CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-740/S008/S013

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 20-740-S008	Application Type: NDA
Sponsor: Bayer	Proprietary Name: Baycol
Investigator: Multiple (Not named)	USAN Name: Cerivastatin
Category:HMG-CoA reductase inhibitor	Route of Administration: oral
Reviewer: S.W. Shen, M.D.	Review Date: 7/06/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
Sept. 22, 1999	Sept. 23,1999	SE-2	

EXECUTIVE SUMMARY:

Cerivastatin is a synthetic, pure enantiomeric pyridine derivative that specifically inhibits HMG-CoA reductase. It was approved for marketing in the US in June 1997. The usual recommended dose was 0.3 mg once daily. The 0.4 mg was approved in 1999. The current submission is to extend the dose range to 0.8 mg per day.

In a pivotal Phase 3 study involving 1170 patients, cerivastatin 0.8 mg administered once daily resulted in statistically significant reductions in plasma low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), apolipoprotein B (Apo B) compared to treatments with placebo and cerivastatin 0.4 mg. No new unexpected adverse events were reported. Comparisons of SGOT/SGPT changes from baseline between cerivastatin dose groups (0.8mg vs. 0.4mg) showed statistically significant differences at each timepoint after baseline. The percentage of patients with CK>ULN were statistically greater at 0.8mg compared to 0.4mg. These statistical results reflect a significant shift in the overall distribution of values at the higher dose. With respect to number and percentage of patients with SGOT/SGPT >3xULN and CK>5xULN, CK>10xULN, none of the pairwise comparisons involving cerivstatin 0.8mg was statistically significant at the 0.05 level. However, the subgroup of female patients $\geq$ 62 years of age with body weights $\leq$ 65kg had increased incidence of CK>10xULN and SGOT/SGPT>3xULN.

Cerivastatin 0.8 mg is a useful addition to the currently marketed doses.

OUTSTNDING ISSUES:

Safety concern in the subgroup patients of females of $\geq$62 years of age with body weights $\leq$65 kg.

RECOMMENDED REGULATORY ACTION:

NDA, Efficacy/Label supplement: Approvable

SIGNATURES Medical Reviewer: /S/ Date 7/06/00

Medical Team Leader: /S/ Date 7/19/00

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List of Abbreviations used in this review:

Alk. Phos.	**Alkaline phosphatase**
ALT	**Alanine aminotransferase (formerly SGPT)**
AST	**Aspartate aminotransferase (formerly SGOT)**
Apo A1	**Apolipoprotein A1**
Apo B	**Apolipoprotein B**
CAD	**Coronary Artery Disease**
CER :	**Cerivastatin**
CK	**Creatine kinase**
HDL-C	**High-density lipoprotein-cholesterol**
HLP	**Hyperlipoproteinemia**
LDL-C	**Low-density lipoprotein-cholesterol**
Lp (a)	**Lipoprotein a**
PLA/PRAVA	**Placebo/Pravastatin**
SIMVA	**Simvastatin**
TOTAL-C	**Total-cholesterol**
TSH	**Thyroid stimulating hormone**
TG	**Triglycerides**
VLDL-C	**Very-low-density-lipoprotein-cholesterol**
ULN	**Upper limit of normal**
UTI	**Urinary tract infecion**

Administrative Background:

The original pivotal study protocol (D97-008) dated 8/12/97 was amended 5 times.

1. Amendment 1 dated 9/5/97: Changed the dose of pravastatin to 40 mg from — mg qd.
2. Amendment 2 dated 10/29/97: The definition of premature menopause and family hx. of premature coronary heart disease were modified and oral anticoagulants were added to the list of excluded concomitant medications.
3. Amendment 3 dated 2/6/98: Modified concomitant therapy to permit treatment with omeprazole and cimetidine.
4. Amendment 4 dated 3/1/98: Allowed Center 14 to enroll women of childbearing potential, provided they were using a double-barrier contraceptive method.
5. Amendment 5 dated 12/15/98: Shortened the duration of the study to 52 weeks from — weeks.

Clinical Background:

Multiple epidemiological studies have established that elevation of serum cholesterol, specifically LDL-C, is a major risk factor for development of cardiovascular diseases. HMG-Co-A reductase inhibitors have been shown to slow the progression of coronary atherosclerosis and reduce the incidence of myocardial infarction, cardiovascular as well as total mortality. The National Cholesterol Education Program (NCEP) has established treatment goals for LDL-C, which depend on an individual's risk for cardiovascular disease.

Cerivastatin is a synthetic, pure enantipmeric pyridiine derivative that specifically inhibits HMG-CoA reductase. It was approved for marketing in the U.S. in June 1997. 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. The 0.4 mg was approved in 1999. The purpose of the current NDA Supplement is to extend the dose range to 0.8 mg per day.

Chemistry/Manufacturing Controls:

The chemical name is sodium [S-[R*,S*-(E)]]-7-[4-4-flurorophenyl)-5-methoxymethyl)-2,6bis(1-methyethyl-3-pyridinyl]-3,5-dihydroxy-6-heptenoate. For structural formula and other details, please see Chemistry Review.

Human Pharmacology/Pharmacokinetics:

Please see Biopharmacology Review.

Description of Clinical Data Sources:

There were two completed clinical studies, Protocol BAY D97-008, (International Study # 0182) and International Study # 17 which was submitted with the Safety Update.

Int'l Study # Country	Study status Starting Date	Trail Design	RX/Doses	# Subjects	Duration
0182 UA/Canada (D97-008)	Completed 11/4/97	Safety/Eff. Random,DB Para. Group comparison	CER 0.8mg CER 0.4mg PLA/PRAVA 40 mg	774 194 198	52 weeks
17 Multinat. /Germany	Completed 5/12/98	Safety/Eff. Random,DB Para. Group comparison	CER 0.2/0.4/0.8mg SIMVA 10/20/40mg	185 184	12 weeks

D97-008, the pivotal Phase III study, was designed to determine the safety and efficacy of cerivastatin 0.8 mg QD compared to: 1). placebo after 8 weeks of treatment; 2). 0.4 mg QD after 8 and 24 weeks; 3). placebo/pravastatin 40 mg QD after 24 weeks of treatment; 4). and long-term comparison (44-52 weeks) between cerivastatin 0.8 mg QD,0.4 mg QD and pravastatin 40 mg QD.

International Study 17 was a small (369 subjects), short-duration (12 weeks) study comparing CER (0.2/0.4/0.8mg) against Simvastatin (10, 20, and 40mg) once daily in patients with hypercholesterolemia.

Integrated Summary of Safety:

The two completed clinical studies form the basis of this Integrated Summary of Safety. However, this Integrated Summary of Safety is primarily based on the analysis of one pivotal Phase III study, Study D97-008, which was to assess the safety and efficacy of CER 0.8mg compared to CER 0.4mg and placebo/pravastatin 40mg over 52 weeks. Study 17 was submitted as part of the Safety Update. It was a forced-titration study from CER 0.2 mg to 0.4 mg and to 0.8 mg in 185 patients. The exposure to 0.8 mg was only during the last 4 weeks.

A. Number of patients:

1. Study D-97-008: Of the 1170 patients randomized into this study, 1166 were valid for safety (776 were randomized to CER 0.8mg, 195 to CER 0.4mg and 199 to the PLA/PRAVA 40ng treatment.
2. Study 17: 185 patients were randomized to CER-treatment from 0.2 mg, 0.4 mg and 0.8 mg.

B. Duration/extent of exposure: The number of patients' exposure by duration and by treatment /dose is shown:

Study 17			
Cerivastatin	0.2 mg N=185	0.4 mg N=185	0.8 mg N=184
Duration	4 weeks	4 weeks	4 weeks
Study D97-008			
Duration (days)	Treatment		
	PLA/PRAVA 40 mg	CER 0.4 mg	CER 0.8 mg
Mean	332	333	328
Maximum/Minimum	———	———	———

C. Adverse Events: The accumulated experience in this class of drugs, HMG-CoA reductase inhibitor, has demonstrated that the adverse events of particular clinical concern are abnormal liver function tests and CK elevation leading to the possible development of rhabdomyolysis. Therefore, this Integrated Summary of Safety will focus on these treatment-emergent adverse events. Other aspects of the safety will be reviewed in the individual study reviews. The mechanism by which statins cause elevations in transaminases is unknown. The incidence of persistent elevations >3XULN is generally dose related across the class.

1. **The percentage of patients who developed increased SGOT during the studies regardless of baseline status is shown.**

   a). **Study 17**:An analysis of serum SGOT (AST) elevations through Week 12 regardless of baseline status in patients valid for safety is shown:

	CER n=184	SIMVA n=184
Any elevation	55 (29.9%)	49 (26.6%)
>ULN to ≤3xULN	55 (29.9%)	48 (26.1%)
>3xULN to ≤5xULN	0 (0%)	1 (0.5%)
>5xULN	0 (0.%)	0 (0%)

The incidence of any serum SGOT elevations in CER-treated patients was higher than in SIMVA-treated patients (29.9% vs. 26.6%). However, all SGOT elevations in the CER-treated patients were <3xULN. Bilirubin was not measured in this study. No patient developed clinical evidence of cholestasis.

   b). **Study D97-008**: :The percentage of patients who developed increased SGOT through Week 52 regardless of baseline status is shown: (Week 8 in parenthesis).

	CER 0.4mg n-194	CER 0.8mg n=774	PLA/PRAVA 40mg n=198
Any elevation	39.7% (25%)	49% (33%)	32% (18%)
>ULN to <3XULN	38.7% (24%)	47% (32%)	31% (18%)
>3XULN	1% (1%)	2% (1%)	1% (0%)
Repeat >3xULN	0.5%	0.5%	0%
Sustained high*	17% (6%()	27% (14%)	16% (7%)

* >ULN at two consecutive visits or patient's last visit.

The development of any SGOT elevation at Week 8 and Week 52 was higher in CER 0.8mg patients compared to CER 0.4mg and PLA/PRAVA 40mg-treated patients.

Repeat >3xULN elevations were higher in the CER-treated patients than PLA/PRAVA 40 mg-treated patients (0.5% vs. 0%). There was no difference between the CER-0.4 and CER-0.8 mg groups.

Sustained SGOT >ULN were higher in patients receiving CER 0.8mg compared to patients receiving CER 0.4mg or PLA/PRAVAS 40mg at Week 52. Of the 191 CER 0.8mg-treated patients with sustained elevations prior to their last visit, 118 (62%) had a normal value at their last visit; 73 (38%) had an SGOT that remained >ULN. All but one of the 73 patients had SGOT elevations < 2XULN at their final observation (the remaining patient had an SGOT of 2.1XULN).

Treatment-emergent SGOT elevations in CER 0.8mg-treated patients occurred most frequently in the first 2 months of therapy.

2. **The percentage of patients who developed increased SGPT during the studies regardless of baseline status is shown.**

   a). **Study 17**:An analysis of serum SGPT (ALT) elevations through Week 12 regardless of baseline status in patients valid for safety is shown:

	CER n=184	SIMVA n=184
Any elevation	40 (21.7%)	50 (27.2%)
>ULN to ≤3xULN	40 (21.7%)	49 (26.6%)
>3xULN to ≤5xULN	0 (0%)	1 (0.5%)
>5xULN	0 (0.%)	0 (0%)

SGPT elevations in CER-treated patients were less frequent than in patients treated with SIMVA.

No patient in the CER-treatment group had >3xULN elevation in SGPT. Bilirubin was not measured in this study. No patient developed clinical evidence of cholestasis.

b). Study D97-008: Elevation of SGPT The percentage of patients who developed increased SGPT through Week 52 regardless of baseline status is shown: (Week 8 in parenthesis).

	CER 0.4mg n-193	CER 0.8mg n=770	PLA/PRAVA 0mg n=198
Any elevation	33% (17%)	38% (21%)	30% (13%)
>ULN to<3XULN	32% (16%)	36% (20%)	30% (13%)
>3XULN	1% (1%)	2% (1%)	1% (0%)
Repeat >3xULN	0.5%	0.3%	0%
Sustained high*	19% (9%()	23% (12%)	13% (4%)

* >ULN at two consecutive visits or patient's last visit.

The development of any SGPT elevation at Week 8 and Week 52 was higher in CER 0.8mg patients compared to CER 0.4mg and PLA/PRAVA 40mg-treated patients.

Repeat >3xULN elevations in the CER-treated groups were higher than the PLA/PRAVA 40 mg group (CER-0.4 mg: 0.5% and CER-0.8 mg: 0.3% Vs 0%).

Sustained SGPT >ULN were higher in patients receiving CER 0.8mg compared to patients receiving CER 0.4mg or PLA/PRAVAS 40mg at Week 52. Of the 159 CER 0.8mg-treated patients with sustained elevations prior to their last visit, 77 (48%) had a normal value at their last visit; 82 (52%) had an SGPT that remained elevated. All but four of the 82 patients had SGPT elevations < 2XULN at their final observation (the 4 remaining patients had SGPTs of <2.5XULN).

Treatment-emergent SGPT elevations in CER 0.8mg-treated patients occurred during the first two months of therapy. For CER 0.8mg-treated patients with SGPT elevations >3XULN, 80% of the events occurred by week 6 and all occurred by week 24.

The number of patients with elevations of SGOT and/or SGPT>3XULN at two or more occasions (not necessarily consecutive) regardless of baseline status were: 4/774 (0.5%) in CER 0.8mg-treated patients, 1/194 (0.5%) in CER 0.4mg-treated patients and 0/198 (0%) in PLA/PRAVA 40mg-treated patients. One patient in the CER-0.4 mg group and 2 patients in the CER-0.8mg group had elevations in both SGOT and SGPT while 2 other patients in the CER-0.8 mg group had elevations in SGOT alone. In the Safety Update, one additional patient (Patient 27046) had repeat elevations in SGOT and SGPT≥.3xULN.

All these patients had concomitant serum CK elevations >10xULN. Changes in transaminases are a function of the hepatic exposure since about 70% of the administered drug is extracted by the liver and only 5% of the administered dose is reflected in the plasma drug concentration. SGOT/SGPT elevations are much less correlated with the plasma drug concentration than CK. This will be further assessed in conjunction with CK elevations.

Most of the elevations occurred within the first 6 weeks, resolved after discontinuation of the study drug, and were not associated with cholestasis. Only one patient (Patient 50017) in the CER-0.8 mg group had concomitant bilirubin elevation. This 53-year-old male had baseline bilirubin of 1.50 (1.4xULN on Day -21) and bilirubin levels fluctuated between 1.1-1.8xULN during the course of therapy. It decreased to ———— (0.7 and 0.8xULN) on Days 262 and 264 of treatment.

Pooling D97-008 study with all CER lower dose US studies (D91-012, D91-016, D92-010, D/X/Y/Z91-031, D96-008, D94-021, SB001, SB002, and D96-007), a total of 3776 patients were treated with CER over the dose range of 0.025mg to 0.8mg for a mean treatment duration of 11 months. 18/3776 CER-treated patients had elevations of SGOT and/or SGPT >3XULN at two or more occasions (not necessarily consecutive) regardless of baseline status:

1/192 (0.5%0 of CER 0.05mg-treated patients.
1/771 (0.1%) of CER 0.2mg-treated patients.
4/913 (0.5%) of CER 0.3mg-treated patients.
8/900 (0.9%) of CER 0.4mg-treated patients
4/774 (0.5%) of CER 0.8mg-treated patients.

These elevations usually occurred within the first 6 weeks of treatment, resolved after discontinuation of the drug, and were not associated with cholestasis and were in most cases asymptomatic.

3). The percentage of patients with any treatment-emergent elevations of serum CK is examined:

a). Study 17: Number and percentage of patients who developed elevation of CK through week 12 regardless of baseline status is shown:

	CER n=184	SIMVA n=184
Any elevation	42 (22.8%)	37 (20.1%)
>ULN to ≤3xULN	37 (20.1%)	34 (18.5%)
>3xULN to ≤5xULN	4 (2.2%)	2 (1.1%)
>5xULN to ≤10xULN	1 (0.5%)	1 (0.5%)
>10xULN	0 0%)	0 (0%)

The percentage of patients with any elevation in the CER-treatment group was

higher than those in the SIMVA-treatment group. Most of the elevations were ≤3xULN and the patients had no muscle-related symptoms except patient # 8018 in the SIMVA 40mg group who had a CK of 2.7xULN. reported back pain but continued in the study.

Both patients with CK elevations>3xULN to <5xULN in the SIMVA treatment group (# 3002 ,# 13013) were on SIMVA 10mg. Patient # 13013 complained of myalgia and was discontinued from the study.

All CER-treated patients (4 with CK elevations >3xULN<5xULN and 1 with >5xULN <10xULN) were on 0.8mg dose and were without any muscle-related symptoms. The one SIMVA patient (#9009) with CK>5xULN to <10xULN was on SIMVA 20mg and did not report any symptoms.

Conclusion: In Study 17, there were no significant differences between CER- and SIMVA-treated patient with respect to CK elevations.

b). Study D97-008: The percentage of patients with any treatment-emergent elevations of serum CK through Week 52 (Week 8 in parenthesis) regardless of Baseline Status is examined below:

	CER 0.4 mg (n=193)	CER 0.8mg (n=770)	PLA/PRAVA 40mg (n=198)
Any elevation*	38% (28%)	49% (35%)	35% (22%)
>ULN to ≤3xULN	30% (22.7%)	40% (29.7%)	30.3% (20.2%)
>3xLN to ≤5xULN	3.6% (2.1%)	4.3% (2.8%)	2.0% (1.0%)
>5xULN to<10xULN	2.6% (2.1%)	2.5% (1.3%)	2% (1.0%)
>10xULN	1.5% (1.0%)	2.1% (1.3%)	0.5% (0.0%)
>10xULN with symptoms	1.5% (1.0%)	1.0% (0.9%)	0.0% (0.0%)
Sustained High+	18% (11%)	27% (17%)	16% (7%)

* Normal Range: 0 to 120 U/L

\+ >ULN at 2 consecutive visits or patient's last visit.

The development of CK elevation ≥10xULN at Week 8 and Week 52-week time-points were higher in CER 0.8mg patients compared to CER 0.4mg and PLA/PRAVA 40mg-treated patients. There were 20 patients (1 in the PLA/PRAVA group, 3 in the CER-0.4 mg group, and 16 in the CER-0.8 mg group) with CK elevation>10XULN post-randomization. 11/20 patients reported concurrent (within 1 week of the elevated CK) muscle-related symptoms and all were in the CER-treated groups. In all but 2 patients, the symptomatic CK elevations occurred within the first 8 weeks. CK elevations >10XULN is of concern since it maybe associated with the possible

development of rhabdomyolysis. These 20 patients are therefore evaluated in details in the table below:

RX Group	Patient ID	Age	Body weight (kg)	Gender	Highest CK value	Symptoms	Exercise (yes/No)	Discontinued from study)
PLA/PRAVA 40mg	21001	34	83.0	M	2540	None	Yes	Yes
CER 0.4mg	11015	66	80.3	F	1375	Back Pain	No	No
CER 0.4mg	24016	58	87.5	M	1657	Leg cramps	No	Yes
CER 0.4mg	48007	67	68.5	F	17220	Myalgia	No	Yes
CER 0.8mg	3010	64	87.1	F	10250	Muscle pain	No	Yes
CER 0.8mg	9029	37	97.5	M	2212	None	Yes	Yes
CER 0.8mg	9046	51	106.1	M	5516	None	Yes	No
CER 0.8mg	16005	63	71.2	F	4000	Muscle weakness	No	Yes
CER 0.8mg	17004	55	86.2	M	1622	None	Yes	Yes
CER 0.8mg	19011	57	84.4	M	1272	None	Yes	Yes
CER 0.8mg	25001	57	97.9	M	4180	None	Yes	No
CER 0.8mg	27043	36	83.5	M	1874	None	Yes	No
CER 0.8mg	27046	75	78.0	F	9020	Myalgia	No	Yes
CER 0.8mg	27047	75	58.9	F	6720	Achiness legs	Yes	Yes
CER 0.8mg	32011	69	66.2	F	1938	Muscle aches	No	Yes
CER 0.8mg	40003	24	85.7	M	1898	None	Yes	No
CER 0.8mg	40070	73	73.5	F	4455	Muscle soreness	No	Yes
CER 0.8mg	41003	73	63.9	F	1428	None	No	Yes
CER 0.8mg	50011	63	58.9	F	2532	Muscle soreness	Yes	Yes
CER 0.8mg	62006	66	66.7	F	3543	Muscle pain	No	Yes

Of the 20 patients with >10XULN elevations, 19/20 were CER-treated patients. These CER-treated patients consisted of 3 patients (1.5%) in the CER-0.4 mg group (patient 48007 was on concomitant gemfibrozil, a protocol violation) and 16 patients (2.1%) of the CER-0.8 mg group. All 3 patients in the CER-0.4 mg group and 8/16 patients in the CER-0.8 mg group had muscle-related symptoms as shown. No patient experienced elevated serum creatinine levels. Urine myoglobin was not measured in any of the patients. None of the patients developed renal insufficiency or renal failure or rhabdomolysis or required hospitalization. Both symptoms and elevated CK levels were reversible upon discontinuation of treatment. All CK levels returned to normal at last follow-up.

Of the 16 patients in CER-0.8 mg group, 7/16 were males and 9/15 were females. The 7 males ranged in age from 24 to 57 years of age but all 9 females were at least 63 years old. The 2 female patients in the CER-0.4 mg group, were both >65 years of age.

The other observation is that all the females among these 16 patients in the CER-0.8 mg group had lower body weights than the males. All but one female with muscle-related symptoms had body weight of 58.9-73.5 kg (Patient 3010 had body weight of 87.1kg). The weight range for the 7 males was from 83.5-106.1 kg. The mean weight of the study patients were 81, 80 and 82 kg for CER-0.4 mg, CER-0.8 mg and PLA/PRAVA 40 mg group respectively.

The preponderance of females >63 years of age led to further analysis. Patients with CK elevation >5 to 10xULN and >10xULN by age/sex group are shown below:

			CK—Multiple of ULN					
			>5 to ≤10x ULN			>10xULN		
Sex-Age	Treatment Group	N	Week 8	Week 24	Week 52	Week 8	Week 24	Week 52
Male≤65	Placebo	112	2 (1.8%)	2 (1.8%)	4 (3.6%)	0	0	1 (0.9%)
	CER 0.4mg	93	3 (3.2%)	3 (3.2%)	4 (4.3%)	0	1 (1.1%)	1 (1.1%)
	CER 0.8mg	388	5 (1.3%)	5 (1.3%)	12 (3.1%)	2 (0.5%)	5 (1.3%)	7 (1.8%)
Male≥65	Pla/Pra 40mg	17	0	0	0	0	0	0
	CER 0.4mg	20	1 (5.0%)	1 (5.0%)	1 (5.0%)	0	0	0
	CER 0.8mg	81	1 (1.2%)	1 (1.2%)	1 (1.2%)	0	0	0
Female≤65	Pla/Pra 40mg	47	0	0	0	0	0	0
	CER 0.4mg	54	0	0	0	0	0	0
	CER 0.8mg	215	0	1 (0.5%)	2 (0.9%)	3 (1.4%)	3 (1.4%)	3 (1.4%)
Female≥65	Pla/Pra 40mg	22	0	0	0	0	0	0
	CER 0.4mg	27	0	0	0	2 (7.4%)	2 (7.4%)	2 (7.4%)
	CER 0.8mg	90	4 (4.4%)	5 (5.6%)	4 (4.4%)	5 (5.6%)	5 (5.6%)	6 (6.6%)

The subgroup of females>65 years of age had the highest incidence rate of CK elevations>10xULN. This is true for both the 0.4 mg- and the 0.8 mg-treated groups. This subgroup represented only 12% (N=90) of the patients in D97-008

study. They accounted for 30% (6/20) of the patients with CK>10xULN. Females patients ≥63 accounted for 45% (9/20) of the patients with CK >10xULN. These women also accounted for 10 of the 11 cases of CK elevations >10xULN with muscle-related symptoms in this treatment group. The reason(s) for this subgroup's increased incidence of CK>10xULN with muscle-related symptoms are not obvious. The possibility that this is due to plasma concentration of cerivastatin can be considered:

(1). Across the statin class of drugs, certain adverse events are correlated with the plasma concentration of the drug. Generally speaking, the plasma concentrations of the drug may increase with the age of the patient (s) (for reasons unknown). Declining renal function (GFR) may be a factor. The sponsor reported that in patients with moderate decreased renal function (Cl_{cr} 31-60 mL/min/1.73m^2), AUC was up to 60% higher, C_{max} up to 23% higher, and $t_{1/2}$ up to 47% longer compared to subjects with normal renal function.

(2). There was a sex difference in the plasma concentration of cerivastatin. The sponsor stated that females' was 12% higher for C_{max} and 16% higher for AUC than males. The basis for this sex-difference is not clear. Perhaps it is related to the difference in body-weights (body-surface-area).

(3). There were dose proportional pharmacokinetics between cerivastatin 0.4 mg and 0.8 mg doses consistent with other clinical studies that measured plasma concentrations. After 8 weeks of treatment, plasma concentrations of cerivastatin at approximately 12 hours after dosing averaged 1.05 ug/L after the 0.4 mg dose, and 2.29 ug/L after the 0.8 mg dose.

Taking all these into account, a hypothesis can be put forth that the subgroup of females ≥63 treated with CER-0.8mg had higher plasma concentration of cerivastatin than other subgroups of females ≤63 years of age/at CER0.4 mg-and 0.8mg doses/and males at CER-0.4 and 0.8 mg doses. This hypothesis can be examined as follows:

(1) If this were the case, other adverse events may show similar increased incidence. Although SGOT/SGPT elevations are much less correlated with the plasma drug concentration than CK elevations, the sponsor had reported that the subgroup of females >62 also had the highest incidence of SGOT/SGPT elevations >3xULN as shown in the following table:

Study D97-008: Patients with SGOT/SGPT Elevations>3xULN during 52 Weeks of Treatment Regardless of Baseline:

Rx Group	Patient	Gender	Age	Highest SGOT	Multiple of ULN SGOT	Highest SGPT	Multiple of ULN SGPT
PLA/.PRAVA. 40mg	9013	M	46	74	3.4		
PLA/PRAVA. 40mg	21001	M	34	102	4.6		
PLA/PRAVA. 40mg	48001	M	55			89	3.6
CER 0.4mg	19015	M	63	74	3.4		
CER 0.4mg	48007	F	67	500	22.7	230	9.2
CER 0.8mg	3010	F	64	231	10.5	81	3.2
CER 0.8mg	4015	F	62	101	4.6	108	4.3
CER 0.8mg	9029	M	37	90	4.1		
CER 0.8mg	16005	F	63	163	7.4	122	4.9
CER 0.8mg	25001	M	57	126	5.7		
CER 0.8mg	25002	M	46	149	6.8	186	7.4
CER 0.8mg	27043	M	36	94	4.3		
CER 0.8mg	27046	F	75	66	3.0	117	4.7
CER 0.8mg	27047	F	69	238	10.8	228	9.1
CER 0.8mg	33004	F	55	75	3.4	95	3.8
CER 0.8mg	39005	M	24			75	3.0
CER 0.8mg	40070	F	73	124	5.6		
CER 0.8mg	44001	M	65			141	5.6
CER 0.8mg	48003	F	63	98	4.5	114	4.6
CER 0.8mg	50011	F	63	129	5.9	143	5.7
CER 0.8mg	50017	M	53			84	3.4
CER 0.8mg	62006	F	66	247	11.2	318	12.7

Of the 18 patients with SGOT elevations>3xULN, 2 each were from the PLA/PRAVA 40mg group and the CER 0.4mg group and 14 from the CER-0.8 mg group (4 males and 10 females). 9/10 patients in the CER 0.8mg group were females ≥62 years of age.

Of the 15 patients with SGPT elevations >3xULN, 1 each from the PLA/PRAVA 40mg group, and CER 0.4mg group. 13 were from the CER-0.8 mg group (4 males and 9 females). 8/9 patients from the CER 0.8mg group, were females ≥62 years of age.

The SGOT elevations maybe partly due to muscle involvement as 11 out of all 18 patients with SGOT>3xULN also had CK >10xULN. 10 out of the 14 patients in the CER-0.8 mg group likewise had CK>10xULN and 7/9 female patients had CK>10xULN. However, the SGOT elevations may also represent adverse hepatic effect.

Although 6 out of all 15 patients with SGPT >3xULN also had CK>10xULN and

all 6 were in the CER-0.8 mg group and ≥62 years of age, the elevated SGPT was unlikely be due to muscle involvement and rather due to direct adverse hepatic effects. It is possible that this subgroup of females ≥62 years of age had greater hepatic exposure to cerivastatin for whatever reason(s).

In summary, the subgroup of female patients ≥62 years of age had increased incidence of both CK and SGOT/SGPT elevations, two of the most serious safety concerns of statin therapy. The mechanism of this increased incidence of CK elevations>10xULN and SGOT/SGPT elevations >3xULN is unknown. Cerivastatin maybe handled differently by females ≥62 years of age. It appears to be an interaction of gender, age ≥62 and perhaps dosage (0.8mg). The basis for these increased incidences of CK>10xULN with concomitant SGOT/SGPT >3xULN can be hypothesized to be due to higher plasma concentration of cerivastatin in females ≥62-65 years of age. This hypothesis can be tested by doing further pharmacokinetic studies specifically designed to evaluate the effects of gender, age and body weight (body-surface-area) on the plasma concentration of cerivastatin. This safety concern can then be appropriately addressed in the Labeling. Please also refer to the Statistical Review

Review of Individual Clinical Studies:

The principal clinical study was Protocol BAY D97-008, a pivotal Phase 3 study designed to compare the safety and efficacy of Cerivastatin 0.8 mg/day and placebo after 8 weeks of treatment in patients with primary hyercholesterolemia .

Protocol BAY D97-008: This was a Phase 3, multicenter, randomized, double-blind, parallel-design study.

I. Objectives:

The primary objective:

Compare the safety and efficacy of cerivastatin 0.8 mg qd. And placebo after 8 weeks of treatment.

The Secondary Objectives:

1. Compare the safety and efficacy of cerivastatin 0.8 mg qd. And 0.4 mg qd. After 8 and 24 weeks of treatment.
2. Compare the safety and efficacy of cerivastatin 0.4 mg qd and placebo after 8 weeks of treatment.
3. Compare the safety and efficacy of cerivastatin (0.8 mg and 0.4 mg qd) and of placebo/pravastatin 40 mg qd after 24 weeks of treatment.
4. Compare the safety of long-term (44-52 weeks) treatment with cerivastatin 0.8 mg qd, cerivastatin 0.4 mg qd, and pravastatin 40 mg qd.

II. Patient Selection:

1. Inclusion Criteria:

1). Men or women (not of childbearing potential) between the ages of 18 and 75 years with documented primary hypercholesterolemia .
2). Randomization criteria:
(a). In patients with no atherosclerotic disease and no risk factor Calculated mean plasma LDL-C value of Visit 3 (week –4) and Visit 4 (Week –2) >160 mg/dL.
(b). In patients with definite atherosclerotic disease (coronary heart disease or peripheral vascular disease, including symptomatic carotid artery disease): calculated mean plasma LDL-C >130 mg/dL.
(c). In patients with 2 or more cardiovascular risk factors (men>45 years, women >55 years of age; family hx of premature coronary heart disease; current cigarette smoking; hypertension; plasma HDL-C <35 mg/dL): Calculated mean plasma LDL-C>130 mg/dL.
3). At Visit 3 (Week –4) and Visit 4 (Week –2), LDL-C values could not differ from the mean plasma LDL-C for these visits by more than >12.5% and the mean plasma TG<400 mg/dL.
4). At Visit 4 (Week –2), a patient had to be compliant with the AHA Step 1 diet and have a Food Record Rating score <15.

2. Exclusion Criteria:

1). History (within 3 months of Visit 1) of myocardial infarction (MI), unstable angina, cerebral vascular accident (CVA), transient ischemic attack (TIA), or uncontrolled hypertension.
2). History (within 6 months of Visit 1) of coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA).
3). For hypertensive patients, change in diuretic or beta-blocker therapy (medication or dose) within 2 months of Visit 1.
4). History of diabetes mellitus (fasting glucose >140 mg/dL at Visit 1 or during run-in or treatment for diabetes mellitus) or of other endocrine diseases (except for hypothyroidism – see below).
5). Thyroid-stimulating hormone (TSH) >1.5 times the ULN at Visit 1. Patients with a history of hypothyroidism receiving a stable dose of thyroid replacement therapy for at least 2 months before Visit 1 could be enrolled if TSH was <1.5 times the ULN at Visit 1.
6). Unstable ophthalmic abnormalities expected to require medical or surgical intervention within 18 months or patients whose best corrected visual acuity was less than 20/50 in either eye because of cataracts. Patients whose cataracts had been removed could be enrolled.
7). History of malignancy (except squamous or basal cell skin cancer) or psychosis.

8). Active liver disease or unexplained persistent elevations of SGOT or SGPT.
9). SGOT or SGPT >1.5 times the ULN at Visit 1, or at any other time during the run-in period (before randomization), confirmed by repeat testing.
10). Weight >140% of ideal body weight.
11). History of hypersensitivity to cerivastatin, pravastatin or other HMG-CoA reductase inhibitors.
12). History of gastrointestinal disorder that could impair absorption of study drugs.
13). Homozygous familial hypercholesterolemia.
14). Other significant laboratory abnormalities (defined as serum creatinine >2 mg/dL, serum creatine kinase ³3 times the ULN or serum amylase >1.5 the ULN) at Visit 1 or at any time during the run-in period before randomization, and confirmed by repeat testing. Any other laboratory abnormality judged clinically significant by the investigator had to be reviewed with Bayer Corporation.
15). Current use of corticosteroids (except for the inhaled asthma preparations fluticasone <440 mg/day; flunisolide <1000 mg/day; beclomethasone <880 mg/day), erythromycin (or other macrolide antibiotics), rifampin, oral anticoagulants, androgens, immunosuppressants, H2 blockers other than cimetidine, or azole antifungals. Postmenopausal women on stable doses of hormone replacement therapy (cyclical or non-cyclical replacement of estrogen and/or progesterone) for at least 2 months before Visit 1 could be enrolled.
16). Concomitant treatment with other hypolipidemic drugs within 10 weeks of randomization. Probucol must not have been used within 6 months of randomization.
17). Concomitant use of fish oil capsules, psyllium, or bran (for the purpose of cholesterol reduction), or of niacin >100 mg/day.
18). Drug or alcohol abuse or current intake of more than 14 standard alcoholic drinks per week. A standard drink was defined as 1 oz of liquor, 12 oz of beer or 6 oz of wine.
19). Pregnancy or breast-feeding. Women of childbearing potential were excluded. The protocol was amended to allow the entry, at Center 14, of women of childbearing potential who were using double-barrier contraception. Women who were surgically sterile or more than one year postmenopausal could be enrolled.
20). Night shift work (eg, 11 pm to 7 am shift) resulting in reversal of normal sleep/wake cycle.
21). Treatment with another investigational product within 30 days of Visit 1.
22). Other medical conditions that could interfere with a patient's participation in the protocol or with the assessment of the trial investigational products.
23). Treatment with cerivastatin for more than 10 days within 6 months of Visit 1.

III. Study Design and Procedures:

This was a multicenter (49 US and 10 Canadian centers), randomized, double-blind, parallel group design. The study began with a 10-week run-in period during which time patients stopped taking any lipid-lowering medications and followed AHA Step 1 diet. At the end of the 10 -week run-in, 1170 patients were randomized into one the following dosage groups:

1. 776 patients to cerivastatin 0.8 mg qd.
2. 195 patients to cerivastatin 0.4 mg qd.
3. 199 patients to placebo treatment and after 8 weeks these patients were switched to pravastatin 40 mg qd.

The detailed study procedures are shown below:

Table II-1: Flow Chart

Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Week	-	-6	-4	-2	0	2	4	6	8	12	16	20	24	32	40	52
Diet counseling	*	*	*	*					*				*			*
Vital signs																
Body weights	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Full lab testing	*		*		*		*		*	*	*		*	*	*	*
Beta HCG	*				*								*			
Fasting lipid profile	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
TSH	*				*								*			
Activity level alcohol consumption	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Adverse events		*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Compliance			*	*	*	*	*	*	*	*	*	*	*	*	*	*
Plasma cortisol					*								*			

III.A. Patient Characteristics: Patients valid for the intent-to-treat (ITT) analysis required a baseline and at least one plasma lipid value after randomization. Patients valid for efficacy analysis required a baseline and at least one lipid value after 3 weeks of double-blind therapy following randomization, and had no major protocol deviation. Demographic data by treatment group is summarized in Table III-1:

Table III-1. Selected Demographic and Baseline Characteristics for the valid for efficacy population:

	CER 0.4mg (n=177)	CER 0.8mg (n=656)	Placebo/ PRAVA 40mg (n=166)
Male ≤65	93	388	112
Male ≥65	20	81	17
Female ≤65	54%	215	47
Female ≥65	27	90	22
% with Family hx of hyperlipidemia	45%	44%	46%
% with family hx of CAD	57%	56%	59%
Mean age at enrollment (yrs)	57	57	56
Mean weight at enrollment kg	81	80	82
Mean duration of HLP (yrs)	9	9	9
Hypertension	52 (31%)	177 (27%)	55 (31%)
Female climacteric state	33 (20)	142 (22%)	34 (19%)
Compliance	96%	95%	95%

The values were similar for the valid-for-safety population (patients who took at least one dose of study medication and who had post-randomization data). Across the 3 treatment groups, the demographic and baseline characteristics were similar. Males represented 59%, 63% and 65% of the study population in CER-0.4 mg, CER-0.8 mg and PLA/PRAVA 40-mg group respectively.

III.B: Disposition of patients: Of the 1170 patients randomized to double-blind treatment, 978 completed the study. Across the 3 treatment groups the rates and reasons for discontinuation are shown in Table III-B-1:

Table III-B-1: Disposition of Patients and Premature Discontinuations

	Placebo/Pravastatin. 40 mg	CER 0.4 mg	CER 0.8 mg
# randomized	199	195	776
# completed study	163 (82%)	168 (86%)	647 (83%)
Adverse event	16 (8%)	18 (9%)	66 (9%)
Noncompliance	0 (0%)	0 (0%)	6 (<1%)
Consent withdrawn	11 (6%)	6 (3%)	23 (3%)
Insufficient effect	2 (1%)	0 (0%)	2 (<1%)
Lost to follow-up	4 (2%)	3 (2%)	14 (2%)
Protocol violation	2 (1%)	0 (0%)	15 (2%)
Patient terminated in error	0 (0%)	0 (0%)	1 (<1%)
Center closed prior to study end	1 (<1%)	0 (0%)	2 (<1%)
Total discontinuat.	36(18%)	27 (14%)	129 (17%)

The rate of total discontinuation and any specific reason for discontinuation were similar across the treatment groups.

IV. Results:

A. Safety:

1. **Deaths, other serious events or discontinued due to an adverse event**: The incidence by treatment groups is shown in Table IV-1:

Table IV-1: # of Patients Who Died, Had a Serious Adverse Event or Discontinued due to an Adverse Event:

	PLA/PRAVA 40mgN=198	CER 0.4mg N=194	CER 0.8mg N=774
Death	0 (0%)	1 (<1%)	0 (0%)
Any serious event	22 (11%)	15 (8%)	70 (9%)
Discontinued d/t adverse event	66 (9%)	16 (8%)	18 (9%)

One patient, (ID # 31012, CER 0.4mg group), a 44-year-old man with family history of premature CAD, suffered a fatal MI 88 days after the start of double-blind treatment while playing softball.

The overall incidence of discontinuations due to adverse events was similar between the treatment groups at Weeks 24 and 52 timepoints. During the first 8weeks the incidence was higher in the CER-treated groups compared to the placebo group.

2. **Potentially Serious Adverse Events**: Patients experiencing serious or potentially serious adverse events are summarized :

Study Drug	Weeks 0-8	Weeks 8-24	Weeks 24-52	Cumulative
Placebo*	2 (1%) n=198	12 (6%) n=191	8 (5%) n=176	22 (11%) n=198
CER 0.4mg	5 (3%)..n=194	7 (4%) n=185	4 (2%) n=173	6 (8%) n=194
CER 0.8mg	16 (2%) n=774	23 (3%) n=727	31 (5%) n=682	70 (9%) n=774

* Patients were treated with PLA for the first 8 weeks followed by PRAVA 40mg for the remaining 44 weeks.

The incidence of serious adverse events in the placebo-controlled period of Weeks 0-8 was similar across the treatment groups. The incidence rates during the treatment periods of weeks 8-24 and 24-52 were similar as was the cumulative rates. Of the patients experiencing serious adverse events, 4, 13, 1, 1, and 3 patients respectively from the CER 0.4mg, CER 0.8mg, Placebo and PRAVA groups discontinued from the study.

3. Discontinuations from the study due to all causes during the cumulative 52-week treatment period of the pivotal study D97-008 are summarized:

	CER 0.4 mgN=194	CER 0.8 mgN=774	PLA/PRAVA 40m*N=198*
Completed study	168 (87%)	647 (84%)	163 (82%)
Reasons for Premature Discontinuation through 8 and 24 weeks by treatment group			
Adverse Events	8(9%)	66(9%)	16(8%0
Non Compliance	0(0%)	6(1%)	0(0%)
Consent withdrawn	5(3%)	23(3%)	11(6%)
Insufficient Rx effect	2(1%)	0(0%)	2(<1%)
Lost to follow up	3(2%)	12(2%)	3(2%)
Protocol violation	0(0%)	15(2%)	2(1%)
Other	0(0%)	3(<1%)	1(1%)

* Patients treated with PLA for 8 weeks followed by PRAVA 40mg for the remaining 44 weeks.

Discontinuations due to all causes were similar across the treatment groups (13%, 16% and 18% respectively). The Week 8 (5%. 6%, 4%, respectively) and cumulative Week 24 (11%, 12%, 11% respectively) discontinuation rates were also similar across the treatment groups. Discontinuations from adverse events up to week 52 were likewise similar across all treatment groups

4. **The over-all incidence rate of selected adverse events** occurring in at least 2% of patients is shown below:

Incidence Rate of selected adverse events (by dose) up to week 52 and week-8:

	PLA/PRAVA 40 mg (n-198)		CER 0.4 mg (n=1194)		CER 0.8 mg (n=774)	
	Week 52	Week 8	Week 52	Week 8	Week 52	Week 8
Any event	178 (90%)	116 (59%)	181 (93%)	113 (58%)	691 (89%)	470 (61%)
Headache	24 (11%)	13 (7%)	31 (16%)	15 (8%)	95 (12%)	50 (6%)
Flu syndrome.	21 (11%)	5 (3%)	19 (10%)	4 (2%)	80 (10%)	20 (3%)
Back pain	22 (11%)	11 (6%)	21 (11%)	8 (4%)	73 (9%)	18 (2%)
Leg pain	12 (6%)	4 (2%)	13 (7%)	5 (3%)	50 (6%)	21 (3%)
Asthenia	12 (6%)	5 (3%)	11 (6%)	6 (3%)	51 (7%)	30 (4%)
Abd. Pain	11 (6%)	5 (3%)	9 (5%)	3 (2%)	47 (6%)	15 (2%)
Infection	7 (4%)	3 (2%)	4 (2%)	1 (<1%)	36 (5%)	9 1%)
Pain	8 (4%)	2 (1%)	8 (4%)	3 (2%)	25 (3%)	9 (1%)
Hyperten.	10 (5%)	4 (2%)	6 (3%)	0 (0%)	31 (4%)	9 (1%)
Angina	4 (2%)	NA	1 (<1%)	NA	2 (<1%)	NA
Diarrhea	13 (7%)	2 (1%)	15 (8%)	5 (3%)	46 (6%)	26 (3%)

Dyspepsia	14 (7%)	4 (2%)	14 (7%)	6 (3%)	46 (6%)	25 (3%)
Constipat.	5 (3%)	1 (<1%)	11 (6%)	5 (3%)	36 (5%)	17 (2%)
Nausea	15 (8%)	6 (3%)	8 (4%)	4 (2%)	36 (5%)	16 (2%)
Flatulence	8 (4%)	6 (3%)	6 (3%)	1 (<1%)	28 (4%)	13 (2%)
Arthralgia	26 (13%)	6 (3%)	26 (13%)	8 (4%)	101 (13%)	31 (4%)
Myalgia	15 (8%)	7 (4%)	15 (8%)	7 (4%)	57 (7%)	19 (2%)
Arthritis	7 (4%)	3 (2%)	5 (3%)	3 (2%)	31 (4%)	11 (1%)
Leg cramps	4 (2%)	3 (2%)	10 (5%)	4 (2%)	16 (2%)	8 (1%)
Dizziness	10 (5%)	5 (3%)	11 (6%)	4 (2%)	37 (5%)	17 (2%)
Insomnia	8 (4%)	4 (2%)	7 (4%)	2 (1%)	20 (3%)	6 (<1%)
Rhinitis	42 (21%)	8 (4%)	35 (18%)	10 (5%)	150 (19%)	42 (5%)
Pharyngitis	30 (15%)	9 (5%)	33 (17%)	9 (5%)	135 (17%)	43 (6%)
Sinusitis	18 (9%)	3 (2%)	16 (8%)	4 (2%)	76 (10%)	21 (3%)
Rash.	17 (9%)	4 (2%)	14 (7%)	5 (3%)	61 (8%)	23 (3%)
UTI	4 (2%)	NA	8 (4%)	NA	29 (4%)	NA

During the Week-8 placebo-controlled period, the adverse events were generally mild and occurred in similar frequency compared to patients receiving placebo, CER 0.4 mg. And CER 0.8 mg. In the 52-week analysis, constipation, pharyngitis and increased CK occurred more frequently in the CER 0.8 mg- and 0.4 mg-treated patients compared to patients receiving PLA/Prava 40 mg.

5. **The incidence rates of treatment-emergent serum electrolyte and chemistry abnormalities greater than the upper limit of normal (ULN)** for selected variables of clinical interest in study D97-008 are shown below:

Treatment-Emergent Serum Electrolyte/Chemistry Abnormalities through Week 24 (and through Week 8 in parenthesis

Lab Variable Elevated	CER 0.4mg n=194	CER 0.8mg n=774	PLA/PRAVA 40mg n=198
Glucose (mg/dL)	24% (11%)	32% (20%)	28% (12%)
Alk.Phophatase (U/L)	5% (4%)	8% (6%)	4% (<1%)
Total Bilirubin (mg/dl)	3% (2%)	6% (3%)	4% (2%)
SGPT (U/L)	21% (11%)	26% (14%)	18% (6%)
SGOT (U/L)	26% (18%)	39 (26%)	20% (12%)
LDH (U/L)	14% (5%)	18% (10%)	12% (6%)
CK (U/L)	26 (22%)	36% (27%)	23% (17%)

Cerivastatin-0.8 mg-treated patients were more likely to have had abnormally high CK, SGOT, SGPT, alkaline phosphatase, LDH and glucose. For elevated SGOT/SGPT/ and CK, please refer to the Integrated Summary of Safety where they were extensively reviewed.

a. The percentage of patients with elevations of serum LDH was greater in CER 0.8mg-treated patients (10%) compared to patients treated with placebo (6%) and CER 0.4mg (5%) at the Week 8 timepoint. The event rate remained higher in the CER 0.8mg-treated patients compared to patients treated with CER 0.4mg and PLA/PRAVA 40mg at Week 24 and Week 52. Of the patients with an LDH elevation >3XULN, all had associated elevations of serum CK, SGOT and SGPT as summarized below:

Patient ID	Max. LDH (mg/dl) ULN=100U/L	CK (multiple of ULN=120U/L)	SGOT(multiple of ULN=22U/L)	SGPT(multiple of ULN=25U/L)
CER 0.8 mg				
#16005	331	33X	7X	5X
#27046	304	5X	2X	5X
#27047	410	56X	11X	9X
#62006	530	30X	11X	13X
CER 0.4 mg				
#48007	477	129X	23X	9X

Since these patients clinically did not have myocardial infarction, the likely explanation for this constellation of elevations is due to hepatic toxicity as discussed in the Integrated Summary of Safety.

All other patients had LDH elevations <u>≤1.2xULN</u> (ULN=100 MU/ML) and of little clinical significance. The following patients had LDH elevations >1.5xULN to <3xULN.

(1). PLA/PRAVA 40 mg group:

Patient 9035, 51 y/o male had LDH of 196 on day 58, decreased to 76 on day 71 and remained normal.

(2). CER-0.4mg group:

Patient 40024, 41 y/o male had LDH of 240 on day 93, decreased to 84 on day 122 and remained normal.

Patient 40069, 51 y/o male had LDH of 165 on day 85, decreased to 71 on day 229 and remained normal.

(3). CER-0.8mg group:

Patient 3010, 64 y/o female had LDH of 289 on day 28, decreased to 89 on day 41 and dropped out of the study.

Patient 9029, 37 y/o male had LDH of 165 on day 113, decreased to 78 on day 122 and dropped out of the study.

Patient 9046, 51 y/o male had LDH of 187 on day 81, decreased to 76 on day 85 and remained normal.

Patient 17004, 55 y/o male had LDH of 151 on day 83, gradually decreased to 91 on day 280 and remained normal.

Patient 20016, 65 y/o male had LDH of 153 on day 29, decreased to 93 on day 57 and remained normal.

Patient 40002, 70y/o male had LDH 163 on day 57, decreased to 76 on

day 85 and remained normal.

Patient 41003, 73 y/o female had LDH of 154 on day 36, decreased to 113 on day 50, and dropped out of the study.

Patient 50011, 63 y/o female had LDH of 291 on day 30, gradually decreased to 78 on day 153 and dropped out of the study. This patient and all other patients who dropped out of the study had no other associated symptoms or abnormal lab findings. The reasons for dropping out were not stated.

b). There was greater incidence rate of elevated total bilirubin in the 0.8mg-treated patients compared to the 0.4mg- and PLA/PRAVA 40mg treated patients. The elevations of total bilirubin in most of the patients were in the order of 1.1xULN (ULN=1.1 mg/dl). The highest bilirubin in the PLA/PRAVA 40 mg group was 1.7 mg/dl (patient # 10006) on day 341 and decreased to 0.9 mg/dl on day 351. The highest bilirubin level in the 0.4 mg group was 1.45 mg/dl (patient # 33012) on day 49 and decreased to 1.03 mg/dl on day 109. The highest bilirubin level in the 0.8 mg group was 1.83 mg/dl (patient # 39006) on day 113 and decreased to 1.13 mg/dl on day 379. None of these patients who had normal bilirubin levels at baseline, developed concomitant elevations of SGOT/SGPT >3xULN.

Only one patient (Patient 50017) in the CER-0.8 mg group whose bilirubin was 1.50 (1.4xULN on Day –21) developed SGPT of 84 (3.4xULN). His bilirubin fluctuated between 1.1-1.8xULN during the course of therapy. It decreased to 0.78 and 0.92 (0.7 and 0.8xULN) on Days 262 and 264 of treatment.

c). The percentage of patients with elevated alkaline phosphatase was greater in the CER-0.8 mg group (6%) compared to patients treated with CER-0.4 mg (4%) and PLA-treated group (<1%) at Week 8 timepoint. At Week 24, the differences persisted. All the elevations were ≤1.2xULN (ULN=72 MU/ML) and of little clinical significance. The following patients had greater elevations:

(1). 0.4mg group:

Patient 28001, 51 y/o female had alk. phos. of 134 on day 84, decreased to 62 on day 112.

(2). 0.8mg group:

Patient 38003, 72 y/o female had alk. phos. of 163 on day 74, decreased to 47 on day 102 and remained normal.

Patient 44001, 65 y/o male had alk. phos. of 139 on day 184, decreased to 60 on day 239, and remained normal.

Patient 46001, 68 y/o male had alk. phos. of 83 and 93 on day 337. Patient had no other associated symptoms or lab. abnormalities.

Patient 52003, 65 y/o male had alk. phos. of 93 on day 196, decreased to 65 on day 259 and remained normal.

d). The percentage of patients with elevations of fasting glucose was greater in

CER 0.8mg group (20%) compared to patients treated with placebo (12%) and CER 0.4mg (11%) at the Week 8 timepoint. At Week 24, the incidence rate was similar in the 0.8mg Week 8 timepoint. At Week 24, the incidence rate was similar in the 0.8mg-treated patients (32%) and patients treated with PLA/PRAVA 40mg (28%) and lower in CER 0.4mg-treated patients. However, after up to 52 weeks of therapy, the event rate was similar across all the treatment groups (CER 0.4mg: 35%, CER 0.8mg: 41%, PLA/PRAVA 40mg: 40%). Most of the elevations were ≤120 mg/dL. (the ULN for fasting glucose was 100 mg/dL). Detailed analysis of patients with higher elevations are shown below:

Patient ID	Days on therapy	Fasting Glucose value
PLA/PRAVS 40 mg		
23001	33	132
	63	165
	91	85
6006	112	147
	168	145
	299	95
CER 0.4 mg Treatment		
22023	90	122
	114	95
30024	99	119
	120	83
CER 0.8 mg Treatment		
5015	368	1114
	371	92
120334	58	119
	247	110
	297	126
20017	57	114
	86	105
24006	288	114
	351	102
290006	57	115
	113	113
	288	119
	372	102
3350224	284	116
	365	101
41003	36	122
	50	95
56007	95	112
	150	114
	183	116

None of the elevations are of the magnitude that causes clinical concerns. The highest elevations (in the PLA/PRAVA 40-mg group) were 165 mg/dL and 147 mg/dL and both decreased to normal levels

6. Hematological abnormalities:

There were no clinically significant hematological changes. Specifically, there was no patient with significantly low platelets and no clinical bleeding episode.

7. Hormonal Studies:

In a substudy of D97-008, cortrosyn stimulation testing was performed in males and females at baseline and after 24 weeks of therapy with either CER-0.4mg, 0.8mg or PRAVA 40mg 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. Similarly, there were no significant abnormalities among patients undergoing HCG stimulation testing.

B. Efficacy:

1. Efficacy at Week 8:

a. The primary efficacy endpoint was percentage change from baseline in mean LDL-C in the CER 0.8mg group vs. the placebo group at at Week 8 endpoint.

Table IV-B-1: Mean Percent Change in LDL-C at Week 8 Endpoint (ITT population)

Treatment Group N	Baseline (mg/dL)	Endpoint mg/dL	Mean % change	P-value*
Placebo N=197	184.6	183.8	-0.3%	
CER 0.4mg N=193	189.8	123.3	-34.9%+	P<0.0001
CER 0.8 mg N=770	189.0	111.4	-40.8% +, **	P<0.0001

* P-value for difference between treatment groups. All significance tests were 2-sided with an alpha level of 0.05. The primary method specified for comparing groups was the least square means from ANOVA model with effects for drug and center.

\+ Significantly different from placebo group.

** Significantly different from CER 0.4 mg group.

The primary efficacy objective was achieved: CER 0.8mg was significantly better than placebo in reducing mean plasma LDL-C at the Week 8 endpoint. There was a significant treatment-by-sex interaction (p=0.046). Females had greater percent reduction s in LDL-C (compared to placebo) on either dose of cerivastatin than male subjects. Please see Statistical Review for more details.

The secondary efficacy objective was also achieved: mean percent reduction in plasma LDL-C achieved with CER 0.8mg was significantly greater than that achieved with CER 0.4mg.

b. The other secondary efficacy parameters, mean changes from baseline in total-C, HDL-C and TG, are shown in Table IV-B-2:

Table IV-B-2: Mean % Changes in Total-C, HDL-C and TG at Week 8 Endpoint (ITT population)

Lipid Variable	Placebo n=197	CER 0.4mg n=193	CER 0.8mg n=770
Total-C	0.6	-24.3*	-29.1**
HDL-C	3.4	7.3*	9.0**
TG	+1.72	-11.38*	-17.88**

* Significantly different from placebo

** Significantly different from placebo and CER 0.4mg

The CER 0.8mg –treated group had significantly greater reduction in Total-C, HDL-C and TG than either placebo or/and CER 0.4mg-treated groups. Both HDL-C and TG responses seem to be baseline-level dependent. This is can be more readily demonstrated in TG. responses. TG responses can be further analyzed by baseline TG levels as shown:

Table IV-B-3: Mean and Median % Change in TG at Week 8 Endpoint by Baseline TG Values (ITT population)

Baseline TG (mg/dL)		Placebo	CER 0.4 mg	CER 0.8 mg
Baseline <150	N	80	60	261
	Mean % change	+5.9	-8.0	-8.7
	Median % change	-1.9	-9.1	-12.1
150<baseline<250	N	95	99	381
	Mean % change	-2.0	-12.6	-21.3
	Median % change	-3.8	-16.1	-25.1
Baseline >250	N	23	34	128
	Mean % change	+2.6	-14.2	-26.5
	Median % change	-3.3	-15.8	-28.2

The median percent reduction in TG at the Week 8 endpoint were slightly greater than the mean percent reductions. However, the magnitude of the

changes relative to placebo, CER 0.4mg and CER 0.8mg treatment groups were similar.

Generally, the higher the baseline TG levels, the greater the mean and median percent reductions observed with cerivastatin. Since TG is not normally distributed and the levels tend to fluctuate widely over time, a better measure TG response may be the cumulative distribution function. And this is shown below:

Percentile of the Cumulative Distribution Function for TG for ITT patients at Week 8 endpoint:

	Percentile		
Treatment	25th	50th	75th
PLA/PRAVA 40 mg N=198	-16.0	-2.3	+17.4
CER 0.4 mg N=193	-26.7	-14.4	+2.6
CER 0.8 mg N=770	-34.6	-21.6	-6.1

For patients treated with CER-0.8mg, the percentile reductions at 25th, 50th and 75th were greater than that of the CER-0.4mg treated patients.

C. **Special lipid parameter** results at Week 8 endpoint are shown below:

Table IV-B-5: Mean Percent Change in Special Lipid Parameters at Week 8 Endpoint (ITT population)

Variable	Placebo	CER 0.4 mg	CER 0.8 mg
Direct LDL-beta quantitation	+1.911*+	-32.9+	-37.7
Apo A1	+1.33*+	+3.51	+4.41
Apo B	+0.54*+	-28.2+	-32.7
VLDL-C	+6.16*+	-15.7+	+22.6
Lp(a)	+12.7	+14.1	+29.5

* Significantly different from CER-0.4mg.
\+ Significantly different from CER 0.8mg

As expected , the reductions in Apo B and VLDL-C paralleled the reduction in LDL-C. Similarly, the percent change from baseline in Apo A1 paralleled that of HDL-C although only the CER 0.8mg-treated group was significantly different from the placebo-treated group.

2. Efficacy at Week 24: After Week 8, patients in the placebo group were treated with pravastatin 40 mg daily. The major efficacy comparisons at Week 24 were between cervastatin 0.4 mg and 0.8 mg, and between cerivasatin doses and pravastatin 40 mg. Lipid parameter results are summarized:

Table IV B-6: Mean /Median Percent Change in Lipid Parameters from Baseline at Week 24 Endpoint in ITT population (Week 8 data in parenthesis)

Variable	Pravastatin 40mg	CER 0.4 mg	CER 0.8 mg
Mean % change LDL-C	-29.5 (0.0)	-31.8 (-34.9)	-38.6* (-40.8)
Mean % change HDL-C	+6.71 (+3.4)	+9.08 (+7.3)	+9.19+ (+9.0)
Mean % changeTotal-C	-20.3 (0.6)	-22.0 (-24.3)	-27.4* (-29.1)
Median % changeTG++	-7.11 (-2.3)	-11.3 (-14.4)	-16.8 (-21.6)
Mean % change Direct LDL-beta quant.	-26.5 (+1.91)	-29.1 (-32.9)	-35.0* (-37.7)
Mean % change Apo A1	+6.17 (+1.33)	+6.34 (+3.51)	+5.17 (+4.41)
Mean % change Apo B	-23.0 (+0.54)	-25.2 (-28.2)	-30.6* (-32.7)
Mean % change VLDL-C	-12.3 (+6.16)	-15.9 (-15.7)	-24.6* (-22.6)
Median % change Lp(a)++	+11.0 (+1.6)	+7.4 (+1.9)	+12.2 (+7.9)

* Significantly different from pravastatin and CER 0.4 mg.
\+ Significantly different from pravastatin.
++ P-value for Median % change in TG and Lp(a) were not calculated.

Similar to the Week 8 results, CER 0.8-mg treatment resulted in greater reductions in all lipid parameters except HDL-C compared to CER 0.4-mg treatment.

Likewise for the TG responses, median percent changes were slightly greater in magnitude than mean percent changes in all three treatment groups. However, the magnitude of the changes relative to pravastatin, CER 0.4mg and CER 0.8mg treatment groups were similar. And in general, the higher the baseline TG levels, the greater the mean and median percent reductions observed with cerivastatin.

4. Efficacy at Week 52: Following Visit 13 (Week 24), the investigators were unblinded to the LDL-C values in order to allow treatment with open label resin for patients who did not respond adequately to the study drug (either cerivastatin or pravastatin.

Table IV-B-7: Resin Use by Treatment Groups between Weeks 24 and 52 (Valid for Efficacy Population)

	Pravastatin 40 mg n=177	CER 0.4 mg n=166	CER 0.8 mg n=656
Patients (%)	8 (5%)	14 (8%)	28 (4%)
Mean # days on resin	108	96	93
Mean daily dose (g/day)	5.4	5.2	6.5

The original statistical plan did not include formal statistical comparisons of efficacy between the treatment groups for lipid values collected after Week 24. However, statistical analysis and comparisons were performed on the data at 52 weeks and are presented in this submission for descriptive purposes only.

In summary:

1. The primary objective of this trial was achieved: cerivastatin 0.8 mg resulted in statistically significant greater lowering of LDL-C at the Week 8 endpoint than placebo-and cerivastatin 0.4 mg-treatments.
2. Cerivastatin 0.8mg treatment resulted in similarly statistically significant greater reductions in total-C, TG, directly assayed LDL-C and Apo B than CER-0.4 mg treatment.
3. These statistically significant differences of reductions with the CER-0.8mg treatment were maintained at Week 24 and Week 52.

Study 17: This was a multinational, multi-center, randomized, double blind parallel group study.

1. Objectives:

The primary objective: To evaluate the efficacy (in terms of percentage change of calculated LDL-C between baseline and endpoint) and safety of cerivastatin 0.8 mg once daily versus simvastatin 40 mg once daily in patients with primary hypercholesterolemia.

The Secondary objective: To evaluate the percentage change of other lipid parameters (total-C, HDL-C and TG) from baseline to the endpoint. The comparisons between cerivastatin 0.2-mg vs. simvastatin 10 mg and cerivastatin 0.4 mg vs. simvastatin 20 mg will be performed in a descriptive way.

II. Patient Selection: Patient population consisted of ambulatory men or women aged 18-80 years with documented primary hypercholesterolemia. In this study, 50% of the patients were male and 50% were females. At entry, the mean age was 56 years old. Inclusion/Exclusion criteria were similar to that of D-97-008 Study.

III. Study Design and Procedures: The entire course of the study was divided into the following periods:

A. Period A (Run-in period): Visit 1 (week –10) to Visit 5 (week 0): Eligible patients meeting the inclusion/exclusion criteria were enrolled in Visit 1. Patients were required to be on AHA Step 1 diet for at least 4 weeks before they started single-blind placebo treatment at Visit 2. Lipid profiles

(total-C, HDL-C, LDL-C and TG) were taken at Visits 1, 3, 4, and 5. Patients meeting the following randomization criteria will be randomized to one of two parallel treatment groups (CER or SIMVA):

* Mean calculated LDL-C ≥190 mg/dL from levels determined at Visits 3 and 4. For patients with additional risk factors, LDL-C ≥160 mg/dL.
* TG <400 mg/dL.
* Patient compliance with drug intake of 80-120% throughout the run-in period.

B. Period B (Visit 5 (week 0) to Visit 6 (week 4): This period consisted of 4 weeks of double-blind treatment, either with CER 0.2 mg or SIMVA 10 mg. Patients randomized to CER treatment, took 1 tablet of active CER and 1 capsule of placebo matching with encapsulated SIMVA. A lipid profile was taken at Visits 5 and 6.

C. Period C (Visits 6 (week 4) to Visit 7 (week 8): Patients continuing the study would be forced-titrated to a higher dose of treatment (CER 0.4 mg or SIMVA 20 mg with the appropriate matching placebo tablet/capsule as in period B). A lipid profile was taken at Visits 6 and 7.

D. Period D (Visit 8 (week 8 to Visit 9 (week12): Patients were forced-titrated to the highest dose of treatment (CER 0.8 mg or SIMVA 40 mg with the matching appropriate placebo tablet/capsule as previous periods). This period lasted 4 weeks and patients were seen every 2 weeks. A lipid profile was taken at each visit.

In addition, PE with vital signs was performed at Visit 2. Safety laboratory tests for hematology, chemistry and urinalysis were done at each visit as well as adverse events documented. In the case of abnormal results, there were no repeat measurements outside visits scheduled according to the protocol for amylase, CK, AST and ALT. If AST >1.5xULN or ALT>1.5xULN, patients were withdrawn from the study. If amylase >1.5xULN or CK>3xULN were measured, repeat tests were done at the next visits scheduled. If amylase or CK elevation persisted at the next visit, the patients were withdrawn from the study.

IV. Results:

A. Safety:
1. Death: There were no deaths in Study 17.
2. Serious Adverse Events: For the valid for safety population (patients who took at least one dose of study drug and who had post-randomization data):
   a). CER-treated patients: Of the 185 patients, 5 patients (3%) experienced 10 serious or potentially serious adverse events. Of these 5 patients, 4 experienced the events on CER 0.2 mg and one

patient had 3 events post-study. There were no serious adverse events in the CER-.4 mg or CER 0.8-mg groups.

b). SIMVA-treated patients: Of the 184 patients, 3 patients (1.6%) had 3 serious adverse events. All occurred on SIMVA 20 mg; there were no serious adverse events reported on SIMVA 10 mg or SIMVA 40 mg.

3. **Discontinuations** due to all causes are summarized below:

	CER (n=185)	SIMVA (n=184)
Completed study	179 (96.7%)	170 (92.4%)
Premature termination due to:		
Adverse event	3 (1.6%)	5 (2.7%)
Patient non-compliance	1 (0.5%)	2 (1.1%)
Consent withdrawn	1 (0.5%)	0 (0%)
Patient lost to follow-up	1 (0.5%)	4 (2.2%)
Protocol violation	0 (0%)	3 (1.6%)
Total	6 (3.2%)	14 (7.6%)

The overall discontinuation rate was higher in the SIMVA group (7.6%) compared to the CER group (3,2%). Discontinuations due to adverse events were also lower in CER-treated patients (1.6%) compared to patients on SIMVA (2.7%). The following table summarizes the reasons for discontinuation:

Patient	Dose @ Discontinuation	'Events Investigator term
8-039	CER 0.2 mg	Eczema, pruritus, Quincke's edema
12-004	CER 0.2 mg	Intense irritation of skin and mucous membrane
8-009	CER 0.4 mg	Muscle pain
5-001	SIMVA 10 mg	Weight increase; pain and swollen fingers, knees.
9-001	SIMVA 10 mg	Pain in the back, pain & stiffness in knees
11-040	SIMVA 10 mg	Headache, dizziness
13-013	SIMVA 20 mg	Muscle pain, CPK elevation
9-017	SIMVA 40 mg	Headache, gastroenteritis

4. All treatment-emergent adverse events occurring in >2% of the patients are showing below:

Adverse event	CER N=185	SIMVA N=184
Flu syndrome	21 (11.4%)	21 (11.4%)
Headache	8 (4.3%)	9 (4.9%)
Abdominal pain	6 (3.2%)	6 (3.3%)
Bronchitis	6 (3.2%)	3 (1.6%)
Creatine phosphokinase increased	6 (3.2%)	2 (1.1%)
Insomnia	5 (2.7%)	5 (2.7%)
Diarrhea	4 (2.2%)	6 (3.3%)
Flatulence	4 (2.2%)	5 (2.7%)
Asthenia	3 (1.6%)	4 (2.2%)
Constipation	2 (1.1%)	5 (2.7%)
Back pain	2 (1.1%)	6 (3.3%)
Accidental injury	1 (0.5%)	6 (3.3%)
Nausea	1 (0.5%)	5 (2.7%)
Myalgia	1 (0.5%)	4 (2.2%)
Pharyngitis	1 (0.5%)	4 (2.2%)

The incidence of back pain, accidental injury, and nausea were greater in the SIMVA group compared to the CER group, while that of CK increased was greater in the CER group.

5. The incidence rates of treatment-emergent high serum chemistries/electrolytes through week 12 are shown below:

Lab Variable	CER N=185	SIMVA N=184
Uric acid (mg/dl)	1.4%	0.7%
Calcium (mg/dl)	0.0%	0.0%
Phosphorus (mg/dl)	3.8%	2.9%
Sodium (meq/L)	0.6%	1.2%
Potassium (meq/L)	1.8%	1.3%
Creatinine (mg/dl)	0.6%	0.0%
BUN (mg/dl)	7.0%	1.4%
SGOT (U/L)	19.6%	21.3%
SGPT (U/L)	13.9%	17.8%
LDH (U/L)	16.2%	19.9%
Alkaline phosphatase (U/L)	6.4%	6.3%
Amylase (U/L)	1.7%	1.1%
CK U/L)	13.9%	13.1%

1 male patient (# 8074) and 2 female patients (# 11045, 17015) had increased uric acid levels. The increase were <10% ULN and of no clinical significance.

2 male and 5 female patients developed increased phosphorus. 3 patients developed increased sodium and 5 patients developed increased potassium

levels. The increases were ≤10% of ULN and of no clinical significance.

1 patient had increased creatinine of 1.50 mg/dl (ULN=1.4). 13 patients developed increased BUN which ranged from ——— (Normal 5 to 20 mg/dl). No clinically significant increases were observed.

30 patients developed increased LDH levels (most of them during Period D on CER 0.8mg). In all but 7 patients the increases were <10% of ULN (normal range 40-100 mU/mL). The increases in the 7 patients ranged from ——— mU/mL. and returned to normal at the end of the study except in one patient.

12 patients developed increased alkaline phosphatase levels (mostly during Period D on CER-0.8mg). All the increases were ≤10% of ULN and of no clinical significance.

4 patients developed increased amylase levels. Except for patient #12006 who had a level of 111.0 U/L (normal range=0 to 88 U/L), the other increases were ≤10% ULN.

Elevated SGOT/SGPT and CK were already reviewed in the Integrated Summary of Safety.

6. Hematological Changes:

There were no clinically significant hematological changes except one patient (#15013) had platelets counts of 101.0 (K/cu mm). She had no clinical bleeding episode.

B. Efficacy: No efficacy results were submitted. Study 17 was primarily a Safety Up-date submission.

Integrated Summary of Efficacy

The integrated summary of efficacy supporting the cerivastatin 0.8mg once daily supplemental new drug application (sNDA) is comprised of one pivotal study (D97-008) performed in the US and Canada. To define the CER dose response across the 0.1mg to 0.8mg range of doses, the following studies are summarized:

Region/Study Number	Description	Doses (once daily)	# of Patients Randomized/ Valid for ITT /Completed	Study Duration (weeks)
US/Canada D97-008 (0182)	Pivotal,placebo/active controlled; pravastatin comparison	CER 0.8mg CER 0.4mg PLA/PRAVA 40mg	776/774/686 195/194/175 199/198/178	52
US D91-031 (0124)	Pivotal, placebo/active controlled; lovastatin comparison	CER 0.3mg CER 0.2mg CER 0.1mg CER 0.05mg PLA LOV 40mg	156/154/134 159/159/143 157/154/139 159/158/140 154/152/1361 54/153/137	24
US D96-008 (0162)	Pivotal,placebo/active controlled; fluvastatin comparison	CER 0.4mg CER 0.3mg PLA/FLUVA 40mg	456/448/408 229/225/205 223/220/199	24
US D94-021 (0152)	Placebo-controlled lovastatin comparison	CER 0.3 mg PLA LOV 40mg	38/37/33 37/37/34 42/42/35	24
Non-US (0149)	Pivotal, placebo-controlled	CER 0.4mg CER 0.3mg PLA	138/138/134 140/140/137 72/71/70	8
Non-US (0120)	Pivotal, placebo-controlled; simvastatin comparison	CER 0.2 mg CER 0.1 mg CER 0.05 mg CER 0.025mg PLA SIMVA 20mg	197/191/179 197/190/181 195/187/178/ 196/193/179 193/187/181 188/183/174	12
Non-US (0132)	Pivotal, placebo-controlled; gemfibrozil comparison	CER 0.3 mg CER 0.2 mg CER 0.1 mg GEM 1200mg PLA	175/168/162 171/167/161 166/160/153 160/154/142 79/75/70	16
Non-US (0161)	Supportive	CER 0.4mg CER 0.2mg	332/330/318 162/162/153	24

Study D97-008 (0182): The relevant features of the study, safety and efficacy have been extensively reviewed in the Integrated Summary of Safety and Individual Studies review.

A. **The primary efficacy endpoint** was the percentage change from baseline in plasma LDL-C. Mean baseline and percentage change from baseline to Week 8 for LDL-C in the ITT population are shown below:

	CER 0.4 mg N=186	CER 0.8 mg N=732	PLA N=188
Baseline (mg/dl)	190.9	189.6	184.5
Week 8 (mg/dl)	123.8	111.1	183.9
% Change	-35.1*	-41.2*+	0.1

*Significantly different from PLA, p=0.0001
+Significantly different from CER 0.4mg,p=0.0001

There were three other lower dose CER pivotal studies to examine the magnitude of the treatment effect of CER 0.8mg vs. that of lower doses. The overall LDL-C results from these pivotal studies are summarized below:

Pivotal Studies D97-008, D96-008, D91-030 and 0149. Least Mean Baseline and Mean Percentage Change of LDL-C from Baseline to Week 8 (ITT population)

	# of Patients	Baseline LDL-C (mg/dl)	% Change
PLA	608	195.2	+0.4
CER 0.1 mg	147	195.8	-21.5*
CER 0.2 mg	151	196.3	-25.0*
CER 0.3 mg	494	200.7	-30.9*
CER 0.4 mg	754	194.3	-34.2*
CER 0.8 mg	732	189.5	-41.8*

* Significantly different from PLA

All CER-treatment, from 0.1mg to 0.8mg resulted in statistically significant reductions of LDL-C compared to placebo treatment and all CER treatment groups were statistically significantly different from each other. Dose-related reductions in LDL-C were present across the CER 0.1mg to 0.8mg dose range at Week 8 endpoint.

B. **The secondary efficacy endpoints** were Total-C, HDL-C, TG and special lipid fractions. Pooling study D97-008 to three lower dose CER pivotal studies, the results are shown in the following tables:

1. **Total-C:**

Pivotal Studies D97-008, D96-008, D91-031 and 0149. Least Mean Baseline and Mean Percentage Change of Total-C from Baseline to Week 8 (ITT population)

	# of Patients	Baseline LDL-C (mg/dl)	% Change
PLA	620	278.4	+0.8
CER 0.1 mg	147	277.8	-14.7
CER 0.2 mg	151	281.9	-17.7*
CER 0.3 mg	497	285.1	-22.0*
CER 0.4 mg	758	279.4	-24.2*
CER 0.8 mg	735	275.5	-29.8*

* significantly different from PLA

Similar to the primary efficacy endpoint, LDL-C, all CER-treatment, from 0.1mg to 0.8mg resulted in statistically significant reductions of Total-C compared to placebo treatment and all CER treatment groups were statistically significantly different from each other. Dose-related reductions in Total-C were present across the CER 0.1mg to 0.8mg dose range at Week 8 endpoint.

2. HDL-C:

Pivotal Studies D97-008, D96-008, D91-031, and 0149. Least Mean Baseline and Mean Percentage Change of HDL-C from Baseline to Week 8 (ITT population)

	# of Patients	Baseline LDL-C (mg/dl)	% Change
PLA	620	49.5	+1.8
CER 0.1 mg	147	48.6	+6.6*
CER 0.2 mg	151	50.5	+8.6*
CER 0.3 mg	496	50.4	+7.7*
CER 0.4 mg	758	49.7	+7.0*
CER 0.8 mg	735	49.0	+9.2*

* significantly different from PLA

Statistically significant percentage increases in mean plasma HDL-C were observed in all CER treatment groups. The increase in CER 0.8mg-treated patients was statistically significantly greater than patients treated with CER 0.4mg.

3. TG:

Studies D97-008, D96-008, D91-031 and 0149. Median (min,max) Percentage Change of TG from Baseline to Week 8 (ITT population)

	# of Patients	% Change (min,max)
PLA	620	-0.4
CER 0.1 mg	147	-9.5*
CER 0.2 mg	151	-15.8*
CER 0.3 mg	497	-15.6*
CER 0.4 mg	758	-16.1*
CER 0.8 mg	735	-22.4*

* significantly different from PLA

Due to the wide variability of TG responses to statin therapy, median changes from baseline (with minimum and maximum) were used to document the dose-related reductions in plasma TG across the CER 0.1 mg to 0.8 mg dose range.

TG reduction with statin therapy is baseline dependent. A larger pool of CER studies in patients with baseline TG>250mg/dl was used to examine the effect of CER on TG in this subgroup.

Studies D97-008, D96-008, D94-021, D91-031, 0120, 0132, 0149 and 0161. Median (min,max) Percentage Change from Baseline to Week 8 in Patients with Baseline TG≥250 mg/dl (ITT Population)

Study Drug	# of Patients	Percentage Change (min,max)
PLA	138	-3.3
CER 0.1 mg	133	-18.1
CER 0.2 mg	129	-22.6
CER 0.3 mg	157	-22.4
CER 0.4 mg	139	-26.2
CER 0.8 mg	125	-30.7

As before, statistically significant reductions were observed in all the CER treatment groups and the reductions in this subgroup of patients with baseline TG>250 mg/dl were greater than patients regardless of baseline TG levels.

Since TG is levels tend to fluctuate widely over time, a better measure TG response may be the cumulative distribution function. And this is shown below:

Percentile of the Cumulative Distribution Function for TG responses in Study D-97-008 at Week 8 endpoint (ITT Population):

	Percentile		
Treatment	25th	50th	75th
PLA/PRAVA 40 mg N=198	-16.0	-2.3	+17.4
CER 0.4 mg N=193	-26.7	-14.4	+2.6
CER 0.8 mg N=770	-34.6	-21.6	-6.1

By this measure, the TG responses to CER-0.8mg were greater than CER-0.4mg and PLA/PRAVA 40-mg.

4. Apolipoprotein B (Apo B): Mean percentage change from baseline to week 8 for plasma apo B are shown:

	CER 0.4mg N=185	CER 0.8mg N=728	PLA N=192
Baseline (mg/dl)	185.3	180.7	176.3
# Change	-28.4*	-32.9*+	+0.6

* Significantly different from PLA; p=0.0001
+ Significantly different from CER 0.4mg; p=0.0001

Dose-related reductions in mean plasma Apo B in CER-0.8mg treated patients were greater than patients treated with placebo and CER-0.4mg since Apo B is a major constituent of LDL-C.

Pooling the results of D97-008 Study to a pool of 3 lower dose CER pivotal studies, the dose response and magnitude of effect of CER on plasma Apo B can be seen:

Pivotal Studies D97-008, D96-008, D91-031 and 0149. Least Square Mean and Mean Percentage Change from Baseline to Week 8 for Apo B (ITT population)

Study Drug	# of Patients	Baseline (mg/dl)	% Change
PLA	619	180.5	+1.3
CER 0.1 mg	147	174.0	-15.3*
CER 0.2 mg	150	174.4	-19.3*
CER 0.3 mg	495	180.3	-23.8*
CER 0.4 mg	755	184.4	-26.9*
CER 0.8 mg	731	181.6	-33.4*

* Significantly different from PLA

Compared to patients treated with PLA, statistically significant differences in the mean percentage change from baseline for plasma Apo B were observed across the CER 0.1mg to 0.8mg dose range.

5. **Special Lipid Variables** (directly measured LDL-C, Apo A1, VLDL-C, Lp(a):

The mean percentage changes from baseline to Week 8 in Study D97-008 for directly measured LDL-C and VLDL-C were greater in patients treated with CER 0.8mg than those treated with CER-0.4mg. There was statistically significant dose-related increases in Apo A1 between CER-treatment groups compared to placebo. There was no statistically significant difference between the two CER-treated groups in Apo A1 or Lp(a).

C. **Efficacy in Demographic Subgroups**: The effects of CER-0.8mg on mean plasma LDL-C by selected demographic subgroups by age, sex, weight, baseline LDL-C and lipid classification are shown below:

Study D97-008 Mean Percentage Change in LDL-C at Endpoint Week 8 by Subgroup (percentage of patients in parenthesis) ITT population:

		CER 0.4mg N=193+	CER 0.8mg N=770+	PLA N=197+
Sex	Males	-34.4 (58%)	-40.4 (61%)	-1.4 (65%)
	Females	-37.0 (42%)	-42.9 (39%)	+0.9 (35%)
Age (years)	≤65	-34.9 (76%)	-40.9 (78%)	+0.4 (81%)
	> 65	-37.3 (24%)	-43.2 (22%)	-50 (19%)
Weight (kg)	≤ 70	-36.8 (76%)	-43.1 (24%)	0.0 (19%)
	>70 to ≤80	-35.8 (24%)	-41.5 (26%)	-0.3 (31%)
	>80 to≤90	-35.3 (33%)	-41.5 (28%)	-3.5 (24%)
	>90	-34.2 (21%)	-39.3 (22%)	+1.2 (25%)
Baseline LDL-C (mg/dl)	≤190	-34.8 (64%)	-40.8 (62%)	+0.2 (67%)
	≥190	-36.8 (36%)	-42.3 (38%)	-2.3 (33%)
Fredrickson's Classification	11a	-35.6 (61%)	-41.2 (64%)	-2.0 (67%)
	11b	-35.6 (39%)	-42.0 (36%)	+1.6 (33%)

The following CER-0.8 mg subgroups had greater percentage reduction in mean LDL-C: female patients, older patients, patients with lesser weight. This is indeed interesting since they are the same subgroup of patients who had greater incidence of SGOT/SGPT>3xULN and CK>10xULN. This subgroup of patients pharmacokinetically behaved as if they were administered a higher than 0.8mg dose. With higher dose, they had greater efficacy and the associated greater/more serious adverse events.

Patients with baseline LDL-C >190 mg/dl had greater lowering than those with baseline LDL-C ≤190 mg /dl. However, Fredrickson's classification of 11a or 11b had no effect on the observed percentage reductions.

D. The findings at Week 24 were similar to the above findings of Week 8.

E. Efficacy Conclusion:

CER-0.8mg administered once daily resulted in statistically significant reductions in plasma LDL-C, Total-C and Apo B compared to treatment with placebo and CER-0.4mg.

Overall Conclusion and Recommendations:

1. This sNDA consisted mainly of a 52-week Phase 3 pivotal study (D-97-008) involving 1170 patients (774 patients treated with CER-0.8mg) and a smaller safety study of 185 patients treated with CER-0.2/0.4/0.8 mg for 4 weeks each. The highest approved and marketed dose of cerivsatatin is 0.4mg/day. The pivotal trail was placebo-controlled for the first 8 weeks. At Week 8, placebo patients were switched to pravastatin 40mg for the remainder of the trial. At Week 24, investigators were unblinded to the LDL-C values so that patients with inadequate LDL-C reduction could be started on resin therapy in addition to cerivastatin. The primary objective of the trail was to compare the safety and efficacy of cerivastatin 0.8mg and placebo after 8 weeks of treatment. The secondary objective was comparing cerivastatin 0.8mg and 0.4mg at 8 and 24 weeks.

2. With respect to efficacy results, cerivastatin 0.8mg was statistically superior to placebo and cerivastatin 0.4mg in the mean percent change in LDL-C. There was a significant treatment-by-sex interaction (p=0.046). Females had greater percent reduction s in LDL-C (compared to placebo) on either dose of cerivastatin than male subjects. The 0.8mg –treated group also had significantly greater reduction in total-C, HDL-C, TG and Apo B than either placebo or/and 0.4mg-treated groups.

3. With respect to safety, no new unexpected adverse events were reported. Throughout the double-blind period (up to Week 24), comparisons of SGOT/SGPT changes from baseline between cerivastatin dose groups showed statistically significant differences at each timepoint after baseline. The percentage of patients with CK values greater than ULN were statistically greater at 0.8mg compared to 0.4mg at Weeks 8, 24 and 52. According to the statistical Reviewer, "the statistical results reflect a significant shift in the overall **distribution** of values at the higher dose." With respect to number and percentage of patients with SGOT/SGPT$\geq$ 3xULN and CK>5xULN, CK>10xULN, none of the pairwise comparisons involving CER-0.8mg was statistically significant at the 0.05 level. However, the subgroup of female patients $\geq$ 62 years of age with body weight $\leq$65kg had increased incidence of CK>10xULN and SGOT/SDGPT>3xULN.

4. Additional pharmacokinetic studies specifically designed to evaluate the effects of gender, age and body weight (body-surface-area) on the plasma concentration

of cerivastatin should be performed to evaluate the apparent increased incidence of CK>10xULN and SGOT/SGPT>3xULN in the subgroup of females>62 years of age, body weight <70 kg.

5. This sNDA is approvable.

Review of Financial Disclosure Forms:

The following financial disclosure information has been submitted:

1. Form FDA 3454 (3/99). The sponsor certifies that Bayer has not entered into any financial arrangement with the clinical investigators named in the lists included in the NDA whereby the value of compensation to the investigator could be affected :

2. List of investigators from whom completed financial disclosure forms were received.
3. The sponsor certifies that all clinical investigators participating in and contributing data to the pivotal study were requested and did provide to Bayer the requisite financial disclosure information.

Comments:

The above financial disclosure information was reviewed and there is no evidence to call into question the overall integrity of the data submitted.

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Labeling

/S/

S.W. Shen, ~~M.D.~~
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/S/ 7-19-00

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