death cited above, occurred during Period B. One patient randomized to placebo had an inguinal hernia operation and continued the study. One patient in the 0.4 mg group had deterioration of his pre-existing arteritis and discontinued the study.
- 5). Elevations of creatinine phosphokinase and hepatic transaminases are

known to occur with HMG-CoA-reductase inhibitors. The frequency of patients with these enzyme elevations during Period B who had normal values during Period A are shown below:

Table 4.1.8.1: Incidence of patients with enzyme elevations who had normal values during Period A (Diet-Run-In Period):

	Placebo n=71	Cerivastatin 0.3 mg n=140	Cerivastatin 0.4 mg n=138
CK			
ULN-<3xULN	7(9.8%)	17(12.1%)	24(17.3)
3xULN<5xULN	1(1.4%)	0	1(0.7%)
>5xULN<10xULN	1(1.4%)	0	1(0.7%)
All>ULN	9(12.6%)	17(12.1%)	26(18.8%)
AS/SGOT			
>ULN<3xULN	1(1.4%)	2(1.4%)	3(2.1%)
ALT/SGPT			
>ULN<2xULN	5(7.0)	4(2.8%)	7(5.0)
>3xULN	0	0	1(<1%)

Comments:

- 1). CK elevations occurred most frequently in the 0.4 mg group, i.e. 18.8% vs. 12.6% and 12.1 % for the placebo and 0.3 mg group respectively. However, 24/26 elevations were <2xULN. Patient 19/148 in the placebo group had a CK value of 799 IU/L (>5xULN) at Week 8 without any symptoms suggestive of rhabdomyolysis. CK was normal at all other times. Patient 4/201 also in the placebo group had CK value of 415 IU/L (>3xULN) at Week 3 and decreased to 157 IU/L (>1xULN) at Week 4. No patient on 0.3 mg had CK elevations of >2xULN. Patient 9/431 in the 0.4 mg group had a CK value of 890 IU/L (>5xULN) at Week 1. This was thought to be due to "hard muscular activity". His value subsequently decreased to 67, 140, 77 and 66 IU/L at Weeks 2, 3, 6 and 8. Patient 19/147 in the cerivastatin 0.4 mg group had a CK value of 421 IU/L (>3xULN) at Week 1. This was attributed to intramuscular injection of diclofenac as therapy for acute lumbago. His subsequent CK values were all within normal range..
- 2). There was no sustained AST/SGOT elevations >3xULN in any of the treatment

groups. There was one sustained ALT/SGPT elevation $>3\times$ ULN in the cerivastatin 0.4 mg group. Patient 06/225 had SGPT of 82, 95, 67, and 78 after 2, 3, 4, and 6 weeks of treatment. His value was 91 on his withdrawal visit.

4.1.9. Reviewer's Comments/Conclusion of the Study Results:

4.1.9.1: Safety:

There were no new/unexpected adverse events reported in this study from the previously submitted safety data and listed in the Labeling. However, this study was only of 8-week duration; perhaps insufficient time for some of the adverse events to develop. Greater weight will be given to the Week 24 and Week 52 endpoints in the D96-008A and D96-008B studies.

4.1.9.2: Efficacy :

- 1). The results of the Intent-to-treat analysis and the Valid-for-efficacy analysis were similar.
- 2). For the primary efficacy parameter, percent reduction from baseline of the calculated LDL-C at Week 8, there was significant difference between the placebo-treated group and the cerivastatin-treated groups. However, the difference between the 0.3 mg and the 0.4 mg groups were not statistically significant.
- 3). Among the secondary efficacy parameters, there were significant differences between the placebo group and the cerivastatin-treated groups with respect to: Total-C, TG, HDL-C, ApoA1, ApoB, and the Atherogenic Index (Total-C/HDL-C). With respect to Lipoprotein AI, only the 0.3 mg group was significantly different from the placebo group. The clinical implication/significance of these changes of the secondary efficacy parameters are yet to be established.
- 4). There was no significant difference between the cerivastatin-treated groups and the placebo group with respect to: Lp(a) and Lipoprotein AI:AIL.

4.2. Clinical Protocol: Study D96-008A (U.S. Study): Study D96-008 is a 3-part study; Part A is a pivotal study for this Supplemental NDA . Part B is a long-term study with extension to 52 weeks. Part C is further extension to 78 weeks.

4.2.1. Objectives:

- 1). To compare the safety and efficacy of cerivastatin 0.4 mg and placebo daily for the first 8 weeks of treatment.
- 2). To compare the safety and efficacy of 0.4 mg cerivastatin QD with that of 0.3 mg QD at Weeks 8 and 24 (Patients in the placebo group were switched to fluvastatin 40 mg/day after the first 8 weeks of treatment)..

4.2.2. Design:

A prospective, randomized, double-blind, multicenter trial with 3 parallel

groups.

4.2.3.1. Study Population:

- a). Inclusion Criteria:
 - 1). Ages 18 to 75.
 - 2). Documented primary hypercholesterolemia.
 - 3). Ambulatory men or women (not of childbearing potential).
- b). Exclusion Criteria:
 - Similar to that of Study 0149 (non-US Study).

4.2.4. Procedures: The study consisted of two assessment periods:

- 1). **The Run-in Period:** The 10- week period from Visit 1 (screening) to Visit 5 (randomization) during which time complete medical hx. PE, 12-lead EKG and baseline chemistry, hematology, U/A and plasma lipid profile were obtained. Special lab. tests of TSH and HCG were also obtained. Patients were placed on AHA Step 1 diet. At Visit 5, eligible patients were randomly assigned in 2:1:1 ratio to cerivastatin 0.4 mg, cerivastatin 0.3 mg or placebo/fluvastatin 40 mg respectively.
- 2). **Double-Blind Treatment Period (24 weeks in duration):**
 - (1). Patients were seen biweekly for the first 4 weeks and then every 4 weeks for the remainder of the treatment period.
 - (2). At each visit, assessments included review of adverse events, concomitant medications, treatment compliance, activity level and alcohol intake, weight, seated blood pressure and pulse, plasma lipid profiles. Special lipid fractions were obtained at Visits and 12 (weeks 8 and 24).
 - (3). Serum chemistries, CBC with differential and platelet count, and U/A were to be performed at Weeks 4, 8, 16, and 24). TSH, plasma cortisol and fibronogen were performed at Weeks 24.
 - (4). At any time during the trial, if a patient had an elevated enzymes (CK, SGOY/SGPT) $>3 \times \text{ULN}$, serial serum values were to be obtained until the values returned to baseline.

4.2.5. Endpoints: The primary efficacy parameter was the relative change (expressed as a percentage) in the calculated plasma LDL-C levels from baseline to the end of 8-week and 24-week treatment periods.

4.2.6. Statistical Considerations: The primary method for comparing groups was to use least-squares means from the ANOVA model with effects for drugs and center.

4.2.7. Results:

4.2.7.1. The baseline characteristics of all patients randomized to treatment are shown in Table 4.2.7.1:

Table 4.2.7.1:

Efficacy population: Demographic Data:			
	Cerivastatin 0.3 mg	Cerivastatin 0.4 mg	Placebo/fluva. 40mg
	n=202	n=409	n=191
sex % male	63	57	61
race % Caucasian	97	92	94
smoking %	17	12	13
alcohol % non-drink	34	34	28
fam.hx. HLP % yes	43	44	39
fam.hx,CAD % yes	58	54	55
mean age (years)	57	58	57
mean weight (kg)	81	80	82
mean du.HLP(yrs)	9	8	9
hypertension %	23	33	25
female climacteric state (%)	17	23	24
Efficacy population : Lipid Profiles:			
L.S.-mean	Cerivastatin 0.3 mg	Cerivastatin 0.4 mg	Placebo/fluva. 40mg
LDL-C	191.4	187.4	191.6
Apo-B	186.5	184.2	185.2
TG	186.0	182.4	179.4
Apo-AI	153.8	155.8	152.2
Total-C	276.6	272.5	274.6
Lipoprot. A	35.6	36.6	37.7

LDL/HDL ratio	4.2	4.0	4.2
VLDL-C	41.6	40.5	38.3
HDL-C	48.5	48.9	48.1

Comments:

- 1). The treatment groups were similar with respect to most of these characteristics. The randomization process was successful.
- 2). Of the 229 patients randomized to 0.3 mg, 202 (88%) were valid for safety and efficacy evaluation, 225 (98%) valid for safety and Intent-to-Treat analysis. Of the 456 patients randomized to 0.4 mg, 409 (90%) were valid for safety and efficacy evaluation, 448 (98%) were valid for safety and Intent-to-Treat analysis. Of the 223 patients randomized to placebo/fluvastatin 40 mg, 191 (86%) were valid for safety and efficacy evaluation, 220 (99%) were valid for safety and Intent-to-Treat analysis. The reasons for invalidity for efficacy were: disqualifying baseline lipid values, inadequate drug compliance, disqualifying concomitant medications, physician data disqualified and any other reason.

4.2.7.2. Efficacy Endpoint Outcomes: The efficacy endpoint outcomes consist of 2 parts: at Week 8 endpoint (0.4 mg cerivastatin vs. 0.3 mg cerivastatin vs. placebo); and at Week 24 endpoint (the efficacy of 0.4 mg cerivastatin QD, of 0.3 mg QD and fluvastatin 40 mg/day). The efficacy endpoint outcomes will be presented and evaluated separately.

4.2.7.2.1. Primary Efficacy Analysis (I): The lipid values at baseline and at Week 8 and the mean percentage changes from baseline in LDL-C during treatment are shown in Table 4.2.7.2(I):

Table 4.2.7.2(I): Changes in calculated LDL-C and Mean Percentage Change from Baseline at Week 8 Endpoint:

Valid for Efficacy Patients			
	Baseline (mg/dL)	Week 8 (mg/dL)	Mean % change
Placebo N=190	191.7	191.0	-2.1
Cerivastatin 0.3mg N=200	191.8	132.9	-30.8
Cerivastatin 0.4 mg N=408	187.4	124.2	-33.6
Intent-to-Treat Patients			
Placebo N=219	191.1	190.7	-0.12
Cerivastatin 0.3mg N=223	191.8	133.5	-30.1
Cerivastatin 0.4mg	187.0	125.2	-33.0

N=448			
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Comments:

- 1). The results of the Valid for Efficacy analysis and the Intent-to-Treat analysis are similar.
- 2). There was significant difference between the cerivastatin-treated groups and the placebo-treated group(p-value for difference between cerivastatin 0.4 mg group and placebo group was $p < 0.0001$).
- 3). The difference between the cerivastatin 0.3 mg and 0.4 mg groups were also statistically significant.

4.2.7.2.1. Primary Efficacy Analysis (II): The mean % changes from baseline in LDL-C at Week 24 are shown in Table 4.2.7.2(II)

Table 4.2.7.2(I): Changes in calculated LDL-C and Mean Percentage Change from BL at Week 24 Endpoint:

Valid for Efficacy Patients			
	Baseline (mg/dL)	Week 24 (mg/dL)	Mean %change
Fluvastatin 40mg N=185	190.1	146.1	-22.9
Cerivastatin 0.3mg N=194	191.3	134.3	-29.9
Cerivastatin 0.4 mg N=385	187.3	124.6	-33.4
Intent-to-Treat Patients			
Fluvastatin 40mg N=208	190.4	147.4	-22.3
Cerivastatin 0.3mg N=213	190.9	136.3	-28.6
Cerivastatin 0.4mg N=427	186.6	125.3	-33.0

Comments:

- 1). The results of the Intent-to-treat analysis and the Valid-for-efficacy analysis were similar.
- 2). Both the cerivastatin-treated groups and the fluvastatin-treated groups showed significant changes in LDL-C from baseline.
- 3). The cerivastatin-treated groups showed statistically significant greater mean % changes than the fluvastatin 40mg-treated group.
- 4). The 0.4 mg cerivastatin-treated group showed statistically significant greater mean % change than the 0.3 mg-group.

4.2.7.2.2. Secondary Efficacy Endpoints: The secondary efficacy parameters, total-C, HDL-C, TG, Total-C/HDL-C, and LDL-C/HDL-C ratios, at Week 8 are shown below in Table 4.2.7.3(I):

Table 4.2.7.3(I): Secondary Efficacy Parameters At Week 8 Endpoint (% change from Baseline):

Patients Valid for Efficacy			
Parameter	Cerivastatin 0.3 mg n=200	Cerivastatin 0.4 mg n=408	Placebo n=190
HDL-C (Baseline)	48.5	48.9	48.1
HDL-C (% change)	+7.8*	+8.1*	+1.1
Total-C (Baseline)	277.1	272.4	274.0
Total-C (% change)	-21.5*+	-23.5*	+0.5
Total/HDL-C (diff. From BL)	-1.6*	-1.7*	-0.0
LDL/HDL-C (diff. From BL)	-1.5*	-1.5*	-0.0
TG (Baseline)	186.0	182.3	179.1
TG (mean % change)	-11.3*	-12.0*	+4.5
TG (median % change)	-14.9*	-15.9*	-0.4
Intent-to-Treat Population			
Parameter	Cerivastatin 0.3 mg n=223	Cerivastatin 0.4 mg n=448	Placebo n=219
HDL-C (Baseline)	48.6	49.1	48.4
HDL-C (% change)	+7.8*	+8.0*	+1.6
Total-C (Baseline)	276.6	272.5	274.6
Total-C (% change)	-21.1*+	-22.9	+0.7
Total/HDL-C (diff. From BL)	-1.6*	-1.7*	-0.0
LDL/HDL-C (diff. From BL)	-1.4*	-1.5*	-0.0
TG (Baseline)	186.7	183.8	176.7

TG (mean % change)	-11.5*	-11.2*	+4.8
TG (median % change)	-15.0*	-15.9*	-0.6

Comments:

*=denotes significantly different from placebo.

+ =denotes significantly different from cerivastatin 0.4 mg.

- 1) The results of the Intent-to-treat analysis and the Valid-for-efficacy analysis were similar.
- 2) At the Week 8 endpoint, the cerivastatin-treated groups had statistically significant greater changes in HDL-C, Total-C, Total/HDL-C and LDL.HDL-C ratios than the placebo-treated group.
- 3) There was no statistically significant difference between the 0.3 mg and 0.4 mg groups with respect to these secondary efficacy parameters except for Total-C.
- 4) There was statistically significant difference in the mean percent change of TG between the cerivastatin-treated groups and the placebo group. The median percent change between the groups showed similar results. And there was no significant difference between the 0.3 and 0.4 mg groups presumably due to large spontaneous fluctuation in TG independent of the treatments.

Table 4.2.7.3(II): Secondary Efficacy Parameters At Week 24 Endpoint Mean % change from Baseline:

Intent-to-Treat Population			
Parameter	Cerivastatin 0.3 mg n=213	Cerivastatin 0.4 mg n=448	Fluvastatin 40 mg n=219
HDL-C (Baseline)	48.5	49.0	48.3
HDL-C(mean % change)	+6.8	+7.3	+5.3
Total-C (Baseline)	276.6	272.5	274.6
Total-C(mean % change)	-19.2*+	-22.4*	-15.2
Total/HDL-C (diff. from BL)	-1.5*+	-1.6*	-1.1
LDL/HDL-C (diff. From BL)	-1.4*+	-1.5*	-1.1
TG (Baseline)	185.5	183.3	177.3

TG (mean % change)	-3.5+	-9.1*	-4.2
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comments:

*=-denotes significantly different from fluvastatin 40 mg.

+=denotes significantly different from cerivastatin 0.4 mg.

- 1) The results of the Intent-to-treat analysis and the Valid-for-efficacy analysis were similar. Only the Intent-to-treat results are shown above.
- 2) At the Week 24 endpoint, the cerivastatin-treated groups had statistically significant greater changes in Total-C, Total/HDL-C and LDL.HDL-C ratios than fluvastatin 40 mg group.
- 3) There was no statistically significant difference between the 0.3 mg and 0.4 mg groups with respect to these secondary efficacy parameters except for Total-C, Total/HDL-C, and LDL/HDL-C ratios..
- 4) There was statistically significant difference in the percent change of TG between the 0.4 mg cerivastatin-treated group, the 0.3 mg group and the fluvastatin 40 mg group. There was no statistically significant difference between the 0.3 cerivastatin group and the fluvastatin 40 mg group.

Table 4.2.7.4: Special Lipid Parameters Results @ Week 8 and Week 24 (% Change from Baseline) in Intent-to-treat Patients:

Variable	Cerivastatin 0.3mg		Cerivastatin 0.4mg		Placebo	Fluvast. 40mg
Direct LDL-beta Quantitation						
	Week 8 N=223	Week 24 N=213	Week 8 N=448	Week 24 N=427	Week 8 N=219	Week 24 N=208
Baseline	190.2	190.2	187.3	186.3	191.6	190.1
% change	-27.0*^+	-25.6*^+	-30.1*^	-29.7*^	+1.20	-20.1*
Apolipoprotein AI						
	Week 8 N=218	Week 24 N=212	Week 8 N=444	Week 24 N=416	Week 8 N=217	Week 24 N=203
Baseline	153.8	153.9	155.8	155.9	152.2	152.2
% change	+3.51*^	+3.48*^	+3.51*^	+2.74*^	-0.42	+1.73*
Apolipoprotein B						
	Week 8 N=218	Week 24 N=212	Week 8 N=444	Week 24 N=416	Week 8 N=217	Week 24 N=203
Baseline	186.5	186.6	184.2	183.3	185.2	184.4
% change	-24.4*^+	-23.8*^+	-25.9*^	-27.5*^	+0.07	-17.9*
ApoB/ApoAI ratio						

	Week 8 N=218	Week 24 N=212	Week 8 N=444	Week 24 N=416	Week 8 N=217	Week 24 N=203
Baseline	1.25	1.25	1.22	1.21	1.25	1.24
% change	-1.34* [^]	-0.33* [^]	-0.35* [^]	-0.24* [^]	+0.01	-0.24*
Lipoprotein A						
	Week 8 N=215	Week 24 N=209	Week 8 N=442	Week 24 N=414	Week 8 N=216	Week 24 N=202
Baseline	35.6	35.7	36.6	37.2	37.7	38.8
% change	-1.04 [^]	+2.58 [^]	+1.13	+5.13* [^]	+7.05*	+13.38*
VLDL-C						
	Week 8 N=218	Week 24 N=209	Week 8 N=435	Week 24 N=412	Week 8 N=214	Week 24 N=200
Baseline	41.6	41.7	40.5	40.3	38.3	38.6
% change	-20.30* [^]	-12.29*	-19.09* [^]	-17.86* [^]	+3.63*	+13.38*

Comments:*=**significant change from baseline.**[^]=**significant change from fluvastatin 40 mg group.**+=**significant change from 0.4 mg cerivastatin group.****1). For the 0.3 mg cerivastatin-treated group:**

- a). Direct LDL-beta quant., ApoB, Apo B/ApoAI ratio, ApoAI all showed significant differences from baseline values and from placebo/fluvastatin groups both at the Week 8 and Week 24 endpoints.
- b). Lipoprotein A showed no significant change from baseline at Week 8 or Week 24. VLDL-C showed significant change from baseline both at Week 8 and Week 24.

2). For the 0.4 mg cerivastatin-treated group:

- a). Direct LDL-beta quant., ApoB, Apo B/ApoAI ratio, ApoAI, and VLDL-C all showed significant differences from baseline values and from placebo/fluvastatin groups both at the Week 8 and Week 24 endpoints
- b). There were statistically significant greater changes in Direct LDL-beta quant. and Apo B than the 0.3 mg group both at Week 8 and Week 24.
- c). Lipoprotein A showed significant change from baseline only at Week 24.

4.2.8. Safety Outcomes:

- 1). There were two deaths in this study. Patient 981, assigned to the placebo /fluvastatin group, died following a coronary artery stent placement complicated by stent-occlusion, emergent coronary artery bypass surgery. Similarly, patient 118, assigned to the 0.4 mg group, suffered a sudden cardiopulmonary arrest 30 days after an urgent coronary artery bypass. Both these deaths were likely to be due to the underlying disease rather than to the study drug.
- 2). The majority of serious events were due to cancer (prostate, basal cell

skin cancer), surgical procedures and admission for complications of atherosclerosis. None of these raised particular safety concerns about the study drug.

- 3). Rates of treatment-related elevations of CK, SGOT, and SGPT at Weeks 8 are shown below:

Table 4.2.8.1: Elevations of CK, SGOT, SGPT regardless of baseline values: Week 8 and Week 24:

Lab. Variable	Cerivastatin 0.3mg		Cerivastatin 0.4mg		Placebo	Fluva.
	Week 8 N=225	Week 24 N=225	Week 8 N=448	Week 24 N=448	Week 8 N=220	Week 24 N=220
CK						
>3xULN to 5xULN	3(1%)	5(2%)	4(<1%)	13(3%)	0(0%)	2(<1%)
>5xULN to 10xULN	0(0%)	2(<1%)	0(0%)	3(<1%)	1(<1%)	3(1%)
>10xULN	0(0%)	3(1%)	1(<1%)	2(<1%)	0(0%)	0(0%)
SGOT						
>3xULN to 5xULN	0(0%)	0(0%)	1(<1%)	1(<1%)	1(<1%)	3(1%)
>5xULN to 10xULN	0(0%)	0(0%)	1(<1%)	1(<1%)	0(0%)	1(<1%)
>10xULN	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
SGPT						
>3xULN to 5xULN	0(0%)	0(0%)	3 (<1%)	5(1%)	0(0%)	2(<1%)
>5xULN to 10xULN	0(0%)	0(0%)	0(0%)	1(1%)	0(0%)	2(<1%)
>10xULN	0(0%)	0(0%)	0(0%)	0(0%)	1(<1%)	1(<1%)

Comments:

- 1). At Week 8: the 0.4 mg group had more elevations of CK, SGOT and SGPT than the 0.3 mg and the placebo groups:
 - a). Patient 643 of the cerivastatin 0.4 mg group had CK of 2550 (21.3xULN) on Day 34 of treatment. No adverse event or concomitant medications were reported within 10 days prior to elevation. His CK value decreased to 82(0.7xULN) within 30 days without any clinical complaints and no other CK elevations for the remainder of the study.
 - b). Patient 52 of the cerivastatin 0.4 mg group had persistent CK elevations: CK of 409 after 2 week of treatment Repeat values 4 weeks and 6 weeks later were 476 and 546 .Study drug was discontinued, and CK return to normal off drug.
 - c). Three patients (patients 922, 914, and 893) were discontinued from the study due to elevation of SGOT/and or SGPT.):
 - (1). Patient 914 had SGPT of 59 and SGOT of 42 on Day 15 of treatment. The study drug was temporarily discontinued for two weeks and the repeat values

were still elevated with SGPT of 33 and SGOT of 25mU/ml. Study drug was discontinued permanently on Day 45 and SGPT returned to normal with SGOT still elevated at 23mU/ml off drug.

(2) Patient 922 had persistent SGPT elevations : SGPT of 81 (3.2xULN) on Day 17 of treatment. On Day 21, the SGPT was 215(8.6xULN) and at Day 23 was 110(4.4xULN). The patient was dropped from the study. Off drug her value returned to normal two weeks later..

(3). Patient 893 had SGPT of 78(3.1xULN) and was dropped from the study due to this abnormality.

d). Patient 452 had SGOT of 124(5.6xULN) and SGPT of 107(4.3xULN) on Day 31 of treatment. At Day 38, the SGPT was 30 and remained within normal limits for the duration of the study.

2). The 24 weeks treatment-related adverse enzymes elevations will also be evaluated in details when the entire Study D96-008 is reviewed.

4.2.8.1. Evaluation of basal and stimulated hormone levels: Statins act by inhibiting HMG-CoA reductase, the rate limiting enzyme in the cholesterol biosynthesis. Theoretically, a reduction in cellular cholesterol synthesis may lead to deficiencies in steroid synthesis. Hence, a number of plasma hormone assessments were performed at randomization and compared to values at Week 8, and/or Week 24. The assessments were made at centers 31 and 34. The data from at least one determination was available for a total of 24 patients.

4.2.8.1. The results of the stimulated cortisol levels are shown below:

Table 4.2.8.1: Stimulation Test: % change from baseline at Week 24:

Male Patients				
		Cerivastatin 0.3 mg	Cerivastatin 0.4 mg	Fluvastatin 40 mg
		N=2	N=8	N=4
Cortisol,AUC	MEAN	6.6	1.2	-14.0
	SD	3.7	9.1	25.9
	MIN	4.0	-10.8	-46.9
	MEDIAN	6.6	0.9	-11.9
	MAX	9.2	18.5	14.6
Cortisol,PEAK	MEAN	3.3	3.0	-15.0
	SD	4.9	14.3	18.5
	MIN	-0.2	-7.4	-39.4
	MEDIAN	3.3	-1.5	-12.8
	MAX	6.8	36.4	5.2
Female Patients				
		N=3	N=4	N=1
Cortisol,AUC	MEAN	8.9	41.9	19.8
	SD	11.1	84.9	19.8

	MIN	-1.9	-15.4	19.8
	MEDIAN	8.3	7.7	19.8
	MAX	20.3	167.6	19.8
Cortisol,PEAK	MEAN	11.6	48.8	4.5
	SD	13.6	104.4	-
	MIN	-3.9	-13.5	4.5
	MEDIAN	16.7	1.9	4.5
	MAX	21.9	204.9	4.5

Comments:

- 1). The sponsor had defined " a clinically significant change as a 50% difference between baseline and follow-up values". As can be seen from above, the group mean difference between the baseline and Week 24 were less than 50%. As for the HCG-stimulated testosterone, HCG-stimulated estradiol , basal aldosterone, basal plasma DHEA-S and basal free testosterone, basal FSH, LH and ACTH , very few patients had changes which exceeded the defined limit for significance. However, the rationale/justification for this definition was not submitted.
- 2). In most cases, the number of patients in each treatment group is less than 5 and the SDs were very large. The comparison between the groups are therefore not very meaningful/significant.
- 3). For the reasons listed above, the data submitted by the sponsor on the basal and stimulated hormone levels are inadequate for any conclusion to be drawn. However, clinical experience with other HMG-CoA-reductase inhibitors has not shown any clinically significant hormonal changes,

4.2.9. Reviewer's Comments/Conclusion of the Study Results:**4.2.9.1: Safety:**

There were no new/unexpected adverse events in this study as outlined in Safety Outcomes above. More detailed evaluation will be done in conjunction with D96-008B study which provided the long-term safety data.

4.2.9.2: Efficacy:

- 1). For the primary efficacy parameter, the calculated LDL-C at week 8 , was statistically different between the cerivastatin-treated groups and the placebo-treated group. ($p < 0.001$).
- 2). Unlike Study 0149 (n0jn-US study), the difference between the 0.3 mg and the 0.4 mg groups were also statistically significant in the direct LDL-beta quant. and the calculated LDL-C at both Week 8 and Week 24 endpoints.
- 3). For the secondary efficacy parameters, the cerivastatin-treated groups had statistically significant greater changes in HDL-C, Total-C, Total/HDL -C and LDL/HDL-C ratios than the placebo-treated group (at Week 8) and the fluvastatin 40 mg-treated group (at Week 24)..
- 4). There was no statistically significant difference between the 0.3 mg and 0.4 mg groups with respect to these secondary efficacy parameters except

for Total-C.

- 5). For TG, there was significant difference in mean percent change (also median percent change) between the cerivastatin-treated groups and the placebo-treated group and there was no statistically significant difference between the 0.3 and 0.4 mg groups at Week 8. At Week 24, only the 0.4 mg group showed statistically significant difference from the 0.3 mg and the fluvastatin groups.

4.3. Clinical Protocol: Study D96-008B (U.S. Study):

4.3.1. Objectives:

To compare the safety and efficacy of 0.4 mg cerivastatin QD with that of 0.3 mg QD, and with that of fluvastatin 40 mg QD at 52 weeks of the trial.

4.3.2. Study Population:

This is the extension of Protocol D-96-008A for the subset of patients, (n=650 of the original 908 patients who were randomized in Protocol D-96-008A), who discontinued prematurely, or who completed 52 week of treatment.

4.3.3. Study Design/ Procedures: Continuation of D96-008A Protocol.

4.3.4. Endpoints: The primary efficacy parameter was the change (expressed as a percentage) of the calculated LDL-C levels from baseline to the end of the 52 -week extension period.

4.3.5. Statistical Considerations: Analysis of variance (ANOVA) was used to calculate the least-square mean percent changes from baseline of the calculated LDL-C and other lipid parameters.

4.3.6. Results:

4.3.6.1. Baseline Characteristics: For all patients randomized to treatments are shown in Table 4.3.6.1.

**Table 4.3.6.1: Baseline Characteristics of Efficacy Population:
Demographic Data**

	Cerivastatin 0.3 mg n=142	Cerivastatin 0.4 mg n=289	Fluvastatin 40mg n=139
sex:(% male)	62	55	58
race (% Caucas.)	96	93	94
smoking(% curr, smoking)	16	13	11
alcohol (% non-drinker)	36	37	26
fm. hx. HLP: % yes	43	45	45
fm. hx. CAD:% yes	62	58	56

mean age (years)	57	58	57
mean weight (kg)	81	80	82
mean durat. HLP (years)	8	8	9
hypertension (% yes)	22	29	26
female climacteric (%)	17	18	25

Comments:

- 1). The patient-groups were similar with respect to most the baseline characteristics. The baseline lipid profiles are the as in D-96-008A since this is the 52-week extension.
- 2). Of the 655 patients enrolled in this 52-week extension, 164 were randomized to 0.3 mg, 328 to 0.4 mg cerivastatin, and 163 to Fluvastatin 40 mg groups respectively.
- 3). Of these, 160/164 of the cerivastatin 0.3 mg group; 320/328 of the 0.4 mg group and 160/163 of the fluvastatin group were valid for safety and efficacy evaluation. All 15 patients enrolled by investigator at Center 9, who was alleged to have fabricated patient data, were declared invalid for the analysis for both safety and efficacy.

4.3.6.2. Efficacy Endpoint Outcomes: Lipid parameter results at Weeks 52 endpoints are summarized below:

Table 4.3.6.2: Lipid Parameter Results at Weeks 52 Endpoints for Patients Valid for Intent-to-Treat % Change from Baseline:

Variable	Cerivastatin 0.3mg N=148	Cerivastatin 0.4mg N=300	Fluvastatin 40mg N=148
LDL-C			
Baseline	191.2	187.9	191.8
% change	-29.9* [^]	-31.3* [^]	-22.8*
+/- SE	1.20	0.90	1.20
HDL-C			
Baseline	48.8	48.7	48.5
% change	+9.0*	+8.3*	+6.5*
+/- SE	1.08	0.81	1.08
Total-C			
Baseline	276.9	273.5	275.8
% change	-19.5* [^]	-20.6* [^]	-14.5*
+/- SE	0.94	0.70	0.94
TG			
Baseline	185.9	184.4	177.9
% change	-2.79 [^]	-4.28*	+4.89

+/- SE	2.82	2.12	2.82
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Comments:

*= denotes significantly different from baseline .

^=denotes significantly different from fluvastatin 40 mg-treated group.

- 1). Analysis for the valid for efficacy population and the intent-to-treat population gave similar results. Only the Intent-to-treat patients are shown above.
- 2). All the active-treated groups (cerivastatin and fluvastatin) showed statistically significantly greater changes in LDL-C, HDL-C and Total-C from baseline values. The cerivastatin-treated groups had statistically significantly greater reductions than the fluvastatin 40 mg group in LDL-C and Total-C. However, there was no statistically significant difference between the 0.4 and the 0.3 mg cerivastatin-treated groups in LDL-C, Total-C and HDL-C..
- 3). Only 0.4 mg Cerivastatin-treated group had statistically significantly greater percent change from baseline in TG at the week 52 endpoint.

4.3.6.3: Safety Outcomes: This study provided the long-term (52 weeks) safety data of Cerivastatin 0.4 mg.

4.3.6.1. Extent of Exposure: Treatment duration by drug groups for patients valid for safety evaluation is shown below:

Table 4.3.7.1: Treatment Duration by Drug Groups:

	Cerivastatin 0.3mg	Cerivastatin 0.4mg	Fluvastatin 40mg
	N=160	N=320	N=160
Mean (days)	323	327	314
SE	106	100	109
Minimum	4	14	2
Maximum	411	429	407

Comments:

- 1). 73%, 75%, and 65% of the patients assigned to the cerivastatin 0.3 mg, 0.4 mg and fluvastatin groups received the assigned study drug for greater than 360 days.
- 2). The actual exposure to fluvastatin 40mg was shorter because the patients in this group were on placebo for the first 8 weeks.

4.3.6.2. Adverse Events: A summary of the adverse events can be seen in the table below:

Table 4.3.6.2: Summary of Adverse Events:

	Cerivastatin 0.3mg	Cerivastatin 0.4mg	Fluvastatin 40mg
	N=160	N=320	N=160
Death	0 (0%)	1 (<1%)	1 (<1%)
Any adverse event	142 (89%)	293(92%)	134(84%)

Any drug-related event	70(44%)	157(49%)	71(44%)
Any serious event	9 (6%)	20(6%)	12(6%)
Discontinued due to adverse event	18(11%)	32(10%)	11(7%)

Comments:

- 1). There were two deaths in this study. They were the same two patients who were already described in Study D96-008A. Both deaths were more likely due to the underlying disease rather than the study drug.
- 2). The adverse events causing patients' discontinuation were mostly digestive system events, and joint/musculoskeletal complaints as in the study report of D96-008A. However, 1 patient in the 0.3 mg group, 4 patients in the 0.4 mg group and 2 patients in the placebo/fluvastatin 40mg group had LFT elevations resulting in discontinuation. Similarly, 1 patient in the 0.3 mg group and 2 patients in the 0.4 mg group had CK elevations resulting in discontinuation. These elevations are examined in detail in the table below:

Table 4.3.6.3: Elevations of CK, SGOT, SGPT during treatment through Week 52 regardless of baseline values:

Variable	Cerivastatin 0.3mg N=225	Cerivastatin 0.4mg N=448	Fluvastatin 40mg N=220
CK			
>3xULN<5xULN	2(1%)	14(4%)	1(0.6%)
>5xULN<10xULN	4(2%)	4(1%)	2(1%)
>10xULN	2(1%)	1(0.2%)	0(0%)
SGOT			
>3xULN<5xULN	0(0%)	2(0.4%)	2(1%)
>5xULN<10xULN	0(0%)	1(0.2%)	2(1%)
>10xULN	0(0%)	0(0%)	0(0%)
SGPT			
>3xULN<5xULN	1(0.6%)	3(0.7%)	2(1%)
>5xULN<10xULN	0(0%)	1(0.2%)	2(1%)
>10xULN	0(0%)	0(0%)	0(0%)

Comments:

- 1). The cerivastatin-treated groups had more CK elevations than the fluvastatin-treated group. 4 patients each in the 0.3 and 0.4 mg group had elevations >5xULN<10xULN. 2 patients each in the 0.3 and 0.4 mg group had elevations >10xULN
 - a). Patient 592 of the cerivastatin 0.3 mg group had sustained CK elevations of 1950 (16.3xULN) and 397 (3.3xULN) on Days 127 and 131 of treatment. He complained of "pain" only and CK decreased to 123 (1xULN) 9 days later.
 - b). Patient 135 of cerivastatin 0.3 mg group had CK of 1367(11.4xULN) on Day 138 of treatment and decreased to 60(0.5xULN) 7 days later.

- c). Patients 44, 154, 729, 822 of the cerivastatin 0.3 mg group all had transient CK elevations $>5xULN$ and decreased to $<1.2xULN$ without any clinical symptoms. .
- d). Patient 643 of the cerivastatin 0.4 mg group had CK of 2550($21.3xULN$) on Day 34 of treatment only and was already discussed in Week 8 safety evaluation on p. 19 of the Review.
- e). No patient in the cerivastatin 0.4 mg group had sustained CK elevations. 4 patients (patients 128, 202, 459, and 501) had only transient elevations of $>5xULN$ and decreased to $<1.3xULN$ without any symptoms.
- 2). The cerivastatin 0.4 mg-treated group had more SGOT/SGPT elevations than the cerivastatin 0.3 mg group and the fluvastatin 40 mg group. However, none had $>10x ULN$ elevations of either SGOT or SGPT.
- a). Patient 452 had SGOT of 124($5.6xULN$) and SGPT of 107($4.3xULN$) on Day 31 of treatment. Similarly Patient 922 also had SGOT of 92 ($4.2xULN$) and SGPT elevation of 81($3.2xULN$) on Day 21 of treatment. Both patients were previously discussed on pp.19-20 of this Review.
- b). Patient 231 of cerivastatin 0.4 mg group had transient SGOT elevation of 95($4.3xULN$) and SGPT of 217($8.7xULN$) . He was noted to have anemia. Both values decreased to 19($0.9xULN$) and 51($2.0xULN$) 20 days later without any hepatic symptoms.
- c). Patient 610 of cerivastatin 0.4 mg group had sustained SGPT elevations of 79($3.2xULN$) and 80($3.2xULN$) on Days 171 and 176 of treatment. She was asymptomatic and her value decreased to 52($2.1xULN$) 9 days later and remained about $1.0xULN$ for the remainder of the treatment.
- 3). A new treatment-related laboratory finding was serum glucose changes. The details can be seen from the table below:

Table 4.3.6.4: Mean Serum Glucose Values (mg/dL) in Valid for Safety Population:

Cerivastatin 0.3 mg N=225				
Variable	MEAN	STD	MINIMUM	MAXIMUM
Baseline	98.0	9.8	77.0	140.0
Week 8	98.8	11.2	74.0	143.0
Week 24	99.4	12.2	61.0	176.0
Week 52	99.9	12.7	76.0	150.0
Cerivastatin 0.4 mg N=448				
Variable	MEAN	STD	MINIMUM	MAXIMUM
Baseline	98.1	10.5	73.0	137.5
Week 8	99.3	11.1	73.0	143.0
Week 24	99.3	12.2	52.0	153.0
Week 52	100.8	12.5	74.0	146.0
Placebo/Fluvastatin 40 mg N=220				
Variable	MEAN	STD	MINIMUM	MAXIMUM
Baseline	97.8	10.2	74.0	142.0
Week 8	98.1	12.7	54.0	156.0
Week 24	99.6	13.6	68.0	171.0

Week 52	100.7	14.5	77.0	171.0
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Comments:

- 1). The maximum glucose values were 176 mg/dL in a patient in the 0.3 mg group, 171 mg/dL in a patient in the fluvastatin group. The incidences were <1% of the treated patients. All values decreased to <1.2xULN (N=100 mg/dL) or normal in subsequent visits.
- 2). These glucose elevations were of little clinical significance. Patients with diabetes mellitus (fasting glucose >140mg/dL or treatment for diabetes) were excluded from the study. Statins are seeking to broaden their indications for treatment of Fredrickson Type IV patients who have a high percentage of glucose-intolerance. Treatment for Type IV patients and in diabetics may require monitoring of glucose levels during treatment.

4.3.7. Reviewer's Comments/Conclusion of the Study Results:**4.3.7.1: Safety:** This study is of value since it provided the long-term (52 weeks) safety data:

- 1). The cerivastatin-treated groups had more CK elevations than the fluvastatin-treated group. The incidence of >10xULN elevations were 1% or less and none developed clinical rhabdomyolysis.
- 2). The incidence of SGOT/SGPT elevations were 1% or less as in the previous studies. None of the treated patients had >10xULN of either SGOT or SGPT or developed clinical symptoms/signs of hepatic cholestasis
- 3). Patients in the cerivastatin-treated groups and placebo-fluvastatin 40 mg-treated group had treatment-related glucose elevations. However, these elevations occurred in <1% and were minimal, of little clinical significance.
- 4). The hormonal data submitted were inadequate to permit a meaningful evaluation as discussed.

4.3.7.2: Efficacy:

- 1). For the primary efficacy parameter, (calculated LDL-C) and the secondary efficacy parameters (Total-C and HDL-C), the cerivastatin-treated groups had statistically significantly greater reductions at Week 52 from baseline values. However, there was no statistically significant difference between the 0.3 and 0.4 cerivastatin groups.
- 2). For TG, only the Cerivastatin 0.4 mg group had statistically significantly greater percent change from the baseline value at the week 52 endpoint.

5. Supportive Studies: Supportive evidence for the safety and efficacy of cerivastatin 0.4 mg is provided by the following studies:**5.1. US D97-001 Study:**

5.1.1. Procedures: This was a randomized, double-blind, placebo-controlled, parallel-group study of cerivastatin 0.8 mg vs. placebo for 28 days in 41 patients with primary hypercholesterolemia, (baseline LDL-C of 174 and 176 mg/dL respectively).

5.1.2. Efficacy Endpoints: LS mean percent change from baseline was used as efficacy parameter.

5.1.3. Results:

5.1.3.1: Efficacy:

- 1). In the 0.8 mg cerivastatin group, LDL-C (directly measured), calculated LDL-C, and Total-C decreased by 41.0%, 44.0% and 30.8% respectively. These mean changes were statistically different compared to that of the placebo group, ($p < 0.0001$).
- 2). For TG, the mean percent change was -11.2% vs. +15.9%, also statistically significantly different ($p = 0.013$).
- 3). No significant differences were demonstrated in the other lipid parameters.

5.1.3.2: Safety:

- 1). There was no death in this study. One serious adverse event of presumed salpingitis was considered not to be related to cerivastatin 0.8 mg treatment.
- 2). 4/28 (14%), 2/28 (7%) of the 0.8 mg cerivastatin-treated patients had SGOT, SGPT elevations respectively compared to 0/13 (0%). 1/13 (8%) of the placebo group. But none of the elevations exceeded 3xULN.
- 3). Similarly, 4/28 (4%) in the 0.8 cerivastatin group had 2-5 xULN CK elevation compared to 1/13 (8%) in the placebo group. One patient had 8xULN CK elevation on one day after the last dose.

5.1.4. Reviewer's Evaluation:

5.1.4.1: Efficacy:

- 1). This was a small, (28 patients in the 0.8 mg cerivastatin group and 13 patients in the placebo group) and of 28 days duration. The finding of 41-44% decrease in LDL-C is of interest in that it is greater than the 32.5-35.8% reduction obtained with 0.3 and 0.4 mg/day treatment studies. Much larger and longer duration studies are needed to confirm this preliminary efficacy finding.
- 2). The mean percent change in TG was also found to be statistically different. However, in view of small number of patients and large spontaneous fluctuations in TG, a more useful parameter would be percent change in median TG. Therefore, the TG finding maybe of little clinical significance.
- 3). Sponsor submitted data in an attempt to correlate the change in LDL-C at Day 29 with the pharmacokinetic parameters. Obviously a larger study is needed and data should be submitted to Biopharmacology for evaluation.

5.1.4.2: Safety:

- 1). Safety concerns, particularly with respect to transaminases and CK elevations, also require larger and longer duration studies. This is underscored by the finding of 8xULN CK elevation in one patient. Patient 1017 had CK of 137-125 on days 15 and 22 of treatment. It further increased to 1024 U/L one day after the last dose and it decreased to 888U/L and 173 U/L four and seven days after the last dose. Urine protein was normal and she did not develop clinical signs /symptoms of rhabdomyolysis.

5.2. Study 0161 (non-US Study):

5.2.1. Procedures: A multinational, multicenter, randomized, double-blind study comparing cerivastatin 0.2 and 0.4 mg in patients with primary hypercholesterolemia. 494 patients were randomized and week 24 data were obtained in 330 and 162 patients in the 0.4 and 0.2 intent-to-treat groups respectively

5.2.2. Results:**5.2.2.1: Efficacy:**

- 1). LS mean percent change from baseline was used as efficacy parameter.
- 2). In the 0.4 mg group, calculated LDL-C and Total-C decreased by 37.9% and 25.6 % respectively. In the 0.2 mg group, the decreases were 30.2% and 20.6% respectively. These differences were statistically significant.
- 3). The treatment differences for TG and HDL-C were not statistically significant.

5.2.2.2: Safety:

- 1). There were no serious treatment-related adverse events.
- 2). 5/287 (2%) patients treated with 0.4 mg cerivastatin, who had normal CK pre-randomization, had CK elevations 5-10xULN. No patients had an elevation >10xULN.
 - a). 3 patients had 2 or more episodes of CK elevation: Patient 5448 had CK of 181 at Visit 11(8/19/97) and increased to 1013 one month later at Visit 12. CK values at Visits 13&14 were normal, but was 227 at Visit 15(3/21/98). The patient continued the study until Visit 16(6/23/98) and the CK was within the normal range. Patient 8199 had two episodes of CK elevation, CK of 668 at Visit 7(4/30/97) and 328 at Visit 10 (7/24/97). CK decreased to within normal range at all other visits and he completed the study. Patient 9218 had two episodes of CK elevation, 195 at Visit 9 (6/12/97) and 626 at Visits 13 (10/29/97). CK decreased to within normal range at all other visits to the end of the study.
 - b). 2 patients had transient CK elevation. Patient 2356 had CK of 618 and patient 9211 had CK of 628 at Visit 7. Both

- patients completed the study without further CK elevation.
- 3). One patient each of the 0.2 mg and the 0.4 mg cerivastatin group with normal ALT pre-randomization, had sustained ALT elevations at 2 or more scheduled visits. No patients had an elevation $>5xULN$.
 - a). Patient 13070 of the cerivastatin 0.2 mg group had 4 episodes of ALT elevation. Only one was 114 ($>3xULN$) and the others were 29, 30 and 31 IU/L. ALT value was below upper limit of normal at all other visits.
 - b). Patient 2357 of the cerivastatin 0.4 mg group had 3 episodes of ALT elevation. Only one was 85 ($>3xULN$; accompanied by an AST of 71) and the others were 44 and 37 IU/L. She completed the study without any further ALT elevation.
 - 4). Two patients in the cerivastatin 0.4 mg group who had normal AST pre-randomization, had AST elevations sustained at 2 or more scheduled visits. No patient in the cerivastatin 0.2 mg group had sustained AST elevation and no patient in either group had an elevation $>5xULN$.
 - a). Patient 2357 had 4 episodes of elevation of AST, only one was 71 ($>3xULN$ and accompanied by an ALT elevation of 85). The other elevations were 23, 31, and 25 IU/L. AST value was below the upper limit of normal at all other visits and she completed the study without any symptoms.
 - b). Patient 15572 had AST of 25 (1.04xULN) on visit 6 and was 67 ($>3xULN$) at visit 9 (2 months later). His value decreased at the next visit and AST remained below upper limit of normal at all other times.

5.2.3. Reviewer's Evaluation:

5.2.3.1: Efficacy:

- 1). For the primary efficacy parameter, LDL-C, statistically significant changes from baseline were observed in both treatment groups after 2 weeks of treatment. The maximum effect was obtained after 4 weeks of treatment and was sustained until 24 weeks. Furthermore, the difference between the groups achieved statistical significance ($p < 0.0001$). This was also true for the secondary efficacy parameter, Total-C.
- 2). For the other secondary efficacy parameters, HDL-C and TG, statistically significant changes from baseline were observed in both treatment groups after 2 weeks of treatment. The maximum effect was obtained after 12 weeks (2 weeks for TG) of treatment and was not sustained at Week 24. However, the difference between the groups was not statistically significant, ($p = 0.60$ and $p = 0.87$ respectively). The clinical implication/significance of these changes is yet to be determined.

5.2.3.2: Safety:

- 1). The cerivastatin 0.4 mg group had 5 CK elevation >5-10x ULN and none in the than the 0.2 mg group.
- 2). One patient each in the 0.2 mg and 0.4 mg group had 3-4 episodes of ALT elevation >3xULN..
- 3). Two patients in the cerivastatin 0.4 mg group had 2-4 episodes of AST elevation >3xULN and none in the cerivastatin 0.2 mg group.
- 4). All CK, ALT/AST elevations decreased to normal levels during the remainder of the study . No patient developed hepatic cholestasis or rhabdomyolysis.

5.3. Study Z91-031:

5.3.1: Procedures: This was a multicenter, double-blind study in patients previously treated with cerivastatin 0,2 mg (for up to 2 1/2 years). This protocol had 3 extensions (X-, Y-, and Z-). Patients were randomized to be given 2X 0.2 mg cerivastatin or lovastatin 40 mg in the evening. The mean treatment duration was 29 weeks.

5.3.2: Results:**5.3.2.1: Efficacy:**

- 1). The LS mean percent change from baseline in LDL-C was the primary efficacy parameter. LS mean percent change from baseline in Total-C, HDL-C, and TG were secondary efficacy parameters.
- 2). Cerivastatin 0.4 mg and lovastatin 40 mg treatments resulted in clinically significant reductions in LDL-C, (-33.0% and -33.8% respectively). Similarly. Comparable reductions in Total-C, TG and increases in HDL-C were obtained in both treatments.

5.3.2.2: Safety:

- 1). There were no deaths in this study.
- 2). 13/398 (3%) of the patients on 0.4 mg cerivastatin discontinued the study due to adverse events. Except for three patients,(one had increased CK and two had abnormal liver function tests), all the others were not drug-related.
- 3). Of the 186 patients valid for safety and had normal CK at baseline, 1 (1%) developed CK >3xULN to 10xULN; compared to 0% for lovastatin 40 mg group. None had elevation >10xULN. Patient 7010 had CK of 789 (6.5xULN) in the Y-91-031 extension and decreased to near normal 15 days later (CK=144). However, he had CK of 329 on Day 1 of Z-extension and was discontinued from the study.
- 4). Of the 218 patients valid for safety and had normal SGOT at baseline, 1 (<1%) developed SGOT >3xULN to 5xULN; compared to 0% for the lovastatin 40 mg group. 1 patient had sustained elevations of SGOT and SGPT. Patient 3072 had SGOT of 98(4.4xULN) and SGPT of 183(7.6xULN) on

Day 230 of treatment. Repeat testing 2 days later, SGOT was 74 and SGPT was 140. His alkaline phosphatase and serum bilirubin were also elevated at this date. There were no follow-up lab. but he completed the study without further incident.

- 5). Of the 222 patients valid for safety and had normal SGPT at baseline, one additional patient, besides Patient 3072, developed elevated SGPT. Patient 29012 had SGPT of 79 and SGOT of 89 on Day 183 of treatment. He also had an elevated temperature and was dropped from the protocol. His temperature came down to normal 12 days later and 6 weeks later both SGPT and SGOT were normal.

5.3.3. Reviewer's Evaluation/Comments:

5.3.3.1: Safety: The adverse events profile was similar to other studies.

Although the incidences of elevation CK, SGOT and SGPT were more numerous in the 0.4 mg cerivastatin group than the lovastatin 40 mg group, the rate was 1% or less. No patient had CK elevation >10xULN, or SGOT>5xULN and only 1 patient (<1%) had SGPT>5xULN.

5.3.3.2: Efficacy:

- 1). Cerivastatin 0.4 mg and lovastatin 40 mg resulted in comparable changes in LDL-C, Total-C, TG., HDL-C to the other studies already presented/reviewed.
- 2). All the patients had been on 0.2 mg cerivastatin for up to 2 1/2 years. Unfortunately, so data were presented to enable a comparison between the 0.2 and 0.4 mg dosages.

6. Safety Update: On 11/13/98, sponsor submitted Four-Month Safety Update to NDA 20-740- S002. It contained Part C of Study D96-008, the study population consisted of patients who had received cerivastatin 0.4 mg for 52 weeks and continued therapy through 78 weeks.

6.1. Updated Cerivastatin Patient Exposure:

Table 6.1: Number of cerivastatin 0.4 mg-Treated Patients in Completed US Studies by Treatment Duration and Dose (Patients Valid for Safety)

Dose	4 weeks	24 weeks	52 weeks	78 weeks
0.3 mg	219	207	191	48
0.4 mg	443	412	385	100

6.2. Adverse Events:

6.2.1: Deaths: There was one death in this study, D96-008C. A 58-year-old female was found dead at home after 433 days treatment with 0.3 mg

cerivastatin. This was attributed to the underlying coronary heart disease, not to the study drug.

6.2.2: **Treatment-related adverse events:** Of particular concern is the treatment-related changes in CK, SGOT and SGPT. It is of interest to compare the incidence of these changes in terms of "through 52 weeks" vs. "after 52 weeks" in this subgroup of patients. The data submitted by the sponsor on 1/27/99(with errors corrected) is shown below:

Table 6.2 : Comparisons of Elevations of CK, SGOT,SGPT by Treatment Duration ("through 52 weeks vs. "after 52 weeks"):

Variable	Cerivastatin 0.3 mg N=48				Cerivastatin 0.4 mg N=100				Place/Fluva.40mg N=47			
	Thru 52 weeks		After 52 weeks		Thru 52 weeks		After 52 weeks		Thru 52 weeks		After 52 weeks	
	n	%	n	%	N	%	n	%	n	%	n	%
CK												
Normal	32	67	41	85	63	63	78	78	36	77	43	91
>ULN to 3xULN	15	31	7	15	32	32	20	20	10	21	4	9
>3xULN to 5xULN	0	0	0	0	3	3	1	1	0	0	0	0
>5xULN to 10xULN	1	2	0	0	2	2	1	1	1	2	0	0
SGOT												
Normal	30	63	38	79	70	70	80	80	35	74	39	83
>ULN to 3xULN	18	37	10	21	28	28	17	17	12	26	8	17
>3xULN to 5xULN	0	0	0	0	1	1	2	2	0	0	0	0
>5xULN to 10xULN	0	0	0	0	1	1	1	1	0	0	0	0
SGPT												
Normal	33	69	42	88	71	71	83	83	39	83	44	94
>ULN to 3xULN	15	31	6	13	24	24	12	12	7	15	3	6
>3xULN to 5xULN	0	0	0	0	3	3	4	4	1	2	0	0
>5xULN to 10xULN	0	0	0	0	2	2	1	1	0	0	0	0

Comments:

In this subgroup of patients who completed 78 weeks of treatment, the incidence of treatment-related elevations of CK, SGOT and SGPT changed over time. As will be seen from the detailed narrative summaries to follow, nine patients developed

elevations after 52 weeks of treatment:(1 with CK>5xULN, 3 with SGOT>3xULN and 5 with SGPT>3xULN elevations). Therefore, monitoring of these adverse events should be undertaken throughout the entire therapy period.

7. Reviewer's Evaluation of Study D96-008 :

7.1. Safety Evaluation:

- A). There was no death attributable to the study-drug.
- B). There was no new/unexpected adverse event reported in these studies. One new adverse finding was elevated serum glucose which was minimally elevated and of little clinical significance.
- C). **Serious Adverse Events:** The entire Study D96-008 (Part A, Part B with the extension to 52 weeks and Part C with extension to 78 weeks) will be reviewed. The following information was extracted from the results of the entire D96008 Study based on the actual data submitted.
 - 1). Of the 448 patients randomized to cerivastatin 0.4 mg, 43 (10%) discontinued due to adverse events. Of 225 patients in the 0.3 mg group, 21 (9%) discontinued and 5/220 in the fluvastatin 40 mg group discontinued due to adverse events. Most of these events were of "digestive", "musculoskeletal/joint" in nature. However, 7 patients in the cerivastatin groups were discontinued from the study due to elevated CK or LFTs.
 - (a). **In the 0.3 mg group, two patients were discontinued:**
 - Patient 366 had SGOT of 44 and SGPT of 77 on Day 99 of treatment. The study drug was discontinued several days later and the value decreased the day after discontinuation (SGOT of 24 and SGPT of 45). The study drug was permanently discontinued. 3 weeks later the values returned to normal.
 - Patient 729 had moderate CK elevations during the placebo-run-in phase(182-215mU/ml). On Day 13 of the treatment, study drug was discontinued for 27 days. During this period, CK values decreased but were still elevated at 157-174. About 4 months later, CK values were markedly elevated at 912mU/ml and the patient was discontinued from the study. After 2 months of follow-up, CK decreased but were still elevated at values of 140-188.
 - (b). **In the 0.4 mg group, five patients were discontinued:**
 - Three patients, (Patients 893, 914, and 922), had been discontinued due to elevation of SGOT/and or SGPT. One patient (Patient 52), was discontinued due to persistent CK elevations. They were previously reviewed in details on pp.19-20 of this Review.
 - One patient, patient 261 had CK of 211 on Day 173 of treatment and experienced moderate body cramps. The study drug was discontinued 4 days later and repeat CK in one month was normal.

- 2). In addition to discontinuations, there were **treatment-related changes in CK, SGOT and SGPT.**
- (a). In general, cerivastatin 0.4 mg-treated groups had more CK elevations than the 0.3 mg group and the fluvastatin 40 mg treated group.
- (1). In the cerivastatin 0.3 mg group, patient 44 had CK of 694U/L (5.8xULN) on Day 113 of treatment. She was asymptomatic and decreased to 86 U/L (<1xULN) 8 days later. Her CK values remained <2xULN for the remainder of the treatment.
- (2). In the 0.4 mg group, 2 patients had CK elevations on more than one occasion:
- Patient 60 had CK of 482(4xULN) on Day 113 of treatment. His CKs fluctuated between 297 (2.5xULN) to 527 (4.4xULN) until Day 527 of the treatment. He was asymptomatic all these times.
 - Patient 428 had CK of 6315 (52.6xULN) on Day 455 of treatment. Repeat CK 2 days later was still 1227(10.2xULN). His LFTs were also elevated and he complained of myalgia on these dates. He did not develop rhabdomyolysis and CK decreased to 63(0.5xULN) on Day 475.
- (3). In the cerivastatin 0.4 mg group, 2 patients had CK>5xULN to <10xULN:
- Patient 128 had CK of 890(7.4xULN) on Day 281 of treatment and decreased to 160(1.3xULN) 3 days later. Patient 459 had CK of 956(8xULN) on Day 362 of treatment and decreased to 84(0.7xULN) 8 days later. Both patients had no clinical symptoms. See detailed discussion in Week 52 safety evaluation on p26.
- (4). In the cerivastatin 0.4 mg group, 4 patients had CK>3xULN <5x ULN:
- Patient 104 had CK of 452(3.8xULN) on Day 463 of treatment. He was asymptomatic and his CK decreased to 73 on Day 561 of treatment.
 - Patient 321 had CK of 385(3.2xULN) on Day 281 of treatment and decreased to 201(1.7xULN) 7 days later without any symptoms.
 - Patient 370 had CK of 586(4.9xULN) on Day 116 of treatment. He was asymptomatic and his CK decreased to 205(1.7xULN) 2 days later.
 - Patient 99 had CK of 409(3.4xULN) on Day 29 of treatment and complained of myalgia. His CK decreased to 84(0.7x ULN) 6 days later.
- (b). Re SGOT, cerivastatin 0.3 mg group and placebo/fluvastatin 40 mg group had no patient with >3xULN elevations.
- (1). The Cerivastatin 0.4 mg group had 2 patients with SGOT elevations on more than one occasion:
- Patient 528 had SGOT of 86(3.9xULN) and 77(3.5xULN) on

- Days 385 and 393 of treatment and decreased to 21(1xULN) 13 days later without any hepatic signs/symptoms.
- Patient 428 had SGOT of 186(8.5x ULN) and 73 (3.3xULN) on Days 455 and 457 of treatment. He was also had elevated CKs and complained of myalgia only.
- (2). Patient 452 had SGOT of 124(5.6xULN) on Days 31 and decreased to 20(0.9x ULN) 7 days later without any clinical hepatic signs/symptoms. See previous discussion on p20.
 - (3). 2 patients had SGOT elevations >3xULN<5xULN(both patients also had CK elevations, see previous discussion on p.35):
 - Patient 104 had SGOT of 90(4.1xULN) on Day 561 of treatment and decreased to 19(0.9xULN) 13 days later.
 - Patient 231 had SGOT of 95(4.3xULN) on Day 256 of treatment and decreased to 19(0.9xULN) 20 days later.
- ©. Re SGPT, the cerivastatin 0.3 mg group and the placebo/fluvastatin 40 mg group had no elevations>3xULN while the cerivastatin 0.4 mg group had:
- (1) 2 patients with SGPT elevations on more than one occasion:
 - Patient 528 had SGPT of 88(3.5xULN) and 121(4.8xULN) on Days 385 and 393 of treatment, he also had SGOT elevations on these dates. Both SGPT and SGOT decreased to 22(0.9x ULN) and 21(1xULN) 13 days later without any clinical hepatic signs/symptoms.
 - Patient 610 had SGPT of 79(3.2xULN) and 80(3.2xULN) on days 171 and 176 of treatment and decreased to 52(2.1xULN) and 27(1.1xULN) 9 and 18 days later. See previous discussion on p.26.
 - (2). 3 other patients had SGPT elevations>5xULN:
 - Patient 104 had SGPT of 186(7.4xULN) ON Day 561 of treatment and decreased to 24(1xULN) 13 days later.
 - Patient 146 had SGPT of 204(8.2xULN) on Day 224 of treatment and decreased to 39(1.6x) and 19(0.8xULN) 6 and 60 days later without any clinical hepatic signs/symptoms..
 - Patient 231 had SGPT of 217(8.7xULN) on Day 256 of treatment and decreased to 51 (2.xULN) 20 days later.
 - (3). 6 patients had SGPT>3xULN<5xULN:
 - Patient 233 had SGPT of 91(3.6xULN) on Day 532 of treatment and decreased to between 50(2xULN) to 65(2.6xULN) during the remainder of the treatment without any clinical hepatic signs/symptoms.
 - Patient 428 had SGPT of 79(3.2xULN) on Day 455 of treatment. She also had elevated SGOT and CK as well as complaining of myalgia. Her SGPT decreased to 73(2.9xULN) and 17(0.7x ULN) over the next 2-17 days without any other signs/symptoms.
 - Patient 452 had SGPT of 107(4.3xULN) on Day 31 of treatment

and decreased to 30(1.2xULN) 7 days later. He was asymptomatic and had elevated SGOT at the same time. See previous discussion on p.20.

-Patient 657 had SGPT of 110(4.4xULN) on Day 174 of treatment and complained of vomiting, nausea and abdominal pain. Her value decreased to 36(1.4xULN) 5 days later without any other complaints.

-Patient 99 had SGPT of 97(3.9xULN) on Day 91 of treatment and decreased to 42(1.7xULN) 7 days later.

7. Reviewer's Overall Evaluation :

7.1. Safety Evaluation:

- 1). There was no death attributable to the study-drug.
- 2). There was no new/unexpected adverse event reported in these studies. One new adverse finding was elevated serum glucose which was minimally elevated and of little clinical significance.
- 3). In the treatment-related adverse events, in almost all the studies, (the pivotal studies and the supportive studies), there were more elevations of CK, SGOT and SGPT in the 0.4 mg-treated groups than either the 0.2/0.3 or placebo/fluvastatin/lovastatin-treated groups. However, most of the elevations were transient. Even in patients with persistently elevated levels no clinical signs/symptoms of hepatic cholestasis or rhabdomyolysis.

7.2. Efficacy Evaluation:

- 1). **Primary Efficacy parameter(LDL-C):**
 - a). At **Week 8 endpoint**, both pivotal studies showed reductions of -33.0--35.9 %, statistically significantly different from the placebo groups. There was statistically significant difference between the 0.3 and the 0.4 mg groups in the D96-008A study, not in the 0149 study
 - b). At **Week 24 endpoint**, statistically significant differences were present between the fluvastatin 40mg group and the cerivastatin-treated groups. Furthermore, statistical significant differences were present between the 0.3 and 0.4 mg groups.
 - c). At **Week 52 endpoint**, the difference between the 0.3 and 0.4 mg groups were no longer statistically significant.
- 2). **Secondary Efficacy parameters:**
 - a). At **Week 8**, statistically significant differences were present only in Total-C, HDL-C and TG (mean percent change) between the placebo groups in both pivotal studies. In the D96-008A study only, the difference in Total-C between the 0.3 and 0.4 mg groups was also significant. No statistically significant differences were found between the cerivastatin groups in terms of HDL-C and TG. Furthermore, in the D96-008A study, the median percent change in TG between the cerivastatin groups was not significant presumably due to the large spontaneous fluctuations of TG independent of the treatments
 - b). At **Week 24**, statistically significant differences were present in Total-C,

and ApoB between the fluvastatin 40mg group and the cerivastatin-treated groups. Furthermore, the difference in Total-C and ApoB between the 0.3 and 0.4 mg groups were also significant.

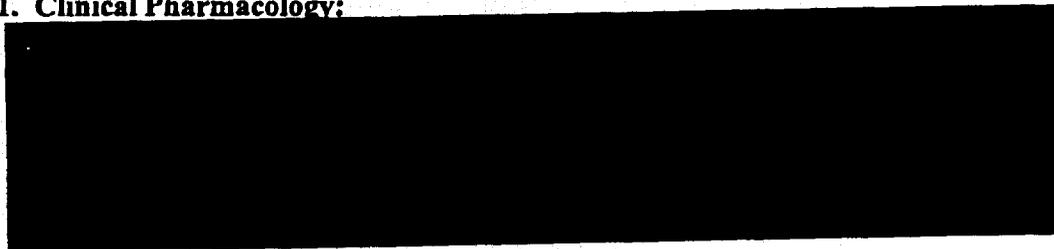
- c). At Week 52, there were still statistically significant difference between the cerivastatin-treated groups and the fluvastatin-treated group in Total-C.

7.3: Conclusions/Recommendations:

- 7.3.1. With 0.4 mg dose, there were no new/unexpected clinically significant adverse events reported in the studies submitted.
- 7.3.2. After 8 weeks of treatment with 0.4 mg once daily, there were significant greater changes of LDL-C, total-C, HDL-C and in TG than the 0.3 mg-treated group. These differences were maintained at week 24. However, there was no significant difference between the 0.3 and 0.4 mg groups with long-term treatment (52 weeks) in the primary efficacy endpoint (calculated LDL-C) or any of the secondary efficacy parameters. There were sufficient number of patients in the study (385 and 191 patients in the 0.4 mg and 0.3 mg group respectively) to detect a statistical significant difference. On the other hand, there were more frequent treatment-related changes in CK and SGOT/SGPT as discussed in Overall Safety Evaluation. From the benefit/risk analysis point of view, cerivastatin 0.4 mg cannot be recommended for administration over cerivastatin 0.3 mg. However, cerivastatin 0.4 mg treatment did significantly lowered LDL-C compared to placebo-treatment. Therefore, from a regulatory point of view, cerivastatin 0.4 mg maybe approved.
- 7.3.3. Recommendation: This Efficacy Supplement may be approved and cerivastatin 0.4 mg may be added to the approved dosages

8. Labeling: Only the proposed changes in the package insert will be commented:

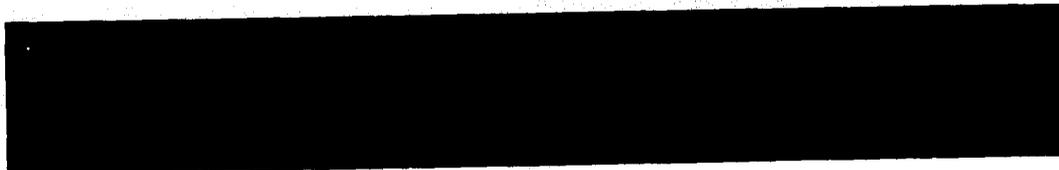
8.1. Clinical Pharmacology:

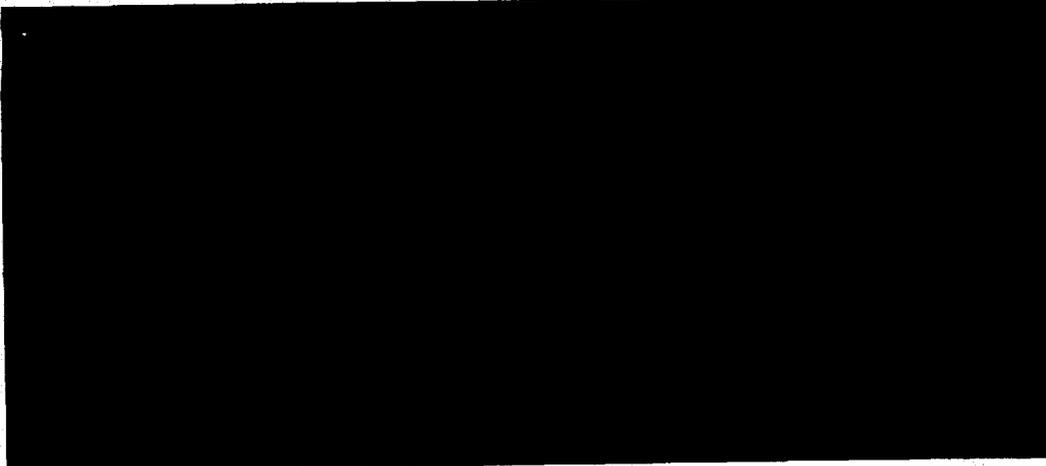


8.1.2: Pharmacokinetics:

Metabolism: Please refer to Biopharmaceutics Review.

8.2. Clinical Studies: The whole section should be revised as follows:





The paragraph " In a pool of seven studies in patients" should be deleted :
Dr. David Hoberman, the biostatistician, states:

"In principle, the sponsor's method of pooling the data from these studies is questionable for the following reasons: 1). There is a substantial variation in mean baseline TG among the studies, so that pooling may be inappropriate. 2). Not all the studies had the same dosage arms so that some of the comparisons are between arms that are in different studies. 3). The sponsor has stratified on "country" instead of "study". A more appropriate approach would have been to have gotten an estimate the desired parameter from each study, separately, and then use some kind of weighted average over the seven studies. "

In response to this reviewer's request, the sponsor, in the 12/7/98 submission, included trend analysis of TG values for all patients in the seven trials and trend analysis for patients who had baseline TG values >250 mg/dL in the seven trials pooled for Figure 1 of the proposed package insert. These data were referred to Dr. David Hoberman for evaluation and he states:

"The sponsor's 12/7/98 submission contains an analysis of variance of the percentage change of TG from baseline to 8 weeks which stratifies on country. The purpose is clearly to determine whether or not the percentage change in TG from baseline to 8 weeks increases with increasing dose. The Table on page 13 of that submission reports p-values of pair-wise comparisons of 0.2 mg, 0.3 mg and 0.4 mg, together with each active dose's comparison to placebo. None of the pair-wise comparisons between active doses is statistically significant even at the nominal 0,05 level. Thus there is no statistical evidence that there is a dose-related response to percentage change in TG from baseline to 8 weeks. Figure 1 on page 14 of the package insert is therefore misleading."

The paragraph, "In a large clinical study, the number of patients meeting their NCEP-ATP II target....." should be omitted for the following reasons:

- 1). It is promotional rather than informative/instructional.

- 2). Table 2 is misleading in that the results are individual and population dependent:
 - a). Whether or not an individual reaches the target goal depends on the mean baseline LDL-C level;
 - b). The actual percentage of patients reaching the target goal depends on the number of patients in a given trial.
 - c). The NCEP-ATP II goals are not based on actual data. Therefore, the clinical benefit of having reached the target goal is yet to be demonstrated.
- 3). The Agency is re-considering similar statements/tables from the package inserts of other lipid-lowering agents.

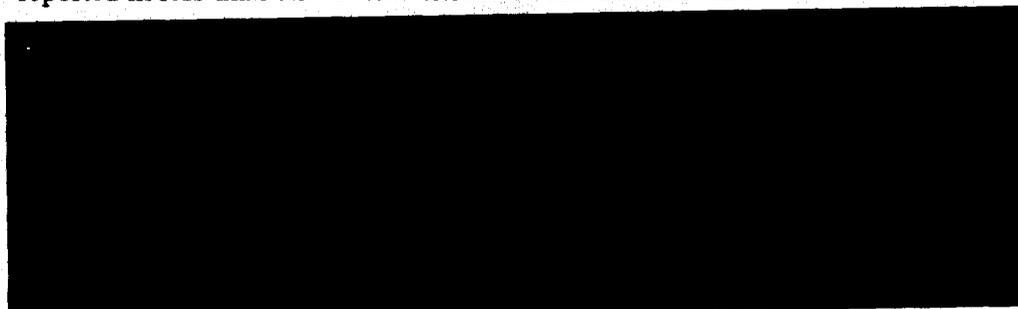
The paragraph, "In a separate dose-scheduling study....." should be omitted since it is no longer needed. In **DOSAGE AND ADMINISTRATION**, it is stated, "The recommended dose is 0.4 mg once daily in the evening."

8.3. **INDICATIONS AND USAGE:** No comments.

8.4. **COUNTERINDICATIONS:** No comments.

8.5. **WARNINGS:**

8.5.1. **Liver Enzymes:** Beginning with the sentence ending with "...have been reported in less than 0.5 %" should be modified as follows:



8.6. **Precautions:** No comments.

8.6.5. **CNS and other toxicities:** Please see Pharmacology/ Biopharmaceutic Reviews re C_{max}/free statements and clinical implication of this ratio.

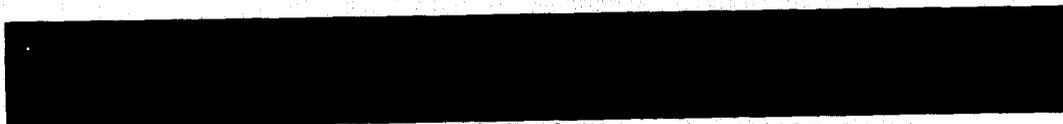
8.6.6. **Pregnancy:** Pregnancy Category X: Please see Pharmacology Review.

8.7. **ADVERSE REACTIONS:** No comments.

8.8. **OVERDOSAGE:** No comments.

8.9. **DOSAGE AND ADMINISTRATION:**

To the sentence, "The recommended dose is 0.4 mg once daily in the evening...."
The following should be added:



/S/



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

3/24/09

CC:
Original NDA
HFD-510-Files
HFD-510-SWSHEN.
HFD-510-MSIMONEAU

/S/



APPEARS THIS WAY ON ORIGINAL

15.55