

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-740/S008/S013**

**STATISTICAL REVIEW(S)**

**NDA:** 20-740/SE2-008  
**Sponsor:** Bayer Corporation Pharmaceutical Division  
**Drug:** Baycol (cerivastatin sodium) tablets  
**Indication:** 800 µg dose for hypercholesterolemia  
**Documents reviewed:** Submissions dated 9/23/99 (electronic document room) and 6/27/00  
**Medical Reviewer:** Shaio-Wei Shen, M.D. (HFD-510)  
**10-month User Fee date:** July 23, 2000

The sponsor has submitted a 52-week randomized, placebo-controlled, double-blind, parallel group clinical trial (D97-008) in support of an 800 µg once-daily dose of Baycol (cerivastatin). The highest approved and marketed dose of cerivastatin is 400 µg. Eligible subjects consisted of men and women not of child-bearing potential between the ages of 18 and 75 with documented hypercholesterolemia. Patients meeting any of the following additional criteria

- Mean (Weeks -4 and -2) LDL-C ≥ 159 mg/dL and no atherosclerotic disease and no cardiovascular risk factors, or
- Mean (Weeks -4 and -2) LDL-C ≥ 130 mg/dL in patients with definite atherosclerotic disease, or
- Mean (Weeks -4 and -2) LDL-C ≥ 130 mg/dL in patients with 2 or more of the following risk factors: age (men ≥ 45, women ≥ 55 or premature menopause), family history of premature coronary disease, current cigarette smoking, hypertension, or low plasma HDL-C >35 mg/dL at Weeks -8 and -6

were randomized in a 4:1:1 ratio to Baycol 800 µg, Baycol 400 µg and placebo/pravastatin if they also met all of the following additional criteria: Week -4 and -2 LDL-C values not different from the mean LDL-C for these visits by > 12.5%, plasma triglycerides (TG) ≤ 400 mg/dL at Weeks -4 and -2, and compliance with the AHA Step 1 diet at Week -2 and a food rating score ≤ 15. The study design is summarized in Table 1.

**Table 1: Study design**

Study number (dates)	# of centers (country)	Treatment/dose	# of pts randomized	Treatment periods
D97-008 (11/97 - 7/99)	59 (49 US, 10 CAN)	Cer 400 µg, Cer 800 µg, Plb/prava 40 mg	776 195 199	4 weeks diet only 6 weeks SB diet + placebo 24 weeks DB 28 weeks partial blind <sup>2</sup>

<sup>1</sup> The primary endpoint was unblinded at Week 24. Treatment assignment remained blinded for the duration of the trial

The trial was placebo-controlled for the first eight weeks. At Week 8, placebo patients were switched to pravastatin 40mg for the remainder of the trial. At Week 24, investigators were unblinded to LDL-C values so that patients with inadequate lipid reduction could be started on open-label resin therapy in addition to the test drug. Treatments continued to be dispensed in a double-blind manner.

The primary objective of the trial was to compare the safety and efficacy of cerivastatin 800 µg and placebo after 8 weeks of treatment. Secondary objectives were comparing cerivastatin 800 µg and 400 µg at 8 and 24 weeks, and cerivastatin 400 µg vs placebo at 8 weeks.

Lipids were measured five times before randomization and 11 times after randomization at Weeks 2, 4, 6, 8, 12, 16, 20, 24, 32, 40 and 52. The primary endpoint was the percent change from baseline in LDL-C at Week 8. Baseline was computed as the mean of values at Weeks -4, -2 and 0 (Visits 3, 4 and 5). Secondary endpoints included HDL-C, total-C, TG, and ratios of total-C to HDL-C and LDL-C to HDL-C. Several lipid fractions were measured. This review will examine Apo-B since this was the only fraction that was included in the label.

### Patient disposition and demographics

Table 2 shows demographic characteristics for the set of randomized patients. Patients were generally well-balanced on all variables.

**Table 2: Baseline demographic characteristics**

	Placebo/prava (n=199)	Cer 400 µg (n=195)	Cer 800 µg (n=776)
Sex (% men)			
Females	35%	42%	40%
Males	65%	58%	60%
Race			
Asian	2%	2%	1%
Black	4%	4%	4%
Caucasian	90%	90%	92%
Hispanic	3%	3%	2%
Other	2%	2%	1%
Age			
<65	76%	71%	73%
≥65	24%	29%	27%
Median (min, max)	56 (27, 75)	58 (29, 75)	58 (24, 76)
Baseline LDL (mg/dL)			
Mean (sd)	184 (35)	190 (51)	189 (40)
Median (min, max)	177 ———	176 ———	181 ———

Table 3 shows completion rates by study Week. Completion rates for the 8-week placebo-controlled portion of the trial were high, at least 94% in each treatment group.

**Table 3. Completion rates<sup>1</sup>**

	Placebo/prava	Cer 400 µg.	Cer 800 µg	Total
Randomized	199 (100%)	195 (100%)	776 (100%)	1170 (100%)
Subjects completing				
Week 2 (V6)	197 (98%)	193 (99%)	768 (99%)	1158 (99%)
Week 4 (V7)	197 (98%)	191 (98%)	760 (98%)	1148 (98%)
Week 6 (V8)	194 (97%)	188 (96%)	741 (95%)	1123 (96%)
Week 8 (V9)	191 (96%)	186 (95%)	731 (94%)	1108 (95%)
Week 24 (V13)	179 (90%)	175 (90%)	686 (88%)	1040 (89%)
Week 52 (V16)	163 (82%)	168 (86%)	647 (83%)	988 (84%)

<sup>1</sup> Completion status for each patient determined by sponsor using information about last day on drug, date of visit, length of time between visits and physician comments.

### Efficacy results

Table 4 shows efficacy results at 8 weeks. With respect to the primary objective of the trial, cerivastatin 800 µg was statistically superior to placebo in the percent change in LDL-C. Not shown in the Table is the Week 24 comparison between cerivastatin 800 µg and cerivastatin 400 µg, a secondary objective of the trial, which was statistically significant in favor of 800 µg at p=.0001.

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**Table 4. Efficacy results at 8 weeks**

	Placebo (n=198)	Cer 400 µg (n=193)	Cer 800 µg (n=770)
<b>LDL-C</b>			
Baseline	185	190	189
% change <sup>1</sup>	-1	-36	-41
p-value <sup>2</sup> vs placebo		.0001	.0001
p-value <sup>2</sup> vs 400 µg			.0001
<b>Total cholesterol</b>			
Baseline	267	276	275
% change	0	-25	-29
p-value vs placebo		.0001	.0001
p-value vs 400 µg			.0001
<b>HDL-C</b>			
Baseline	48	49	49
% change	+3	+7	+9
p-value vs placebo		.0001	.0001
p-value vs 400 µg			.045
<b>TG<sup>3</sup></b>			
Baseline	167	181	187
% change	-2	-14	-22
p-value vs placebo		.0001	.0001
p-value vs 400 µg			.001
<b>Apo B</b>	(n=195)	(n=189)	(n=749)
Baseline	177	186	181
% change	0	-29	-33
p-value vs placebo		.0001	.0001
p-value vs 400 µg			.0001

<sup>1</sup> Percent change based on raw means

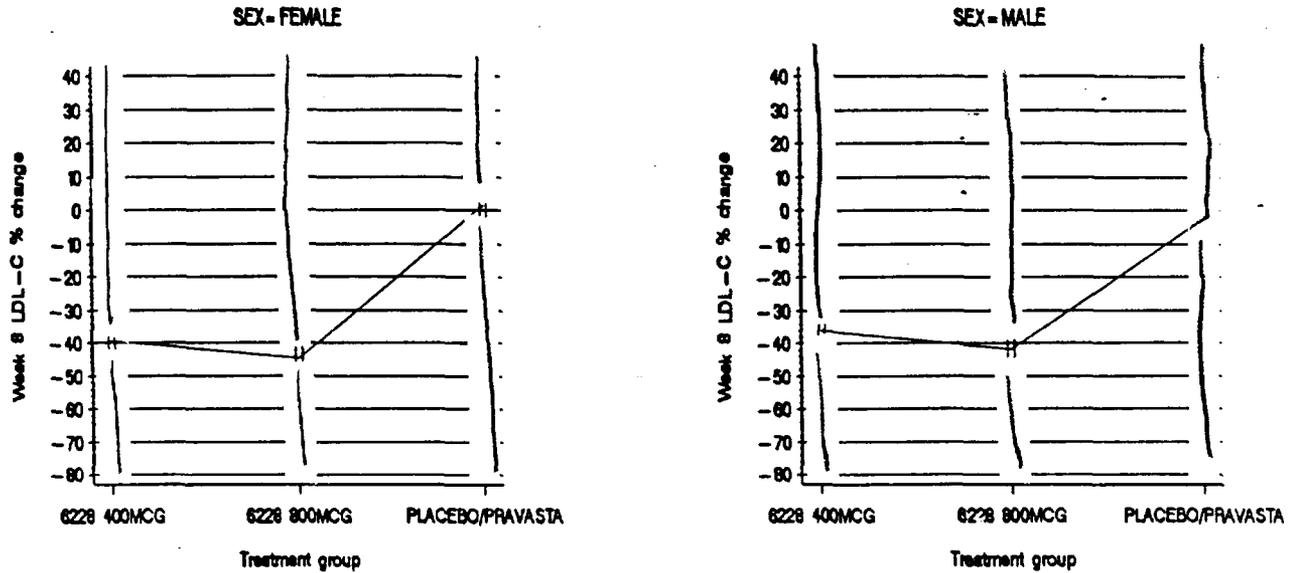
<sup>2</sup> P-values from ANOVA with terms for treatment and study site

<sup>3</sup> Summarized as medians

This reviewer examined response by subgroups for age (<65, ≥65), sex and race (white, black, other) on the primary endpoint, LDL-C at Week 8. There was a nominally significant treatment-by-sex interaction (p=.046). Females had greater treatment differences (larger percent reductions in LDL-C on either dose of cerivastatin compared to placebo) than did male subjects. The interaction, quantitative in nature, is illustrated in the **Figure** below which shows box plots of the distributions by sex and treatment group. Median values for different treatments are connected by a solid line for clarity. The mean treatment difference (800 µg minus placebo) was -39% for males and -44% for females.

Subgroups defined by age and race did not show significant differences between treatments.

**Figure  
LDL-C % change by gender**



**Safety**

Based on discussions with the Medical Officer, this reviewer conducted statistical analyses of three laboratory parameters: ALT, AST and CPK. These parameters were measured at Weeks -10, -4, 0 (randomization), 4, 8, 12, 16, 24, 32, 40, and 52. **Table 5** shows the percent of patients with AST, ALT and CPK values above the Upper Limit of Normal (ULN)<sup>1</sup> at selected timepoints. Due to the design of the trial, the different time periods permit only certain types of comparisons. For example, statistically valid comparisons with placebo can be made at Week 8 which cannot be obtained after this timepoint due to the addition of pravastatin to the placebo group. The values at Week 52 may reflect the influences of unblinding and resin therapy for some patients.

**Table 5. ALT, AST and CPK  
Percent of patients with values above the ULN at randomization and by week on study**

Week	ALT			AST			CPK		
	Plb/pr	400µg	800µg	Plb/pr	400µg	800µg	Plb/pr	400µg	800µg
0	9%	9%	9%	11%	8%	11%	10%	8%	13%
4	6%	8%	11%	7%	11%	17%	9%	11%	19%
8	6%	9%	13%	7%	11%	17%	8%	14%	18%
24	10%	12%	16%	8%	10%	20%	8%	9%	17%
52	7%	13%	13%	8%	11%	13%	11%	11%	17%

<sup>1</sup> ULNs were 22, 25 and 120 mu/ml for AST, ALT and CPK, respectively (sponsor's 6/27/00 submission)

ALT and AST values were similar between the groups at randomization. Throughout the double-blind period (up to Week 24), the percent of patients with AST and ALT values greater than the ULN increased over time in the cerivastatin 800 µg dose group but not at 400 µg. Comparisons of AST and ALT changes from baseline between cerivastatin dose groups showed nominally statistically significant differences at each timepoint after baseline. ANOVAs of the ranks of the change from baseline endpoint were nominally significant at p<.05 except for ALT at 52 weeks. The statistical results reflect a significant shift in the overall distribution of values at the higher dose.

The percentages of patients with CPK values greater than the ULN were statistically greater at 800 µg compared to 400 µg at Weeks 4, 24 and 52. However, CPK values were also higher at 800 µg for 2 of the 3 pre-treatment visits including the randomization visit (Week 0) shown in the Table. There was no time-related change in the percent of patients with values above the ULN in any treatment group. ANOVA (ranks) of the change from baseline did not show any statistically significant differences between cerivastatin dose groups.

Table 6 shows the number and percentage of patients with AST and ALT elevations at least 3 times the ULN. The Table examines three timepoints: 8, 24 and 52 weeks.

**Table 6. ALT and AST**  
Number (%) of patients with elevations > 3 x ULN at anytime on treatment

Week	Placebo (n=198)	400 µg (n=194)	800 µg (n=774)
<u>AST</u>			
8	0 (0%)	2 (1.0%)	10 (1.3%)
24	1 (0.5%)	2 (1.0%)	12 (1.6%)
52	2 (1.0%)	2 (1.0%)	14 (1.8%)
<u>ALT</u>			
8	0 (0%)	1 (0.5%)	8 (1.0%)
24	1 (0.5%)	2 (1.0%)	11 (1.4%)
52	1 (0.5%)	2 (1.0%)	13 (1.7%)

None of the pairwise comparisons involving 800 µg was statistically significant at the .05 level.

Table 7 shows the number and percentage of patients with CPK elevations at least 5 and 10 times the ULN. A patient with a CPK value at least 10 times the ULN is included in the corresponding (5 x ULN) cell as well.

**Table 7. CPK****Number (%) of patients with elevations > 5 x ULN and > 10 x ULN at anytime on treatment**

Week	Placebo/prava (n=198)	Cer 400 µg (n=193)	Cer 800 µg (n=770)
<u>8</u>			
> 5 x ULN	2 (1.0%)	6 (3.1%)	20 (2.6%)
> 10 x ULN	0 (0%)	2 (1.0%)	10 (1.3%)
<u>24</u>			
> 5 x ULN	2 (1.0%)	7 (3.6%)	25 (3.3%)
> 10 x ULN	0 (0%)	3 (1.5%)	13 (1.7%)
<u>52</u>			
> 5 x ULN	5 (2.5%)	8 (4.1%)	35 (4.5%)
> 10 x ULN	1 (0.5%)	3 (1.5%)	15 (1.9%) <sup>1</sup>

<sup>1</sup>Exact chi-square test, p=.051 vs placebo

Only the 800 µg vs placebo comparison of the proportion of patients with CPK values at least 10 x ULN yielded a nominally significant difference (p=.051).

### Comments for labelling

### Summary and conclusion

Baycol 800 µg was statistically superior to Baycol 400 µg in reducing LDL-C at 8 weeks, the primary timepoint (-41% vs -36%). The 800 µg dose also demonstrated superior efficacy at 8 weeks for the secondary endpoints total cholesterol, HDL-C, TG and Apo B. Females receiving 800 µg experienced an average 5% greater LDL-C percent reduction compared to placebo than did male subjects. Treatment differences were -44% and -39%, respectively.

AST and ALT values were nominally statistically higher at 800 µg compared to 400 µg, reflecting a shift in the **distribution** of values at the higher dose. Using a different metric which characterizes the extreme values of the distributions (the percent of patients with values above certain multiples of the ULN), AST, ALT and CPK were not statistically different between cerivastatin dose groups.

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Mathematical Statistician

Concur: Dr. Nevius **/S/** 7-4-00

Cc:  
Orig. NDA 20-740/SE2-008  
HFD-510/division file  
HFD-510/WKoch, SShen  
HFD-715/division file, TSahlroot

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