CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-740/S008/S013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUL 14 2000

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-740	SUBMISSION DATE: 09-22-1999
BRAND NAME:	Baycol
GENERIC NAME:	Cerivastatin sodium 0.8 mg tablets
REVIEWER:	Xiaoxiong (Jim) Wei, M.D., Ph.D.
SPONSOR:	Bayer, West Haven, CT
TYPE OF SUBMISSION:	Efficacy supplement

SYNOPSIS:

On September 22, 1999, Bayer submitted an efficacy supplement to NDA20-740 for extension of recommended dose up to 0.8 mg per day from current 0.4 mg per day. This supplement is an electronic submission with hard copies.

In this submission, the sponsor demonstrated dosage form equivalence between the existing 0.4 mg tablets and newly formulated higher strength, 0.8 mg tablets as well as the dose proportionality up to 0.8 mg per day. The sponsor also demonstrated that there is no accumulation of cerivastatin after multiple dose therapy. The study of effects of food and administration time on pharmacokinetics of cerivastatin showed that there was no difference between the morning or evening administration of a single dose of 0.8 mg cerivastatin under both fasting and fed conditions. In a drug interaction study of a single dose 0.8-mg cerivastatin with multiple doses of itraconazole, 200 mg once a day for 5 days, the sponsor indicated that the increase in mean AUC of cerivastatin is about 27%. The main goals of this review are to try to answer the following important questions:

1. Are the 0.8-mg cerivastatin tablets dosage form equivalent to 0.4-mg tablets? Is the dose proportionality extended to 0.8 mg from 0.4 mg?
2. Is there any accumulation of cerivastatin after multiple dose treatment?
3. Does food and the administration time have effect on the pharmacokinetic parameters of cerivastatin?
4. Is there any clinically relevant change in pharmacokinetic parameters of cerivastatin after itraconazole treatment of 200 mg once a day for 5 days?

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 20-740 Barcol 0.8-mg tablets submitted on September 22, 1999. The submission is acceptable to OCPB. The labeling comment (p.6) should be sent to the sponsor as appropriate.

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1. Are the 0.8-mg cerivastatin tablets dosage form equivalent to 0.4-mg tablets? Is the dose proportionality extended to 0.8-mg cerivastatin from 0.4-mg?

The sponsor conducted a three-way crossover study to investigate the bioequivalence of 2 x 400 µg tablet and 800 µg tablet cerivastatin as well as the dose proportionality of 400 µg and 800 µg tablets of cerivastatin after single, oral administration in 24 healthy volunteers (Study #80175). The subjects were given single oral doses of either 1 tablet of 800 µg cerivastatin, of 1 tablet of 400 µg cerivastatin, or of 2 tablets of 400 µg cerivastatin. The treatment sequence was given by a randomlist. The drug was given each dosing day between 7 p.m. and 7:36 p.m. The results are summarized in the Table 1.

Table 1. Descriptive statistics for cerivastatin pharmacokinetic Parameters (geom. Mean/SD, N=24)

Parameter	Dose and Strength		
	0.4 mg	0.8 mg	2 X 0.4 mg
AUC (µg.h/L)	17.9/1.4	38.6/1.4	36.8/1.4
AUCnorm (kg.h/L)	3.64/1.3	3.91/1.4	3.73/1.4
Cmax (µg/L)	2.64/1.3	6.04/1.4	5.58/1.5
Cmax norm (kg/L)	0.535/1.3	0.613/1.5	0.566/1.5

AUCnorm (kg.h/L): AUC X body weight/dose

The following Table 2 summarizes point estimates and 90 % confidence intervals derived from the analyses of variance for cerivastatin:

Table 2. Mean Ratios and 90 % confidence intervals for the appropriate comparisons for cerivastatin.

Parameter	Comparison	Estimated Ratio	90 % C.I. for Ratio
AUC norm	0.8 mg : 0.4 mg	1.07	1.00, 1.15
	0.8 mg : 2 X 0.4 mg	1.05	0.98, 1.12
Cmax norm	0.8 mg : 0.4 mg	1.14	1.02, 1.28
	0.8 mg : 2 X 0.4 mg	1.08	0.96, 1.21

Since the ratios of AUC and Cmax for tablets 0.8 mg : 2 X 0.4 mg were 1.07 and 1.05, respectively with 90% confidence intervals within 0.8 to 1.25, this reviewer agrees with the sponsor that a single oral dose of 0.8 mg cerivastatin tablet is bioequivalent to a single oral dose of 2 x 0.4 mg cerivastatin tablets.

AUC_{norm} was estimated to be 7 % higher for 0.8 mg than for 0.4 mg (mean ratio: 1.07) with a 90 % confidence interval of [1.00, 1.15]. The mean ratio for $C_{max,norm}$ was 1.14 with a 90 % confidence interval of [1.02, 1.28]. This reviewer agrees with the sponsor that a dose-proportional behavior of cerivastatin may be concluded.

2. Is there any accumulation of cerivastatin after multiple dose treatment?

The sponsor conducted a study to investigate if there is any accumulation of cerivastatin after multiple dose therapy (Study # D96-039). The primary objectives of this study included the determination of single-dose and 10-day steady-state pharmacokinetics of 800 µg cerivastatin. The pharmacokinetic parameters assessed included AUC_{0-24}, C_{max}, t_{max} and $t_{1/2}$. On Day 1 and Days 8 to 17, subjects were administered 800 µg of cerivastatin given as 2 x 400 µg tablets once each evening between the hours of 5 and 6 p.m. The results are summarized in the following table:

Table 3. Geometric Means (geom. SD)		
PK Parameter	800 µg (Day 1)	800 µg (Day 17*)
AUC_{0-24} (µg•h/L)	59.27 (1.35)	53.19 (1.37)
C_{max} (µg/L)	12.20 (1.32)	9.55 (1.37)
t_{max} (hours)	2.07 (1.33)	2.58 (1.29)
$t_{½}$ (hours)	3.59 (1.24)	3.79 (1.13)
*Steady-state, after 10 days dosing		

No statistically significant differences were observed between single dose and steady-state pharmacokinetics of cerivastatin 800 µg for AUC_{0-24} and $t_{½}$. The ratio of Day 17 to Day 1 values for these variables were 0.897 and 1.054 for AUC_{0-24} and $t_{½}$, respectively. Therefore, the sponsor concluded that there was no accumulation following 10 days of dosing with 800 µg cerivastatin (mean accumulation ratio was 0.91).

In a multiple dose study of safety, tolerability, pharmacokinetics and pharmacodynamics of 0.8 mg cerivastatin in patiets with hypercholesterolemia (97-001), a steady state pharmcokinetic profiles were measured on Day 28. 27 out of 40 patients were analyzed for multiple dose pharmacokinetics. Patients ranged in age from 28 to 74 years, and in weight from 127 to 248 lbs. There were 39 Caucasian and two Black patients in the study. Fifteen patients were male and 26 patients were female. The multiple dose pharmacokinetic profile is comparable to the study discussed above. (Table 4).

Table 4. Geometric Mean (%CV) of Pharmacokinetic Parameters			
Parameter	Cerivastatin (n = 27)	M1 (n = 14)	M23 (n = 14)
AUC_{0-24} (µg*h/L)[1]	67.0 (30%)	5.54 (48%)	17.0 (54%)
C_{max} (µg/L)	12.7 (41%)	0.55 (50%)	1.4 (47%)
t_{max} (hr)	1.4 (33%)	3.4 (53%)	4.5 (35%)
$t_{1/2}$ (hr)[1]	4.2 (20%)	3.6 (40%)	5.0 (39%)

This reviewer agrees with the sponsor's conclusion from this study. However, this reviewer found that there is great variation for AUC values from different studies in this submission. The following table summarized these AUC values of cerivastatin on Day 1 only from different studies:

Study Protocol #	AUC on Day 1
80175	38.6
10012	———
96-039	59.3

It seems that the difference among studies for AUC values can reach 1.5 fold.

3. Does food and the administration time have effect on the pharmacokinetic parameters of cerivastatin?

The sponsor conducted a single-center, randomized, non-blind, controlled four-way crossover study on the pharmacokinetics of a single dose of 0.8 mg cerivastatin administered in the morning or evening under each fasting or fed conditions (Study #10012).

The primary objective of this study was to evaluate the influence of food and administration time of dosing on bioavailability and pharmacokinetics of cerivastatin following oral administration of 0.8 mg single doses each. The sponsor assessed 36-hour pharmacokinetic profiles of the plasma concentrations for cerivastatin and the metabolites M-1 and M-23.

The study design was as follows:
A: at 8 a.m. following an overnight fast of at least 10 hours
B: at 8 a.m. within 5 min after a high-fat breakfast
C: at 6 p.m. within 5 min after a low-fat evening meal
D: at 10 p.m. 4 hours after a low-fat evening meal.

The study results were summarized below.

Descriptive statistics for cerivastatin pharmacokinetic parameters (geom. mean/g.SD, N = 24)

Parameter	Treatment			
	A	B	C	D
AUC (mcg*h/L)	43.5/1.36	41.6/1.41	44.2/1.39	45.3/1.41
C_{max} (mcg/L)	7.7/1.40	8.7/1.42	7.1/1.41	7.1/1.43
t_{max} (h)*	1.5	2.0	3.0	2.5
$t_{½}$ (h)	2.6/1.22	2.4/1.34	2.9/1.21	2.9/1.16

* median (range)

The following table summarises the main ANOVA results for cerivastatin:

Mean Estimates and 90% confidence intervals (CI) for the various treatment comparisons

Parameter	Comparison	Estimate	90 % CI
AUC [mcg*h/L]	B / A	0.96	[0.90, 1.01]
	C / D	0.97	[0.92, 1.03]
	D / A	1.05	[0.99, 1.11]
	C / B	1.06	[1.00, 1.12]
C_{max} [mcg/L]	B /A	1.12	[1.04, 1.21]
	C / D	1.00	[0.93, 1.08]
	D / A	0.92	[0.85, 0.99]
	C / B	0.81	[0.76, 0.88]

The calculated confirmatory 90 % confidence intervals for cerivastatin AUC for the ratios B/A ([0.90, 1.01]) and C/D ([0.92, 1.03]) were completely contained within the range of 0.80 to 1.25. Consequently, no relevant influence of food on cerivastatin AUC could be detected for both the morning and evening dosing.

This reviewer agrees with the sponsor's conclusion that there was no difference between the morning or evening administration of a single dose of 0.8 mg cerivastatin under both fasting and fed conditions.

4. Is there any clinically relevant change in pharmacokinetic parameters of cerivastatin after itraconazole treatment of 200 mg once a day for 5 days?

Cerivastatin is metabolised by the CYP-450 3A4 to some degree. The sponsor conducted a crossover study evaluated the effect of CYP-450 3A4 inhibition by itraconazole on the metabolism and pharmacokinetics of 0.8 mg cerivastatin and near equi-potent doses of pravastatin and atorvastatin. This study attempted to evaluate the extent of the CYP-450 3A4 interaction of each of these 3 statins. However, atorvastatin data was not included in the submission.

This was a randomized, open-label, 3-way crossover study designed to evaluate the pharmacokinetics of 0.8 mg cerivastatin, 20 mg atorvastatin, and 40 mg pravastatin, alone and in combination with 200 mg itraconazole. The statin-alone dose was given on Day 1 of each period. The combination dosing (statin and itraconazole) occurred on Day 10 after 5 days of once daily itraconazole pretreatment (itraconazole given once daily on Days 6 to10). Between each period there was a 14- to 17-day washout phase. The cerivastatin $AUC_{0-\infty}$, AUC_{0-tn}, C_{max}, t_{max}, and $t_{½}$ are shown in Table 6-1.

Table 6-1. Geometric mean (%C.V.) PK Parameters of Cerivastatin (CER) Given Alone or with Itraconazole (ITRA)

Parameter	n	CER alone	CER + ITRA	Ratio of LS Means ([CER + ITRA]/CER)	90% C. I. About Ratio
$AUC_{0-\infty}$ (µg*h/L)	18	50.2 (15.3)	63.5* (32.2)	1.27	1.12 – 1.43
AUC_{0-tn}(µg*h/L)	18	48.1 (40.8)	61.3* (32.9)	1.27	1.12 – 1.45
C_{max} (µg/L)	18	8.6 (42.9)	10.8* (40.5)	1.25	1.04 – 1.51
t_{max} (hr)	18	2.0 (41.4)	2.0 (33.2)	--	--
$t_{½}$ (hr)	18	2.8 (25.7)	3.4* (16.7)	1.19	1.12 – 1.28
* p<0.05 compared to cerivastatin alone					

The Metabolite M1 AUC_{0-tn} and C_{max} parameters are shown in Table 6-2.

Table 6-2. Geometric mean (%C.V.) PK Parameters of Cerivastatin Metabolite M1 Following Administration of Cerivastatin (CER) Alone or with Itraconazole (ITRA)

Parameter	n	CER alone	CER + ITRA	Ratio of LS Means ([CER + ITRA]/CER)	90% C. I. About Ratio
AUC_{0-tn} (µg*h/L)	15	2.6 (51.9)	1.7* (72.6)	0.63	0.43 – 0.92
C_{max} (µg/L)	17	0.6 (42.8)	0.5 (49.5)	0.81	0.65 – 1.00
* p<0.05 compared to cerivastatin alone					

Slight decreases in both AUC and C_{max} of M1 were observed with concurrent itraconazole.

The Metabolite M23 AUC_{0-tn} and C_{max} are shown in Table 6-3.

Table 6-3. Geometric mean (%C.V.) PK Parameters of Cerivastatin Metabolite M23 Following Administration of Cerivastatin (CER) Alone or with Itraconazole (ITRA)

Parameter	n	CER alone	CER + ITRA	Ratio of LS Means ([CER + ITRA]/CER)	90% C. I. About Ratio
AUC_{0-tn} (µg•h/L)	18	11.5 (39.0)	16.1* (31.8)	1.40	1.24 – 1.57
C_{max} (µg/L)	18	1.4 (33.6)	1.6 (37.9)	1.17	0.98 – 1.38
* p<0.05 compared to cerivastatin alone					

The effects of itraconazole on M23 resembled those on parent drug, namely, a modest but statistically significant increase in AUC, and a lesser increase in C_{max}.

Itraconazole produced a significant increase in pravastatin AUC, which averaged 51% resulting in a much broader 90% confidence interval, with an upper limit just above 2. There was a mean increase in C_{max} of 24%, but because of the greater variability associated with pravastatin, this effect was not statistically significant. The 3-OH metabolite exhibited the greatest changes from itraconazole co-administration, with mean AUC and C_{max} values that were almost twice those found with pravastatin alone.

The effects of itraconazole on the pharmacokinetics of 0.8 mg cerivastatin were consistent with previously reported results obtained with 0.3 mg cerivastatin given with either itraconazole or erythromycin, another potent CYP450 3A4 inhibitor. In those studies, mean increases in AUC of 38% and 50% were found with itraconazole and erythromycin, respectively. The corresponding increase is C_{max} were 12% and 24%. In the current study, the mean increase in AUC was 27%, and the mean increase in C_{max} was 25%.

M1 is formed primarily via CYP-450 3A4, so inhibition of this enzyme by itraconazole would be expected to decrease the formation of this metabolite. On the other hand M23 is formed primarily through CYP-450 2C8, so it is not surprising that in the context of decreased CYP-450 3A4 activity, more of the cerivastatin dose would be subject to this alternative pathway. The increased formation of M23 (about 40% higher AUC) offsets the decreased formation of M1 (about 40% lower AUC). Although both metabolites are pharmacologically active, only the M23 metabolite has similar activity as cerivastatin. M1 possesses about 50% of the activity of the parent. Additionally, metabolites M1 and M23 are present in much lower concentrations.

The mean increase in pravastatin AUC by itraconazole was approximately 50%. The most pronounced changes were seen with the 3-OH metabolite of pravastatin, for which the AUC almost doubled when given with itraconazole. However, the impact of the increase is mitigated by the fact that the 3-OH metabolite of pravastatin possesses only 1/10 the potency of pravastatin itself.

The sponsor concluded that the pharmacokinetics of both cerivastatin and pravastatin are only slightly affected by inhibition of hepatic CYP-450 3A4 by itraconazole. Single doses of cerivastatin and pravastatin given alone or in combination with itraconazole after 5 days of pre-treatment were well tolerated. This reviewer agrees with the sponsor 's conclusion in this clinical setting with a single CYP3A4 inhibitory drug. We are more concerned about multiple drug interactions, specifically when both CYP3A4 and CYP2C8 metabolic pathways are inhibited.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☛ indicates an explanation only and is not intended to be included in the labeling)

Pharmacokinetics/Metabolism Section:

The major circulating blood components are cerivastatin and the pharmacologically active M1 and M23 metabolites. The relative potencies of metabolites M1 and M23

Following a 0.8-mg dose of cerivastatin to male and female patients, mean steady state Cmax values for cerivastatin, M1, and M23 were 12.7, 0.55, and 1.4 ug/L, respectively. Therefore, the cholesterol-lowering effect is due primarily to the parent compound, cerivastatin.

☛ the relative potencies of cerivastatin and its metabolites M1 and M23 are indicated in the current labeling and should be there in modified labeling.

Precaution/Drug interactions Section:

/S/

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Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 9/14/00

CC: NDA 20-740 (orig.,1 copy), HFD-510 (Simoneau), HFD-850 (Lesko), HFD-870 (Wei, Ahn, Huang), CDR.

Code: AP

Attached: study summary 80175.

Study synopsis (80175)

Title of the study:	Randomized, non-blind, three-way crossover study to investigate the dose proportionality of 400 µg and 800 µg tablets of BAY w 6228 (Cerivastatin) as well as the bioequivalence of 2 x 400 µg tablet and 800 µg tablet BAY w 6228 (Cerivastatin) after single, oral administration in 24 healthy volunteers. (BAY w 6228/0183)
Investigators:	W. Wingender, M.D., H. Adelmann, M.D., M. Böttcher (physician), D. Kubitzka, M.D., G. Lemm, M.D., J. Nagelschmitz, M.D., U. Schühly, M.D., G. Wensing, M.D.
Study center:	Bayer AG, Pharma Research Center, Institute of Clinical Pharmacology, 42096 Wuppertal, Germany
Publications (references):	Not applicable
Period of study:	20th October-1997 - 24th November 1997
Clinical phase:	I
Objectives:	The primary objective of this study is to investigate the dose proportionality of 400 µg and 800 µg tablets of BAY w 6228 (Cerivastatin) as well as the bioequivalence of 2 x 400 µg tablet and 800 µg tablet BAY w 6228 (Cerivastatin). The secondary objective is to investigate the safety and tolerability of BAY w 6228.
Methodology (design of study):	This was a single-center, randomized, non-blinded, cross-over trial.
Number of healthy subjects /patients:	24 healthy male subjects were enrolled into the study and randomly allocated to one of the 6 sequence groups. None of the subjects dropped out of the study. 24 subjects were valid for the safety analysis 24 subjects were valid for pharmacokinetic analysis
Diagnosis and main criteria for inclusion:	Healthy male caucasian subjects, aged between 18 to 45 years.
Test product, dose and mode of administration, batch number:	BAY w 6228 (Cerivastatin): - Tablets BAY w 6228 of 800 µg, Development number: — Batch No.: 521 226T/8 (BAYER AG) route of administration: orally
Duration of treatment:	The appropriate BAY w 6228 doses were given as single oral doses at about 7 p.m. at the profile day in each period according to the random plan.
Reference therapy, dose and mode of administration, batch number:	BAY w 6228 (Cerivastatin): - Tablets BAY w 6228 of 400 µg, Development number: — Batch No.: 521 226T/8 (BAYER AG) route of administration: orally
Criteria of evaluation:	Criteria for assessment of the pharmacokinetic profiles were the plasma concentration time curves of BAY w 6228 and its main metabolites M1 and M23 and the following pharmacokinetic parameters: Primary parameters: AUC, AUC_{norm}, C_{max}, $C_{max,norm}$ for BAY w 6228. Secondary parameters: t_{max}, MRT, $t_{1/2}$ for BAY w 6228 and AUC, AUC_{norm}, C_{max}, $C_{max,norm}$, $t_{1/2}$, MRT, t_{max}, Ae_{ur} and CL_{ren} for the metabolites. Criteria to assess safety and tolerability were adverse events, cardio-vascular parameters (systolic and diastolic blood pressure,

	mean arterial pressure, heart rate), ECG parameters (PR, QRS, QTc duration, heart rate) and laboratory data (haematology, clinical chemistry, urinalysis).
Statistical methods:	Pharmacokinetic data of the unchanged drug BAY w 6228 were to be evaluated according to the Bayer Guideline 'Harmonization of Data Evaluation in Pharmacokinetics' Point estimates and associated 90 % confidence intervals were constructed for the primary PK parameters for the ratios '800 µg/2 x 400 µg' and '800 µg/400 µg' using the intra-individual standard deviation determined by analysis of variance appropriate for the cross-over design. All safety parameters were evaluated descriptively.

Summary and Conclusions:

Results:

Safety

24 subjects with the random numbers 01 to 24 participated in each of the three periods of the study.

The dose proportionality of 400 µg and 800 µg tablets of BAY w 6228 (Cerivastatin) as well as the bioequivalence of 2 x 400 µg tablet and 800 µg tablet BAY w 6228 (Cerivastatin) were investigated in a 3 x 3 crossover study design by administration of either 1 tablet of 800 µg BAY w 6228, of 1 tablet of 400 µg BAY w 6228, or of 2 tablets of 400 µg BAY w 6228. The drug was given each dosing day between 7 p.m. and 7.36 p.m. and was staggered between the subjects.

The demographic characteristic of the study group is given in table I next page.

Summary and Conclusions:

table I: demographics

total study population, N=24

age	mean	35.0
(years)	sd	4.75
	range	(28 - 44)
race	Caucasian	24
weight	mean	81.5
(kg)	sd	8.36
	range	(66 - 101)
height	mean	182.21
(cm)	sd	5.70
	range	(170 - 193)
Broca-Index	mean	0.99
	sd	0.10
	range	(0.84 - 1.15)

11 of 24 subjects (i.e. 46 % of the study population) reported adverse events after initiation of 400 µg BAY w 6228, after 2 x 400 µg 5 of 24 subjects (i.e. 21 %) suffered from any adverse event and following 800 µg adverse events were observed with 9 of 24 subjects (i.e. with 38 % of the

population). The incidence rates of any adverse event (which is equal to the ratio "number of subjects reporting any event with a start after treatment/total number of subjects") were 29 % (400 µg), 8 % (2 x 400 µg) and 21 % (800 µg).
There were no deaths, other serious adverse events or other significant adverse events in this study.
In case of the headache of subject no. 10 which was of moderate intensity and was accompanied by vomiting and nausea a relationship to drug administration cannot be excluded. But as the drug administration in this study took place in the evening and blood samples were to be taken during the night the sleep of the volunteers was disturbed and this could be another possible explanation for this adverse event. In all other cases a relationship to drug substance seems not to be possible. In case of the cold diseases or the cold related symptoms like rhinitis or sore throat which occured during the study it has to be kept in mind that the study was conducted in October and November

Summary and Conclusions:
when cold diseases are very common in the area around the study site. In other cases a relationship can be excluded as they started prior to drug administration or very late after drug administration which holds true for most cases of headache which were reported and for the gastroenteritis in case of subject no. 3. A tabulated summary of the adverse event is given in table II below.

Table II: Adverse events occuring after initiation of study drug

	400 µg	2 x 400 µg	800 µg
Subjects with any event after initiation of study drug Observed / total (rate)	11/24 (46 %)	5/24 (21 %)	9/24 (38 %)
Subjects with any treatment-emergent event Observed / total (rate)	7/24 (29 %)	2/24 (8 %)	5/24 (21 %)
Adverse event			
Headache	no. 7, 9, 10, 15++	no. 9*	no. 22
Cold disease	no. 5*	no. 6*	no. 6*, 10*, 22
Rhinitis	no. 17*, 24*	no. 17	no. 12, 17*
Sore throat	no. 5*, 18, 23		
Cough	no. 14*	no. 14*	no. 14*
Whistling in the ears			no. 12
Abdominal pain	no. 6		no. 8
Pain right thorax			no. 9
Pain in the shoulder		no. 3*	
Intercostal neuralgia		no. 9	
Gastroenteritis			no. 3
Nausea	no. 10		
Vomitus	no. 6, 10		
Meteorism			no. 9
Soft stool			no. 8

++ random number
* denotes an event which was not treatment-emergent

Summary and Conclusions:
No pronounced individual changes in laboratory parameters could be recognized which could be attributed to BAY w 6228 treatment. If laboratory parameters were abnormal they were not of clinical relevance because they were only slightly changed, already present prior to first drug administration, were of a short duration and normalized during the further course of the study, or were within the same range for all measurement for the respective subject.
In several parameters there was a slight mean decrease from -11 hours to +13 hours and then an increase up to the base level after +37 hours (AST, ALT, AP, GLDH, LDH, HBDH, urea, uric acid, total protein, potassium and platelet). There was a mean decrease in LDL for all dosing groups from -11 hours to +37 hours. Mean leukocytes, neutrophils and triglyceride values increased from -11 hours to +37 hours in each dosing group.
A relationship of the changes of these parameters to the drug administration seems to be rather impossible as they occured shortly after the drug administration and went back to the baseline the next day. It must be kept in mind that several blood samples were taken during the night which disturbed the sleep of the subjects. The in-house situation could have changed some of the parameters, too.
No systematic treatment effect on vitals signs and ECG was apparent. In this study the administration of the study medication was performed at 7:00 pm. Thus the profile measurements

during the night (up to 13 hours after dosing) showed a decrease in the vital parameters which was not related to the study drug.
The tolerability of the study drug was in general good. Adverse events after the higher doses were neither increased in the number nor in the intensity. In most cases they were not related to drug administration and of mild to moderate intensity. No safety relevant alterations of vital signs, physical findings, laboratory parameters, or ECG-findings could be found. Therefore it can be concluded that the administration of BAY w 6228 was safe and well tolerated in all doses investigated.
Pharmacokinetic analysis
Plasma samples were analysed for the parent drug BAY w 6228 and its metabolites M1 and M23 by

— The limit of quantification was ——— for BAY w 6228, and —— for the metabolites.

Summary and Conclusions:

Descriptive statistics for BAY w 6228 pharmacokinetic parameters

(geom. mean/SD, n = 24)

	400 µg	800 µg	2x400µg
AUC (µg*h/L)	17.9 / 1.4	38.6 / 1.4	36.8 / 1.4
AUC_{norm} (kg*h/L)	3.64 / 1.3	3.91 / 1.4	3.73 / 1.4
C_{max} (µg/L)	2.64 / 1.3	6.04 / 1.4	5.58 / 1.5
$C_{max,norm}$ (kg/L)	0.535 / 1.3	0.613 / 1.5	0.566 / 1.5
$t_{1/2}$ (h)	3.46 / 1.2	3.22 / 1.2	3.36 / 1.2
MRT (h)	7.04 / 1.3	6.36 / 1.3	6.71 / 1.2
t_{max} (h)#	3.0 ———	2.5 ———	3.0 ———

median (range)

The following table summarizes point estimates and 90 % confidence intervals derived from the analyses of variance for BAY w 6228 and its metabolites M1 and M23:

Mean Ratios and 90 % confidence intervals for the appropriate comparisons for BAY w 6228

Substance	Parameter	Comparison	Estimated Ratio	90 % C.I. for Ratio
BAY w 6228	AUC_{norm}	800mcg : 400 mcg	1.07	(1.00, 1.15)
		800 mcg : 2 x 400 mcg	1.05	(0.98, 1.12)
	$C_{max,norm}$	800mcg : 400 mcg	1.14	(1.02, 1.28)
		800 mcg : 2 x 400 mcg	1.08	(0.96, 1.21)
M 1	AUC_{norm}	800mcg : 400 mcg	0.90	(0.59, 1.36)
		800 mcg : 2 x 400 mcg	1.10	(0.87, 1.38)
	$C_{max,norm}$	800mcg : 400 mcg	0.97	(0.82, 1.15)
		800 mcg : 2 x 400 mcg	1.08	(0.92, 1.27)
M 23	AUC_{norm}	800mcg : 400 mcg	0.98	(0.88, 1.09)
		800 mcg : 2x400 mcg	1.05	(0.95, 1.16)
	$C_{max,norm}$	800mcg : 400 mcg	1.05	(0.98, 1.13)
		800 mcg : 2 x 400 mcg	1.08	(1.00, 1.16)

Summary and Conclusions:
It can be concluded that a single oral dose of 800 µg BAY w 6228 tablet is bioequivalent to a single oral dose of 2 x 400 µg BAY w 6228 tablets.
It cannot be formally concluded that a single oral dose of 800 µg BAY w 6228 tablet is dose-proportional in all respects to a single oral dose of 400 µg BAY w 6228 tablets. AUC_{norm} was estimated to be 7 % higher after 800 µg relative to 400 µg (mean ratio: 1.07) with a 90 %

confidence interval of [1.00, 1.15]. So it was completely contained within the bioequivalence range of [0.80, 1.25]. The mean ratio for $C_{max,norm}$ was 1.14 with a 90 % confidence interval of [1.02, 1.28], however, thus with an upper limit of 1.28 being slightly higher than the upper limit of the bioequivalence range. Considering this marginal violation of the formal criteria, assumed to be of no clinical relevance, a dose-proportional behaviour of BAY w 6228 may be concluded.
Although the pharmacokinetic characteristics of M1 and M23 were not the primary targets in this study (please see chapter 5.10.2 of the protocol) and the sample size estimation did not regard these variables an exploratory statistical assessment was made also for the metabolites in plasma.
For the metabolite M1 neither bioequivalence nor dose-proportionality can be concluded. However, it should be taken into account that the point estimators for all ratios are close to 1, and that the intra-subject variability was markedly larger (CV of 39 % for AUC_{norm} and 35 % for $C_{max,norm}$) than anticipated in the sample size estimation for BAY w 6228 with a CV of 22.5 %. Furthermore AUC_{norm} could be determined in only 5 of 24 subjects for the 400 µg dose, in 19 subjects for the 800 µg dose and in 20 subjects of the 2 x 400 µg dose. In particular only 4 subjects were available for the comparison 400 µg versus 800 µg.
For the metabolite M23 a single oral dose of 800 µg BAY 6228 tablet is bioequivalent to a single oral dose of 2 x 400 µg BAY w 6228 tablets and dose-proportional to a single oral dose of 400 µg BAY w 6228.
Conclusion
The drug was safe and well tolerated.
Single oral dose of 800 µg and 2 x 400 µg BAY w 6228 (Cerivastatin) can be concluded to be bioequivalent concerning BAY w 6228 and the metabolite M23. Single oral doses of 400 µg and 800 µg were found to be dose-proportional with respect to M23. Concerning BAY w 6228 dose

Summary and Conclusions:
proportionality could be demonstrated for AUC; the C_{max}-ratio was found to be 1.14 with a 90 % CI of (1.02, 1.28) slightly exceeding the bioequivalence criteria of (0.80, 1.25). Considering this marginal violation of the formal criteria, assumed to be of no clinical relevance, dose-proportional behaviour of BAY w 6228 can also be concluded.
For M1 all estimate ratios were close to 1 with 90 % confidence intervals exceeding the bioequivalence limits, as variability was large due to restricted number of subjects to be evaluable. Time to reach C_{max} (t_{max}) and elimination half-lives remained unaltered for both parent drug and metabolites over the dose range 400 to 800 µg and were comparable for all treatments.

2. Study synopsis

Title of study:	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multiple Dose Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of 800 µg Cerivastatin in Patients with Hypercholesterolemia.
Investigators:	Evan Stein, MD, PhD and Randall Stoltz, MD
Study centers:	[redacted]
Publication (references):	Safety, Tolerability, and Efficacy of the 0.8 mg Dose of Cerivastatin, a New HMG-CoA Reductase Inhibitor. Stein, Isaacsohn, Stoltz et al, J. Amer. College of Cardiology, Vol. 31, Suppl. A, 1998, p. 281A
Period of Study:	March 30, 1997 - July 3, 1997
Clinical Phase:	Phase I/II
Objectives:	The primary objective of the study was to evaluate the safety and tolerability of cerivastatin 800 µg given once daily for 28 days to patients with primary hypercholesterolemia. The secondary objective was to obtain data on the multiple-dose pharmacokinetics (PK) and pharmacodynamics (PD) of cerivastatin in patients with primary hypercholesterolemia.
Methodology:	This was a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study of cerivastatin 800 µg (2 X 400 µg tablets) versus placebo in patients with primary hypercholesterolemia. Following a two to four-week run-in, the last two weeks of which patients received single-blind placebo, eligible patients were randomized to cerivastatin 800 µg or placebo once daily for 28 days. Randomization was 2:1, active to placebo. Patients were screened within six weeks of receiving the first dose (Visit 5.1) of double-blind drug. All cholesterol-lowering medications were discontinued at Screening, and patients were to be off cholesterol-lowering medications for at least four weeks prior to randomization. Anti-hypertensive medication was permitted, provided the dose regimen remained unchanged during the four-week period prior to randomization. Tests and procedures done during the screening period included the following: complete medical history and physical exam; vital signs including blood pressure (BP), heart rate, temperature, respiration, height and weight; PA and lateral chest x-ray (if a written report confirming a normal chest x-ray within

the last year was not available); clinical laboratory tests including hematology, chemistry and urinalysis, hepatitis, HIV and urine drug screens, and a serum pregnancy test for women aged 55 years and younger who were not surgically sterile or postmenopausal.

Patients were seen by a registered dietician, given diet instructions and began the American Heart Association (AHA) Step I diet at Screening and at Visit 1. The four-week run-in was used to establish compliance with the diet. During the 4-week run-in, patients were seen weekly by a dietician and given further dietary instructions. At each visit, patients were given a diary and asked to record dietary information obtained over a 3-day period. The diaries were returned at weekly intervals and a Food Record Rating (FRR) score was calculated.

At Visit 1, if patients were not taking cholesterol-lowering medication for at least two weeks and were following the AHA Step 1 diet, the run-in period could be shortened to the two-week placebo run-in (Visit 3). At Visit 3, all patients began single-blind placebo once daily in the evening for two weeks.

Patients were seen weekly during the run-in period. Brief physical exams and vital signs were done at each visit. On the mornings of Visits 3, 4 and 5, fasting lipid profiles and safety labs were obtained. A baseline ophthalmic exam was done during the two-week period prior to dosing (Visit 5.1). Following evaluation of the Visit 5 labs, qualified patients were randomized (Visit 5.1) to cerivastatin 800 μg or placebo once daily for 28 days. Visit 5.1 was also designated as Day 1 of the double-blind period.

To qualify for randomization, the following criteria were to be met:

- plasma low density lipoprotein-cholesterol (LDL-C, calculated) was $\geq$ 160 mg/dl, or $\geq$ 130 mg/dl with documented coronary artery disease (CAD).
- male $\geq$ 45 years or female $\geq$ 55 years with premature menopause and no estrogen replacement therapy and an LDL-C $\geq$ 130 mg/dl in the presence of one or more cardiovascular risk factors (per 1993 NCEP guidelines): hypertension, current cigarette smoking, family history of premature CAD (myocardial infarction, onset of typical angina or significant angiographic disease before age 60), or low high density lipoprotein-cholesterol (HDL-C), defined as < 35 mg/dl at Screening.
- At Visit 4 and Visit 5, the plasma LDL-C must not differ from the mean plasma LDL-C value for these visits by > 12%.
- At Visit 4 and Visit 5, the plasma triglycerides (Trig) must be < 400 mg/dl.
- Compliant with the AHA Step 1 diet with an FRR score $\leq$15 at Visit 5.

Patients were seen weekly during the double-blind period. Tests and procedures performed during the double-blind period included the following: complete physical exam on Day 30 and brief physical exams at all other visits; vital signs; 12-lead ECG and an ophthalmic examination (Day 28, 29 or 30). On the mornings of Days 8, 15, 22 and 28, patients had blood drawn for fasting laboratory tests (as described for screening) and lipid profiles. Patients were to maintain the AHA Step I diet throughout the double-blind treatment phase of the study; 3-day diet diaries were collected and evaluated on Day 14 and on Day 28 (last day of treatment)

	On Days 7, 14, 21 and 28, patients returned to the clinic at approximately 5:00 PM. Patients were given their study medication and platelet aggregation studies were done two hours after dosing. A baseline platelet aggregation study was done pre-dose on Day 1. Plasma samples for the analysis of cerivastatin concentrations were collected immediately pre-dose on Day 1, and on Day 28, samples were collected immediately pre-dose and at 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24 and 36 hours post-dose. On Day 1, urine was collected over a 24-hour period for cerivastatin assay. A urine sample was collected immediately pre-dose and at the following intervals: 0 - 6, 6 - 12 and 12 - 24 hours post-dose. Patients were confined to the clinic from the morning of Day 1 through the morning of Day 2, and from the evening of Day 28 through the morning of Day 30.
Number of patients:	Fifty patients were enrolled in the run-in and 41 patients were randomized. Forty-one patients completed the 28-day double-blind treatment period, but only 40 patients completed the Day 28 to Day 30 PK sampling period. Patient 2009 who received 800 µg cerivastatin opted not to remain in the clinic and undergo the 36-hour PK profile because of discomfort related to an adverse event (pelvic inflammatory disease). Patients ranged in age from 28 to 74 years, and in weight from 127 to 248 lbs. There were 39 Caucasian and two Black patients in the study. Fifteen patients were male and 26 patients were female.
Test product, dose, mode of administration, batch number:	During the two-week single-blind run-in, patients took placebo (two tablets) once daily in the evening. The placebo tablets were identical in appearance to the cerivastatin tablets. During the 28-day double-blind period, patients took cerivastatin 800 µg (2 x 400 µg) or placebo (2 tablets) once daily in the evening at mealtime between 5:00 and 7:00 PM. The following batch numbers were used: Test Product — Batch # cerivastatin 400 µg tablets — 521226T placebo tablets — 529181
Duration of treatment:	Patients received single-blind placebo for two weeks and double-blind study drug (cerivastatin 800 µg or placebo) for 28 days.
Reference therapy, dose and mode of administration, batch number:	Not applicable, no reference treatment was used

Criteria for evaluation: Pharmacokinetics and Pharmacodynamics:

The principal PK variables to be evaluated included AUC_{0-24}, C_{max}, t_{max}, and $t_{1/2}$ on Day 28. The pharmacodynamic (PD) variables to be evaluated included total cholesterol, direct LDL-C, calculated LDL-C, HDL-C, lipoprotein (a) and triglycerides. For all PD variables, the change and percent change from baseline (Visit 5) were to be evaluated. The primary PD parameter that was to be evaluated was LDL-C by [redacted] method (direct LDL-C).

Safety:

All observations pertinent to the safety of cerivastatin were recorded on the CRF. Safety parameters evaluated included the results of the physical and ophthalmology exams, vital signs, ECGs, adverse events, platelet aggregation studies and laboratory tests.

Statistical methods: **Pharmacokinetic, pharmacodynamic and safety measurements**

The following PK parameters were evaluated: area under the concentration curve (AUC_{0-24}), maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), and elimination half-life ($t_{1/2}$).

The following PD parameters were evaluated: total cholesterol (t-Chol), both direct and calculated low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Trig), and lipoprotein (a) [Lp (a)].

Summary statistics were to be presented for all PK and PD variables. The PD variables were analyzed using analysis of variance (ANOVA) with terms for center and treatment. The primary PD parameter evaluated was LDL-C by [redacted] however, for comparative purposes, the calculated LDL-C values are also presented.

Summary statistics for baseline and demographic variables were to be presented by treatment group. For the two treatment groups, frequencies of adverse events were to be evaluated as well as summary statistics for changes from baseline in vital signs and ECGs. Laboratory data were to be listed with abnormal values flagged.

Summary and conclusions:

Summary of safety

Cerivastatin given as 800 µg daily for 28 days resulted in no changes on physical examination with the exception of one patient diagnosed with PID on Day 26 of the study. No clinically significant changes were observed in vital signs, electrocardiogram, or ophthalmic examination during the study. Adverse events occurred in 18 of 28 (64%) patients given cerivastatin and in 7 of 13 (54%) of patients given placebo. All events were mild or moderate in intensity with the exception of moderate to severe abdominal pain reported by a patient diagnosed with PID. Headache was the most common event reported. No patient discontinued treatment because of an adverse event or for any other reason.

Elevations in transaminase and CK levels were observed with slightly greater frequency in the patients treated with cerivastatin than in those treated with placebo. One patient treated with cerivastatin had a clinically significant elevation of CK (8 times the ULN) at the end of 28 days of treatment; this patient was asymptomatic and reported no adverse events throughout the study. There were no clinically relevant changes in any other laboratory tests, including PT and PTT. There were no clinically relevant changes in platelet aggregation measurements conducted predose on Day 1 and weekly throughout the 28-day double-blind phase of the study. Overall, 800 µg cerivastatin given as a 28-day multiple dose regimen was well tolerated.

Summary of Pharmacokinetics

Results are shown below for the 27 patients valid for pharmacokinetics.

Geometric Mean (%CV) of Pharmacokinetic Parameters

Parameter	Cerivastatin (n = 27)	M1 (n = 14)	M23 (n = 14)
$AUC_{0\text{-}24}$ (µg*h/L)[1]	67.0 (30%)	5.54 (48%)	17.0 (54%)
C_{max} (µg/L)	12.7 (41%)	0.55 (50%)	1.4 (47%)
t_{max} (hr)	1.4 (33%)	3.4 (53%)	4.5 (35%)
$t_{1/2}$ (hr)[1]	4.2 (20%)	3.6 (40%)	5.0 (39%)
24-hr Ae_{ur}(µg)	–	17.5 (37%)	51.8 (32%)

[1] n = 13 for M1

The pharmacokinetic results observed for the 800 µg cerivastatin dose were consistent with previously reported results at lower doses, i.e., cerivastatin AUC and C_{max} increased approximately in proportion to dose (300, 400 and 800 µg). There was no evidence of accumulation or nonlinearity. Metabolite concentrations of M1 and M23 were considerably lower than the that of parent compound, cerivastatin, so that these active metabolites which have approximately 50 and 100%, respectively, the activity of cerivastatin itself, contribute only minimally (about 20%) to the overall efficacy attributable to cerivastatin.

Summary of Pharmacodynamics

Treatment with 800 µg cerivastatin once daily for 28 days produced mean reductions of 41% in LDL-cholesterol ——— 44% in LDL-cholesterol (calculated), 31% in total cholesterol, and 11% in triglycerides. These mean percent changes from baseline in cerivastatin group were statistically significantly different from those in placebo group at the 5% level. A non-significant increase of 3% was seen in HDL-C.

A responder analysis was conducted for the percent change in LDL-cholesterol (calculated). At Day 28, 24 of 28 patients (86%) who received 800 µg cerivastatin showed a decrease from baseline in LDL-cholesterol of over 25%. At the same time point, 21 of 28 patients (75%) who received 800 µg cerivastatin showed a decrease in LDL-cholesterol of over 35%.

A correlation analysis was performed in an attempt to correlate the percent change from baseline at Day 29 for LDL-cholesterol (calculated) with the pharmacokinetic parameters, AUC_{0-24} and C_{max}. The Pearson's correlation coefficients for LDL-C versus AUC_{0-24} was -0.26 ($p = 0.2066$), and for LDL-C versus C_{max} it was --0.34 ($p = 0.0952$). Spearman's correlation coefficients showed similar results. The PK/PD correlation results indicate a slight negative correlation between AUC_{0-24} and LDL-C as well as between C_{max} and LDL-C. These results are consistent with the expectation that higher plasma levels of cerivastatin lead to increased pharmacodynamic effect (efficacy).

Conclusions

An 800 µg dose of cerivastatin given daily for 28 days was well tolerated. Adverse events were mild to moderate except for one case of salpingitis (PID) considered unrelated to cerivastatin. Mild (<2 x the upper limit of normal) elevations in transaminases and transient mild to moderate elevations in CK were seen in both the cerivastatin and the placebo group nearly equally. One patient treated with cerivastatin had a clinically significant elevation of CK (8 times the ULN) at the end of 28 days of treatment; this patient was asymptomatic and reported no adverse events throughout the study. There were no clinically relevant changes in any other laboratory tests, including PT and PTT. The 800 µg dose of cerivastatin was not associated with clinically relevant changes in platelet aggregation measurements conducted predose on Day 1 and weekly throughout the 28-day double-blind phase of the study.

The 800 µg dose of cerivastatin given daily for 28 days demonstrated excellent capacity to lower total cholesterol (-31%) and calculated LDL-C (-44%). These mean decreases were significantly different ($p < 0.0001$) from the placebo group changes. This dose of cerivastatin was effective enough to lower LDL-C by greater than 35% in 3 out of 4 patients (75%).

2 Study synopsis

Title of the study:	A single-center, randomized, non-blind, controlled four-way crossover study on the pharmacokinetics, safety and tolerability of a single dose of 0.8 mg BAY w 6228 administered in the morning or evening under each fasted or fed conditions.(BAY w 6228/10012)
Investigators:	R. Frey, M.D., D. Kubitza, M.D., J. Nagelschmitz, M.D., U. Schühly, M.D., Ch. Wandel, M.D., G. Wensing, M.D.
Study center:	Bayer AG, Pharma Research Center, Institute of Clinical Pharmacology, 42096 Wuppertal, Germany
Publications (references):	none to date
Period of study:	15-DEC-1998 - 15-FEB-1999
Clinical phase:	I
Objectives:	The primary objective of this study was to evaluate the influence of food and day time of dosing on bioavailability and pharmacokinetics of BAY w 6228 following oral administration of 0.8 mg single doses each. The primary objective was assessed by considering a 36-hour pharmacokinetic profile of the plasma concentrations for BAY w 6228 and the metabolites M-1 and M-23, and also (optionally) the concentrations of M-1, and M-23 in the urine. Secondary objective of this study was the assessment of the safety and tolerability of treatments.
Methodology (design of study):	A single-center, randomized, non-blind, controlled four-way crossover study in 24 healthy, young male volunteers with a single dose administration of 0.8 mg BAY w 6228 tablet P. O. under following dosing conditions: A: at 8 a.m. following an overnight fast of at least 10 hours B: at 8 a.m. within 5 min after a high-fat breakfast C: at 6 p.m. within 5 min after a low-fat evening meal D: at 10 p.m. 4 hours after a low-fat evening meal.

Methodology (design of study):	The study consisted of four periods. Each period started with a residential phase on the morning of profile day (day 1) for baseline safety measurements, followed by a 36-hour pharmacokinetic profile starting with administration of the test drug. All subjects began fasting at 10:00 p.m. on day –1. The subjects that were randomized for fasting (A) had to remain fasted until four hours after dosing, at which time they had been served a low-fat lunch and a low-fat dinner in the evening. The subjects that were randomized for a high-fat breakfast (B) had their breakfast followed by a low-fat lunch four hours after dosing and a low-fat dinner in the evening. The other subjects (C+D) had a low-fat breakfast and the same low-fat lunch on the profile day before they took their low-fat dinner before dosing.
Number of healthy subjects /patients:	24 healthy subjects were randomized. 24 healthy subjects were valid for the safety and the pharmacokinetic analysis.
Diagnosis and main criteria for inclusion:	Healthy male, Caucasian subjects, aged between 18 and 55 years.
Test product, dose and mode of administration, batch number:	BAY w 6228 tablets 0.8 mg, development number: —— Batch No.: 523939K oral administration
Duration of treatment:	The study consisted of four periods with one treatment day. The washout phase between the periods was to be about one week (minimum: two days)
Reference therapy, dose and mode of administration, batch number:	None

Criteria of evaluation:	Pharmacokinetic analysis: plasma concentrations of BAY w 6228, M-1 and M-23. Primary target parameters: • AUC, C_{max} for BAY w 6228 • 90 % confirmatory confidence intervals for the ratio of treatments B/A and C/D of BAY w 6228 AUC; Secondary kinetic variables: • AUC_{norm}, C_{max}, t_{max}, $t_{1/2}$, MRT for BAY w 6228; AUC, AUC_{norm}, C_{max}, $C_{max,norm}$, t_{max}, $t_{1/2}$, MRT, Ae_{ur}, CL_R for the metabolites M-1 and M-23 • 90 % exploratory confidence intervals for the ratio of D/A and C/B of BAY w 6228 AUC; • 90 % exploratory confidence intervals for the ratio of B/A, D/A, C/D and C/B of M-1 and M-23 AUC; • 90 % exploratory confidence intervals for the ratio of B/A, D/A, C/D and C/B of C_{max} and $t_{1/2}$ for BAY w 6228, M-1 and M-23. Secondary target parameters: Adverse events, vital signs, ECG, laboratory parameters Clinical observations: Physical examination, adverse events, vital signs, ECG, clinical chemistry, haematology, urinalysis.

Statistical methods:	For quantitative variables descriptive statistics including mean values, standard deviations (SD), minimum, median and maximum values were calculated. For qualitative variables frequency tables were provided. Additionally, descriptive statistics for pharmacokinetic variables including geometric mean values, geometric standard deviations (SD) and coefficients of variation (CV). The ANOVA procedure was performed to estimate the following ratios and to calculate the corresponding 90% confidence intervals: B/A and C/D of BAY w 6228 AUC (confirmatory) D/A and C/B of BAY w 6228 AUC (exploratoy) B/A, D/A C/D, C/B of M-1 and M-23 AUC (exploratory) B/A, D/A C/D, C/B of C_{max} and $t_{1/2}$ for BAY w 6228, M-1 and M-23 (exploratory)

Summary and Conclusions:

Results

Pharmacokinetic analysis

Plasma samples were analyzed for the parent drug BAY w 6228 and its metabolites M-1 and M-23 by ——— The limit of quantification was —— for BAY w 6228, and ——— for the metabolites.

The following tables present the geometric means/geom. SD for the derived pharmacokinetic parameters for BAY w 6228 and its metabolites M-1 and M-23:

Descriptive statistics for BAY w 6228 pharmacokinetic parameters (geom. mean/g.SD, N = 24)

Parameter	Treatment			
	A	B	C	D
AUC (mcg*h/L)	43.5/1.36	41.6/1.41	44.2/1.39	45.3/1.41
C_{max} (mcg/L)	7.7/1.40	8.7/1.42	7.1/1.41	7.1/1.43
t_{max} (h)*	1.5 ———	2.0 ———	3.0 ———	2.5 ———
$t_{½}$ (h)	2.6/1.22	2.4/1.34	2.9/1.21	2.9/1.16

* median (range)

Descriptive statistics for M-1 pharmacokinetic parameters (geom. mean/g.SD, N = 24)

arameter	Treatment			
	A	B	C	D
AUC (mcg*h/L)	4.2/1.31	4.0/1.48 [1)]	4.3/1.45	5.0/1.42
C_{max} (mcg/L)	0.6/1.51	0.7/1.42	0.5/1.50	0.7/1.29
t_{max} (h)*	3.0 ———	4.0 ———	4.0 ———	4.0 ———
$t_{½}$ (h)	3.7/1.58	2.8/1.87 [1)]	4.9/1.41	4.2/1.52
Ae_{ur} (%)	2.7/1.30	2.7/1.40	2.4/1.28	2.3/1.30

* median (range) [1)] N = 22

Summary and Conclusions:

Descriptive statistics for M-23 pharmacokinetic parameters (geom. mean/g.SD, N = 24)

Parameter	Treatment			
	A	B	C	D
AUC (mcg*h/L)	14.1/1.38	13.9/1.46	15.7/1.37	16.8/1.32
C_{max} (mcg/L)	1.6/1.40	1.8/1.45	1.5/1.43	1.5/1.34
t_{max} (h)*	4.0 ———	4.0 ———	6.0 ———	6.0 ———
$t_{½}$ (h)	4.0/1.42	4.2/1.57	5.0/1.33	4.9/1.34
Ae_{ur} (%)	8.9/1.26	8.9/1.29	8.3/1.23	8.2/1.27

* median (range)

The following table summarizes the main ANOVA results for BAY w 6228:

Mean Estimates and 90% confidence intervals (CI) for the various treatment comparisons

Parameter	Comparison	Estimate	90 % CI
AUC [mcg*h/L]	B / A	0.96	[0.90, 1.01]
	C / D	0.97	[0.92, 1.03]
	D / A	1.05	[0.99, 1.11]
	C / B	1.06	[1.00, 1.12]
C_{max} [mcg/L]	B /A	1.12	[1.04, 1.21]
	C / D	1.00	[0.93, 1.08]
	D / A	0.92	[0.85, 0.99]
	C / B	0.81	[0.76, 0.88]
$t_{1/2}$ [h]	B /A	0.91	[0.84, 0.98]
	C / D	1.00	[0.93, 1.08]
	D / A	1.12	[1.04, 1.21]
	C / B	1.24	[1.14, 1.34]

A: at 8 a.m. following an overnight fast of at least 10 hours

B: at 8 a.m. within 5 min after a high-fat breakfast

C: at 6 p.m. within 5 min after a low-fat evening meal

D: at 10 p.m. 4 hours after a low-fat evening meal

Summary and Conclusions:

The calculated confirmatory 90 % confidence intervals for BAY w 6228 AUC for the ratios B/A ([0.90, 1.01]) and C/D ([0.92, 1.03]) were completely contained within the range of 0.80 to 1.25. Consequently, no relevant influence of food on BAY w 6228 AUC could be detected for both the morning and evening dosing.

BAY w 6228 AUC was estimated similar after the administration four hours after a low-fat evening meal (treatment D) and under fasting conditions in the morning (treatment A) as well as after the administration within five minutes after a low-fat evening meal (treatment C) and after administration within five minutes after a high-fat breakfast (treatment B). Therefore, no relevant influence of daytime on BAY w 6228 AUC could be detected.

No relevant food effect could be detected for BAY w 6228 C_{max} and $t_{1/2}$.

A marginal daytime effect could be detected for BAY w 6228 C_{max} and $t_{1/2}$: C_{max} was estimated 19 % higher after the administration within five minutes after a high-fat breakfast (treatment B) compared to the administration within five minutes after a low fat evening meal (treatment C); $t_{1/2}$ was estimated 24 % shorter after the administration within five minutes after a high-fat breakfast (treatment B) compared to the administration within five minutes after a low fat evening meal (treatment C).

Safety

There were no serious adverse events or deaths or dropouts during this study. In total, 19 adverse events occurred for 13 subjects i.e. there were 11 subjects without any adverse events during all of the treatment periods. Three complaints at baseline were reported for subjects 4, 5 and 21. All adverse events were judged as mild (17) or moderate (2). The outcome of all adverse events was judged as resolved up to one event (Headache in subject 12; outcome = improved). The relation to study drug was judged as not related in 12 cases, as unlikely five times and as possible two times.

Summary and Conclusions:

No significant differences could be detected among the four treatment groups concerning the number of subjects, who reported adverse events or other safety parameters. The following table gives an overview about the number of subjects with treatment emergent AEs by treatment group:

Treatment	Number of subjects reporting adverse events
A	7
B	3
C	2
D	5
Total	13
none (baseline complaint)	3

Summary and Conclusions:

Table: Incidence of treatment emergent adverse events (COSTART terms) following a single dose of BAY w 6228

Body system adverse event	BAY w 6228 fasted treatm. A N=24	BAY w 6228 Am. breakfast treatm. B N=24	BAY w 6228 with dinner treatm. C N=24	BAY w 6228 4h after dinner treatm. D N=24
number of subject with any adverse event total n=13	7	3	2	5
body as a whole				
headache	#1(mild)	#21(mild)	#2(mild)	#15(mild)*
total n=10	#8(mild)		#17(mild)	#18(mild)
	#12(moderate)			#21(mild)*
	#13(mild)			
	#18(moderate)			
skin				
urticaria				#20(mild)
abscess	#23(mild)			
digestive system				
flatulence				#12(mild)
respiratory				
herpes simplex		#18(mild)		
rhinitis	#10(mild)*			
pharyngitis (sore throat)		#6(mild)		

- # denotes subject identification number
- * denotes subjects with an AE 6 to 7 days after drug intake and short time before drug intake of the next period

Subjects without any adverse events: #3, 7, 9, 11, 14, 16, 19, 22, 24

Subjects who reported only one AE before the first administration of the drug at all: #4, 5

Summary and Conclusions:

The number of patients not reporting any adverse events was lower if the study drug was administered immediately after a meal.

Headache was the most common adverse event reported 13 times by 10 subjects, mainly during the profile days. This might be due to caffeine withdrawal on the profile days.

Subjects # 4 suffered from sinusitis frontalis at the beginning of the study before the planned start of his first period. Therefore he was discharged from the ward and started one week later. He was without complaints at the beginning of his first treatment (C). Subject # 20 had a mild urticaria during his first period, which could not be observed during the following three treatments. Medication was not needed and given. Therefore this adverse event was judged as not related to study drug. Subjects # 21 suffers of migraine symptoms several times per year. He complained typical migraine symptoms during daytime before his first treatment at 10 p.m.. In the evening at study drug administration he was without complaints. Subject # 23 suffered in his fourth and last period of a sudoriparous abscess of the left axilla. He reported this to the investigator 10 hours after drug intake although the onset as a small pustula was already 1 or 2 days before study drug administration. He has in general a tendency for these kind of abscesses. This abscess was treated by his surgeon through incision and was judged as not drug related. With respect to adverse events, the study drug cerivastatin was well tolerated.

The parameters of haematology stayed within or nearby the upper and lower limit of normal without any hint of clinically relevant abnormalities.

The parameters of clinical chemistry stayed in general within or nearby the upper and lower limit of normal without any clinically relevant abnormalities. These minor elevations returned to normal spontaneously. Following values above the upper limit of normal will be mentioned:

LAP (ULN 35U/L): Subject # 7, period (p) 1 +36 h 51U/L, p2 +24 h 87 U/L without any symptoms, period 3 and 4 within normal limits.

Amylase (ULN 120 U/L) & Lipase (ULN190 U/L): Subject # 24 demonstrated in period 3 +48 h peack values for amylase of 353 U/L and lipase with 1895 U/L without any symptoms or complaints.

Triglycerides: Subject # 7 p2 +24 h 7,6 mmol/L singular peack

Summary and Conclusions:

Total bilirubin (ULN 18,8 µmol/L): Three subjects # 11, 19, 21 had continuously elevated levels between 20 and 45 µmol/L before and during the study. For all three a mild form of a Morbus Meulengracht should be considered.

CK (ULN 80 U/L): The following subjects reported physical activity, mostly in the gymnasium, which was followed by mild CK elevations: Subject # 2 period (p) 3 – 10 h 212 U/L, # 3 p 3 - 14 h 110 U/L and p4 0 h 98 U/L, # 5 p2 +48 h 139 U/L, # 12 p2 –14 h 165 U/L and p3 0 h 235 U/L & +24 h 95 U/L, # 16 p1 0 h 170 U/L, p2 0 h 133 U/L & +24 h 176 U/L, & +48 h 176 U/L; during period 3 and 4 within normal limits. At the end of the fourth and last period all CK measurements were within normal limits.

There was no obvious difference between treatment groups with respect to heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure.

There was no obvious difference between treatment groups with respect to axis ECG heart rate, P-duration, PR-duration, QRS-duration, QTc-duration and QRS-angle and qualitative findings.

No clinically relevant deviations from normal were found on physical examinations.

In total, BAY w 6228 (cerivastatin sodium) 0.8mg was safe and well tolerated in this single dose food effect study.

Conclusion

Single oral doses of 0.8 mg BAY w 6228 in the morning or evening under both fasted and fed conditions were safe and well tolerated. Lack of influence of food could be demonstrated according to guidelines, thus validating the current recommended posology for BAY w 6228, i.e. drug intake in the evening at dinner or at bed time, respectively.

2. Study synopsis

Title of the study:	Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of 800 µg Cerivastatin after Single and Multiple Dosing (D96-039)
Investigator(s):	[redacted]
Study center(s):	[redacted]
Publications (references):	Manuscript in preparation
Period of study:	November 15, 1996 to January 14, 1997 (First subject enrolled - Last subject's observation)
Clinical phase:	Phase I
Objectives:	The purpose of this study was to evaluate the safety, tolerability and pharmacokinetics of 800 µg cerivastatin after single and multiple dosing and to evaluate the pharmacodynamics of 800 µg cerivastatin after multiple dosing.
Methodology (design of study):	This study was designed as a single-center, randomized, double-blind, placebo-controlled study assessing the safety, tolerability and pharmacokinetics of cerivastatin administered as a single dose (800 µg) and as multiple doses (800 µg daily for 10 days) to healthy subjects. The pharmacodynamics of cerivastatin was also to be assessed after the multiple dose regimen. Subjects were screened by physical examination, electrocardiogram (ECG) and laboratory testing, and randomized to cerivastatin or placebo on a 2:1 basis. On Day -1, qualified subjects entered the clinic to begin a 2-day confinement. Subjects were given a single dose of 800 µg cerivastatin or placebo on Day 1. One week later, on the morning of Day 8, subjects re-entered the clinical and began once-daily dosing with 800 µg cerivastatin or placebo (same assignment as Day 1) for 10 consecutive days; subjects were discharged from the clinic on the evening of Day 19. Blood samples were collected for measurement of cerivastatin and its metabolites as 24-hour pharmacokinetic plasma profiles beginning the evening of Days 1 and 17. Platelet aggregation studies were performed predose and 2 hours postdose on Day 1, and every other day during the multiple-dose treatment phase (Days 8 to 14); an end-of study evaluation was performed on Day 17.

	Lipid parameters including total-, LDL-, and HDL-cholesterol and triglycerides were evaluated on Day 8 (predose baseline), Day 14, and Day 18, after 10 days of multiple dose treatment. Safety parameters, including adverse events, vital signs, ECGs, clinical laboratory tests, and physical examinations with funduscopy, were monitored throughout the study.
Number of patients:	In total, 17 subjects were enrolled in Study D96-039 including 14 males and 3 females. Eleven of the 17 subjects received cerivastatin and six received placebo. All 17 subjects were valid for safety analysis. Two subjects, one in each treatment group, who discontinued the study prematurely for administrative reasons, were excluded from the pharmacokinetic and pharmacodynamic evaluations.
Diagnosis and main criteria for inclusion:	Healthy male or female subjects between the ages of 18 and 49 years, inclusive, with plasma LDL-cholesterol 110 mg/dL or above were selected for enrollment.
Test product, dose and mode of administration, batch number:	On Day 1 and Days 8 to 17, subjects were administered 800 µg of cerivastatin given as 2 x 400 µg tablets once each evening between the hours of 5 and 6 p.m. Tablets were swallowed intact without chewing with 120 mL of tap water at ambient temperature. The batch number of cerivastatin used in this study was 521226T.
Duration of treatment:	Each subject participated in the trial for approximately 19 days. Subjects were confined to the clinic for a total of 13 overnight stays. Subjects who completed the entire study received a total of 11 doses of cerivastatin 800 µg or placebo (Days 1 and 8 to 17).
Reference therapy, dose and mode of administration, batch number:	Placebo doses were administered as two tablets, identical in appearance to the cerivastatin tablets. Placebo was administered in an identical manner to cerivastatin. The batch number of placebo tablets used in this study was M951102.
Criteria of evaluation:	The primary objectives of this study included the determination of single-dose and 10-day steady-state pharmacokinetics of 800 µg cerivastatin. The pharmacokinetic parameters assessed included AUC_{0-24}, C_{max}, t_{max} and $t_{1/2}$. Pharmacodynamics was evaluated after 10 days of 800 µg cerivastatin dosing as the percent change from baseline (assessed predose on Day 8) to the morning of Day 18 in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides. Safety was evaluated by examining the incidence of adverse events and

	laboratory abnormalities, as well as changes in vital signs, physical examination results including funduscopy, and ECGs. The percent change from baseline (assessed predose on Day 1) to Days 8 and 17 in collagen-initiated platelet aggregation study results was performed as part of the safety assessment.
Statistical methods:	For all pharmacokinetic parameters, logarithmically (natural log) transformed estimates for each subject were analyzed using two-way analysis of variance (ANOVA) with terms for day and subject. Log-scale least square means and log-scale differences were exponentiated to obtain geometric least squares means and ratio estimates. Lower and upper limits based on 90% confidence intervals are presented, as are significance levels at which 80% equivalence from below and 125% equivalence from above can be claimed. The overall significance level for two-sided equivalence is the maximum of these two p-values. Pairwise two-sided tests for treatment inequality are also presented. The percent change from baseline for total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and collagen-initiated platelet aggregation study results were analyzed using one-way ANOVA with a term for treatment.
Summary and conclusions: Summary of pharmacokinetics: PK parameters are summarized in the table below for both Day 1 and Day 17.	

Geometric Means (geom. s.d.)		
PK Parameter	**800 µg (Day 1)**	**800 µg (Day 17*)**
AUC_{0-24} (µg•h/L)	59.27 (1.35)	53.19 (1.37)
$AUC_{0-24,norm}$ (g•h/L)	5.60 (1.34)	5.02 (1.40)
C_{max} (µg/L)	12.20 (1.32)	9.55 (1.37)
$C_{max,\ norm}$ (g/L)	1.15 (1.29)	0.90 (1.41)
t_{max} (hours)	2.07 (1.33)	2.58 (1.29)
$t_{½}$ (hours)	3.59 (1.24)	3.79 (1.13)

*Steady-state, after 10 days dosing

No statistically significant differences were observed between single dose and steady-state pharmacokinetics of cerivastatin 800 µg for AUC_{0-24} and $t_{½}$. The ratio of Day 17 to Day 1 values for these variables were 0.897 and 1.054 for AUC_{0-24} and $t_{½}$, respectively, with confidence limits that were within the limits of 80% and 125%. The Day 1 C_{max} of 12.2 µg/L was slightly higher than the Day 17 value (9.6 µg/L) and the Day 1 t_{max} (2.1 h) was lower than the Day 17 t_{max} (2.6 h). There was no accumulation following 10 days of dosing with 800 µg cerivastatin (mean accumulation ratio was 0.91).

Pharmacokinetic results following a single dose of 800 µg cerivastatin were consistent with those obtained following lower doses of 200 µg and 400 µg examined in previous studies with AUC_{0-24} values of 14.2, 24.5, and 59.3 µg•h/L and C_{max} values of 2.3, 5.4, and 12.2 µg/L for the 200, 400, and 800 µg doses, respectively. These results indicate that the pharmacokinetics of cerivastatin are linear over the dose range 200-800 µg. At steady-state, the pharmacokinetic results essentially paralleled the single dose observations.

Summary of pharmacodynamics:
Statistically significant decreases from baseline in both LDL-cholesterol and total cholesterol were observed after 10 days of dosing in subjects in the 800 µg cerivastatin group as compared to subjects in the placebo group. For LDL-cholesterol, subjects in the cerivastatin group had a 32.7% decrease from baseline compared to an 11.0% decrease in the placebo group ($p = 0.0002$); for total cholesterol the decreases were 21.6% and 10.6% for the cerivastatin and placebo groups, respectively ($p = 0.0182$). There were no statistically significant differences between the treatment groups for change from baseline in HDL-cholesterol or triglycerides.

Summary of safety:
All 17 subjects enrolled in the study completed the single dose phase; 15 subjects completed the 10-day dosing phase including 10 subjects in the cerivastatin group and 5 in the placebo group. Two subjects, one in each treatment group, discontinued the study due to administrative reasons: one subject had baseline LDL-cholesterol that was less than the protocol entry criterion of 110 mg/dL and one requested discharge to be with a family member who was involved in a motor vehicle accident.

Adverse events were reported by 3 (27.3%) of the 11 subjects who received 800 µg cerivastatin; none of the six subjects in the placebo group experienced adverse events. Five events were reported in these 3 subjects: headache (2 subjects), abdominal pain, neck pain and amblyopia. All events were judged by the investigator to be mild in intensity with the exception of one episode of headache classified as moderate; all events resolved prior to discharge. No serious adverse events were reported during the study and none of the subjects discontinued the study due to adverse events.

All laboratory parameters were reviewed by the principal investigator and the sponsor. The outcome of this review revealed no clinically significant changes in laboratory parameters monitored during the study; there were no laboratory abnormalities reported as adverse events. Transient elevations in serum transaminases (SGOT and SGPT) were observed in 4 subjects in the cerivastatin group. Only one subject had an elevation that was 2X the upper limit of normal; Subject 1005 had an SGPT value

of 100 U/L (normal range 3-50 U/L) on the last day of dosing; the value had returned to normal (19 U/L) at the time of the follow-up evaluation. All other elevations in SGOT and SGPT were mild (<2 x ULN).

No clinically significant changes were observed in the percent change from baseline in collagen-initiated platelet aggregation studies conducted following the single dose phase (Day 8) or following the 10-day multiple dose phase of the study (Day 17).

There were no significant changes detected on physical examination during the study; all subjects had normal funduscopic findings post-study. Changes in vital signs parameters were small and not clinically relevant and no significant changes were detected by ECG.

Conclusions:
Cerivastatin given as a single dose and as a 10-day multiple dose regimen of 800 µg was well tolerated. In general, linear pharmacokinetics was observed at this dose as compared to lower cerivastatin doses. As expected for a drug with a short half-life, no accumulation was observed after 10 days of dosing with 800 µg cerivastatin. Although this study was of short duration and was not diet-controlled, subjects receiving 800 µg cerivastatin administered once each evening for 10 days showed a statistically significant decrease (placebo-subtracted) in total cholesterol of approximately 10% and in LDL-cholesterol of approximately 20% compared to subjects receiving placebo.