CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020740

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	**20-740**
SUBMISSION DATE:	**August 30, 1996** **June 26, 1996** **January 28, 1997** **February 10, 1997** **February 14, 1997** **March 6, 1997**
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:	**Original NDA (NME)** **Code: 1S**

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 50 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 50, 100, 200 and 300 µg.

Cerivastatin is well absorbed following oral dosing. The absolute bioavailability of a 200 µg oral dose given as 2 x 100 µg tablets is 60% and mean relative bioavailability is about [redacted] The pharmacokinetics of cerivastatin are linear over the dose range of 50 to 400 µg. The elimination half-life [redacted] and cerivastatin reaches its T_{max} during this same time frame. No drug accumulation has been observed with once daily dosing. The pharmacokinetics are similar under fed and fasted conditions.

The drug is extensively metabolized and biliary secretion is a major pathway of elimination. Three metabolites have been identified in humans; M1, M23 and M24 and their presence in plasma, urine and feces occurs in varying degrees.

However, the half-lifes are similar.

The metabolites have pharmacologic activity, however because of the low levels in the bloodstream they probably do not contribute significantly to efficacy/toxicity. Cerivastatin has been shown to be metabolized by CYP3A4, however other pathways have not been ruled out. The metabolic pathways for the metabolites were not elucidated.

Several bioequivalence studies have been conducted to evaluate manufacturing changes and the various dosage strengths.

However, a bioequivalence study has not been conducted but a study comparison of the two formulations appears not to be significantly different (Note: only tablets manufactured with mannitol have been used in the clinical trials).

Studies were conducted to evaluate dosage form equivalence between the 2 x 50 µg tablets and the 1 x 100 µg tablet. Dose proportionality studies were conducted using the 100-400 µg tablets that were not proportional formulations, but dose proportionality was established.

In vitro, cerivastatin is highly bound (>99%) to plasma proteins (mostly serum albumin (80%) and acidic alpha-1-glycoprotein (15%)) with minimal partitioning into erythrocytes. However, the unbound drug's partitioning capability is high.

Age and gender have no clinically significant effects on the pharmacokinetics of cerivastatin. Renal impairment patients have higher C_{max} and AUC values than healthy volunteers. However, there is no clear relationship between plasma drug levels and the degree of renal impairment. The effect on pharmacokinetics appears to plateau in moderately impaired patients with no further changes with an increase in renal impairment. The sponsor has not conducted a hepatic impairment study.

Several drug interaction studies have been conducted and cerivastatin has been shown to have no effect on the pharmacokinetics of warfarin or digoxin. Coadministration of Maalox® and cimetidine have no impact on cerivastatin pharmacokinetics, but cholestyramine reduces the bioavailability of cerivastatin 20%. This phenomenon can be reduced by giving cholestyramine before the evening meal and cerivastatin every evening at bedtime.

Cerivastatin reduces baseline LDL-cholesterol 13.5% and 28.6%, and Total cholesterol 9.6% and 19.9% in the 50µg and 300 µg groups, respectively. A dose-response relationship is evident.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-740 submitted August 30, June 26, 1996, January 28, February 10, 14 and March 6, 1997. The following dissolution method and specification is recommended on an interim basis.

However, it is recommended that the sponsor submit dissolution

The Human Pharmacokinetics Section is acceptable. Please convey recommendation, general comments (p.53) and labeling comments (p.53) to the sponsor as appropriate.

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(Appendices and Attachment available from DPE-II upon request)

BACKGROUND:

Multiple epidemiologic studies have established that elevated serum cholesterol, specifically elevated low density lipoprotein cholesterol (LDL-C), and decreased high density lipoprotein cholesterol (HDL-C) are risk factors for the development of cardiovascular disease. Recent studies have shown that HMG-CoA reductase inhibitors significantly reduce the incidence of myocardial infarction and death from cardiovascular causes in men with moderate hypercholesterolemia and no history of myocardial infarction, and have shown significant reduction in all-cause mortality, especially that from coronary disease, in men and women with hypercholesterolemia and angina pectoris or previous myocardial infarction.

Cerivastatin sodium is sodium [S-[R*,S*-(E)]]-7-[4-(4-fluorophenyl)-5-methoxymethyl)-2,6 bis(1-methylethyl)-3-pyridinyl]-3,5-dihydroxy-6-heptenoate. Its formula is $C_{26}H_{33}FNO_5Na$ and its molecular weight is 481.5. The drug is enantiomerically pure and is a white to off-white hygroscopic amorphous powder that is soluble in water, methanol, ethanol, and very slightly

soluble in acetone.

Baycol® was initially submitted to the agency by Bayer Corporation as IND .

The NDA submission included 34 Phase I clinical pharmacology studies, 4 Phase II studies and 3 pivotal Phase III studies. Twenty-one supportive and long-term studies were also conducted. Cerivastatin is neither marketed, registered nor pending approval in any countries.

During the course of the development of this drug several meetings were held with the Agency. Points relevant to the Office of Clinical Pharmacology and Biopharmaceutics were as follows: 1)The sponsor was asked to provide a list of formulations and batch numbers used in the development program and to conduct a bioequivalence study between old and new (mannitol) formulations---April 28, 1992, 2)FDA suggested that a bioequivalence study evaluating various strengths of cerivastatin be conducted and a single, distinct tablet be used for a given dosage regimen, 3)a dose proportionality study would be included in the NDA, and 4)additional PK studies would be conducted to evaluate the 50 µg strength.

Protocol Number	Title	Page
0138	Investigation of the absolute bioavailability of Bay w 6228 after single administration of 100 µg I.V. as a bolus in comparison to 200 µg p.o. (Non-blind, randomized, crossover). . Report 24731.	12
	Expert opinion Bay w 6228: Formulation change /mannitol tablets during clinical development.	13
0153	A study to evaluate the bioequivalence of a 100 µg Bay w 6228 tablet vs. a 100 µg Bay w 6228 tablet vs. a 100 µg Bay w 6228 tablet Report 1319.	15
0133	Bioequivalency test for BAY w 6228 50 µg and 100 µg tablets.	16
0148	Bioequivalency study between BAY w 6228 and 50 µg and 150 µg tablets. Report 6546.	16

106	A controlled, double-blind, parallel group, ascending, single dose study of the safety and tolerability of the HMG-CoA reductase inhibitor BAY w 6228. Report 6134.	16
107	A controlled, double-blind, parallel group, ascending, multiple-dose study of the safety and tolerability of the HMG-CoA reductase inhibitor BAY w 6228. Report 6003.	18
123	Safety and tolerability of BAY w 6228 300 µg once daily in patients with hypercholesterolemia. Report 5787.	20
108	An open randomized 4-way crossover study of the safety, tolerability and pharmacokinetics of 200 µg BAY w 6228 given as morning or evening doses under fasted or fed conditons. Report 1153.	22
111	A double-blind, placebo-controlled dose scheduling study of BAY w 6228 in doses of 100 µg twice daily with breakfast and dinner compared to 200 µg once daily with dinner or at bedtime in patients with hypercholesterolemia. Report 1215.	23
151	Elucidation of metabolism, determination of the excretion pattern and of the excretion balance after single oral administration of [^{14}C] BAY w 6228 non-blinded, non-controlled study. Report 24824.	24
	Biotransformation in human liver microsomes in vitro. Characterization of primary metabolism pathways and of cytochrome P450 isozymes involved. Report 24571.	25
	[^{14}C] BAY w 6228: Biotransformation in humans. Report 25040.	25
	Investigation of BAY w 6228 metabolites in plasma and urine. Report 25087.	25
135	Phase I study of BAY w 6228-multiple dosing of BAY w 6228 300 µg for 7 days in healthy volunteers in an open, non-randomized study. Report 24807.	27
154	A study to evaluate the dose proportionality of 100 µg, 200 µg and 300 µg BAY w 6228 tablets. Report 1334.	27
155	A study to evaluate the dose proportionality of 50 µg and 100 µg BAY w 6228 tablets and the dose strength equivalence of one 100 µg versus two 50 µg BAY w 6228 tablets. Report 1344.	28

150	A non-blinded study in subjects with different degrees of renal impairment compared to healthy volunteers to assess potential differences of pharmacokinetic parameters after single-dose administration of BAY w 6228 300 µg. Report 24930.	29
D96-019	Influence of renal function on the pharmacokinetics of cerivastatin tablets after single and multiple dosing.	31
114	A controlled double-blind, parallel group, multiple-dose study of the safety, tolerability and pharmacokinetics of the HMG-CoA reductase inhibitor BAY w 6228 in young vs. elderly volunteers. Report 6135.	32
118	A controlled double-blind, parallel group, multiple-dose study of the safety, tolerability and pharmacokinetics of the HMG-CoA reductase inhibitor BAY w 6228 in male vs female volunteers. Report 6147.	34
	Clinical-pharmacological expert opinion: BAY w 6228 pharmacokinetics-interethnic comparison.	36
	[^{14}C] BAY w 6228. Binding to plasma proteins and erythrocyte plasma partitioning in vitro for rat, dog and man. Report 20067.	37
	[^{14}C] BAY w 6228. Investigation of the binding to plasma proteins: characteristics of the binding and interaction studies in vitro. Report 20649.	38
117	Influence of Maalox® 70 on the pharmacokinetics of BAY w 6228. Report 6313.	39
116	Investigation on the influence of cimetidine on the pharmacokinetics of BAY w 6228. Report 23395.	39
125	Influence of cholestyramine on the pharmacokinetics of BAY w 6228. Report 23396.	40
129	Study on the influence of a pretreatment with cholestyramine in the pharmacokinetics of BAY w 6228 after oral administration of both drugs at different time points in healthy male volunteers. Report 6315.	42
119	A study to evaluate the potential reciprocal interaction between BAY w 6228 and digoxin. Report 1240.	43

128	A randomized, double-blind cross-over trial to determine the effects of BAY w 6228 on the pharmacokinetics of a single-dose of concomitantly administered warfarin on the steady-state pharmacokinetics of BAY w 6228, in healthy male volunteers. Report 24315.	46
123	Safety and tolerability of BAY w 6228 300µg once daily in patients with hypercholesterolemia. Report 5787.	47
124 D91-031	A double-blind, dose ranging study of BAY w 6228 in doses of 50 µg, 100 µg, 200 µg and 300 µg once daily compared to placebo and to lovastatin 40 mg once daily in patients with hypercholesterolemia. Report 1304.	50
110	A double-blind, pilot dose ranging study of BAY w 6228 in doses of 25 µg, 50 µg, 100 µg and 200 µg once daily compared to placebo and to simvastatin 20 mg once daily in patients with hyperlipidemia.	52

DRUG FORMULATION:

Cerivastatin tablets which were used for nearly all of the clinical trials were manufactured both in the U.S. at Bayer Corporation and in Germany at Bayer AG by a process utilizing lyophilized drug substance. The three pivotal clinical trials which were conducted in the United States (Study #D91-031/124), the United Kingdom (Study #120) and in France (Study # 132) used tablets manufactured mostly at the Leverkusen, Germany facility. The manufacturing process was modified to use a cerivastatin substance in the manufacture of the to-be-marketed tablet. A bioequivalence study was conducted and is discussed on p. 15.

Two formulations were used in the development of cerivastatin sodium. One formulation was referred to as Bay w and the other Bay w 6228 mannitol (to-be-marketed formulation). The major differences between the two were the substitution of mannitol for , and in magnesium stearate in the to-be-marketed formulation. Since all of the pivotal clinical studies used the mannitol formulation a bioequivalence study was not conducted. One clinical study, a double-blind, placebo-controlled dose scheduling study comparing twice daily dosing of cerivastatin to once daily dosing, used the formulation. Eleven pharmacokinetic studies (100µg and 200µg safety and tolerability, ascending single and multiple doses, age, Maalox™, food, drug interaction and diurnal effect) were conducted which used the formulation.

Batch sizes for most of the pharmacokinetic and clinical studies were greater than tablets per batch. However, a few of the initial pharmacokinetic studies were conducted using tablets from a tablet batch. According to SUPAC, acceptable pilot scale batches should be at a

minimum, one-tenth that of full production or 100,000 tablets whichever is larger. The studies conducted using this smaller batch were safety and tolerability 100µg, 200µg, ascending single dose and multiple dose safety and tolerability, food and diurnal studies (Study Nos. 103-108).

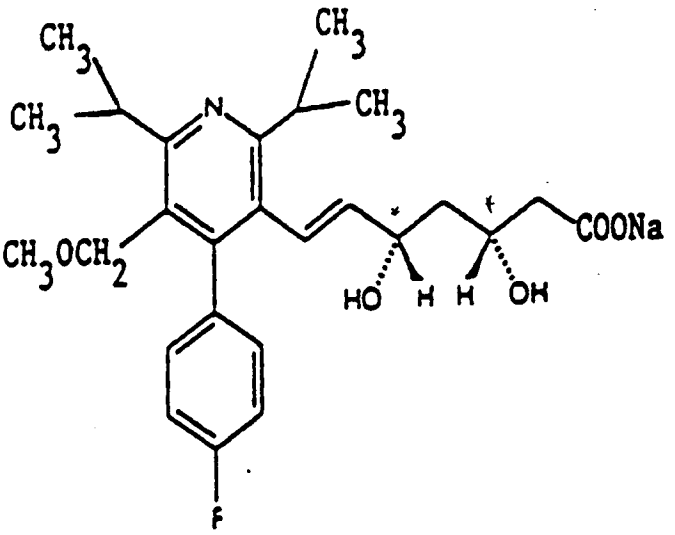

Figure 1: The chemical structure of cerivastatin sodium (BAYCOL®).

The formulations were not dose proportional as evidenced by Table 1 below.

Table 1 : Cerivastatin Composition (UNIT FORMULA)				
Ingredient	**Quantity (mg/Tablet)**			
Bay w 6228	**50µg**	**100µg**	**200µg**	**300µg**
Crospovidone				
Magnesium Stearate				
Mannitol				
Sodium Hydroxide				
Methyl Hydroxy propyl cellulose				
Titanium hydroxide				
Ferric Oxide				

DISSOLUTION:

The company did not submit any dissolution data in media other than which they are proposing in their dissolution specification. No dissolution data was provided for the lots manufactured with compared to the lots manufactured with mannitol. Nor was a comparison

The sponsor suggested the following dissolution method and specification:

The tablet is more than using this proposed method. These parameters do not yield a very discriminating dissolution method which makes the evaluation of other media that much more critical. (See Figure 2).

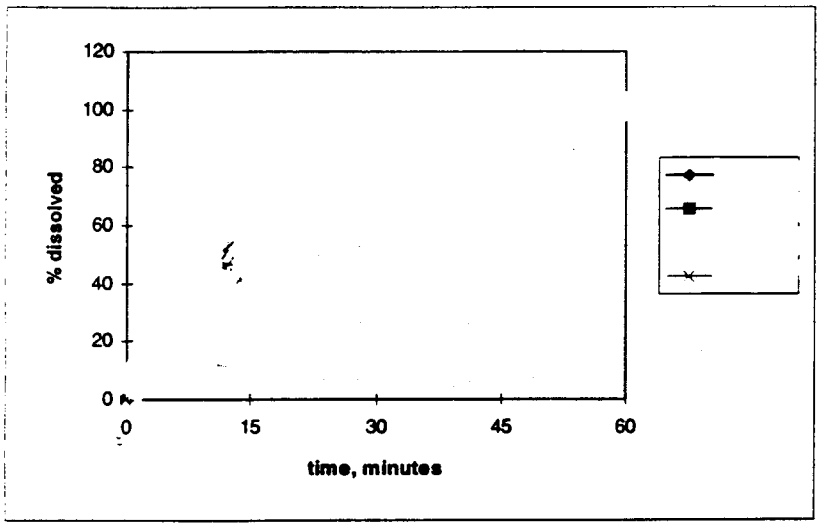

FIGURE 2. Dissolution Characteristics of mg of cerivastin in

Table 2. The Solubility of Cerivastatin Sodium in Various Aqueous Media

Medium	Solubility at Saturation Point (mg/ml)

ANALYTICAL METHODOLOGY:

This difference was attributed to the cross-reacting metabolites.

Specific assays were also developed for the quantitation of the metabolites M1, M23 and M24 in plasma and urine. These metabolites were also analyzed using an with

TABLE 3 . Analytical Methods Used in the Analysis of Cerivastatin in Plasma and Urine Samples

TABLE 4. Analytical Methods Used in the Analysis of Cerivastatin Metabolites in Plasma and Urine Samples		
	Plasma	**Urine**

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

Absolute and relative bioavailability were investigated in a single-dose, randomized, non-blind, crossover study in 7 healthy male volunteers ranging in age from 18 to 45. A 100 µg IV bolus dose, 200 µg oral dose (2 x 100 µg tablets) and a 200 µg oral solution were evaluated. The absolute bioavailability was for the tablet. The mean relative bioavailability of the tablet compared to the solution was with virtually identical mean plasma concentration time curves.

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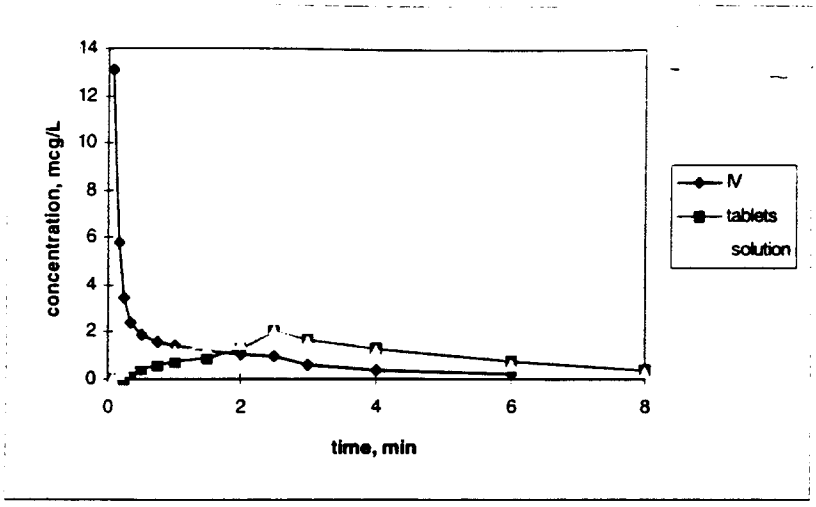

FIGURE 3: Mean cerivastatin plasma levels versus time after oral administration of 200 µg as both tablets and an oral solution, and IV administration of 100 µg (1 minute infusion) to 7 healthy volunteers.

TABLE 5
Mean Pharmacokinetic Parameters of Cerivastatin After Oral (200 µg tablet and solution) and IV (100 µg, 1-min infusion) Administration to 7 Healthy Volunteers

Parameters	Oral tab	Oral soln	IV
C_{max} (kg/L) $_{norm}$	0.72	0.74	
C_{max} (µg/L)	2.02	2.06	
t_{max} (h)	2.5	2.5	
AUC(µg·h/L)	9.34	9.27	7.77
AUC (kg·h/L) $_{norm}$	3.34	3.31	5.56
$t_{½}$p (h)	2.13	2.19	1.77

B. Bioequivalence

Two formulations were used in the clinical development of cerivastatin. The initial formulation which was used in early Phase I and Phase II trials contained [redacted] as the main excipient. A new tablet formulation containing mannitol instead of [redacted] was developed to improve long-term stability of the product. This switch in filler occurred prior to Phase 2b. In a meeting with the Division of Metabolism and Endocrine Drug Products (April 28, 1992), the FDA requested that a bioequivalence study be conducted between the [redacted] and mannitol formulations. The sponsor did not conduct a bioequivalence study to evaluate this change. In lieu of a bioequivalence study, the sponsor performed a retrospective review of studies which used the two excipients. The studies used in the retrospective analysis are discussed in Table 6.

Table 6. Cerivastatin Tablets Used in Phase I Studies (European and U.S.)

Ingredient	Batch No.	Study No.
[redacted]	526301 (100 µg) 527549	103, 104, 105 Pilot studies 106, 107 Ascending dose (single and multiple dose) 108 Food effect 114 Age 118 Gender
Mannitol	527762 529056 529176 529406	116 Cimetidine interaction study 117 Maalox interaction study 119 Digoxin interaction study 125 Cholestyramine interaction study 128 Warfarin interaction study 129 Cholestyramine varied with time 138 Bioavailability

The means and standard deviations were presented, but no descriptive statistics nor confidence intervals were calculated. The confidence intervals for the retrospective study were calculated by the reviewer, and bioequivalence was established between the two formulations

The data that was used in the reviewer's analysis was assayed using

The results of the retrospective study are presented in Tables 7 & 8.

Table 7. Results of Pharmacokinetic Data Pool Analysis for Dose-Normalized AUC and Cmax and tmax After Single-Dosing (g. Means/SD, ar. Means ±SD, median (range)

Single-dose	**Mannitol Tablets (N=69)**
$AUC_{dose\text{-}norm}$ (h/L)	0.059 / 1.43 0.063±0.026 0.059
$C_{max\ dose\text{-}norm}$ (L^{-1})	0.011 / 1.39 0.012±0.005 0.011
t_{max} (h)	2.5

Table 8. Results of Pharmacokinetic Data Pool Analysis for Dose Normalized AUC, Cmax and tmax after Multiple-dosing (g. means/SD, ar. means ±SD, median (range)

Multiple-dose	Mannitol Tablets (N=22)
$AUC_{dose\text{-}norm}$ (h/L)	0.059 / 1.30 0.062 ±0.019 0.057
$C_{max\ dose\text{-}norm}$ (L^{-1})	0.010 / 1.37 0.011 ±0.004 0.010
t_{max} (h)	2.25

The sponsor stated the *in vitro* characteristics were "virtually identical." However, the supporting documentation was not included in the original NDA. The reviewer has requested this information.

A single dose, three period crossover, nonblinded, randomized bioequivalence study was conducted in 29 healthy male volunteers ranging in age from 19 to 38 years to evaluate whether modifications in the manufacturing process and site changes impacted the performance of the drug products.

All three products contained mannitol as the excipient. Drug was administered 2 hours after the evening meal. No significant differences between the two processes and sites were observed. The point estimates and 90% confidence intervals for bioavailability parameters for log-transformed ratios of the formulation means are given in Table 9.

TABLE 9
90% Confidence Interval, for Comparison of Cerivastatin Pharmacokinetic Parameters, of the Ratio

Parameter	German) Tablet	US) Tablet	Ratio*	90 % C.I.
$AUC_{0-\infty}$, (µg·h/L)	7.53±1.53	7.40±1.44	1.009, 1.028, 1.019	0.94-1.09 0.95-1.11 0.95-1.10
C_{max}, (µg/L)	1.33±1.51	1.39±1.38	1.075, 1.026, 0.954	0.98-1.18 0.94-1,12 0.87-1.04

*Calculated from geometric least squares mean

Two additional bioequivalence studies were conducted. The objectives were to evaluate 1) 2 x 50 µg tablets versus 1 x 100 µg tablet and 2) 3 x 50-µg versus and 1 x 150 µg tablet. In both studies, healthy Japanese volunteers were administered cerivastatin under fasting conditions as an open-label, randomized, crossover trial. The tablets were manufactured in Germany using the process (clinical trial) and mannitol as the excipient. Both studies demonstrated dosage form equivalence.

II. Pharmacokinetics

Values for volume of distribution and systemic clearance were obtained following iv dosing. The volume of distribution at steady-state of about 0.3 L/kg indicated that the drug penetrated only moderately into tissues. With a clearance of about 13 L/h cerivastatin could be regarded as a low-clearance drug.

A. Single vs. Multiple Dose Administration

The pharmacokinetics of cerivastatin are linear based on the results of single dose and multiple dose studies. Single dose pharmacokinetics of cerivastatin were investigated in 48 healthy male volunteers ranging in age from 18 to 43. The study was conducted as a randomized, placebo-controlled, parallel group, ascending dose design (100 µg, 200 µg, 300 µg and 400 µg). The mean plasma concentration profiles are plotted in Figure 4.

The results for AUC and C_{max} suggested dose proportionality over the range studied. (See Tables 10 & 11).

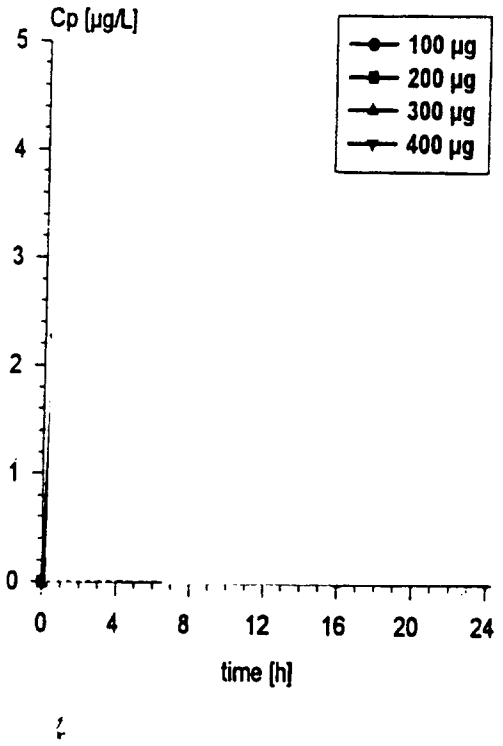

FIGURE 4. Cerivastatin plasma concentrations (g. means) assayed by following single doses of 100-400 µg to separate groups of healthy males (N=12 per group)

Table 10. Pharmacokinetic Parameters (g. mean/GSD) of a Single Dose Ascending Study (N=12 subjects/dose) of Cerivastatin

Parameter/Dose	100 µg	200 µg	300 µg	400 µg
AUC (µg*h/L)	6.25 / 1.52	11.71 / 1.28	20.52 / 1.60	22.45 / 1.25
AUC_{norm} (kg*h/L)	4.61 / 1.50	4.37 / 1.32	4.87 / 1.55	4.31 / 1.28
C_{max} (µg/L)	1.01 / 1.56	2.15 / 1.32	3.55 / 1.53	4.04 / 1.17
t_{max} (h)	1.5 - 4.0	1.0 - 3.0	1.5 - 3.0	0.5 - 3.0
$t_{½}$ (h)	3.37 / 1.42	3.08/ 1.51	4.89 / 1.45	4.23 / 1.60

A small percentage of subjects (4.2%) experienced abdominal pain and elevation of clinical markers (serum CPK---2 subjects (1 active and 1 placebo), amylase---3 subjects (2 active and 1 placebo), serum transaminase---4 subjects (all on active treatment; 1-100µg, 1-200µg, 2-400µg). The adverse events and elevation were not dose-related.

Cerivastatin multiple dosing was investigated in 48 healthy male volunteers in a randomized, placebo-controlled, parallel group, ascending dose design study where 100-400 µg were given as multiple oral doses over 7 days. The following dose regimens were used: 100 µg, 200 µg, 300 µg and 400 µg qd; and 100 µg and 200 µg bid. Results for the qd and bid regimens are presented in Tables 11 & 12 and Figure 5.

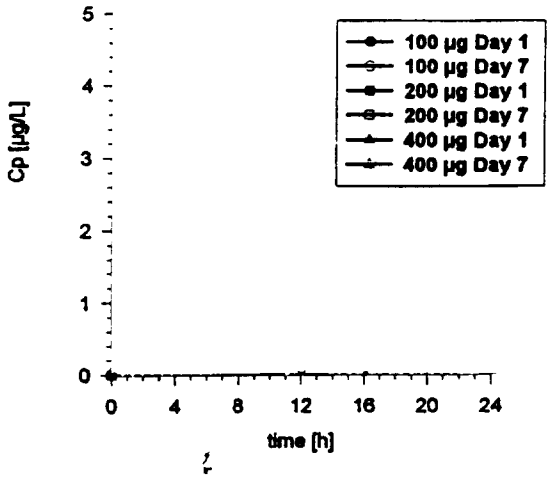

FIGURE 5. Cerivastatin plasma concentrations (g. means) assayed by after 100, 200 and 400 µg q.d. for 7 days to separate groups of male volunteers (N=8 per group).

Table 11
Primary pharmacokinetic parameters (g. mean/GSD, n = 8 per dose) for cerivastatin after multiple dosing of 100, 200, 300 and 400µg qd for Day 1 and Day 7

	100µg qd	200µg qd	300µg qd	400µg qd
Day 1				
AUC [µg•h/L]	6.49 / 1.31	13.07 / 1.33	18.90 / 1.25	24.60 / 1.17
C_{max} [µg/L]	1.28 / 1.59	2.61 / 1.16	4.08 / 1.38	5.45 / 1.27
t_{max} [h] #				
$t_{1/2}$ [h]	2.76 / 1.24	2.79 / 1.29	3.60 / 1.18	3.60 / 1.20
Day 7				
AUC_{0-T} [µg•h/L]	6.33 / 1.39	12.40 / 1.34	21.73 / 1.21	24.67 / 1.15
C_{max} [µg/L]	1.14 / 1.33	2.31 / 1.33	3.96 / 1.43	4.41 / 1.43
T_{max} [h] #				
$t_{1/2}$ [h]	3.19 / 1.41	2.74 / 1.22	3.79 / 1.17	5.16 / 1.20

(range)

Geometric mean Day 7 $AUC_{0-\tau}$ ranged from 6.33 to 24.67 μg•h/L for the q.d. regimens (100 - 400 μg) and from for the b.i.d. regimens (100 & 200 μg). The mean time to peak concentration t_{max} was approximately 2 hours for all dose groups on both Day 1 and Day 7. The q.d. data suggested dosage proportionality with no accumulation with chronic administration (accumulation ratios for the various doses were 0.97, 0.949, 1.15). For the b.i.d dosing, the 100 µg arm suggested minor accumulation, however, the trend was not seen with the 200 µg dose (Table 12).

Table 12
Primary pharmacokinetic parameters (g. mean/GSD, n = 8 per dose) for cerivastatin after multiple dosing of 100 and 200μg bid for Day 1 and Day 7

	100μg bid		200μg bid	
Day 1/2	pm	am	pm	am
$AUC_{0-\tau}$ [μg•h/L]	5.51 / 1.50	5.85 / 1.52	13.71 / 1.26	13.37 / 1.20
C_{max} [μg/L]	1.41 / 1.46	1.40 / 1.62	3.30 / 1.20	3.06 / 1.24
t_{max} [h] *				
Day 7/8	pm	am	pm	am
$AUC_{0-\tau}$ [μg•h/L]	6.95 / 1.50	6.85 / 1.51	13.41 / 1.26	13.42 / 1.25
AUC_{0-24} [μg•h/L]**	13.81 / 1.50		26.85 / 1.25	
C_{max} [μg/L]	1.40 / 1.41	1.60 / 1.55	2.81 / 1.25	2.98 / 1.23
t_{max} [h] *				
$t_{1/2}$ [h] ***	3.58 / 1.71		6.40 / 1.19	

* (range) ** sum of both dosing intervals *** within first dosing interval

Cerivastatin achieved steady-state in 3 days. Small differences in trough concentrations were observed between evening and morning administration. However, these differences were not present in C_{max} and AUC data.

Comparison of evening and morning pharmacokinetics indicated no circadian effects for either AUC or C_{max}.

Day 7/8 analysis of AUC 0-24 for b.i.d. and q.h.s. regimens was also performed for the equivalent total daily doses of 100 µg b.i.d. and 200 µg q.h.s., and 200 µg b.i.d. and 400 µg q.h.s. The data in Table 13 indicated dose proportionality. The two regimens were not bioequivalent at the 90% confidence interval (100/200- and 200/400-
However, these small differences between the two dosage regimens were probably not clinically significant.

Table 13. Summary Statistics for Day 7/8 AUC_{0-24} for b.i.d. and q.h.s. Regimens			
Dose Group	Geometric Mean±SD	N	Dose Ratio
100 BID 200 QHS	13.81±1.50 12.40±1.34	8 8	1.114
200 BID 400 QHS	26.85±1.25 24.67±1.15	7 6	1.088

Pharmacodynamic results were also measured with a percent change from baseline for lipid parameters total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides after 6 days dosing. This particular study was not a diet controlled study and the study duration was only 7 days. However, noticeable changes from baseline were observed for Total cholesterol and LDL cholesterol. No dose response was observed, but that was probably due to the short duration of the study.

Table 14. Pharmacodynamic Results (% Change From Baseline) for Cerivastatin				
Dose (SEM)	Total Cholesterol	LDL-Cholesterol	HDL-Cholesterol	Triglycerides
Placebo	10.0 (2.7)	12.8 (3.0)	8.87 (2.6)	10.0 (14.9)
100 µg QHS	-22.0 (2.6)	-30.4 (3.1)	0.2 (4.6)	-15.1 (10.3)
200µg QHS	-20.8 (2.8)	-30.7 (2.2)	-9.3 (3.4)	14.7 (17.5)
100 µg BID	-26.3 (3.3)	-34.0 (4.1)	-14.5 (3.9)	2.4 (11.7)
300 µg QHS	-23.6 (1.6)	-33.1 (2.5)	-5.8 (3.9)	-3.8 (14.9)
200 µg BID	-24.9 (1.7)	-36.4 (2.8)	2.2 (2.9)	-18.1 (7.5)
400 µg QHS	-22.3 (2.0)	-36.3 (4.1)	5.1 (4.0)	-6.1 (7.3)

Twenty-two subjects on active treatment and 9 placebo treated subjects reported adverse events. Four subjects had events that were probably not study related. The most commonly reported events were headache, asthenia, abdominal pain and dizziness. One serious adverse event of extremely elevated CPK and liver function tests in one subject in Stage III (400µg arm) of the study was reported. This event caused termination of the study after 20 of 24 expected subjects were randomized to treatment.

B. Healthy volunteers vs.Hypercholesterolemic patients

A Phase-IIa study was conducted to evaluate the safety and tolerability of 300 μg cerivastatin administered once daily for 28 days in patients with hypercholesterolemia using a placebo-controlled, double-blind, parallel group design. Pharmacokinetic profiles of cerivastatin were obtained from 23 subjects who received active drug. The results indicated that cerivastatin was absorbed quite rapidly, with a mean t_{max} of 2.1 hours C_{max} averaged 3.9 μg/L

elimination was characterized by a half-life of approximately 3 hours) and AUC of 24.6 µg•h/l compared to 21.9 µg•h/l in healthy volunteers. There was only modest intersubject variability with respect to each of the pharmacokinetic parameters. Coefficient of variation (inter-subject variability) was approximately 35% for both AUC and C_{max}.

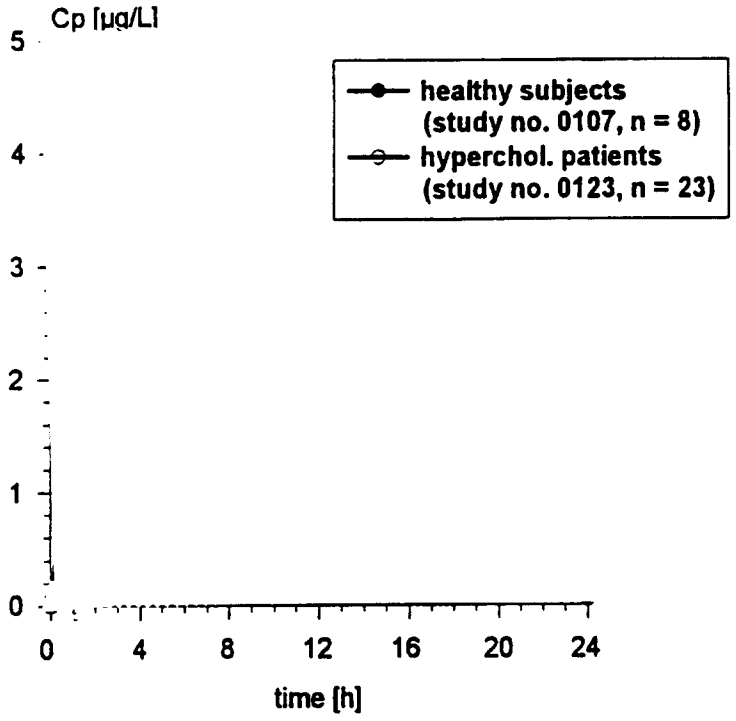

FIGURE 6. Cerivastatin plamsa concentrations (g. means) assayed by on day 7 (healthy subjects) or on day 5 (hypercholesterolemic patients) of a 300 µg q.d. dose regimen

These pharmacokinetic data in the target patient population are relatively consistent with the pharmacokinetic characteristics observed in healthy subjects, as indicated in Figure 6 above.

C. Animal Pharmacokinetics

Data from animal studies showed that cerivastatin had a low affinity for tissues other than liver tissue. Penetration of radioactivity across the blood brain barrier occurred only to a small extent.

In rat experiments, radioactivity from [^{14}C]cerivastatin also crossed the placental barrier. The estimated amount of radioactivity excreted with milk was 1.16% of the dose within 48 hours after administration. Both pregnancy and breast-feeding are contraindicated for cerivastatin due to the potential harm of reduced cholesterol biosynthesis to the fetus and infant.

D. Food Effects

The influence of food on the oral absorption of cerivastatin was studied with tablets manufactured with lactose. The study was a randomized open-label single-dose 4-way crossover study in 31 healthy male volunteers ranging in age from 18 to 45. The four treatment arms were: 1) administration of 200 µg (2 x 100 µg tablets) in the morning after an overnight fast, 2) administration of tablets with a high fat breakfast, 3) administration of tablets with a low fat evening meal and 4) administration of tablets 4 hours after the evening meal. The results indicated that the AUC of cerivastatin was decreased 11-15% when the drug was given in the morning compared to the evening. C_{max} was 18% greater when administered with breakfast compared to the fasted state. This change was not observed with evening administration. No diurnal variations were observed in C_{max} irrespective of whether the patient was fed or fasted. Differences in $t_{½}$ and T_{max} were not observed. Period differences were observed with Period 1 yielding the greatest differences. Values 9% lower for AUC and 20% lower for C_{max} compared to the other periods were observed. The sponsor suggested the possibility that the occurrence was related to the assay schedule which involved the analysis of cohorts within a period, rather than analyzing samples for a particular subject across all periods in a given run. However, this comment was only conjecture.

Thirteen subjects reported a total of 24 adverse events. The events occurred in all four phases; however twice as many occurred in the evening compared to the morning. This phenomenon could be related to the higher AUCs in the evening. There was no difference in occurrence between the fasted or fed state.The most commonly reported adverse event was headache and it occurred more often when cerivastatin was taken in the fasted state. The second most common adverse event was rhinitis and it occurred more often in the fed state. An unexplained clinical anomaly occurred half-way through the study. Twenty-nine subjects experienced abnormal levels of bilirubin. The sponsor provided no explanation for this occurrence.

TABLE 15
Mean (SD) Pharmacokinetic Parameters of Cerivastatin After Administration of Single Oral Doses of 200 µg under Fasted/Fed Conditions in the Morning and Evening (g. mean/GSD, N=31)

Parameters	Modality			
	a.m. fasted	a.m. fed	p.m. fasted	p.m. fed
$AUC_{0-\infty}$ (µg·h/L)	14.36(1.26)	14.19(1.25)	16.15(1.25)	16.99(1.26)
C_{max} (µg/L)	2.27(1.25)	2.88(1.29)	2.58(1.29)	2.78(1.38)
t_{max} (h)				
$t_{½}$ (h)	3.20(1.22)	3.26(1.37)	3.05(1.18)	3.33(1.20)

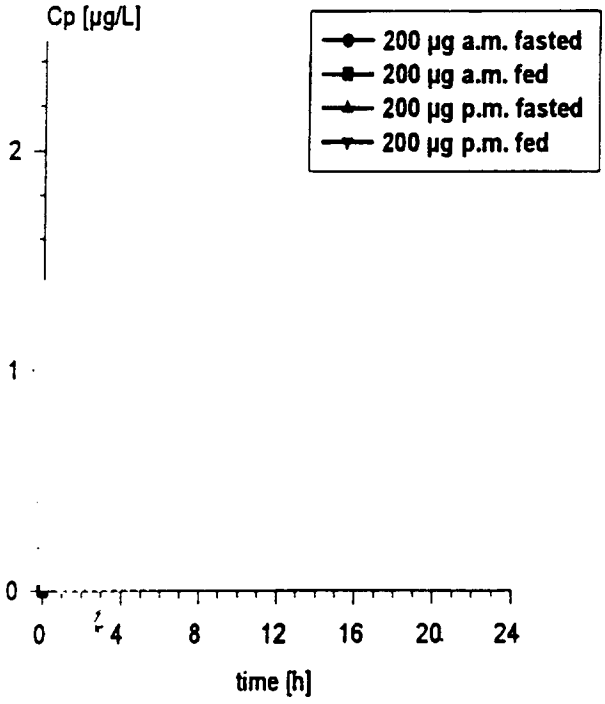

FIGURE 7. Cerivastatin Plasma Concentration (g. means) Assayed by S.D. to 31 Healthy Male Volunteers under Different Dosing. **after 200µg**

A double blind, placebo-controlled dose scheduling study of cerivastatin in doses of 100 µg twice daily (breakfast and dinner) compared to 200 µg once daily (with dinner or at bedtime) in patients with hypercholesterolemia was conducted. The study was 14 weeks in duration (4 weeks dietary run-in, 6 weeks placebo, 1 week each of active treatment arm). No pharmacokinetic evaluation was performed. However, a pharmacodynamic lipid profile was determined. The database was 60% male and contained 308 patients with a median age of 52. Ninety-three percent were Caucasian. Average decrease in LDL-cholesterol was 28.4% and total cholesterol 21%, respectively. However, the decrease associated with the administration of 100µg b.i.d. was 14% lower than amounts achieved with the single administration of 200 µg. No difference in lipid profile was observed between the evening meal and at bedtime administration.

The food effect should have been conducted at the maximum dosage that the company plans to administer. A greater difference in pharmacokinetic values and adverse events might have been observed. The assumption that minimal clinical effects between time of dosing and food status would occur was not adequately evaluated in the current studies. Currently, the sponsor is proposing an evening administration, so time of day is currently not an issue.

TABLE 16

Pharmacodynamic Parameters of Cerivastatin Administered as 100 µg Twice Daily with Breakfast and Dinner Compared to 200µg Once Daily with Dinner or at Bedtime in Patients with Hypercholesterolemia

Parameters	100µg bid	200µg qpm	200µg qhs	PLA
LDL-cholesterol	-25.7	-29.4	-30.4	1.4
Total cholesterol	-18.9	-21.9	-22.1	-0.01
Triglycerides	-11.6	-11.6	-10.9	-3.1
HDL-cholesterol	5.3	2.3	3.2	-1.2

The incidence of adverse events was twice as great in the evening. The most commonly reported events were headache and rhinitis. Elevation of liver enzymes was also observed. The administration of cerivastatin appeared more effective in lowering cholesterol in females compared to males (31.5% F vs. 26.4% M). This phenomenon will be further elucidated in a gender study discussed later in this report.

III. Metabolism

The metabolism of cerivastatin was investigated in human liver microsomes in vitro. Two major metabolites were formed within one hour, M1 (BAY w 5679) and metabolite M23 (BAY 17-5111),

The minor metabolite M24 (BAY 19-3103),

In humans, M23 represented the major metabolite. The reaction was very stereoselective yielding the

The effects of all three metabolites on hepatic cholesterol synthesis was studied in rats. Both M23 and M24 inhibited the accumulation of cholesterol in rat livers in a dose-dependent fashion. M1 did not show a dose-response effect. The ED_{50} of M23 and M24 was similar to the parent compound, but M1 was not as effective.

The proposed metabolic pathway for cerivastatin in man is shown in Figure 8.

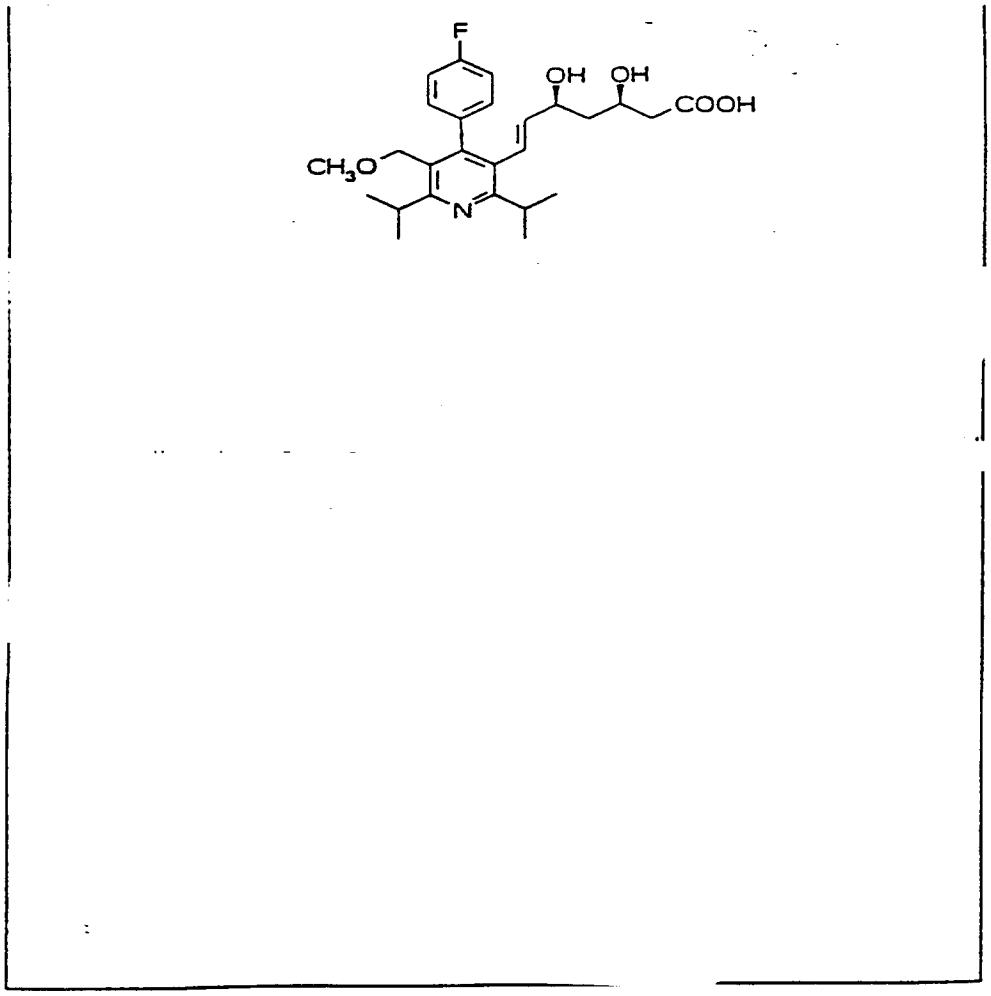

FIGURE 8. Metabolic pathways for cerivastatin and its metabolites

In vitro inhibition studies showed that isozyme CYP3A4 was involved in the metabolism of cerivastatin. CYP2D6 was shown not to have a role. Other isozyme involvement has not been fully determined. The metabolite metabolic pathways were not elucidated.

A detailed evaluation of the metabolism and excretion patterns in humans was conducted as a where four healthy male volunteers 50 years of age and older were dosed with 400μg cerivastatin as a solution under fasting conditions. Metabolite M23 was the major metabolite in plasma, M1 was also detected in plasma, but in lower concentrations: in plasma was accounted for by parent drug plus both metabolites M1 and M23. Metabolite M24 was not detected in plasma for any subject The recovery in urine and feces for each subject is presented below. The parent compound

accounts for less than No indication for racemization or chiral inversion of cerivastatin was observed. The plasma half-lives were similar between the parent compound and the M1 and M23 metabolites (2.6, 4.1, and 3.1 h, respectively).

Table 17
Summary of excretion of total cerivastatin plus metabolites M1, M22 (of M1), M23, M31 (of M23) and M24, given as % of administered dose

	Vol. 1	Vol. 2	Vol. 3	Vol. 4
	% Dose Excreted in Urine			
M1				
M22				
M23				
M24				
Total				
	% Dose Excreted in Feces			
M1				
M22				
M23				
M31				
M24				

Vol=volunteer

Urinary excretion . On the average. found in urine could be attributed to known structures (M1, M23 and their corresponding M22, M31, respectively, and M24).

Total excreted in the feces accounted for On the average M1, M22, M23, M31 and M24 represented of the dose). The total excreted within was greater than of dose in of the subjects. Cerivastatin was not found in either urine or feces.

Steady-state plasma concentrations and urinary excretion characteristics of the metabolites M1, M23 and M24 were investigated in a multiple-dose study where six healthy young male Japanese subjects were dosed with 300μg cerivastatin qd for seven days.

Table 18
Primary pharmacokinetic parameters (g. mean/GSD, n = 6) for metabolites M1 and M23 after multiple dosing of 300μg qd for Day 1 and Day 7

	M1	M1	M23	M23
	Day 1	Day 7	Day 1	Day 7
AUC [μg*h/L] **	1.61 / 1.08	1.53 / 1.28	4.21 / 1.30	4.4 / 1.17
C_{max} [μg/L]	0.26 / 1.31	0.22 / 1.33	0.58 / 1.31	0.57 / 1.22
t_{max} [h]	4.0 - 6.0	5.0 - 6.0	5.0 - 6.0	5.0 - 8.0
$t_{1/2}$ [h] *				
Ae_{ur} [%]	4.2 ± 1.0	4.4 ± 1.0	9.0 ± 2.1	9.8 ± 2.0

* range ** $AUC_{0-\infty}$ for Day 1, $AUC_{0-\tau}$ for Day 7

Metabolite M24 could not be detected in any of the plasma samples (LOQ: 0.1μg/L). The fraction of dose excreted in urine as M24 was 0.87 ± 0.3% for Day 1 and 1.4 ± 0.3% for Day 7.

IV. Dose and Dosage Form Proportionality

Dose proportionality in cerivastatin from 100 µg to 400 µg administered as multiple 100 µg tablets (Study 106) was shown in dose escalation studies that were previously discussed under the healthy volunteer pharmacokinetic section (Data is repeated in Table 19.)

Table 19. Pharmacokinetic Parameters (g. mean/GSD) of a Single Dose Ascending Study (N=12 subjects/dose) of Cerivastatin

Parameter/Dose	100 µg	200 µg	300 µg	400 µg
AUC (µg*h/L)	6.25 / 1.52	11.71 / 1.28	20.52 / 1.60	22.45 / 1.25
AUC_{norm} (kg*h/L)	4.61 / 1.50	4.37 / 1.32	4.87 / 1.55	4.31 / 1.28
C_{max} (µg/L)	1.01 / 1.56	2.15 / 1.32	3.55 / 1.53	4.04 / 1.17
t_{max} (h)	1.5 - 4.0	1.0 - 3.0	1.5 - 3.0	0.5 - 3.0
$t_{½}$ (h)	3.37 / 1.42	3.08/ 1.51	4.89 / 1.45	4.23 / 1.60

A three-way, open-label, single dose, crossover dose-proportionality study (Study 154) comparing doses of 100 µg, 200 µg and 300 µg administered as single tablets in 32 healthy young male subjects was conducted. This study used cerivastatin tablets that were made in

Germany using the [redacted] derived manufacturing process. Subjects were administered either 100, 200 or 300 µg tablets 2 hours after an evening meal. The parent drug, M1 and M23 metabolites were evaluated in this study. The results confirmed linear pharmacokinetics (Tables 20 & 21).

TABLE 20
Dose Proportionality Results of Cerivastatin in Healthy Male Volunteers in the Dose Range 100 µg to 300 µg (geometric mean/g. SD) (Parent drug)

Parameters	100 µg	200 µg	300 µg
C_{max} (µg/L)	1.29/1.35	2.40/1.34	3.75/1.34
$C_{max\ norm}$ (kg/L)	0.99/1.36	0.92/1.36	0.96/1.37
AUC (µg·h/L)	7.89/1.31	15.33/1.33	24.03/1.32
AUC_{norm} (kg·h/L)	6.07/1.33	5.89/1.34	6.16/1.35
$T_{1/2}$ (h)[d]	3.03/1.17	3.18/1.22	3.06/1.12
tmax (h)	2.65/1.51	2.26/1.53	2.61/1.14

Table 21. C_{max} Comparison for M23 Metabolites

Tablet Strength	Geom. Mean (g. SD)	Comparison	Ratio of Dose Adjusted means	90% CI
100 µg	0.15 (1.66)	200µg/100µg	0.996	0.867-1.145
200 µg	0.30 (1.41)	300µg/100µg	1.014	0.882-1.166
300 µg	0.47 (1.43)	300µg/200µg	1.018	0.885-1.170

The M1 metabolite could not be detected at the 100 µg and 200 µg tablet strengths. C_{max} for the 300 µg strength was 0.21 (1.36) geom. mean (g. SD). The level of this metabolite in the bloodstream compared to the parent drug was approximately 5%. The level of the M23 metabolite in the bloodstream was 12% of the parent drug level.

A third dose proportionality study (Study 155) was conducted in 29 healthy male volunteers using 50 µg and 100 µg doses administered as single tablets. These dosages also showed linearity. The values obtained in these studies were relatively comparable to other dose ascending single and multiple dose studies.

TABLE 22
Dose Proportionality Results of Cerivastatin in Healthy Male Volunteers in the Dose Range 50 µg to 300 µg (geometric mean/g. SD)

Parameters	50 µg*	100 µg*
C_{max} (µg/L)	0.56/1.28	1.11/1.97
$C_{max\ norm}$ (kg/L)	0.88/1.29	0.87/2.00
AUC (µg·h/L)	3.03/1.27	6.38/1.32
AUC_{norm} (kg·h/L)	4.76/1.27	5.02/1.32
$T_{1/2}$ (h)[d]	3.21/1.34	3.17/1.25
tmax (h)	2.01/1.32	1.96/1.63

*Taken from study 155

Special Populations

Renal

A non-blinded, non-randomized parallel design single dose study was conducted to compare the pharmacokinetics of cerivastatin in subjects with varying degrees of renal function. Twenty-four subjects (18 males and 4 females) were assigned to one of four groups. Only males were included in the healthy volunteer group. Subjects received 300 µg of cerivastatin administered as one tablet taken 1 hour before breakfast. Subjects were assigned to a renal function group (6 persons per group) based on a 24 hour creatinine clearance (Cl_{cr}). The criteria for each group were as follows:

Group 1 (normal): Cl_{cr} >90 mL/min/1.73 m^2
Group 2 (mild impairment): Cl_{cr} 61 - 90 mL/min/1.73 m^2
Group 3 (moderate impairment): Cl_{cr} 30 - 60 mL/min/1.73 m^2
Group 4 (severe impairment): Cl_{cr} <30 mL/min/1.73 m^2

The results are summarized below in Tables 23, 24 and 25.

Table 23
Cerivastatin pharmacokinetic parameters (g. mean/GSD)

	Group 1 n = 6	Group 2 n = 6	Group 3 n = 6	Group 4 n = 6
f_u [%] *	0.76 ± 0.08	0.88 ± 0.21	0.80 ± 0.09	1.15 ± 0.19
AUC [μg *h/L]	13.17 / 1.25	19.70 / 1.52	26.87 / 1.68	20.33 / 1.60
AUC_{norm} [kg*h/L]	3.13 / 1.23	6.41 / 1.61	7.01 / 1.82	4.80 / 1.80
C_{max} [μg /L]	2.98 / 1.23	3.71 / 1.27	4.88 / 1.52	3.57 / 1.53
$C_{max, norm}$ [kg/L]	0.71 / 1.24	1.21 / 1.38	1.27 / 1.65	0.84 / 1.69
t_{max} [h] #	2.0	2.0	2.0	1.50
$t_{1/2}$ [h]	2.23 / 1.08	3.09 / 1.38	2.81 / 1.27	3.16 / 1.53

* arithmetic mean ± SD # median (range)

Groups 2 and 3 had significantly higher normalized C_{max} and AUC values (almost 2x higher) relative to Group 1. There was no clear relationship of plasma drug level to the degree of renal impairment, since Group 4 had similar drug levels to those of Groups 2 and 3.

Cerivastatin M23 metabolite profile reflected the observations made with the parent compound; namely, Groups 2 and 3 had the highest plasma concentrations of metabolite, while Group 4 subjects had only slightly higher (or in some cases even lower) AUC and C_{max} values compared to Group 1. M1 metabolite profile was not as clear-cut. AUC was lowest in Group 2 which represented mild impairment. Only Group 3 was significantly different for AUC. However, a clear correlation was observed for the renal clearance of both metabolites (Spearman rank correlation coefficients M1 Cl_{ren}=0.833 and M23 Cl_{ren} =0.894).

Table 24
M23 pharmacokinetic parameters (g. mean/GSD)

	Group 1 n = 6	Group 2 n = 5	Group 3 n = 2	Group 4 n = 5
AUC [μg *h/L]	3.99 / 1.16	6.82 / 1.73	20.37 / 1.30	5.67 / 2.10 [b]
C_{max} [μg /L]	0.50/1.18	0.72 / 1.72	1.85 / 1.77	0.39 / 2.20
$t_{1/2}$ [h]	3.77 / 1.16	4.25 / 1.40	5.94 / 1.26	4.49 / 1.67 [e]
Ae_{ur} [%] *	8.56 ± 1.28	7.81 ± 2.69	3.26 ± 3.12 [c]	0.82 [d]
M24: Ae_{ur} [%] [a] *	0.63 ± 0.23	0.56 ± 0.39 [b]	0.86 ± 0.17	< LOQ [c]

a: all M24 plasma concentrations < 0.1 μg /L b: n = 4 c: n = 6 d: n = 1 e: n = 3
< LOQ = all urine concentrations < 1 μg /L
* arithmetic mean ± SD

Table 25
M1 pharmacokinetic parameters (g. mean/GSD)

	Group 1 (n = 6)	Group 2 (n = 5)	Group 3 (n = 4)	Group 4 (n = 1)
AUC [μg *h/L]	1.31 / 1.33	0.88 / 1.83 [d]	2.59 / 2.13	1.56
C_{max} [μg /L]	0.21 / 1.20	0.17 / 1.43	0.33 / 2.40 [a]	0.16 / 1.32 [b]
$t_{1/2}$ [h]	3.37 / 1.21	2.65 / 1.98 [c]	2.93 / 2.05	3.25
Ae_{ur} [%] *	3.50 ± 0.78	2.28 ± 1.02	1.46 ± 1.02	< LOQ [c]

a: n = 5 b: n = 4 c: n = 6 < LOQ = all urine concentrations < 1 μg /L d: n = 4
* arithmetic mean ± SD

A second multi-center, non-randomized, non-blinded, parallel design, multiple dose study of cerivastatin administered at a dose of 300 µg taken daily at 10:00 pm for 7 days compared patients with mild to severe renal impairment to healthy volunteers. The same criteria for group stratification that was used in the single dose study was used here. A total of 35 subjects participated in the study (see Table 26).

Table 26. Geometric Mean (%CV) Pharmacokinetic Parameters for Cerivastatin

Parameters		Group 1	Group 2	Group 3	Group 4
Day 1	AUC_{0-24} (µg•h/L)	19.2 (25.5)	19.6 (35.5)	30.8 (35.3)	29.0 (50.7)
	C_{max} (µg/L)	3.3 (37.8)	3.4 (56.1)	4.6 (34.5)	5.2 (40.5)
Day 7	AUC_{0-24} (µg•h/L)	21.4 (28.9)	20.8 (28.7)	36.1 (39.6)	30.0 (45.5)
	C_{max} (µg/L)	3.9 (38.8)	3.5 (29.9)	4.6 (42.2)	4.8 (36.7)
	t½ (h)	3.1 (23.9)	3.4 (21.7)	4.4 (25.8)	3.6 (22.0)

Patients in Groups 3 and 4 had AUC values which were 50% higher than Group 1. C_{max} values were 20% higher in these two groups compared to healthy volunteers. No accumulation of drug was observed as a result of renal impairment. The same phenomenon that was apparent in the single dose study is again apparent in this study. That is, the moderate impairment group appeared to be most different from the healthy volunteer.

It appears that differences do exist between the normal subject and the renally impaired patient. However, the body seems to compensate for this condition of renal impairment. The possibility exists that decreased protein binding associated with progressively worse renal function may be partially responsible for the apparent inconsistency between groups, since a greater free fraction would most likely lead to greater clearance. Secondly, cerivastatin is eliminated primarily by metabolism and biliary excretion, so that diminished renal function may not have a major impact on cerivastatin pharmacokinetics. All renally impaired groups had greater pharmacokinetic variability than did healthy volunteers. A clear relationship of plasma drug level to renal impairment was not established since a plateau effect was observed as the degree of renal impairment increased. Cerivastatin should be used with caution in renally impaired subjects.

Age

Safety, tolerability and pharmacokinetics of cerivastatin in elderly vs. young subjects were investigated under single-dose and steady-state conditions after seven days of 100 μg once daily, administered at 6 p.m., immediately after the evening meal. Forty-eight (48) healthy male volunteers participated in this placebo-controlled, randomized group comparison. Age ranged from 65 to 78 years for the elderly group, and 18 to 38 years for the young.

One subject in the young group had unusually low cerivastatin plasma concentrations on Day 7 suggesting non-compliance with dosing on that day. The below graph excludes this subject, while the tabular results below present data with and without this subject.

No significant differences were observed in the elderly compared to the young at steady-state. No accumulation was observed in the young. However, a 14% accumulation was observed in the elderly, which is probably not clinically significant. No significant differences were observed in t_{max} and $t_{½}$ between the young and the elderly.

Table 27
Summary of primary pharmacokinetic parameters in young and elderly male subjects after Cerivastatin multiple dosing of 100 μg qd for Day 1 and Day 7 (g. mean/GSD)

	Elderly, Day 1 (n = 15)	Elderly, Day 7 (n = 14)	Young, Day 1 (n = 8)	Young, Day 7 (n = 8) **
AUC [μg*h/L]	5.31 / 1.38	---	5.66 / 1.27	---
AUC_{norm} [kg*h/L]	4.20 / 1.34	---	4.16 / 1.40	---
AUC_{0-24} [μg*h/L]	5.24 / 1.37	5.98 / 1.36	5.55 / 1.25	4.29 / 2.37 (5.71 / 1.37)
$AUC_{0-24, norm}$ [kg*h/L]	4.14 / 1.32	4.78 / 1.34	4.07 / 1.39	3.15 / 2.46 (4.19 / 1.52)
C_{max} [μg/L]	0.94 / 1.36	1.00 / 1.25	0.93 / 1.34	0.62 /2 .68 (0.87 / 1.28)
t_{max} [h] *				
$t_{1/2}$ [h]	3.52 / 1.17	4.02 / 1.28	3.81 / 1.48	4.06 / 1.59 (3.58/1.17)

* (range) ** results in parentheses exclude outlier subject 1007

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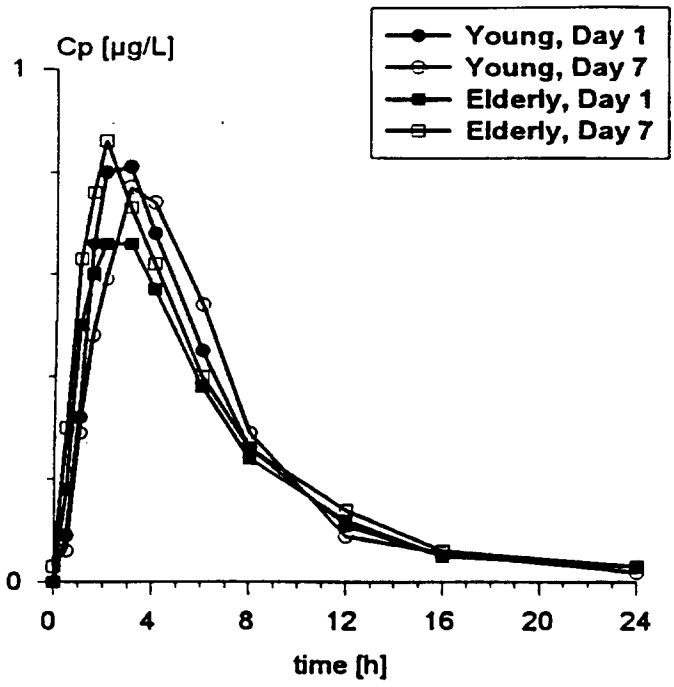

FIGURE 9. Cerivastatin plasma concentrations in young and elderly male subjects on Days 1 and 7 of a 100µg once daily dosing regimen (g. means)

The ability to lower Total and LDL cholesterol was significantly greater in the active group compared to the placebo. Significant differences were especially observed when comparing these two groups in the elderly population. The decreases from baseline for Total cholesterol and LDL-cholesterol were greater for the elderly population compared to the young (~35%) (Table 28).

Table 28. Pharmacodynamic Results for Young vs. Old Subjects Administered 100µg Cerivastatin

	Young		Elderly	
Lipid Parameter	**Placebo Δ (STD)**	**Active Δ (STD)**	**Placebo Δ (STD)**	**Active Δ (STD)**
Total Cholesterol	-8.6 (7.0)	-13.0 (8.1)	-5.8 (8.6)	-17.4 (6.7)
LDL-Cholesterol	-17.9 (5.8)	-20.3 (14.5)	-7.1 (12.6)	-28.1 (8.0)
HDL-Cholesterol	4.1 (19.5)	2.7 (10.5)	0.9 (8.2)	0.53 (7.4)
Triglycerides	16.4 (67.0)	-5.51(19.6)	-10.7 (25.5)	14.1 (75.3)

No differences in the occurrence of adverse events were observed between placebo and active controls. Twice as many adverse events (in total) occurred in the elderly compared to the young. This observation was not surprising due to the physiological changes in the body with age. Major adverse events were headache, digestive upset and pharyngitis. There was no difference in the occurrence of these major events between the young and the elderly. Sixteen subjects experienced elevated clinical values for CPK, SGPT and SGOT. No differences were observed between placebo vs. active and young vs. elderly.

Decrease in physiological function is commonly observed in the elderly, and the observed changes in pharmacokinetic parameters have a small, but statistically significant impact on the pharmacodynamic performance. Since no increased incidence in side effect profile was noted with age, no changes for the 100 µg dosage are being suggested at this time. However, the adverse event profile may change with increasing dosage of the drug.

Gender

The influence of gender on cerivastatin pharmacokinetics was investigated in a placebo-controlled, randomized, double-blind, parallel group multiple-dose study, where healthy female volunteers and age-matched male volunteers received 200 µg once daily at 6 p.m., immediately after the evening meal, for seven days. The results are depicted graphically in Figure 9 and summarized in Table 29.

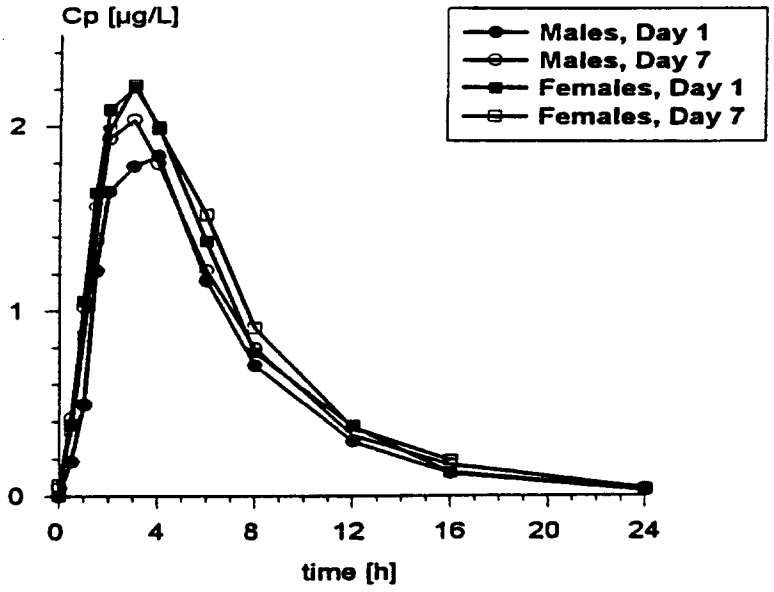

FIGURE 9. Cerivastatin plasma concentrations (g. means) after 200 µg qd for 7 days to healthy male and female volunteers (N=16 each)

Table 29
Summary of primary pharmacokinetic parameters in female and male subjects after cerivastatin multiple dosing of 200 μg qd for Day 1 and Day 7 (g. mean/GSD)

	Female, Day 1 (n = 16)	Female, Day 7 (n = 16)	Male, Day 1 (n = 16)	Male, Day 7 (n = 16)
$AUC_{0-\infty}$ [μg*h/L]	16.77 / 1.40	---	14.40 / 1.24	---
$AUC_{0-\infty,norm}$ [kg*h/L]	5.30 / 1.47	---	5.67 / 1.26	---
AUC_{0-24} [μg*h/L]	16.57 / 1.39	17.31 / 1.59	14.24 / 1.25	15.48 / 1.32
$AUC_{0-24,norm}$ [kg*h/L]	5.23 / 1.46	5.47 / 1.70	5.60 / 1.26	6.09 / 1.34
C_{max} [μg/L]	2.48 / 1.29	2.52 / 1.56	2.31 / 1.35	2.32 / 1.31
t_{max} [h] *				
$t_{1/2}$ [h]	3.40 / 1.17	3.44 / 1.27	3.56 / 1.24	3.67 / 1.20

* (range)

No significant differences in the primary pharmacokinetic variables, AUC_{0-24}, $AUC_{0-24,norm}$ and C_{max} at steady-state (Day 7) were observed between males and females. However, the AUCs were greater in males compared to females in the young group, but the female AUC values were greater in the elderly group. Older subjects had higher AUCs, an observation that was noted in the age study. No apparent dependence of both t_{max} and $t_{1/2}$ on gender was observed. No differences in accumulation between males and females was observed.

Table 30. Lipid Pharmacodynamic Results (% Change from Baseline)

	Females		Males	
Parameter	**Placebo Δ (STD)**	**Active Δ (STD)**	**Placebo Δ (STD)**	**Active Δ (STD)**
Total Cholesterol	-11.8 (6.7)	-17.6 (8.3)	-14.0 (7.1)	-26.8 (6.6)
LDL-Cholesterol	-15.5 (9.5)	-24.2 (10.8)	-19.0 (6.3)	-32.7 (6.7)
HDL-Cholesterol	- 9.5 (17.3)	- 8.6 (8.6)	-14.9 (17.2)	-11.3 (11.6)
Triglycerides	8.9 (36.4)	- 5.1 (27.5)	31.5 (70.0)	-17.2 (22.6)

Forty-nine percent (49%) of subjects reported 44 adverse events. Twice as many adverse events occurred in the active group compared to control. However, no gender differences were observed. The three most common adverse events were headache, dyspepsia and rash. In regards to clinical measurements, no differences in SGOT, SGPT and CPK elevations were

observed in placebo vs active groups. More males than females experienced elevation. In the <65 age group, females experienced elevation. However, in the >65 years of age group elderly males experienced elevations.

Ethnicity

A set of clinical pharmacological studies, similar to the phase-I program for the European and US submissions has been performed in 89 Japanese subjects. The studies included single doses, multiple doses, food effect and age effect. To address the issue of interethnic differences a retrospective pooled analysis of the primary pharmacokinetic parameters AUC, C_{max}, t_{max} and $t_{1/2}$ was performed for Caucasian, Japanese and Black subjects. These subjects were from study centers in the following countries: Germany, South Africa, Japan and the United States (see Tables 31, 32 & 33).

Table 31
Results of cerivastatin pharmacokinetic data pooled analysis for dose-normalized AUC and C_{max}, t_{max} and $t_{1/2}$ after single-dosing (g. means/GSD, median(range))

single dose	Caucasians (n = 181)	Japanese (n = 54)	Black (n = 22)
$AUC_{dose\text{-}norm}$ [h/L]	0.060 / 1.39	0.061 / 1.28	0.066 / 1.30
$C_{max,\ dose\text{-}norm}$ [L^{-1}]	0.011 / 1.40	0.011 / 1.28	0.012 / 1.34
t_{max} [h]*	2.0	3.0	2.0
$t_{1/2}$ [h]	3.13 / 1.42	2.03 / 1.22	3.00 / 1.26

* median (range) only

Table 32
Results of cerivastatin pharmacokinetic data pooled analysis for dose-normalized AUC and C_{max}, t_{max} and $t_{1/2}$ after multiple-dosing (g. means/GSD, median(range))

multiple dose	Caucasians (n = 52)	Japanese (n =16)
$AUC_{dose\text{-}norm}$ [h/L]	0.062 / 1.29	0.070 / 1.30
$C_{max,\ dose\text{-}norm}$ [L^{-1}]	0.011 / 1.37	0.012 / 1.27
t_{max} [h]*	2.0	4.0
$t_{1/2}$ [h]	2.55 /(1.62-6.80)	2.21 /(1.61-4.65)

* median (range) only

No difference in the primary pharmacokinetic parameters AUC and C_{max} for Caucasians, Japanese or Blacks was observed for single or multiple dosing (subject pool of Blacks was too small to be evaluated for multiple dosing).

The performance of key metabolites was also compared in the Japanese and Caucasian populations. Active metabolites M1 and M23 were present in plasma at similar concentrations and M24 was not detectable The Caucasian data was derived from healthy volunteers who participated in the renal impairment study, one of the few studies which evaluated the metabolites. The amount excreted compared favorably between the two populations.

Table 33
Cerivastatin metabolite pharmacokinetic data pooled analysis for dose-normalized AUC and C_{max}, t_{max} and $t_{1/2}$ after single-dosing (g. means/GSD, median(range))

	Caucasians (n = 6)		Japanese (n =6)	
	M23	M1	M23	M1
AUC_{-norm} [kg•h/L]	0.92 / 1.24	0.32/1.34	0.82 / 1.44	0.34/1.24
$C_{max,norm}$ [kg/L]	0.012 / 1.28	0.05/1.25	0.011 / 1.47	0.05/1.46
t_{max} [h]				
$t_{1/2}$ [h]	3.77 /1.16	3.37/1.21	2.61 /1.08	3.04/1.32
Ae_{ur} (%)	8.6±1.3	3.5 ± 1.21	9.0±2.1	4.2 ±1.0
M24 Ae_{ur} (%)	0.6±0.2		0.9±0.2	

* median (range) only

No evidence for any interethnic difference in cerivastatin pharmacokinetics was observed in the different ethnic groups investigated (Caucasians, Japanese and Black population).

Pediatric

The sponsor did not investigate cerivastatin in populations under 18 years of age.

VI. Drug Interactions

A. In vitro

In vitro studies were carried out to assess the protein binding characteristics of cerivastatin. Cerivastatin was highly bound to human plasma proteins (99.1%); mostly serum albumin (80%) and acidic alpha-1-glycoprotein (15%). The binding was independent of drug concentration up to 100 mg/L and relatively independent of pH in the range of 7.0- 8.6 and exhibits no gender

effect. Up to 100 mg/l, there were no signs of saturation of the protein binding. The erythrocyte/plasma partition coefficients were 0.1 for man and 0.16 for rat and dog. The partition coefficient for the unbound drug was high (erythrocyte/plasma water partition coefficients 18-28 for humans).

Cerivastatin did not alter the binding capacity of the highly bound drugs warfarin, imipramine and propranolol. The influence of other drugs on cerivastatin's binding capacity was also evaluated with no impact at therapeutic levels. However, at high concentrations of phenylbutazone, salicylic acid and nicotinic acid, slight increases in the free fraction were observed (see Table 34).

Table 34. Interaction of Different Drugs on the Protein-Binding of Cerivastatin (arith mean and coefficients of variation)

Drug	Concentration	Cerivastatin fraction unbound, %	(CV%)
None		0.82	(3.3)
None		0.99	(3.3)
None		1.03	(14)
Warfarin	3, 15	0.82, 0.81	(6.5, 5.6)
Phenylbutazone	100, 500	1.10, 1.82	(6.0, 0.9**)
Clofibrate	100, 500	0.81, 0.88	(0.8,2.9)
Ibuprofen	50, 250	0.76, 1.05	(8.7, 1.0)
Propranolol	1,5	0.77, 0.79	(11, 3.9)
Imipramine	0.3, 1.5	0.65, 1.04	(3.6, 34)
Gemfibrozil	100, 500	0.69, 1.01	(6.7, 2.5)
Nifedipine	1, 5	0.75, 0.87	(2.8, 7.3)
Salicylic Acid	200, 1000	1.24, 2.88	(33,11**)
Nicotinic Acid	100, 500	0.91, 1.53	(5.8, 7.4**)
Furosemide	0.5, 2.5	0.76, 0.81	(4.6, 14)
Phenytoin	20, 100	0.80, 1.00	(3.4, 4.1)
Digitoxin	0.1, 0.5	0.77, 0.73	(0.8, 1.6)

** $p<0.001$

B. In vivo

Concomitant drug intake may influence the pharmacokinetics of both drugs. The choice of studies to be performed for cerivastatin to elucidate the risk for drug-drug interactions was guided by the following rationale:

- to check for possible influence on the absorption of cerivastatin by changes in pH (antacids, H_2-antagonist).
- to check for possible influence on the absorption of cerivastatin by adsorption to cholestyramine, a basic co-medication in hypercholesterolemic patients.
- to check for possible influence on the metabolism of cerivastatin by the cytochrome P450 inhibitor cimetidine

- to examine the possible influence of cerivastatin on concurrently administered drugs with narrow therapeutic ranges, ie, warfarin and digoxin.

Maalox®

The influence of Maalox® 70, an antacid based on magnesium-aluminum hydroxide, was investigated in eight healthy male volunteers (age: 27-36 years) in a controlled, randomized, non-blind, two-way crossover study. Single oral doses of 200 µg cerivastatin were given under fasting conditions at 8 a.m. (meal 2 h after administration) with or without 10 mL Maalox® 70 suspension together with a small amount of water. Cerivastatin plasma concentration/time profiles were assessed in addition, total immunoactive drug (drug + metabolites) was determined

Table 35
Pharmacokinetic parameters after a single oral dose of 200 µg cerivastatin alone or in combination with Maalox® 70 (g. mean/GSD, n =

	Cerivastatin alone	Cerivastatin + Maalox® 70
AUC [µg•h/L]	11.38 / 1.46	10.44 / 1.46
C_{max} [µg/L]	1.99 / 1.48	1.77 / 1.29
t_{max} [h] *	3.0	3.0
$t_{1/2}$ [h]	2.69 / 1.29	2.67 / 1.24

* median (range)

The ratios of mean AUC and $C_{max\ values}$ (Cerivastatin + Maalox/Cerivastatin alone) and 90%-confidence intervals were 0.918 and 0.888 for the data, and 0.985 and 1.031 The analysis indicated that the simultaneous administration of Maalox® 70 did not have an influence on the pharmacokinetics of cerivastatin. A 10% reduction in AUC and 12% reduction in C_{max} was observed when the drugs were coadministered and this small change will probably have no clinical impact. However, the impact at 300 µg is unknown.

Cimetidine

The influence of the H_2-antagonist cimetidine was investigated in a study of similar design to that cited above. Eight healthy male young volunteers received single oral doses of 200 µg cerivastatin at 8 a.m. alone or on the fourth day of a four-day cimetidine 400 mg b.i.d. treatment regimen. Plasma concentration/time profiles were determined both by

Table 36
Pharmacokinetic parameters after a single oral dose of 200 μg cerivastatin alone or in combination with cimetidine (g. mean/GSD, n = 7)

	Cerivastatin alone	Cerivastatin + Cimetidine	Cerivastatin alone	Cerivastatin + Cimetidine
AUC [μg•h/L]	16.31 / 1.16	16.03 / 1.17	11.04 / 1.17	10.09 / 1.12
C_{max} [μg/L]	3.57 / 1.22	3.26 / 1.14	2.18 / 1.10	2.06 / 1.19
t_{max} [h] *	2.5	3.0	3.0	3.0
$t_{1/2}$ [h] **	1.66 ± 0.45	1.68 ± 0.40	2.14 ± 0.21	1.98 ± 0.31

* median (range) ** ar. mean ± SD

The ratios of mean AUC and $C_{max\ values}$ (Cerivastatin + Cimetidine/Cerivastatin alone) and 90%-confidence intervals were 0.982 , and 0.912 for the and 0.889 and 0.934 respectively, clearly indicating the absence of a pharmacokinetic interaction between cimetidine and cerivastatin.

Cholestyramine

The anionic exchange resin cholestyramine which prevents the reabsorption of bile acids, thus depleting endogenous cholesterol, is a common co-medication in patients treated with a HMG-CoA reductase inhibitor. Therefore, the influence of cholestyramine on cerivastatin pharmacokinetics was investigated in detail in two separate studies employing different dosing times and dosing conditions.

In the first study, twelve healthy male volunteers (age: 18 - 42 years) received single oral doses of 200 μg cerivastatin at 8 a.m. under fasting conditions alone or together with three pouches of cholestyramine (Quantalan®, 4 g per pouch, 12 g in total) in a controlled, randomized, non-blind crossover design. The mean cerivastatin plasma concentration/time curves, assessed by were markedly lower under concomitant cholestyramine dosing. Mean C_{max} was reduced by about 40% and occurred at a later time, and mean AUC was also reduced by about 21%.

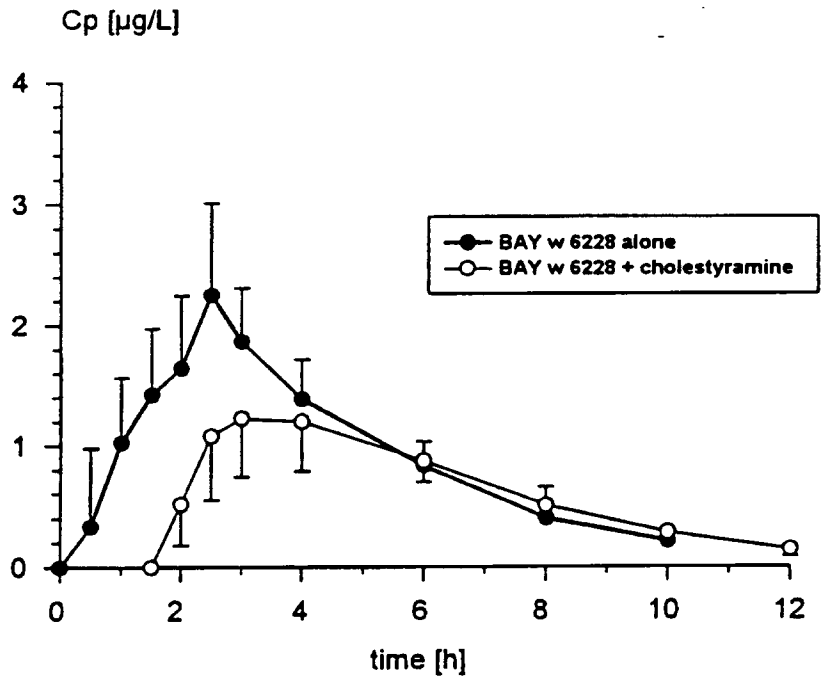

FIGURE 10. Cerivastatin plasma concentrations (g. means/SD) after administration of 200µg single dose to 12 healthy male volunteers with and without concurrent cholestyramine dosing

Table 37
Pharmacokinetic parameters of BAY w 6228 after a single oral dose of 200 µg BAY w 6228 alone or in combination with cholestyramine (g. mean/SD, n = 12)

	Cerivastatin at 8 a.m.	Cerivastatin at 8 a.m. + cholestyramine at 8 a.m.
AUC [µg*h/L]	10.29 / 1.23	8.10 / 1.41
C_{max} [µg/L]	2.28 / 1.31	1.33 / 1.48
t_{max} [h] #	2.5	3.0
$t_{1/2}$ [h]	2.19 / 1.12	2.55 / 1.15

median (range)

The ratios of mean AUC and C_{max} values (cerivastatin + cholestyramine/cerivastatin alone) and corresponding 90%-confidence intervals were 0.787 and 0.585 respectively, indicating that there is a statistically significant difference between the two treatments.

To clarify the clinical relevance of this interaction, an additional investigation was performed where cerivastatin and cholestyramine were evaluated with respect to dosing times and conditions. In a four-way controlled, randomized, non-blind, single-dose crossover study in twelve healthy male volunteers the following different treatments were studied:

- Treatment A (reference for B): 300 μg cerivastatin at 6 p.m. at the beginning of a standard dinner

- Treatment B: 12 g cholestyramine (3 * 4 g Quantalan® 50) at 5 p.m. (1 h before dinner) + 300 μg cerivastatin at 6 p.m. at the beginning of a standard dinner

- Treatment C (reference for D): 300 μg cerivastatin at 10 p.m. before bed time

- Treatment D: 12 g cholestyramine at 5 p.m. (1 h before dinner) 300 μg cerivastatin at 10 p.m. before bedtime

Table 38

Pharmacokinetic parameters after a single oral dose of 200 μg cerivastatin alone or in combination with cholestyramine at different time points (g. mean/GSD, n = 12)

	Treatment A: Cerivastatin at 6 p.m.	Treatment B: Cerivastatin at 6 p.m. + cholestyramine at 5 p.m.	Treatment C: Cerivastatin at 10 p.m.	Treatment D: Cerivastatin at 10 p.m. + cholestyramine at 5 p.m.
AUC [μg•h/L]	20.58 / 1.47	17.23 / 1.45	22.92 / 1.32	21.14 / 1.40
C_{max} [μg/L]	3.78 / 1.50	2.61 / 1.44	4.22 / 1.37	2.87 / 1.34
t_{max} [h] *	1.75	4.0	2.0	3.0
$t_{1/2}$ [h]	3.04 / 1.33	2.92 / 1.28	2.84 / 1.20	3.19 / 1.34

* median (range)

Rate and extent of absorption of cerivastatin were influenced by pretreatment with cholestyramine: The decrease in AUC was about 8-19% depending on the time of pretreatment, and the decrease in C_{max} was about 32%, irrespective of the time of pretreatment. For both timing conditions t_{max} was increased, whereas $t_{1/2}$ was not changed.

The ratios of mean AUC and C_{max} values (cerivastatin + cholestyramine/cerivastatin alone) and the 90%-confidence intervals for the two different time schemes (1-h and 5-h difference between cerivastatin and cholestyramine dosing) were as follows:

Table 39

Statistical evaluation of study of cholestyramine interaction study

Ratio:	B/A*	D/C*
AUC	0.837 (	0.923
C_{max}	0.690	0.680

*See preceding text for definition of treatment abbreviations

The 90%-confidence intervals of the decreased AUC and C_{max} by pretreatment with cholestyramine were not within the range of 80 to 125%. When administered concomitantly, the bioavailability of cerivastatin was reduced by adsorption to cholestyramine. Administering cholestyramine one hour before the evening meal and cerivastatin at bedtime will return plasma levels to normal.

The adverse events associated with coadministration were mostly upset stomach, flatulence and vomiting. Headache was also a major side effect experienced by the subjects. However, the occurrence of the side effects was across the board with no treatment arm having a greater incidence.

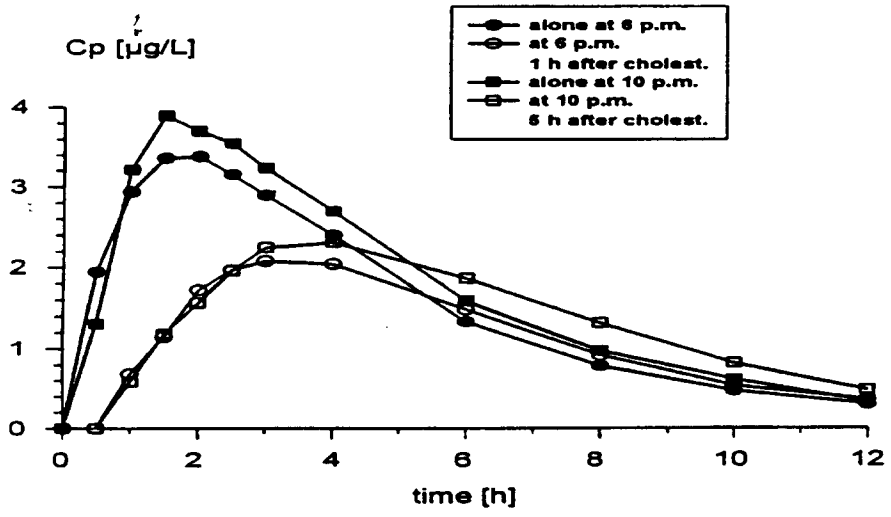

FIGURE 11. Cerivastatin plasma concentration (g. means) after administration of 300 µg single dose to 12 healthy male volunteers with and without concomitant cholestyramine dosing at different time points

Digoxin

Digoxin, a drug widely used for heart failure, has a narrow therapeutic range and the potential of an interaction with cerivastatin was evaluated. Twenty healthy male volunteers ranging in age from 20 to 43 years started the study with only 11 completing. The study was a nonrandomized, nonblinded multiple dose study.

On Day -2 they were given an initial dose of 200 μg cerivastatin at 6:00 pm after the evening meal in order to obtain a single-dose baseline pharmacokinetic profile. Digoxin (Lanoxin®) treatment began on Day 1 and consisted of loading doses of 0.5 mg once daily at 8 a.m. for three days, followed by digoxin maintenance doses of 0.25 mg once daily at 8 a.m. from study Day 4 to Day 30. Cerivastatin was co-administered with 200 μg once daily at 6 p.m. after the evening meal from Day 9 to Day 22.

Plasma digoxin concentrations were obtained 12 hours post-dose on Days 6, 7 and 8 (digoxin alone); on Days 20, 21 and 22 (digoxin + cerivastatin); and on Days 34, 35 and 36 (digoxin alone, post cerivastatin treatment). Twenty-four hour urine concentrations of digoxin were also determined. Cerivastatin plasma concentrations were measured from Day -2 through the next 24 hours. This routine was repeated on Day 9 for cerivastatin.

Table 40 below displays plasma digoxin concentrations, urine digoxin concentrations and calculated results for digoxin clearance (all g. mean/SD) including statistical evaluation for the periods when digoxin was administered alone (mean of Days 6, 7 and 8) and when dosed concurrently with cerivastatin (Days 20, 21 and 22). The digoxin values in the table represent "adjusted digoxin" values which were determined by dividing each individual digoxin concentration by the ratio of its corresponding calibration standard to the internal standard value of 0.7 ng/ml.

Table 40

Digoxin pharmacokinetic results with and without concurrent dosing of 200 μg cerivastatin (g. mean/GSD, n = 13)

	Digoxin alone	Digoxin + cerivastatin	Ratio (combined dosing/alone)	90%-confidence intervals	p-value
Digoxin plasma concentrations [μg/L]	0.594/1.17	0.651/1.18	1.096	1.004 - 1.195	0.086
Urine digoxin concentrations [μg/L]	94.11/1.27	96.10/1.44	1.021	0.912 - 1.143	0.748
Digoxin clearance [mL/min]	115.9/1.45	109.0/1.24	0.941	0.817 - 1.083*	0.453

* n = 6, otherwise n = 13

In addition, the follow-up digoxin measurements on Days 34-36 (seven subjects participated in this optional protocol extension) did not give any evidence for changes in digoxin steady-state pharmacokinetics when compared to period 1 which also represented a digoxin alone study period.

With regard to cerivastatin pharmacokinetics, the ratio of AUC_{0-24} (cerivastatin + digoxin /cerivastatin alone) was 1.034 with a 90% confidence interval of 0.960 - 1.114. t_{max} was decreased 18% when the drugs were coadministered and $t_{1/2}$ remained at 3h. C_{max} was statistically significantly increased (20%) in the presence of digoxin: the ratio was 1.196

Table 41

Cerivastatin pharmacokinetic results with and without concurrent dosing of 0.25 mg of digoxin (g. mean/GSD, n = 13)

Comparison of Day -2 to Day 9 AUC_{0-24} (ng•hr/ml)					
Parameters	**Day -2**	**Day 9**	**Ratio Day 9 vs Day -2**	**90% Confidence Interval**	**P-value**
AUC_{0-24}	14.19/1.36	14.67/1.27	1.0340	0.96-1.11	0.4424
$AUC_{0-\infty}$	14.3/1.36	14.81/1.28			
C_{max}	2.16/1.32	2.58/1.24	1.1959	1.099-1.30	0.0023
t_{max}	3.19/1.36	2.60/1.46			
t½	3.07/1.15	3.14/1.21			

All subjects reported at least 1 adverse event. Sixty percent reported adverse events at times which coincided with cerivastatin administration. The three most frequently reported adverse events were body as a whole (headache), respiratory (rhinitis and pharyngitis) and cardiovascular (abnormal electrocardiogram). The electrocardiogram abnormality occurred during the digitalization period (digoxin alone). Additional adverse events included gynecomastia (side effect of digoxin) and depression in one patient that was thought to be unrelated to the study drugs. A few elevations in serum CPK (2 x normal) (N=6) and liver function tests (N=1) were observed during the administration of cerivastatin.

The mean data indicated there were no statistically significant differences in plasma and urine digoxin concentrations following 14 days of concurrent dosing of cerivastatin and digoxin (Days 20, 21 and 22) compared to initial steady-state digoxin values (Days 6, 7 and 8). In fact, all measured digoxin parameters including plasma and urine concentrations and digoxin clearance were equivalent with respect to the 80-125% confidence limit criteria. However, when looking at the "raw" digoxin levels for subjects, 3 out of 13 had digoxin levels which increased more than 40% during concurrent administration of cerivastatin which suggested a possible interaction, although the mean data did not reflect this.

Because digoxin has such a narrow therapeutic index, the coadministration of these two drugs should not be taken lightly. The sponsor should have conducted this study at 300 µg which is the highest dose that is proposed for marketing. A difference in the pharmacokinetic and adverse event profiles might occur. Monitoring should occur, especially within the first month or two of administration.

The impact on cerivastatin is a lesser concern. The severity of side effects associated with cerivastatin are less severe compared to digoxin. No increases in the incidence of side effects

that are normally associated with cerivastatin were observed. The 20% increase in C_{max} should have no real clinical impact. Finally, a better design for the cerivastatin drug interaction study would have been to check blood levels throughout the coadministration period from Day 9 through Day 22 to ensure no accumulation of cerivastatin was occurring.

Warfarin

Twenty-four healthy male volunteers (age: 18 - 23 years) participated in a controlled, randomized, double-blind, two-way crossover study to determine the possible pharmacodynamic and pharmacokinetic interaction of the concomitant administration of cerivastatin and the anticoagulant warfarin sodium.

The study consisted of two treatment periods of 8 days each, with a 14-day washout period. The treatments included 300 μg cerivastatin or matching placebo once daily at 8 a.m. On study Day 4 of each treatment period, the volunteers also received a single oral dose of 25 mg of warfarin sodium (Coumadin®). The effect of cerivastatin on both the pharmacodynamics (prothrombin time [PT] and clotting factor VII activity) of warfarin sodium and the pharmacokinetics of both warfarin enantiomers was investigated. The effect of warfarin sodium on the pharmacokinetics of cerivastatin was also investigated.

Table 42

Summary of pharmacodynamic data for warfarin after single oral dose of 25 mg warfarin sodium during treatment with 300 μg cerivastatin or matching placebo once daily (g. mean/GSD, n = 21)

Parameter	Warfarin + Cerivastatin	Warfarin + Placebo	mean ratio (90%-confidence interval [%])
$AUC_{0\text{-}96\,h}$ of PT [s*h]	1940 / 1.12	1918 / 1.15	101 (100 - 103)
PT_48 h [s]	23.4 / 1.18	23.5 / 1.21	99 (96 - 102)
$AUC_{0\text{-}96\,h}$ of factor VII [%*h]	3332 / 1.33	3388 / 1.35	99 (95 - 103)
Factor VII_36 h [%]	12.1 / 1.66	12.1 / 1.80	100 (91 - 111)

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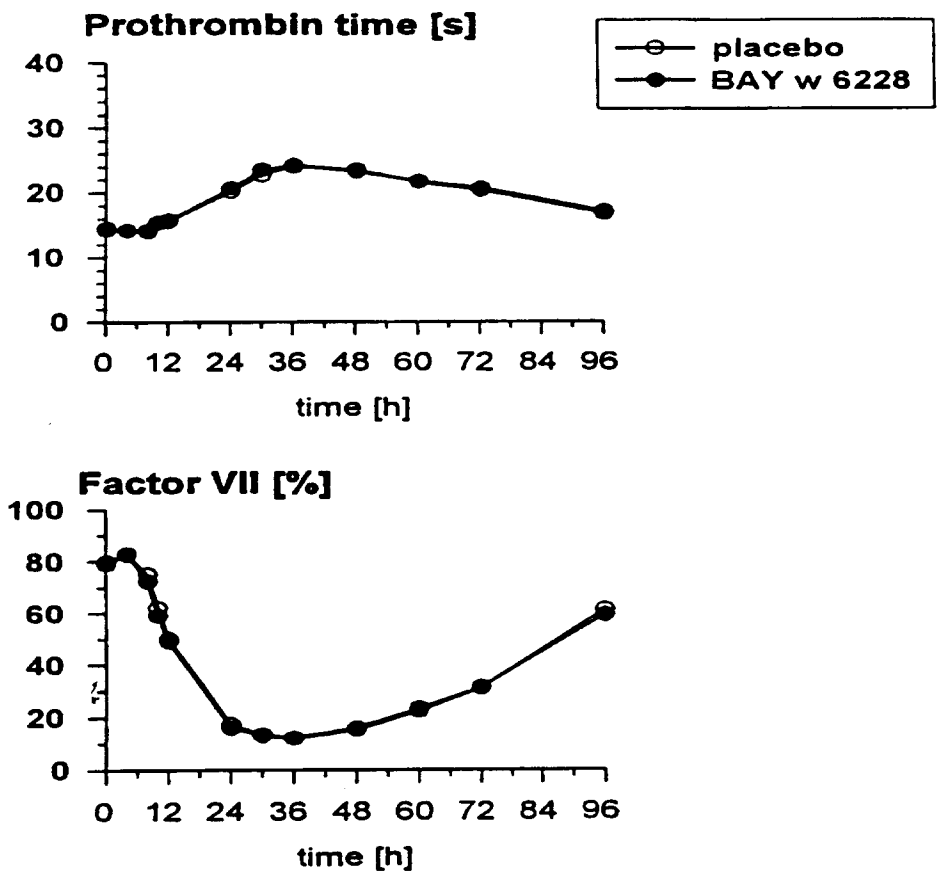

FIGURE 12. Mean clotting factor VII activity and prothrombin time results (g. means) after a single oral dose of 25 mg warfarin sodium on the fourth day of cerivastatin 300µg qd treatment in healthy male volunteers (N=21 each)

The ratios of mean prothrombin time and clotting factor VII activity (cerivastatin + warfarin/warfarin alone) were close to one, with 90% confidence limits of 95 to 105% for PT, and 90 to 111% for factor VII. The concomitant administration of cerivastatin and warfarin sodium, therefore, does not affect the pharmacodynamics of warfarin.

In addition, the pharmacokinetics of both enantiomers of warfarin were not affected by the co-administration of cerivastatin, as presented in Table 43.

Table 43

Summary of pharmacokinetic data for (R)- and (S)-warfarin after a single oral dose of 25 mg warfarin sodium during treatment with 300 μg cerivastatin or matching placebo once daily (g. mean/GSD, n = 21)

Parameter	Warfarin + Cerivastatin	Warfarin + placebo	mean ratio (90%-confidence interval [%])
(R)-Warfarin			
$AUC_{0-\infty}$ [mg•h/L]	94.5 / 1.21	91.8 / 1.24	103 (98.4 - 107)
C_{max} [mg/L]	1.62 / 1.15	1.62 / 1.18	100 (95.2 - 105)
t_{max} [h] *	3.5	2.5	
$t_{1/2}$ [h]	42.5 / 1.18	41.6 / 1.18	102 (96.6 - 108)
(S)-Warfarin			
$AUC_{0-\infty}$ [mg•h/L]	63.9 / 1.31	62.6 / 1.34	102 (98.1- 105)
C_{max} [mg/L]	1.58 / 1.16	1.57 / 1.20	101 (95.2 - 107)
t_{max} [h] *	2.0	2.5 (	
$t_{1/2}$ [h]	31.6 / 1.24	31.1 / 1.31	101 (96.1 - 106)

* median (range)

Similarly, there was no evidence for any interaction of warfarin on cerivastatin pharmacokinetics. The confidence intervals for the ratios of mean values of the parameters AUC, C_{max}, and $t_{1/2}$ were well within the 80 - 125% equivalence range.

TABLE 44. Summary of pharmacokinetic data for 300 μg cerivastatin administered daily for 3 days alone or with 25 mg warfarin daily for 4 days (g. means/SD)

Parameters	Without warfarin	With warfarin	Mean Ratio[1]	90% CI[2]
C_{max} μg/l	3.07/1.38	2.83/1.36	92.1	86.9-97.5
$C_{max\ norm}$ kg/l	0.75/1.35	0.69/1.34		
$AUC_{0-\infty}$ μg•h/l	18.1/1.30	16.3/1.32	90.0	85.4-94.8
$AUC_{0-\infty}$ kg•h/l	4.41/1.27	3.97/1.30		
t_{max} h	2.50	2.50		
$t_{½}$ h	2.19/1.17	2.23/1.11	102	95.2-104

[1]Geometric mean of individual test/reference ratios

[2]90% Confidence interval for the test/reference mean ratio after logarithmic transformation of the data