CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020740

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies

NDA #: 20-740

Applicant: Bayer Corporation Pharmaceutical Division

Name of Drug: Baycol (cerivastatin)

Indication: Hypercholesterolemia

Documents Reviewed: Volumes 1.1-1.2, 1.230-1.570 and 1.675

Medical Input: David Orloff, M.D. (HFD-510)

The sponsor has presented the results of 10 completed controlled clinical trials to establish the efficacy of cerivastatin (an HMG coenzyme A reductase inhibitor) for the treatment of hypercholesterolemia. The proposed dose range for cerivastatin (CER) is 50 μg to 300 μg once daily in tablet strengths of 50, 100, 200 and 300 μg.

A brief description of each of these trials is presented in Table 1 on the following page. Note that the trials are presented in chronological order.

In the first 3 studies listed in Table 1 (Studies 109, 110 and 111), a lactone formulation of cerivastatin was used; for all other studies a mannitol formulation (the marketed formulation) was used.

This review is divided into 3 main sections as follows:

The 2 studies reviewed in Section I are of similar design and defined as pilot studies by the sponsor. The duration of treatment in both these trials is only 4 weeks. The studies reviewed in Section II of this review were defined by the sponsor as pivotal studies. These 3 studies have similar designs and are summarized together. In Section III, the remaining 5 studies are summarized and reviewed separately. For the studies reviewed in Sections I and II, this reviewer requested data from the sponsor and the results presented here are those of the reviewer not the sponsor.

For Section III of this review, this reviewer relied solely on the results presented by the sponsor. By design, none of these 5 studies could provide sufficient evidence of efficacy and therefore, in the opinion of this reviewer, they do not deserve the same attention as the 5 studies reviewed in Sections I and II.

Please note that the US studies were given 2 study numbers; a "D" number and a number compatible with the numbering of the foreign studies.

Table 1. Designs of Double-blind Randomized Controlled Trials
Presented in Chronological Order

Study Number[1] (Dates Conducted)	# of Centers (Locations)	Treatment/Dose[2]	# of Pts. Randomized	Treatment Periods	Page #
109 (D91-012) (8/90-6/91) Pilot Study	11 (US)	CER 25 50 100 200 Lovastatin 40 PLA	35 34 37 33 33 35	4 weeks diet 6 weeks SB placebo + diet **4 weeks DB**	3-4
111 (D91-016) (9/91-2/93) Dose Scheduling Study	13 (US)	CER 100 bid 200 qpm 200 qhs PLA	92 92 89 46	4 weeks diet 6 weeks SB placebo + diet **4 weeks DB**	12-13
110 (11/91-5/92) Pilot Study	22 (Germany, France and UK)	CER 25 50 100 200 Simvastatin 40 PLA	32 35 31 33 31 34	4 weeks diet 6 weeks SB placebo + diet **4 weeks DB**	3-4
123 (D92-010) (3/92-5/92)	1 (US)	CER 300 PLA	24 12	4 weeks DB	14
120 (7/92-6/94)	63 (Europe)	CER 25 50 100 200 Simvastatin 40 PLA	196 194 195 195 186 192	4 weeks diet 6 weeks SB placebo + diet **12 weeks DB** 88 weeks extension	5-11
126 (12/92-8/94) Titration Study	13 (Canada)	CER 50-300 Simvastatin 5-40	259 126	4 weeks diet 6 weeks SB placebo + diet **32 weeks DB**	15-16
124 (D91-031) (2/93-6/94)	38 (US)	CER 50 100 200 300 Lovastatin 40 PLA	158 155 159 155 153 154	4 weeks diet 6 weeks SB placebo + diet **24 weeks DB** 72 weeks extension	5-11
132 (9/93-7/95)	63 (Europe)	CER 100 200 300 Gemfibrozil 1200 PLA	166 171 175 160 79	4 weeks diet 6 weeks SB placebo + diet **16 weeks DB** 88 weeks extension	5-11
139 (8/94-8/95) Familial Hypercholesterolemia	1 (South Africa)	CER 200 300 PLA	18 18 18	4 weeks diet 6 weeks SB placebo + diet **6 weeks DB** 46 weeks extension	17
149 (1/95-11/95)	24 (5 countries in Europe)	CER 300 400 PLA	140 138 71	4 weeks diet 6 weeks SB placebo + diet **8 weeks DB**	18

[1] Study numbers of studies considered pivotal by the sponsor are bolded.

[2] All cerivastatin doses are measured in μg's; all active control doses are measured in mg's.

Section I. Studies 109 (D91-012) and 110

Studies 109 and 110 were dose-response studies conducted by the sponsor early in their Phase III program. Both studies were multicenter trials (11 US centers for 109 and 22 centers in 3 European countries for 110) with 6 parallel treatment arms; placebo, an active control (lovastatin 40 mg for 109 and simvastatin 20 mg for 110), 25 μg, 50μg, 100 μg, and 200 μg cerivastatin (taken with the evening meal). After 4 weeks on the AHA Step I diet, patients were given placebo single-blind for 6 weeks (with diet) followed by randomization and 4 weeks of double-blind treatment.

The objective of both of these studies was to compare each cerivastatin dose to placebo and to the active control. All comparisons to active control favored the active control and henceforth the sponsor is making no claims regarding the efficacy of cerivastatin compared to other marketed statins.

Patient Disposition

In Study 109, 207 patients were randomized to treatment and in Study 110, 196 patients were randomized (Table 2 below).

In each study, there were 6 dropouts during double-blind treatment. In Study 109, 4 of the 6 dropped due to an adverse event; 1 dropped due to myalgia and 1 due to high CPK in the 25 μg group, 1 due to SGPT of 75 and 1 due to SGPT > 3xULN at baseline (after only 4 days of treatment) in the 200 μg group. In Study 110, 3 of the 6 dropped due to an adverse event; 1 due to insomnia and 1 due to abdominal pain (both in the placebo group) and the third patient on 50μg due to a high SGPT at baseline and a doubling of SGPT after 1 week of treatment.

Table 2. Patient Disposition for Studies 109 and 110

	Placebo	25	50	100	200	Active Control
Study 109						
Randomized	35	35	34	37	33	33
Dropouts	1	2	0	0	1	2
ITT	34	35	34	37	33	32
Study 110						
Randomized	34	32	35	31	33	31
Dropouts	3	1	1	1	0	0
ITT	34	32	35	31	33	31

Patient Demographics

The treatment groups within each study were comparable with regard to demographics, medical history and lipoproteins at baseline.

The average age of the patients in each study was about 50 (range of 20 to 66 years); in Study 109, 5% of the patients were 65 years or older and, in Study 110, 2% were 65 years or older. More than 90% of the patients in both studies were Caucasian. About ⅔ of the patients were male.

Efficacy Results

The lipoprotein results for the ITT population are summarized in Table 3 below. Pairwise comparisons (with adjustment for multiple comparisons)[1] of percent change in calculated LDL-C performed by the sponsor and this reviewer comparing placebo to each dose yielded statistically significant differences ($p<.0001$, unadjusted value) for each study at endpoint and at each week on treatment. It is evident from the results shown below that decreases in LDL-C are dose-related; this was confirmed with a trend test.

Secondary analyses of triglycerides (TG), total cholesterol (TC) and HDL-C also revealed statistically significant differences between placebo and each dose of cerivastatin.

Table 3. Studies 109 and 110
Lipoprotein Efficacy Results at Week 4 LOCF (Endpoint)
ITT Population

	Placebo	CER 25	CER 50	CER 100	CER 200	Active Control[2]
LDL-C						
Study 109						
Baseline	201.9	198.4	196.7	198.0	197.5	196.8
% Change	-1.9%	-11.1%	-14.4%	-19.7%	-28.3%	-35.8%
Study 110						
Baseline	243.2	233.3	215.4	246.1	250.4	234.5
% Change	+1.4%	-11.7%	-17.7%	-19.7%	-29.5%	-39.8%
Total Cholesterol						
Study 109						
Baseline	286.9	279.3	279.8	280.6	279.4	278.3
% Change	-0.1%	-7.7%	-10.2%	-13.9%	-20.3%	-26.2%
Study 110						
Baseline	324.6	313.0	298.7	331.4	334.0	321.5
% Change	+1.1%	-8.7%	-12.2%	-15.6%	-21.6%	-29.2%
HDL-C						
Study 109						
Baseline	53.3	48.3	47.4	46.1	48.2	52.0
% Change	0%	-2.0%	+6.7%	+5.2%	+7.9%	+4.4%
Study 110						
Baseline	53.3	57.1	56.8	53.2	56.1	59.8
% Change	-1.4%	-0.5%	+3.6%	-0.5%	+4.5%	+6.2%
TG						
Study 109						
Baseline	157.9	163.1	179.3	182.8	168.4	147.8
% Change	+16.2%	+4.7%	-6.9%	-8.6%	-8.7%	-14.5%
Study 110						
Baseline	140.0	112.9	133.1	158.1	137.6	135.9
% Change	+10.4%	+1.6%	-1.3%	-6.6%	-8.5%	-18.5%

[1] For 109, the sponsor used a sequentially rejective Bonferroni test to adjust for multiple comparisons. For 110, the sponsor used a step-down procedure going from the highest to the lowest dose with no alpha-adjustment. This reviewer used Dunnett's procedure.

[2] Lovastatin 40 mg for 109 and simvastatin 20 mg for 110.

Section II. Studies 120, 124 (D91-031) and 132

Studies 120, 124 and 132 were defined by the sponsor as their Phase 3 pivotal trials. All 3 trials are large multicenter, multiple dose trials (for number of centers in each trial, see Table 1). Studies 120 and 132 were conducted in Europe and Study 124 in the US. Only the results of Study 124 are reported in the sponsor's proposed labeling.

The study designs (Table 4 below) are similar for these 3 studies; all 3 include a short-term double-blind treatment period followed by a long-term extension period. The focus of this review is on the short-term double-blind treatment period.

The primary objective for each trial was to show that each dose of cerivastatin significantly reduces LDL-C compared to placebo. As a secondary objective, cerivastatin was compared to the active control arm. The sponsor is making no claims based on the secondary objective.

All protocols defined a valid case or valid visit analysis as the primary analysis. One criterion for validity was that the patient be on treatment at least 3 weeks. As a secondary analysis, the sponsor performed an ITT analysis which included patients having at least one post-baseline observation. The results for the 2 analyses were consistent and only the ITT results (computed by this reviewer) are presented here. The ITT analyses are generally the preferred analysis since use of the randomized groups validates the statistical tests. One may consider an alternative analysis if, for example, there are considerable dropouts (not the case here) or drug compliance is low (not a problem in these studies since patients were to be dropped if compliance was below 80%). Also, for previously approved statins, only ITT results are presented in the labeling, so to maintain consistency within this drug class, the ITT results should be presented in cerivastatin's labeling, as well.

Table 4. Summary of Designs for Studies 120, 124, and 132

Study	Treatment/Dose	Treatment Periods	Entry Criteria	Primary Endpoint
120	CER 25 50 100 200 Simvastatin 40 PLA	4 wks diet 6 wks SB placebo + diet **12 wks DB** 88 wks extension	LDL-C ≥ 160 OR LDL-C ≥ 130 w/CHD or w/ ≥ 2 risk factors TG ≤ 350 Aged 21-75 years	% reduction in LDL-C at Week 12 (valid case analysis)
124	CER 50 100 200 300 Lovastatin 40 PLA	4 wks diet 6 wks SB placebo + diet **24 wks DB** 72 wks extension	LDL-C ≥ 160 TG ≤ 350 FRR ≤ 15 Aged 18-75 years	% reduction in LDL-C at endpoint (valid visits only)
132	CER 100 200 300 Gemfibrozil 1200 PLA	4 wks diet 6 wks SB placebo + diet **16 wks DB** 88 wks extension	LDL-C ≥ 155 and 190 ≤ TG ≤ 500 Aged 18-80 years	% reduction in LDL-C at endpoint (valid visits only)

Patient Disposition

The number of patients randomized to each treatment group and the number of dropouts during the double-blind treatment period are presented in Table 5 below. The dropout rates were comparable among the treatment groups; in Study 120, about 5-8% of the patients discontinued treatment while in Studies 124 and 132, the rate was slightly higher, 10-15%. The primary reasons for dropout in all groups were patient withdrawal and ADE's. A total of 6 cerivastatin-treated patients in all 3 studies withdrew due to abnormal liver function test results. No relationship between ADE's and dose was evident in these studies.

The number of patients included in this reviewer's ITT analyses are shown in Table 5 below. (These numbers are based on the datasets given to the reviewer by the sponsor.) Note that in Studies 120 and 124, all randomized patients were included in the ITT analyses while in Study 132 about half of the dropouts did not have endpoint data and are therefore not included in the ITT analyses.

Table 5. Patient Disposition for Studies 120, 124, and 132

	Placebo	25	50	100	200	300	Active Control
Study 120							
Randomized	187	193	187	190	191		183
Dropouts	8	18	12	11	13	NA	12
ITT	187	193	187	190	191		183
Study 124							
Randomized	152		158	154	159	154	153
Dropouts	16	NA	18	15	16	20	16
ITT	152		158	154	159	154	153
Study 132							
Randomized	79			166	171	175	160
Dropouts	10	NA	NA	14	11	14	19
ITT	75			160	167	168	154

Patient Demographics

The treatment groups within each study were comparable with regard to demographics, medical history and lipoproteins at baseline.

The 2 European studies (120 and 132) were similar demographically; about 98% of the patients were Caucasian and about 60% were males. The average age at randomization was about 55 years, range of 19-80 with about 18% of the patients 65 or older. In Study 124, the US study, 92% of the patients were Caucasian, 5% Black and 53% of the patients were male. The 124 population was slightly older than the 120 and 132 populations; the average age was 58 years and the range, 24 to 75. About ¼ of the patients in Study 124 were 65 or older.

Efficacy Results

In the tables on this page and the page that follows, the results of this reviewer's ITT analyses are presented. For these analyses, the patient's last lipoprotein value while on double-blind treatment is used. For all treatment groups, the maximum mean response was reached after 4 weeks of therapy and maintained until endpoint; therefore, even though the studies presented here had different completion endpoints, the study results are comparable. These results were found, generally, to be consistent with the sponsor's analysis of valid cases.

Pairwise comparisons of each cerivastatin dose to placebo showed statistically significant treatment differences with adjustments for multiple comparisons (sequentially rejective Bonferroni test) for TC and LDL-C in all 3 studies. Doubling of the dose, on the average, increased the % decrease from baseline by about 4-6%.

Table 6. Total Cholesterol - Mean % Change from Baseline at Endpoint
ITT Results

	Placebo	25	50	100	200	300	Active Control
Study 120							
Baseline	296.9	298.7	293.4	294.3	295.4	NA	296.1
% Change	-0.9%	-9.1%	-12.3%	-18.2%	-22.1%		-28.6%
Study 124							
Baseline	281.4	NA	283.9	279.0	281.7	277.8	285.0
% Change	+1.4%		-9.4%	-12.1%	-16.5%	-18.9%	-22.6%
Study 132							
Baseline	307.6	NA	NA	303.7	296.8	305.0	302.2
% Change	+1.6%			-13.1%	-17.8%	-20.3%	-11.9%

Table 7. LDL-C - Mean % Change from Baseline at Endpoint
ITT Results

	Placebo	25	50	100	200	300	Active Control
Study 120							
Baseline	214.6	217.1	212.5	213.0	214.8	NA	214.3
% Change	-0.6%	-11.9%	-15.9%	-24.0%	-29.5%		-38.6%
Study 124							
Baseline	198.0	NA	199.6	196.7	196.6	193.2	200.1
% Change	+1.2%		-13.3%	-18.0%	-24.0%	-27.5%	-31.7%
Study 132							
Baseline	209.0	NA	NA	206.3	201.4	208.6	206.1
% Change	+1.5%			-18.9%	-25.5%	-27.6%	-9.2%

The results for HDL are less consistent across studies than what was observed for TC and LDL-C. For HDL-C, a dose response relationship is not evident and the lower doses (25 and 50) were not statistically significantly different from placebo. In Study 132, only cerivastatin 300 and the active control significantly increases HDL compared to placebo

Table 8. HDL-C - Mean % Change from Baseline at Endpoint
ITT Results

	Placebo	25	50	100	200	300	Active Control
Study 120							
Baseline	52.6	51.8	52.6	51.1	51.9	NA	53.0
% Change	-1.6%	-0.1%	+0.9%	+3.2%	+2.8%		+4.8%
Study 124							
Baseline	50.1	NA	49.7	49.0	50.1	49.4	50.0
% Change	+3.1%		+5.7%	+7.4%	+9.8%	+9.6%	+10.1%
Study 132							
Baseline	43.9	NA	NA	43.3	43.2	44.2	44.4
% Change	+4.8%			+8.2%	+8.7%	+10.3%	+13.9%

The TG results are inconsistent among the studies and no significant dose response relationship was observed.

Table 9.Triglyceride - Mean % Change from Baseline at Endpoint
ITT Results

	Placebo	25	50	100	200	300	Active Control
Study 120							
Baseline	148.5	148.6	142.5	153.3	144.9	NA	145.7
% Change	+4.0%	-1.8%	-7.2%	-12.0%	-12.6%		-14.2%
Study 124							
Baseline	167.8	NA	173.3	166.5	175.2	176.6	174.8
% Change	+2.0%		-6.1%	-5.3%	-9.7%	-12.0%	-16.4%
Study 132							
Baseline	289.5	NA	NA	284.6	273.1	275.3	272.5
% Change	-0.1%			-11.3%	-12.3%	-19.5%	-45.9%

Subgroup Analyses

Subgroup analyses were performed by this reviewer for all the ITT data combined from Studies 120, 124 and 132 to ascertain consistency of effect across groups defined by gender, age (<65 and ≥65), weight (based on tertiles), LDL-C at baseline (based on tertiles) and lipid class (IIa; TG<200 and IIb; TG≥200) Those results are summarized for LDL-C at endpoint in Tables 10 and 11.

The results suggest a larger response for patients 65 and older compared to patients under 65 (test for interaction p-value=.08). The magnitude of the response difference, however, is small (2-4%). Treatment differences due to weight or gender were not significant.

Table 10. LDL-C - % Change from Baseline at Endpoint by Demographic Subgroups

	Placebo	25	50	100	200	300
AGE						
<65	(n=320)	(n=150)	(n=281)	(n=389)	(n=408)	(n=248)
Baseline	207.3	219.4	208.9	206.9	205.3	201.7
% Change	+0.3%	-10.9%	-14.4%	-19.6%	-26.2%	-26.7%
≥65	(n=89)	(n=43)	(n=64)	(n=107)	(n=103)	(n=68)
Baseline	208.0	209.1	196.7	202.2	203.4	199.0
% Change	+1.0%	-15.5%	-16.2%	-24.4%	-27.8%	-30.8%
GENDER						
Male	(n=209)	(n=107)	(n=191)	(n=299)	(n=297)	(n=194)
Baseline	200.7	215.7	201.3	202.7	202.3	200.1
% Change	+0.9%	-9.9%	-12.8%	-19.7%	-25.1%	-25.7%
Female	(n=200)	(n=86)	(n=154)	(n=197)	(n=214)	(n=122)
Baseline	214.5	218.8	213.2	210.8	208.6	202.7
% Change	-0.1%	-14.4%	-17.1%	-21.9%	-28.4%	-30.4%
BASELINE WEIGHT (kg)						
≤75	(n=144)	(n=118)	(n=104)	(n=175)	(n=170)	(n=55)
Baseline	223.7	220.8	209.9	216.8	213.6	210.0
% Change	-0.5%	-14.1%	-16.0%	-23.2%	-28.8%	-29.8%
76-118	(n=117)	(n=75)	(n=87)	(n=162)	(n=180)	(n=106)
Baseline	200.6	211.2	215.3	203.8	204.4	207.1
% Change	+0.4%	-8.3%	-15.4%	-20.5%	-26.9%	-26.7%
>118	(n=146)	(n=0)	(n=153)	(n=156)	(n=160)	(n=153)
Baseline	196.5		199.5	196.3	196.4	193.1
% Change	+1.3%		-13.4%	-17.8%	-23.7%	-27.3%

The LDL-C results by lipid class and LDL-C at baseline (Table 11) show consistent results across subgroups within treatment groups. There is no relationship between magnitude of response and baseline LDL-C.

Table 11. LDL-C - % Change from Baseline at Endpoint by Lipid-defined Subgroups

	Placebo	25	50	100	200	300
LIPID CLASS[1]						
IIa	(n = 261)	(n = 163)	(n = 260)	(n = 271)	(n = 280)	(n = 127)
Baseline	205.8	218.0	207.6	207.3	206.9	194.4
% Change	+0.3%	-12.2%	-15.2%	-21.5%	-26.8%	-27.9%
IIb	(n = 148)	(n = 30)	(n = 85)	(n = 225)	(n = 231)	(n = 189)
Baseline	210.4	212.4	203.7	204.2	202.4	205.6
% Change	+0.6%	-10.1%	-13.3%	-19.6%	-26.1%	-27.3%
LDL BASELINE						
< 182	(n = 134)	(n = 51)	(n = 123)	(n = 170)	(n = 168)	(n = 104)
Baseline	167.2	165.4	167.8	167.3	166.5	170.2
% Change	+2.1%	-9.6%	-12.4%	-19.6%	-25.4%	-26.2%
182 - < 209.9	(n = 138)	(n = 66)	(n = 108)	(n = 157)	(n = 180)	(n = 121)
Baseline	194.2	194.6	194.8	195.0	194.3	194.2
% Change	+0.2%	-12.4%	-15.6%	-20.0%	-26.5%	-27.3%
≥ 210	(n = 137)	(n = 76)	(n = 114)	(n = 169)	(n = 163)	(n = 91)
Baseline	260.2	271.4	259.6	254.9	256.2	245.6
% Change	-1.1%	-12.9%	-16.3%	-22.2%	-27.7%	-29.5%

[1] IIa is defined as baseline TG < 200 and IIb as baseline TG ≥ 200.

Dose Response

Inspection of the means in Table 7 of this review suggest a relationship between dose and response. The graph below illustrates this relationship further; each box represents the interquartile range of the responses with the median represented by a circle and the shaded area represents the 95% CI about the median. A linear relationship between dose and response is evident, particularly for doses 50, 100 and 200 (statistical tests for linearity confirmed this relationship). Pairwise comparisons of the dose groups revealed that the 300 dose is not a significant improvement over the 200 dose.

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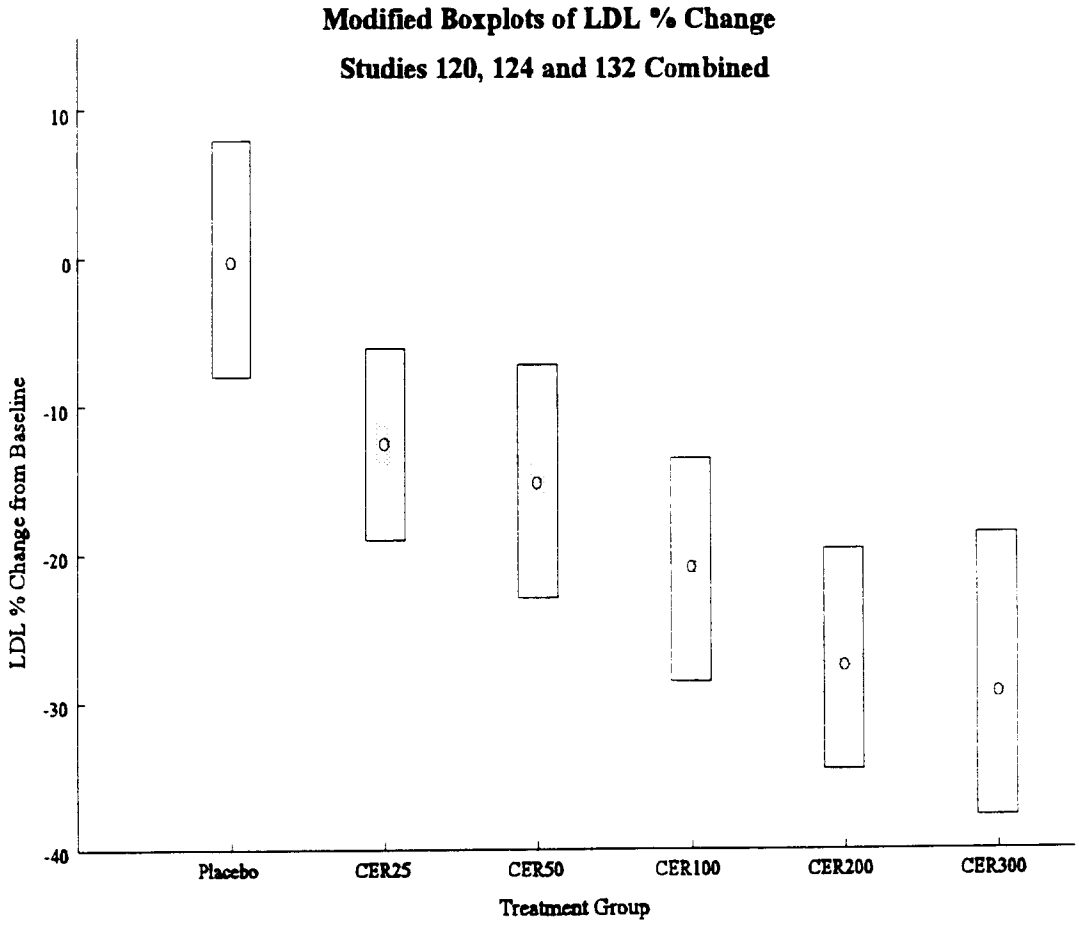

Section III.

Study 111 (D91-016)

The primary objective of Study 111 was to compare once daily evening (with dinner or at bedtime) dosing of 200μg of cerivastatin to twice daily dosing of 100μg of cerivastatin. Patients with primary hypercholesterolemia followed the AHA Step I diet for 4 weeks unblinded and then for an additional 6 weeks were given placebo single-blinded plus diet. After the 10-week lead-in, patients fulfilling the entry criteria[1] were randomized into 4 treatment groups (100μg of cerivastatin twice daily (bid), 200μg of cerivastatin once daily with dinner (qpm), 200μg of cerivastatin once daily at bedtime(qhs) or placebo) in a 2:2:2:1 ratio at 13 centers and treated for a total of 4 weeks.

A total of 848 patients were screened; 319 of these patients qualified for randomization. Table 11 below summarizes patient disposition for this trial. Only 7 patients discontinued treatment; 2 due to adverse events (arm pain (CER 100 bid) and skin rash (CER 200 qpm)). Of these 7 patients, 2 are not included in the efficacy analysis because they did not have a valid LDL value after 1 week on treatment. An additional 9 were not considered evaluable for efficacy; 6 were noncompliant (taking $<70\%$ of drug), 3 did not satisfy entry criteria for LDL . According to the protocol, the primary analysis was to be of the evaluable population with an ITT analysis designated as secondary.

Table 11. Patient Disposition in Study 111

	Placebo	CER 100 bid	CER 200 qpm	CER 200 qhs
Randomized	46	92	92	89
Discontinued	2	2	1	2
Completed	44 (96%)	90 (98%)	91 (99%)	87 (98%)
Efficacy Evaluable	45 (98%)	89 (96%)	88 (96%)	86 (97%)

The treatment groups were balanced with regard to baseline characteristics. About 60% of the patients were male and 93% were Caucasian. Patients ranged in age from 28 to 71 years; mean of about 53 years. About ¼ of the patients were over 60 years old. Compliance, measured by pill counts, was high (mean $>93\%$) in each treatment group.

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[1]Entry criteria included a Food Rating score <15, $160\ mg/dl \leq LDL\text{-}C \leq 250\ mg/dl$ and triglycerides (TG) ≤ 350 mg/dl.

Each of the 2 treatment groups with once-a-day evening dosing (at bedtime or with dinner) showed a statistically significantly larger mean decrease in LDL-C (about 4%) and TC (about 3%) than the 100 bid group (Table 12). These differences were evident at Weeks 2, 3 and 4. The groups were not different with regard to TG; in addition, none of the 3 cerivastatin groups were different from placebo. For HDL, only the 200 qpm group was statistically significantly different from the 100 bid group.

Subgroup analyses based on age, gender, LDL baseline and several other demographic variables produced LDL results consistent with the results shown in Table 12 below.

Table 12. Lipoprotein Results at Endpoint
Study 111 - ITT Population

	Placebo	CER 100 bid	CER 200 qpm	CER 200 qhs
LDL				
Baseline	197	197	197	197
% Change	+1%	-26%	-29%*	-30%*
HDL				
Baseline	45	49	49	52
% Change	-1%	+5%	+2%*	+3%
TC				
Baseline	279	279	281	280
% Change	0%	-19%	-22%*	-22%*
TG				
Baseline	170	164	178	158
%Change	-3%	-12%	-12%	-11%

* = $p < .03$ compared to the 100 BID dose

The sponsor computed 95% confidence intervals for the 3 primary comparisons. A difference of 7% for LDL was considered clinically meaningful according to the protocol. The upper limits for the 95% confidence intervals shown in the first 2 rows of Table 13 below suggest that differences in favor of the evening doses as large as 7 or 8% are consistent with the data further suggesting that the statistically significant results observed in this study, also, may be considered clinically important (according to the sponsor's criterion). The confidence interval on the difference between the 2 once-a-day dosing groups suggests no clinically important difference between the groups.

Table 13. LDL-C Treatment Differences and Confidence Intervals
Endpoint Results - Study 111

Comparison	Difference	95% Confidence Interval
100 bid - 200 qpm	3.7%	0.5%, 7.0%
100 bid - 200 qhs	4.7%	1.5%, 8.0%
200 qpm - 200 qhs	1.0%	-2.3%, 4.3%

Study 123 (D92-010)

Study 123 was a very small study of 36 patients. This study was an early pilot study of the 300 μg dose; subsequent to this study, several fixed dose studies were designed to examine this dose further (Studies 124, 132, 139 and 149). Patients were randomized to placebo or cerivastatin (300 μg given in the evening) and treated for a total of 4 weeks. There was no dietary run-in phase and patients were given no guidelines with regard to diet or exercise. The results are summarized in Table 14 below (no statistical tests were performed by the sponsor or this reviewer). One patient provided no data and so the results are for a total of 35 patients (23 cerivastatin and 12 placebo).

Table 14. Endpoint Results
Study 123

	Placebo (n = 12)	CER 300 (n = 23)
LDL-C		
Baseline	187	181
% Change	-10%	-37%
TC		
Baseline	267	267
% Change	-5%	-25%
HDL-C		
Baseline	47	50
% Change	+5%	+11%
TG		
Baseline	167	176
% Change	+4%	-8%

The effect of the lack of a run-in period is evident in the results shown above. The placebo effects seen here are appreciably larger than the placebo effects observed for the other studies in this NDA. For LDL-C, the usual endpoint placebo effect after a dietary/placebo run-in phase and double-blind treatment is a decrease of less than 1%; in this study, a mean drop of 10% was seen for the placebo group. Likewise the LDL-C effect in the treatment group is about 10% higher than what was generally observed in Studies 124 and 132.

Study 126

Study 126 is a multi-center titration study designed to compare cerivastatin to simvastatin for safety and efficacy. After a 10-week lead-in (4 weeks diet and 6 weeks of diet plus placebo), patients were randomized in a 2:1 ratio to cerivastatin or simvastatin and treated for 32 weeks.

To be eligible for this study, patients were required to have an LDL-C $\geq$ 160 mg/dl, TG $\leq$ 350 mg/dl and an FR score $\leq$ 15. Visits were scheduled every 2 weeks for the first 8 weeks of double-blind treatment and every 4 weeks for the remaining 24 weeks.

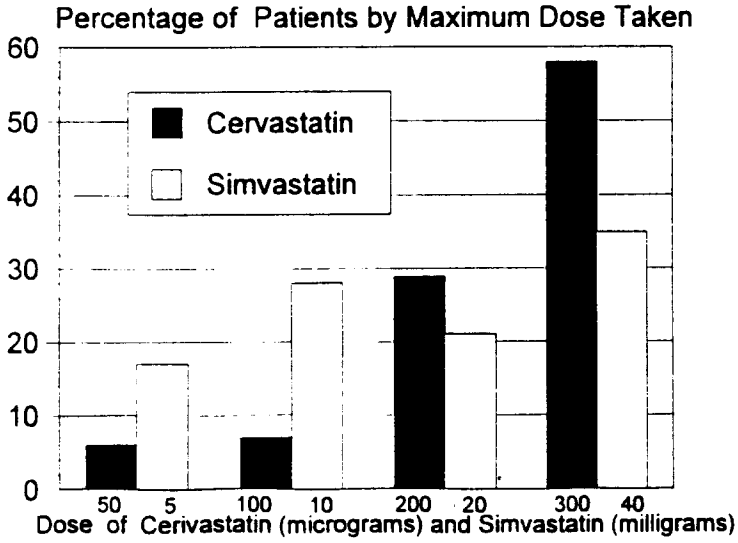
The dose for both groups could be titrated in a stepwise manner at the completion of Weeks 8, 16 and 24 if the LDL-C $\geq$ 130 mg/dl at the previous visit. The maximum dose allowed by week on study is outlined in the Table 15 below.

Table 15. Maximum Dose Allowed by Week on Study

Week on Study	Cerivastatin Maximum Dose (μg)	Simvastatin Maximum Dose (mg)
1-8	50	5
9-16	100	10
17-24	200	20
25-32	300	40

At 13 centers in Canada, 127 patients were randomized to simvastatin and 260 to cerivastatin. (The trial was powered to detect a LDL-C treatment difference of 5%.) A total of 4 patients (1 simvastatin and 3 cerivastatin) dropped out of the study with no on-treatment data and therefore these patients are not included in the ITT population. Fifteen simvastatin and 39 cerivastatin patients did not complete the study. The primary reason for discontinuation in both groups was adverse event (10 SIM and 14 CER). Incidence of ADE's did not appear to be dose-related.

The treatment groups were comparable at baseline with regard to baseline lipoproteins, demographics (with the exception of gender), medical history and dietary intake. The mean age of the patients was 52 years with a range of 25 to 73 years. About 94% of the patients were Caucasian. The treatment groups were imbalanced for gender; 68% of the cerivastatin patients and 46% of the simvastatin patients were male.



The graph to the left shows that a higher percentage of patients in the cerivastatin group (58%) were titrated to the maximum dose allowed compared to the simvastatin group (35%).

Duration of drug exposure was comparable for the 2 groups.

Significantly larger decreases in LDL-C were observed in the simvastatin group compared to the cerivastatin group at each measurement week for the duration of the trial. These differences were evident comparing the treatment group empirical means and means adjusted for center, gender and dose ($p<.0001$). The differences, also, were evident by maximum titrated dose (Table 16 below) and by subgroups defined by gender, race and lipid class. The treatment effects for the 2 groups appeared to be comparable for patients over 65 years but the sample size was small (18 simvastatin and 24 cerivastatin).

Table 16. LDL-C Endpoint Results at Maximum Dose Taken
Study 126

Cerivastatin			**Simvastatin**		
Dose	N	% Change	Dose	N	% Change
50	15	-11%	5	21	-27%
100	20	-24%	10	35	-30%
200	73	-27%	20	26	-35%
300	149	-29%	40	44	-40%

For TC, significantly larger decreases of about 6% were observed for simvastatin compared to cerivastatin.

The treatment groups were comparable with regard to changes in HDL and TG at endpoint.

The safety profiles for both groups were similar. Only one patient in each group had a SGPT or SGOT > 3xULN at more than 1 visit.

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Study 139

Study 139 is a single-center trial in South Africa designed to study the lipid lowering effects of cerivastatin (200 μg and 300 μg) compared to placebo in patients with heterozygous familial hypercholesterolemia. To be eligible for this study, patients needed to be diagnosed with genotyped-heterozygous familial hypercholesterolemia, have an LDL-C ≥ 194 mg/dl, TC ≥ 292 mg/dl, and TG ≤ 350 mg/dl. In addition, the patient or a close relative needed to be diagnosed with xanthomatosis. After a 10-week lead-in (4 weeks of diet and 6 weeks of placebo plus diet), patients were randomized and treated for 6 weeks. Following this double-blind period, patients could continue on study[1] for an additional 46 weeks. Only the data from the double-blind period is presented here.

A total of 55 patients were randomized to treatment. One patient was lost to follow-up and provided no efficacy data. The intent-to-treat population consisted of 18 patients in each treatment group. The treatment groups were balanced with regard to demographics, medical history and baseline lipid parameters. The mean age of the patients was 43 years ; 44% of the patients were male; and 74% were Caucasian.

The endpoint results for the lipid parameters are summarized in Table 17 below. Pairwise comparisons of the cerivastatin groups to placebo yielded statistically significant p-values (using Holm's sequentially rejective Bonferroni test) for those changes starred in the table below. The changes in LDL-C and TC appear to be dose-related.

Table 17. Endpoint Mean Results
6 weeks Double-Blind Treatment Period
Study 139 - Intent-to-Treat

	Placebo (n = 18)	CER 200 (n = 18)	CER 300 (n = 18)
LDL-C			
Baseline	280	281	295
% Change	+11%	-17%*	-23%*
TC			
Baseline	348	351	371
% Change	+9%	-14%*	-19%*
HDL-C			
Baseline	46	45	46
% Change	+10%	+6%	+9%
TG			
Baseline	110	123	149
% Change	+3%	-1%	-20%*

About ¼ of the placebo patients were responders (patients with a ≥ 15% change in LDL-C), while about 70% of the CER 200 and 85% of the CER 300 patients were responders.

In this patient population with heterozygous familial hypercholesterolemia, the lipoprotein responses are less than those observed in patients with homozygous hypercholesterolemia; nevertheless, comparisons to placebo showed statistically significant treatment differences for both doses for LDL-C and TC.

[1] The extension periods consisted of 6 weeks where patients randomized to placebo were switched to CER 200, patients on CER 200 were switched to CER 300 and patients on CER 300 remained on CER 300 and an additional 40 weeks with all patients on CER 300.

Study 149

Study 149 was specifically designed to study the efficacy and safety of cerivastatin 400 μg compared to placebo and cerivastatin 300 μg in patients with hypercholesterolemia. At the time of this study, the 300 μg dose had been studied in several clinical trials and so this study was not designed to compare that dose to placebo.

Patients with baseline LDL-C ≥ 190 mg/dl or LDL-C ≥ 160 mg/dl plus 1 or more risk factors (such as, family history or patient history of CHD, obese, smoker) and TG ≤ 350 mg/dl were eligible for this study. After a 10 week lead-in period (4 weeks of diet alone and 6 weeks of placebo and diet), patients were randomized to one of the 3 treatment arms (placebo, cerivastatin 300 μg, or cerivastatin 400 μg) and treated for 8 weeks. Patients were withdrawn from the study before treatment if they had a single AST or ALT measurement > 1.5 ULN during the placebo lead-in period or at baseline. On treatment, patients were withdrawn if repeat measurements of ALT or AST showed values > 3ULN.

In addition to be being powered for efficacy, this trial, also, was powered to confirm the safety of cerivastatin 400 μg compared to placebo with regard to drug-induced myopathy (CPK > 10*ULN associated with muscular pain at 2 successive visits). A difference of 5% or greater was considered clinically important.

A total of 351 patients were randomized to treatment (71 placebo, 140 cerivastatin 300 μg and 138 cerivastatin 400 μg. Two patients dropped out at baseline and 8 while on treatment (1 placebo, 3 cerivastatin 300 μg and 4 cerivastatin 400 μg). Only 2 patients withdrew due to ADE's; one in each cerivastatin group.

Treatment groups were comparable at baseline regarding demographics and medical history. The mean age of the patients was about 55 years. Sixty percent of the patients were male, 98% were Caucasian.

The sponsor performed analyses of data from an evaluable population (primarily defined as protocol compliers), from completers and from the intent-to-treat population (patients with at least one response on treatment). Only the ITT results are presented here (Table 18). The cerivastatin 400 μg group was statistically significantly different from placebo and the 300 μg group for LDL-C and TC. For TG and HDL-C, the cerivastatin groups were statistically different from placebo but they were not significantly different from each other. The sponsor's safety analysis revealed no significant differences among the treatment groups.

Table 18. Endpoint Results
Study 149 - Intent-to-Treat

	Placebo (n = 71)	CER 300 (n = 140)	CER 400 (n = 138)
LDL-C			
Baseline	232	223	218
% Change	+0.2%	-33%	-36%
TC			
Baseline	314	306	300
% Change	+1%	-24%	-26%
HDL-C			
Baseline	55	55	54
% Change	-0.1%	+6%	+4%
TG			
Baseline	138	142	145
% Change	+9%	-17%	-14%

Section IV. Summary and Labeling Comments

Summary

Cerivastatin significantly reduced LDL-C at each of the proposed dose levels (50 μg to 300 μg) compared to placebo in all the studies presented by the sponsor (see Table 1 for a brief description of each study and Table 19 below for a summary of the results). The magnitude of the response was consistent across studies and across subgroups based on age, gender, weight, lipid class and baseline LDL-C (see Tables 10 and 11).

Pairwise comparisons of cerivastatin to active control favored the active control (see Tables 3, 6, 7, and 16) and henceforth the sponsor is making no claims regarding the efficacy of cerivastatin compared to other marketed statins.

Table 19. LDL-C % Change from Baseline at Endpoint
ITT Results for All Completed Studies

Study	Placebo	25	50	100	200	300
109	-2%	-11%	-14%	-20%	-28%	NA
110	+1%	-12%	-18%	-20%	-30%	NA
120	-1%	-12%	-16%	-24%	-30%	NA
124	+1%	NA	-13%	-18%	-24%	-28%
132	+2%	NA	NA	-19%	-26%	-28%
111	+1%	NA	NA	NA	-30%	NA
123	-10%	NA	NA	NA	NA	-37%
126	NA	NA	-11%	-24%	-27%	-29%
139	+11%	NA	NA	NA	-17%	-23%
149	0%	NA	NA	NA	NA	-33%

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Reviewer's Comments on Labeling (Clinical Studies section)

The Clinical Studies section of the sponsor's proposed labeling presents the results for Studies 124 and 111. The results of Study 124 (as presented in Table 1 of the proposed labeling) are consistent with the results observed in other studies in this NDA and give a fair representation of the efficacy of cerivastatin, however, the sponsor has presented the results for the evaluable population. This reviewer recommends that Table 1 of the proposed labeling be modified and that the ITT results, as shown below, be presented to be consistent with labeling in this drug class.

Dosage	n	Total-C	LDL-C	HDL-C	TG
Placebo	152	+1.4%	+1.2%	+3.1%	+2.0%
Baycol					
0.05 mg qd	158	-9.4%	-13.3%	+5.7%	-6.1%
0.1 mg qd	154	-12.1%	-18.0%	+7.4%	-5.3%
0.2 mg qd	159	-16.5%	-24.0%	+9.8%	-9.7%
0.3 mg qd	154	-18.9%	-27.5%	+9.6%	-12.0%

Following the results of Study 124, the sponsor presents and briefly discusses the results of Study 111. It should be sufficient to state the results for Study 111 and not include the sponsor's Table 2, particularly since the results in Table 2 are not consistent in magnitude with the results in Table 1. Also, wording such as "equally efficacious" and "superior" should be excluded since both would require further elaboration to be interpreted appropriately. Instead, the results could be stated as follows;

> *In a dose-scheduling study, Baycol (cerivastatin sodium tablets) given as a 0.2 mg dose once daily with dinner or at bedtime was compared to 0.1 mg given twice daily (morning and evening). The treatment groups on once daily dosing in the evening showed a statistically significantly larger mean decrease of about 4% of LDL-C than the treatment group on twice daily dosing.*

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In the first paragraph of the Clinical Studies section, the sponsor's proposed labeling states the following;

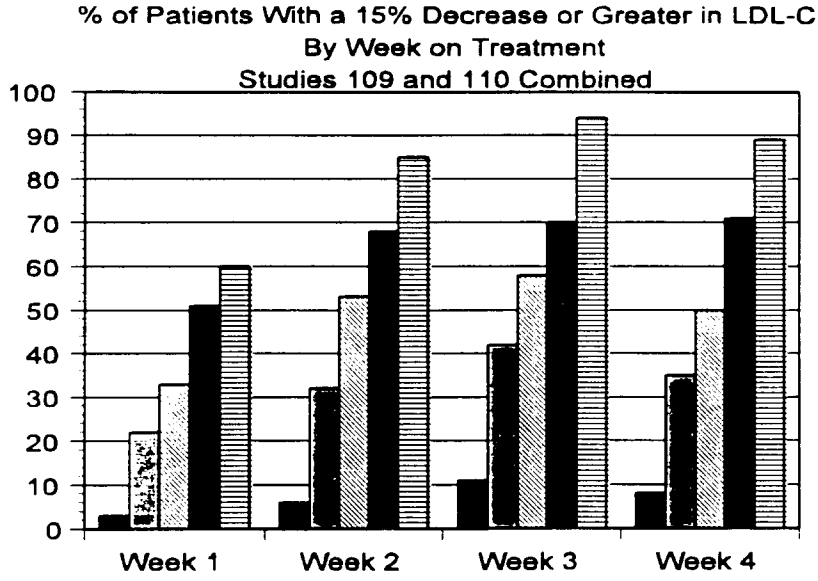
> *"A response in Total-C and LDL-C was evident by one week and the maximum therapeutic response occurred within four weeks."*

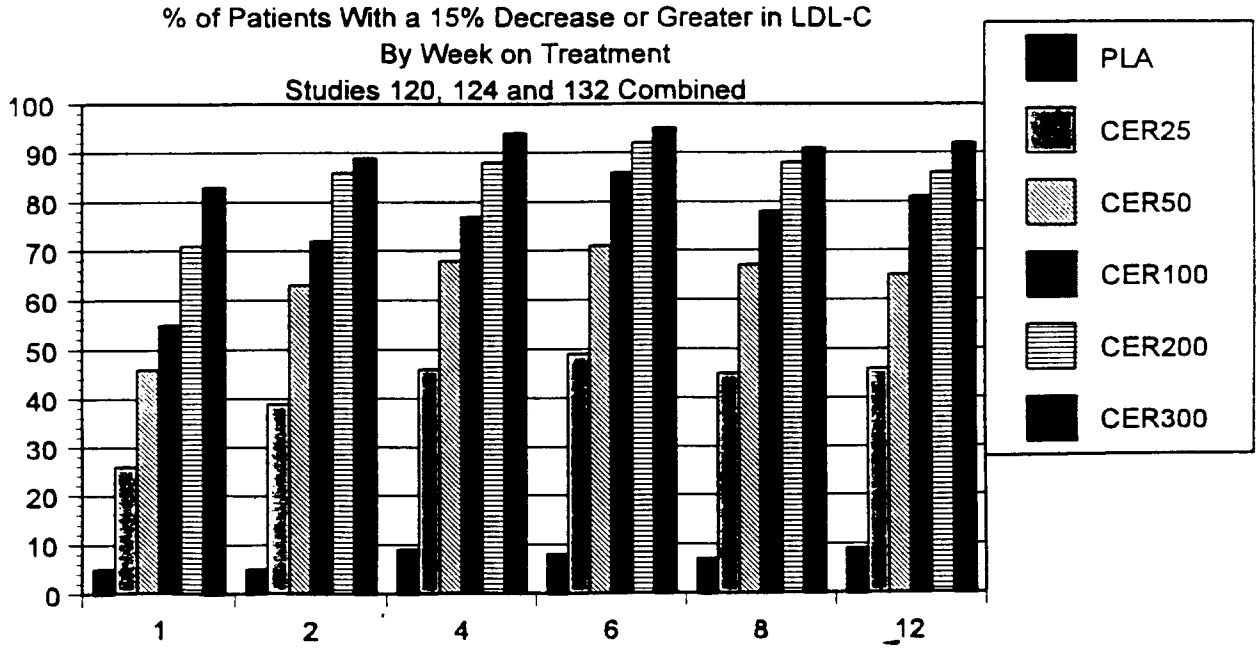
The sponsor supports this statement with plots of mean changes over time. As worded this statement may be misleading since it implies individual patient effects whereas it is supported by mean treatment effects.

This reviewer examined individual patient responses to determine if the majority of patients exhibited a "response" by week 1 and whether their maximum response was observed by Week 4.

To examine the onset of response, a definition of response is needed. The sponsor and

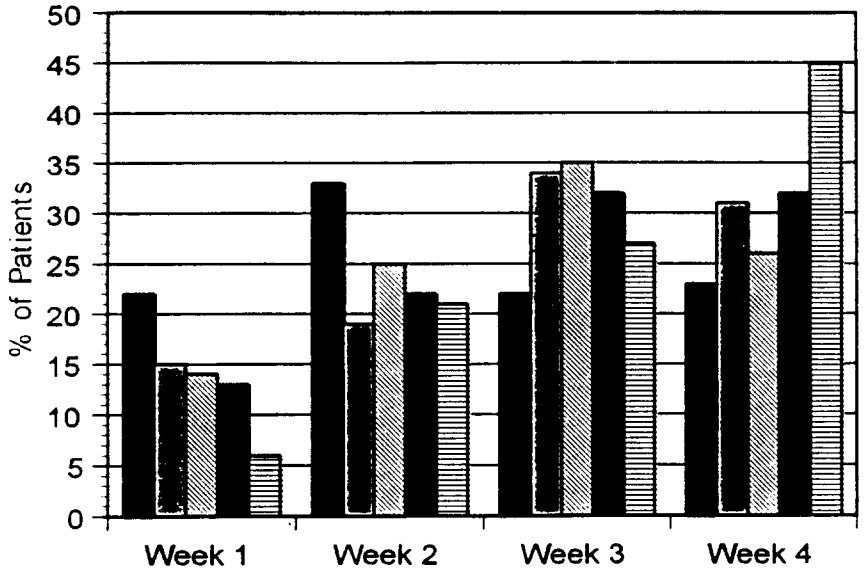
FDA have agreed that a decrease of 15% in LDL-C was indicative of a response so for the analysis which follows, a responder is defined as a patient with a 15% change from baseline or greater in LDL-C. (This definition of a responder was stated also in the protocols of the three main studies.) The figures below illustrate the percentage of responders in the placebo group and each cerivastatin dose group by week on study. In the high dose groups (100, 200 and 300 μg), more than 50% of the patients show a response after one week of therapy in all 5 studies. From Studies 120, 124 and 132, it can be seen that the percentage of responders does not change appreciably after Week 4.



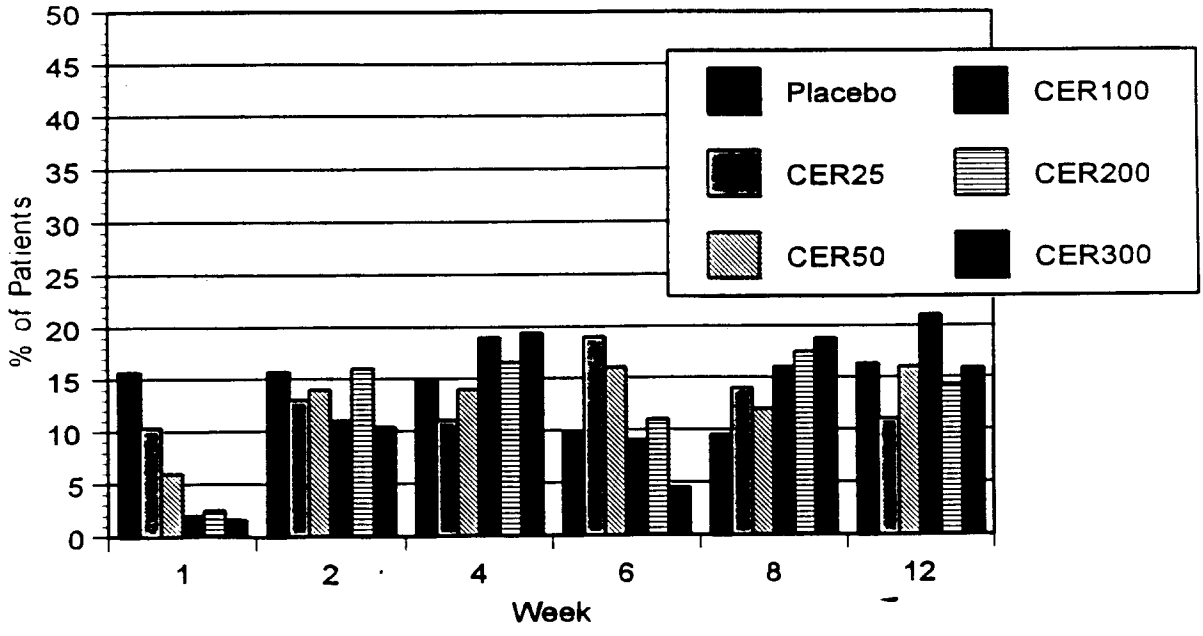


The time of maximum response by dose is summarized below. For Studies 109 and 110, of the patients who reached their maximum response before Week 4, more than 70% of the patients in each cerivastatin dose group sustained a response within 10% of their maximum response at endpoint. These 2 studies cannot support the sponsor's statement that the maximum response occurred within 4 weeks since these studies were only 4 week studies. The results from Studies 120, 124 and 132 do not suggest that a large percentage of patients in each treatment group reach their maximum response by Week 4.

Week of Maximum Response
Studies 109 and 110 Combined



Week of Maximum Response
Studies 120, 124 and 132 Combined



Overall, this reviewer concludes that there is sufficient statistical evidence to support the indication proposed by the sponsor. This reviewer's recommended changes to the Clinical Studies section of the label need to be discussed with the review team.

Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius 5-19-97

Mr. Marticello

cc:
Archival NDA 20-740
HFD-510
HFD-510/DOrloff, GTroendle, SSobel
HFD-510/MSimoneau
HFD-715/Biometrics Division 2 File, DMarticello, JMele, Chron

Mele/x3-3520/WordPerfect Windows-baycol.rev/May 9, 1997

This review consists of 23 pages.

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Clinical Pharmacology and Biopharmaceutics Review

NDA:	**20-740**
SUBMISSION DATE:	**September 20, 1996**
BRAND NAME:	**BAYCOL®**
GENERIC NAME:	**Cerivastatin Sodium (Bay w 6228) Tablets 50µg, 100µg, 200µg and 300µg**
REVIEWER:	**Carolyn D. Jones, Ph.D.**
SPONSOR:	**Bayer Corporation West Haven, CT 06516**
Type of Submission:	**Dissolution Data Review Report**

SYNOPSIS:

BAYCOL® (cerivastatin sodium), a synthetic and pure enantiomer, is a new HMG-CoA reductase inhibitor that competitively inhibits the rate-limiting step of cholesterol synthesis, i.e., the conversion of hydroxymethylglutaryl-CoA to mevalonate. The drug is recommended for use in patients with hypercholesterolemia. The proposed dose range of cerivastatin is 200 µg to 300 µg given once daily in the evening, either with the evening meal or at bedtime. Bayer is proposing to market tablet strengths of 200 and 300 µg.

The sponsor is proposing the following dissolution specification which the Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPEII) agreed to on an interim basis:

pH
Q=

However, it was recommended as part of the review of the original NDA, that as a Phase IV commitment, the sponsor conduct additional studies and submit dissolution profiles at

However, it was understood that although on September 20, 1996 the sponsor had submitted to the agency cerivastatin dissolution data at

STUDY REPORT:

Initially, dissolution tests were conducted using
However, upon development of an the dissolution method was switched to the

Production scale 0.05, 0.1 and 0.3 mg tablets and pilot scale 0.1 mg tablets were evaluated at
The tests were performed using Cerivastatin
was Furthermore,
All profiles showed

Using the same apparatus, the sponsor also investigated the effect of rotation speed using the 0.05 mg and 0.10 mg tablets at
Rotation speed had

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPEII) has reviewed the submission dated September 20, 1996 to NDA 20-740 and deems it acceptable. No further development of a dissolution method is required. The proposed specification

which was originally accepted on an interim basis will be accepted as a final dissolution specification. Please convey this recommendation to the sponsor as appropriate.

COMMENTS NOT TO BE SENT TO THE SPONSOR:

1. The sponsor has not provided dissolution profiles for the 0.20 mg tablets in the three different media nor at the different agitation rates. However, since data was submitted that bracketed this tablet strength (0.10 and 0.30 mg tablets), and no differences were observed, there is no reason to believe that the 0.20 mg tablet will behave differently.

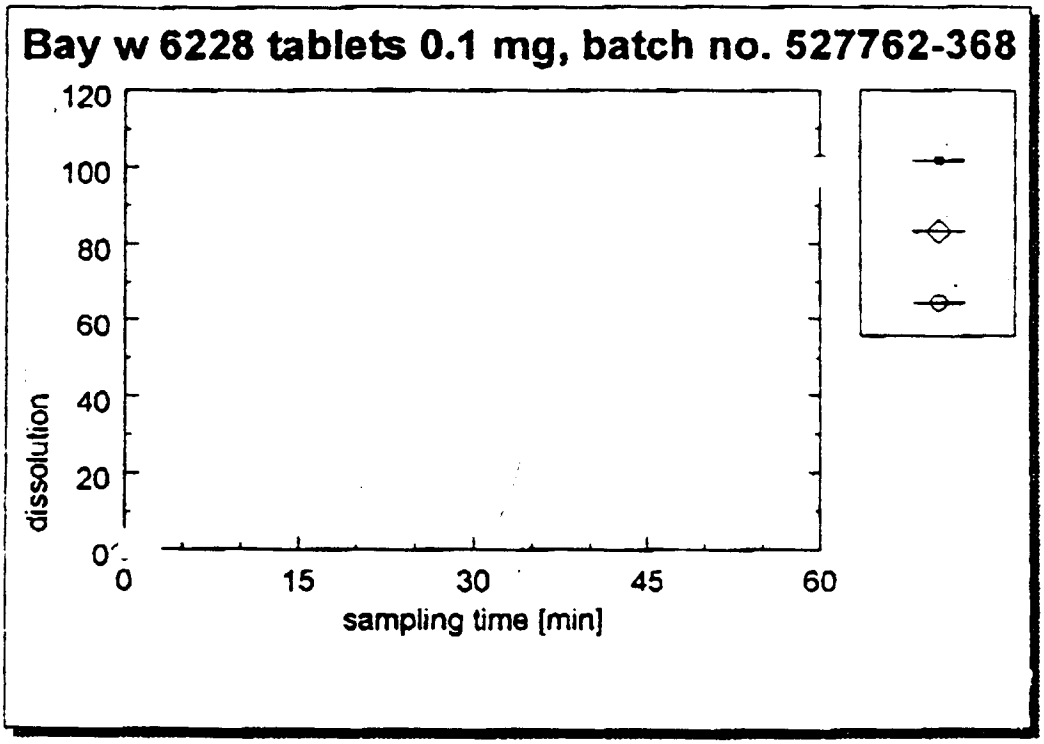
6/3/97
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialed by Hae-Young Ahn, Ph.D., Team Leader_____ 6/4/97

cc: NDA 20-740 (1 copy), HFD-510(Orloff, Simoneau, Barbehenn), HFD-340 (Vishwanathan), HFD-870(Ahn, Jones, M. Chen), CDR(Murphy).

"C M"

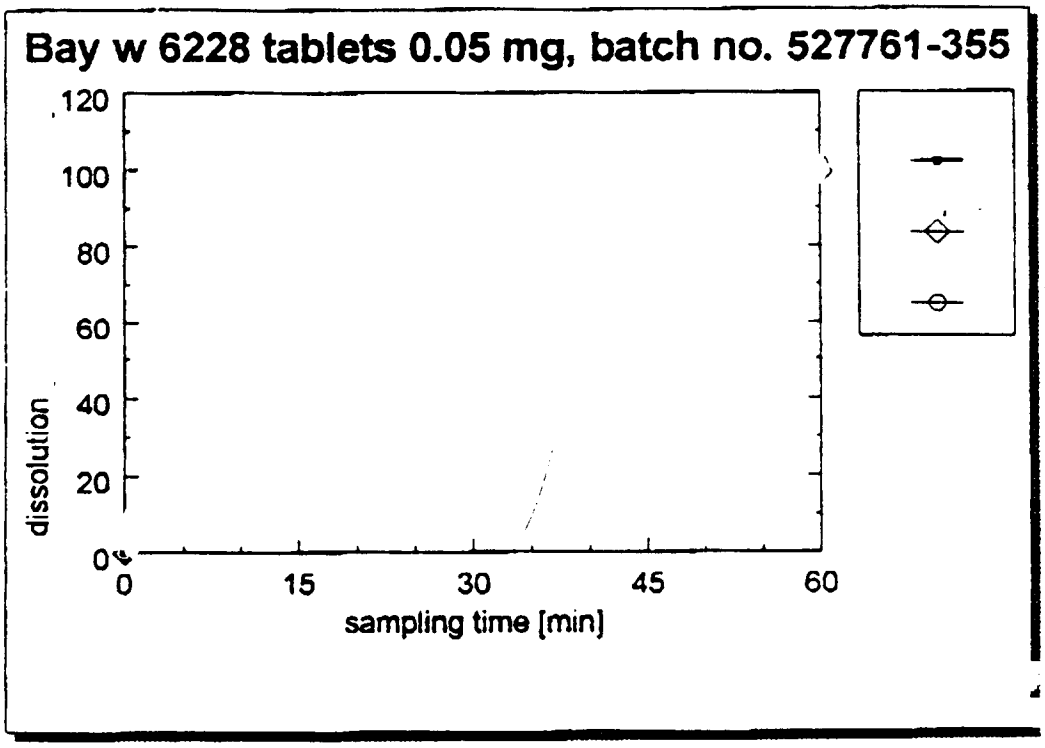
figure 2b: **Influence of the Rotation Speed of the Paddle**



Bay w 6228 tablets 0.1 mg, batch no. 527762-368								
time [min]	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	mean	cv [%]

all results listed in % of labeled content

figure 2a: **Influence of the Rotation Speed of the Paddle**



Bay w 6228 tablets 0.05 mg, batch no. 527761-355								
time [min]	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	mean	cv [%]

figure 1: **Comparison of Different Dissolution Media**

medium	15 min	30 min	45 min	60 min
Bay w 6228 Tabl coated 0.05 mg, batch no.437184D (production scale)				
Bay w 6228 Tabl coated 0.1 mg, batch no.437186A (production scale)				
Bay w 6228 Tabl coated 0.1 mg, batch no.531234E (pilot scale)				
Bay w 6228 Tabl coated 0.3 mg, batch no. 437188K (production scale)				

All tests were performed in

*) the results are decreasing because of the chemical instability of Bay w 6228

STATISTICAL REVIEW AND EVALUATION
(Carcinogenicity Review)

NDA #: 20-740

APPLICANT: Bayer Corporation

MAY 29 1997

NAME OF DRUG: Baycol (cerivastatin tablets)

DOCUMENTS REVIEWED: Volumes 1.25-1.28 (Mouse Study) and 1.38-1.43 (Rat Study) of NDA 20-740. Data on floppy diskettes supplied by the sponsor.

REVIEWING PHARMACOLOGIST: Elizabeth Barbehenn, Ph.D. (HFD-510).

I. BACKGROUND

In this NDA submission, two animal carcinogenicity studies (STD03636 in mice and STD03592 in rats) were included. These two studies were conducted to investigate whether Baycol affects tumor incidence in mice and rats when administered in the diet at some selected dose levels for up to 24 months.

II. THE MOUSE STUDY (STD03636)

IIa. Design

Groups of 50 male and 50 female B6C3F1 mice were treated with Baycol in concentrations of 0 (control), 1 (low), 5 (medium), 25 (high) or 125 (maximum) ppm in the feed for up to 24 months.

IIb. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the papers by Cox (1972) and Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics II. The results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold:
(1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and
(2) To determine the significance of a positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al. (1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 1a and 1b summarize the intercurrent mortality data for the male and female mice respectively. For the male mice, in the time-interval of 92-105 weeks, there appears to be an increased mortality in the high and maximum dose groups as compared to other dose groups. For the female mice, in the time-interval of 92-105 weeks, more animals died in other groups than in the low dose group.

- Figures 1a and 1b depict the Kaplan-Meier survival distributions for males and females respectively. For the male mice, after 105 weeks, there appears to be an increased mortality in the high and maximum dose groups when compared to the other doses. For the female mice, the curves for different dose groups (except the low dose group) intertwine each other suggesting that there is no significant difference between their survival patterns. Mortality is lower in the low dose group as compared to other groups for female mice. The test of homogeneity yields significant results for the male mice (Table 2a in the Appendix).

- Table 2a displays the p-values of the test of homogeneity and of positive linear trends for males and females using the Cox test and the generalized Kruskal-Wallis (Gehan) test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test which gives equal weight to all deaths. The test of homogeneity and the test of linear trend yield significant results for the male mice which confirm the graphical findings of Figure 1a. Table 2b displays p-values for pairwise comparisons (Control=0, Low Dose=1, Medium Dose=2, High Dose=3 and Maximum Dose=4) for both sexes.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of a positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor types were classified as fatal and non-fatal. Table 3 (Part I) displays selected organs and organ codes. Table 3 (Part II) displays tumors and tumor codes.

Following Peto et al. (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused death for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 1, 5, 25, and 125 for the control, low, medium, high and maximum dose groups respectively. This was done in order to reflect the actual dose levels of 0, 1, 5, 25 and 125 ppm of Baycol. The time-intervals used were 0-52, 53-78, 79-91, 92-105, 106 and beyond for males and females.

The tumor analysis results are displayed in the Appendix. Tables 3a and 3b describe the p-values for the test of trend based on the tumor data. The rule proposed by Haseman (1983) could be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by Lin and Rahman (1995) for trend tests was used in this review. This rule for trend tests says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of 1% or less (rare tumors) should be tested at a 0.025 significance level, otherwise (for common tumors) a 0.005 significance level should be used.

On the basis of the rule for trend tests described above, the following significant linear dose tumor-trends were indicated for both the male and the female mice.

The number of males with hepatocellular adenomas and multiple adenomas for the liver for various dose groups is described below (Table 3a).

Male Mice			Tumor Rate					Trend
Organ	Tumor Name	Tumor Type	Control N=50	Low N=50	Medium N=50	High N=50	Maximum N=50	Test p-Value
Liver	Hepatocellular Adenoma	Mixed	7	7	8	14	19	p<0.001
Liver	Hepatocellular Adenoma, Multiple	Incidental	0	0	0	4	5	p=0.001

The number of females with hepatocellular adenomas and multiple adenomas for the liver for various dose groups is described below (Table 3b).

Female Mice			Tumor Rate					Trend
Organ	Tumor Name	Tumor Type	Control N=50	Low N=50	Medium N=50	High N=50	Maximum N=50	Test p-Value
Liver	Hepatocellular Adenoma	Incidental	0	3	2	7	16	p<0.001
Liver	Hepatocellular Adenoma, Multiple	Incidental	0	0	0	0	5	p<0.001

IIc. Additional Statistical Analyses

At the request of the reviewing pharmacologist, three additional tumor analyses were performed for both sexes:

Analysis #1: adenoma and multiple adenoma combined,
Analysis #2: carcinoma and multiple carcinoma combined,
Analysis #3: adenoma, multiple adenoma, carcinoma and multiple carcinoma combined.

Analysis #1

The tumor analysis results for adenoma and multiple adenoma combined are displayed in Table 4a (for males) and 4b (for females).

The number of males with hepatocellular adenomas and multiple adenomas combined for the liver for various dose groups is described below (Table 4a).

Male Mice			Tumor Rate					Trend
Organ	Tumor Name	Tumor Type	Control N=50	Low N=50	Medium N=50	High N=50	Maximum N=50	Test p-Value
Liver	Hepatocellular Adenoma and Multiple Adenoma Combined	Mixed	7	7	8	18	24	p<0.001

The number of females with hepatocellular adenomas and multiple adenomas combined for the liver for various dose groups is described below (Table 4b).

Female Mice			Tumor Rate					Trend
Organ	Tumor Name	Tumor Type	Control N=50	Low N=50	Medium N=50	High N=50	Maximum N=50	Test p-Value
Liver	Hepatocellular Adenoma and Multiple Adenoma Combined	Incidental	0	3	2	7	21	p<0.001

For both sexes, a significant linear dose tumor-trend was indicated for hepatocellular adenomas and multiple adenomas of the liver.

Analysis #2

The tumor analysis results for carcinoma and multiple carcinoma combined are displayed in Table 5a (for males) and 5b (for females).

The number of males with hepatocellular carcinomas and multiple carcinomas combined for the liver for various dose groups is described below (Table 5a).

Male Mice			Tumor Rate					Trend
Organ	Tumor Name	Tumor Type	Control N=50	Low N=50	Medium N=50	High N=50	Maximum N=50	Test p-Value
Liver	Hepatocellular Carcinoma and Multiple Carcinoma Combined	Mixed	0	2	8	13	9	p=0.074

The number of females with hepatocellular carcinomas and multiple carcinomas combined for the liver for various dose groups is described below (Table 5b).

Female Mice			Tumor Rate					Trend
Organ	Tumor Name	Tumor Type	Control N=50	Low N=50	Medium N=50	High N=50	Maximum N=50	Test p-Value
Liver	Hepatocellular Carcinoma and Multiple Carcinoma Combined	Mixed	0	0	0	2	2	p=0.034

For both sexes, no significant linear dose tumor-trend was indicated for hepatocellular carcinomas and multiple carcinomas combined of the liver.

Please note that this reviewer's results are different from those of the sponsor's. The sponsor reported a significant linear dose tumor-trend for hepatocellular carcinomas and multiple carcinomas combined of the liver for male mice ($p < 0.0001$) whereas this reviewer reported a nonsignificant result for the same ($p=0.074$). In order to find out possible causes for this difference in p-values, two teleconferences were conducted with the sponsor in Germany. In turned out that the sponsor's p-value of < 0.0001 was obtained through a contingency table (2x5) chisquare-test of no association between tumor occurrence and dose. Here, a chisquare-test of no association is an inappropriate test. But, when the sponsor performed Peto's test with weight: 0, 1, 5, 25, 125 ppm, they obtained a p-value of 0.0729732 (which was close to this reviewer's p-value of 0.074). In this regard, please refer to a memorandum by Dr. Karl Lin dated May 28, 1997.

Analysis #3

The tumor analysis results for adenoma, multiple adenoma, carcinoma and multiple carcinoma combined are displayed in Table 6a (for males) and 6b (for females).

The number of males with hepatocellular adenoma, multiple adenoma, carcinoma and multiple carcinoma combined for the liver for various doses is described below (Table 6a).

Male Mice			Tumor Rate					Trend Test p-Value
Organ	Tumor Name	Tumor Type	Control N=50	Low N=50	Medium N=50	High N=50	Maximum N=50	
Liver	Hepatocellular Adenoma, Multiple Adenoma, Carcinoma and Multiple Carcinoma Combined	Mixed	7	9	15	28	33	p<0.001

The number of females with hepatocellular adenoma, multiple adenoma, carcinomas and multiple carcinomas combined for the liver for various doses is described below (Table 6b).

Female Mice			Tumor Rate					Trend Test p-Value
Organ	Tumor Name	Tumor Type	Control N=50	Low N=50	Medium N=50	High N=50	Maximum N=50	
Liver	Hepatocellular Adenoma, Multiple Adenoma, Carcinoma and Multiple Carcinoma Combined	Mixed	0	3	2	9	23	p<0.001

For both sexes, a significant linear dose tumor-trend was indicated for hepatocellular adenomas, multiple adenomas, carcinomas and multiple carcinomas combined of the liver.

IId. Summary of Mouse Study (STD03636)

The results of the statistical tests show that, for the male mice, there is an increased mortality in the high and maximum dose groups when compared to the other doses. For the female mice, mortality is lower in the low dose group as compared to other dose groups.

For both sexes, a significant linear dose tumor-trend was indicated for hepatocellular adenomas and multiple adenomas combined of the liver. For both sexes, no significant linear dose tumor-trend was indicated for hepatocellular carcinomas and multiple carcinomas combined of the liver. For both sexes, a significant linear dose tumor-trend was indicated for hepatocellular adenomas, multiple adenomas, carcinomas and multiple carcinomas combined of the liver.

Please note that this reviewer's results are different from those of the sponsor's. The sponsor reported a significant linear dose tumor-trend for hepatocellular carcinomas and multiple carcinomas combined of the liver for male mice ($p < 0.0001$) whereas this reviewer reported a nonsignificant result for the same ($p=0.074$). In order to find out possible causes for this difference in p-values, two teleconferences were conducted with the sponsor in Germany. In turned out that the sponsor's p-value of < 0.0001 was obtained through a contingency table (2x5) chisquare-test of no association between tumor occurrence and dose. Here, a chisquare-test of no association is an inappropriate test. But, when the sponsor performed Peto's test with weight: 0, 1, 5, 25, 125 ppm, they obtained a p-value of 0.0729732 (which was close to this reviewer's p-value of 0.074). In this regard, please refer to a memorandum by Dr. Karl Lin dated May 28, 1997.

III. THE RAT STUDY (STD03592)

IIIa. Design

Groups of 50 male and 50 female Wistar rats were treated with Baycol in concentrations of 0 (control), 0.1 (low), 0.5 (medium), 2.5 (high) ppm, 5.0 ppm (maximum), or with 500 ppm Lovastatin in their diet over 24 months. An MTD (maximum tolerated dose) of 2.5 ppm was established as 5.0 ppm was lethal causing mortality of 50% of female rats and 60% of male rats within the first six months of treatment. On the advice of the Reviewing Pharmacologist, this reviewer decided to analyze only the control, low, medium and high groups of Baycol.

IIIb. Reviewer's Analysis

This reviewer independently performed analyses on the survival and the tumor data provided by the sponsor on a floppy diskette. For survival data analysis, methods described in the papers by Cox (1972) and Gehan (1965) were used. The tumor data were analyzed using the methods described in the paper of Peto et al. (1980) and the method of exact permutation trend test developed by the Division of Biometrics II. The results are included in the Appendix.

Survival Analysis: The purpose of the survival analysis was two-fold:
(1) To examine the differences in the survival distributions among different dose groups (referred to as the test of homogeneity), and
(2) To determine the significance of a positive linear trend in proportions of deaths with respect to dose levels (called the test of linear trend).

For the theoretical background of these analyses, please refer to Lin et al. (1994) and Thomas et al. (1976).

The following results for survival analysis are contained in the Appendix:

- Tables 7a and 7b summarize the intercurrent mortality data for the male and female rats respectively. For the male rats, in the time-intervals of 79-91 weeks and 92-104 weeks, there appears to be an increased mortality in the control group as compared to other dose groups. For the female rats, in the time-intervals of 53-78 weeks, 79-91 weeks and 92-104 weeks, there appears to be an increased mortality in the low dose group as compared to other dose groups.

- Figures 2a and 2b depict the Kaplan-Meier survival distributions for males and females respectively. For the male rats, after 105 weeks, there appears to be an increased mortality in the control group when compared to the other doses. For the female rats, after 105 weeks, mortality is lowest in the high dose group and highest in the low dose group. The test of homogeneity does not yield significant results for the male and the female rats (Table 8a in the Appendix).

- Table 8a displays the p-values of the test of homogeneity and of positive linear trends for males and females using the Cox test and the generalized Kruskal-Wallis (Gehan) test. It is well known that the Kruskal-Wallis test gives more weight to early differences in death rates between groups than the Cox test which gives equal weight to all deaths. The test of homogeneity and the test of linear trend does not yield significant results for the male and the female rats. Table 8b displays p-values for pairwise comparisons (Control=0, Low Dose=1, Medium Dose=2, and High Dose=3) for both sexes. None of the comparisons are significant.

Tumor Analysis: The tumor data analysis was performed to detect, for a selected tumor type in a selected organ/tissue, the significance of a positive linear trend in the proportions of discovered tumors with respect to dose levels. The tumor types were classified as fatal and non-fatal.

Following Peto et al. (1980), this reviewer applied the death-rate method and the prevalence method to fatal and non-fatal tumors respectively. For tumors that caused death for some, but not all animals, a combined analysis was performed. The exact permutation trend test was used to calculate the p-values of all trend tests, except when the tumor was found in both categories, in which case the continuity corrected normal test was used. The scores used were 0, 0.1, 0.5, and 2.5 for control, low, medium, and high dose groups respectively. This was done in order to reflect the actual dose levels of 0, 0.1, 0.5, 2.5 ppm of Baycol. The time-intervals used were 0-52, 53-78, 79-91, 92-104, 105 and beyond for males and females.

The tumor analysis results are displayed in the Appendix. Tables 9a and 9b describe the p-values for the test of trend based on the tumor data. The rule proposed by Haseman (1983) could be used to adjust for the effect of multiple testings in pairwise comparisons. A similar rule proposed by Lin and Rahman (1995) for trend tests was used in this review. This rule for trend tests says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of 1% or less (rare tumors) should be tested at a 0.025 significance level, otherwise (for common tumors) a 0.005 significance level should be used.

On the basis of the rule for trend tests described above, no statistically significant positive linear trend or increased incidence was detected in any of the tested tumor types.

IIIc. Evaluation of Validity of the Design of Rat Study (STD03592)

This reviewer's analyses show that for rat study, there is no statistically significant positive linear trend. However, before drawing the conclusion that the drug is not carcinogenic in rats, it is important to look into the following two issues as having been pointed out by Haseman (1984) in Environmental Health Perspective:

(i) Were enough animals exposed, for a sustained amount of time, to the risk of a late developing tumor?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the rats?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

(i) Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on average, approximately 50% of the animals in the high dose group survived the two-year study period.

(ii) Also, in personal communication with Dr. Karl Lin of Division of Biometrics II, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.

(iii) In addition, Chu, Cueto and Ward (1981) suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy:

(i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the rat carcinogenicity study in the light of the above guidelines.

Validity of Rat Study (STD03592)

Tables 7a and 7b contain survival rates (by subtracting mortality rates from 100%) for male and female rats for all the dose levels and for the times: end of 52 weeks, end of 78 weeks, end of 91 weeks, and end of 104 weeks. From the survival criteria mentioned above, it can be concluded that enough numbers of rats were exposed to the drug for a sufficient amount of time in both sexes.

The sponsor indicated that (p. 51, vol. 1.38) body weights for high-dose (2.5 ppm) males and females were about 6% lower than controls throughout the study. From the weight-gain criteria mentioned above, it can be concluded that the high dose used (2.5 ppm) may be close to the maximum tolerated dose for the both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

IIId. Summary of Rat Study (STD03592)

No statistically significant positive linear trend or increased mortality in the treated groups when compared with the control was detected in either sex.

None of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups when compared with the control.

From the survival criteria, it can be concluded that enough numbers of rats were exposed to the drug for a sufficient amount of time in both sexes. From the weight gain criteria, it can be concluded that the high dose used (2.5 ppm) may be close to the maximum tolerated dose for both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

IV. SUMMARY

Mouse Study (STD03636)

The results of the statistical tests show that, for the male mice, there is an increased mortality in the high and maximum dose groups when compared to the other doses. For females, mortality is lower in the low dose group as compared to other dose groups.

For both sexes, a significant linear dose tumor-trend was indicated for hepatocellular adenomas and multiple adenomas combined of the liver. For both sexes, no significant linear dose tumor-trend was indicated for hepatocellular carcinomas and multiple carcinomas combined of the liver. For both sexes, a significant linear dose tumor-trend was indicated for hepatocellular adenomas, multiple adenomas, carcinomas and multiple carcinomas combined of the liver.

Please note that this reviewer's results are different from those of the sponsor's. The sponsor reported a significant linear dose tumor-trend for hepatocellular carcinomas and multiple carcinomas combined of the liver for male mice ($p < 0.0001$) whereas this reviewer reported a nonsignificant result for the same ($p=0.074$). In order to find out possible causes for this difference in p-values, two teleconferences were conducted with the sponsor in Germany. In turned out that the sponsor's p-value of < 0.0001 was obtained through a contingency table (2x5) chisquare-test of no association between tumor occurrence and dose. Here, a chisquare-test of no association is an inappropriate test. But, when the sponsor performed Peto's test with weight: 0, 1, 5, 25, 125 ppm, they obtained a p-value of 0.0729732 (which was close to this reviewer's p-value of 0.074). In this regard, please refer to a memorandum by Dr. Karl Lin dated May 28, 1997.

Rat Study (STD03592)

No statistically significant positive linear trend or increased mortality in the treated groups when compared with the control was detected in either sex.

None of the tested tumor types showed any statistically significant positive linear trend or increased incidence in the treated groups when compared with the control.

From the survival criteria, it can be concluded that enough numbers of rats were exposed to the drug for a sufficient amount of time in both sexes. From the weight gain criteria, it can be concluded that the high dose used (2.5 ppm) may be close to the maximum tolerated dose for both sexes. However, to draw any final conclusion in this regard, all clinical signs and histopathological effects must be taken into consideration.

Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed)

Concur: Mr. Marticello 5/29/97

Dr. Lin 5/29/97

cc: Archival NDA 20-740
HFD-510/Barbehenn, CSO, Division File
HFD-715/Taneja, Marticello, Lin, Nevius, Division File, Chron.

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