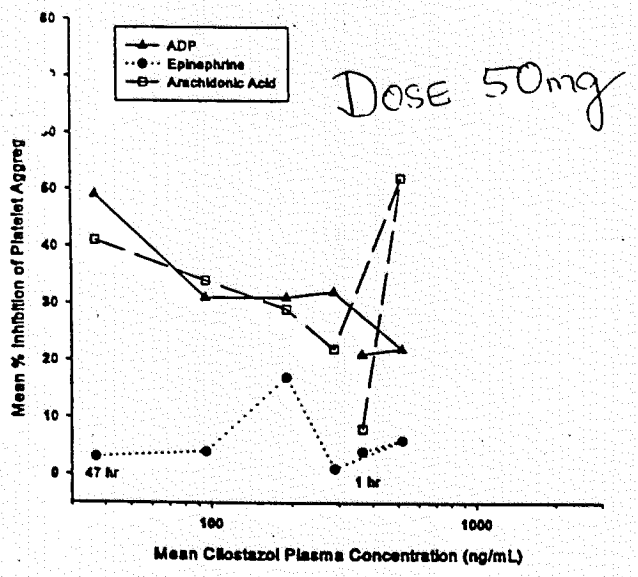
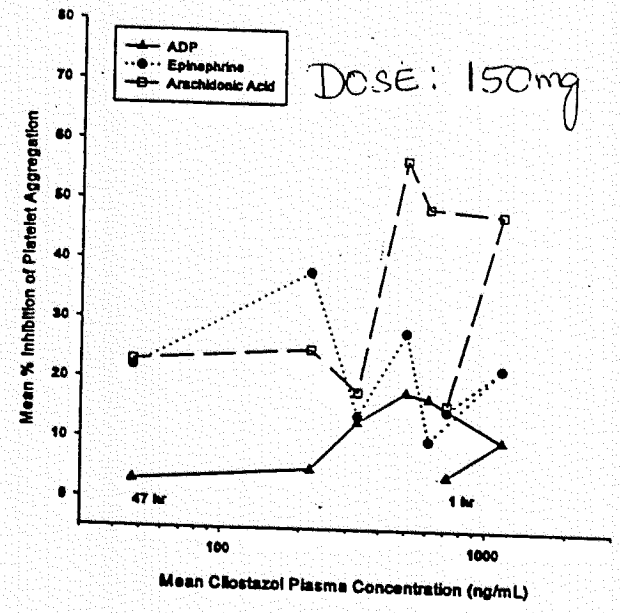
PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS

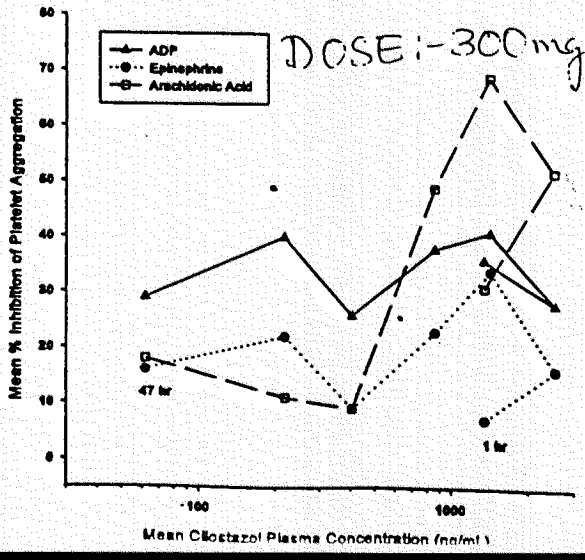
The sponsor carried out an exploratory PK/PD analysis as described below. This analysis was conducted to relate the PK of cilostazol to inhibition of platelet aggregation. There appears to be a relationship between cilostazol plasma concentrations and the inhibition of platelet aggregation induced by arachidonic acid.

A study was conducted in 6 normal volunteers, 5 of whom were administered 50 mg, 150 mg and 300 mg single doses of cilostazol. Plasma concentrations of cilostazol and OPC-13015, and inhibition of platelet aggregation by ADP, arachidonic acid, and epinephrine were determined at various times for 47 hours. Platelet aggregation inhibition was determined by an in vitro method at critical concentrations, 2 times the critical concentrations and at a fixed concentration (the mean of all the critical concentrations) of ADP, arachidonic acid and epinephrine. Critical concentrations were determined in vitro for each subject, and were defined as the minimum concentration of the aggregant which would induce secondary or irreversible platelet aggregation.

The mean % inhibition of platelet aggregation by ADP, epinephrine and arachidonic acid were plotted against the mean plasma concentrations for the 50, 150 and 300 mg doses of cilostazol (see the three figures below).







Visual inspection of the plots indicate the following:

1) ADP and epinephrine did not appear to have a monotonically increasing concentration-response relationship.
2) For arachidonic acid, the inhibition of the platelet aggregation appeared to increase with cilostazol concentrations.
3) There appeared to be a sharp decline in the inhibition of platelet aggregation when cilostazol concentrations were below approximately 500 ng/ml.
4) A counter-clockwise hysteresis was observed, indicating a lag in the effect with respect to the plasma concentration.

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"Population" PK analysis of Cilostazol
Reviewer: Dr. Ahmed El-Tahtawy

Background
The plasma concentration in patients and healthy volunteers were characterized with high variability and a secondary peak. The sponsor precluded parametric modeling of patients of phase III data as the secondary peaks were not captured with the planned 20-hour sampling. Secondary peaks occurs at 20-25 hours post dose.

Objective
Was to identify covariates affecting cilostazol systemic exposure in patients and quantify the influence of these covariates.

Methods
2166 plasma samples for 462 patients receiving 100 cilostazol bid ½ hour before meals in studies 21-92-202, 21-93-201, 201-94-201, 21-94-203 were used in the analysis (number of patients and samples per study are provided in the following table).

Study	# of patients randomized to 100 mg dose	Treatment duration # weeks	Samples per patient up to 'Trough'	'Peak'
21-93-201	95	12	5	2
21-92-202	171	24	8	—
21-94-201	133	24	3	—
21-94-203	119	16	3	2

All patients had to come to the clinic for trough levels (at the end of dose interval right before the next dose), always around the same time. In some of the studies, peak evaluation were also performed. Patients had to take the drug immediately after the trough evaluation and be evaluated 2-4 h later.

The sponsor adopted a non-parametric approach for data analysis, where plasma concentrations were partitioned into observation levels, then categorizing patient exposure into "exposure levels". Patient levels were then correlated with different covariates using regression tree methodology and classical statistical methods. Area under population curve for identifying subpopulation were calculated.

The following Table summarizes the studied covariates.

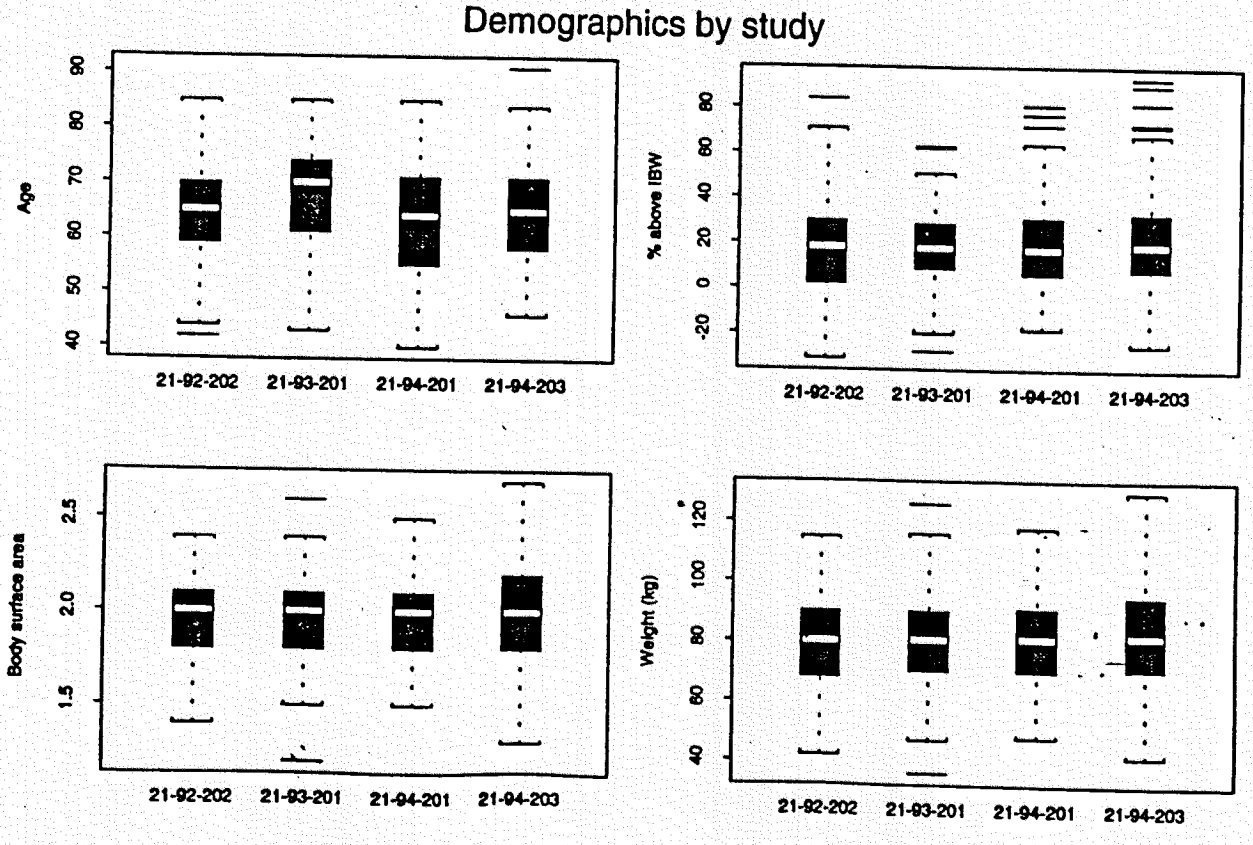
Description of covariates

	Covariate	Type
Demographics	gender, race, obesity[a] (>20% above IBW)	Factor
	age, weight, body surface area (BSA), % above IBW	Continuous
Lifestyle	smoking(never/ previously/current), alcohol (never/ previously/current)	Ordered Categorical
Medical history	diabetes, myocardial infarction, cerebro-vascular event	Factor
Disease state	duration of disease[b] (0.5 to 1/ 1 to 5 / 5 to 10/ >10 YRS), baseline walking distance[c] (Mild/ Moderate/ Severe impairment)	Ordered Categorical
Concomitant medications and medical conditions	drugs and therapeutic subclasses of drugs used by ≥ 25 patients[d]	Factor
Study design	study[e]	Factor

Results

Table below gives the distribution of categorical demographic covariates across the studies. The patients demographics are also depicted in the following figure.

Boxplots of Continuous Variables by Study



Distribution of categorical demographic covariates across the studies.

Covariate/ levels (p-value)[a]	Study N (%)				Total N (%)
	92-202	93-201	94-201	94-203	
# patients	157	88	116	101	462
Gender:					
Males	119(75.8)	76 (86.4)	88 (75.9)	79 (78.2)	362 (78.4)
Females	38(24.2)	12 (13.6)	22(19)	28 (27.7)	100 (21.6)
Race:					
Caucasian	137(87.3)	77 (87.5)	106 (91.4)	91 (90.1)	411 (89.0)
Other	20(12.7)	11(12.5)	10 (8.6)	10 (9.9)	51 (11)
Obesity					
No	83 (52.9)	49 (55.7)	63 (54.3)	52 (51.5)	247 (53.5)
Yes	74(47.1)	39 (44.3)	53(45.6)	49 (48.5)	215 (46.5)
Current smoking:					
No	97(61.9)	52(59.1)	56(48.3)	56(55.5)	261(56.5)
Yes	60(38.2)	36(40.9)	60(51.7)	45 (44.5)	201 (43.5)
Alcohol consumption:					
Never	22(14)	14 (15.9)	21(18.1)	23 (22.7)	80 (17.3)
Previous	44(28)	26 (29.5)	25(21.5)	22 (21.8)	117 (25.3)
Current	91 (58.0)	48(54.6)	70 (60.3)	56 (55.5)	265 (57.4)
Amount of alcohol:					
Seldom	26 (28.5)	19(39.6)	27(38.6)	19 (33.9)	91 (34.3)
Sometimes	35 (38.5)	21(43.8)	17(24.3)	20(35.7)	93(35.1)
Daily	30 (33.0)	8(16.7)	26(37.1)	17(30.4)	81(30.6)
Disease state*** (0.001):					
Mild	15(9.6)	50(56.8)	11(9.5)	39 (38.6)	115 (24.9)
Moderate	79(50.3)	24(27.3)	52(44.8)	42(41.6)	197 (42.6)
Severe	63(40.1)	14(15.9)	53(45.7)	20(19.8)	150 (32.5)
Duration of illness:					
6MO to 1YR	19(12.1)	6 (6.8)	5 (4.3)	6 (5.9)	36 (7.8)
1YR to 5YRS	66(42.0)	42(47.7)	60(51.7)	48(47.5)	216 (46.8)
5YRS to 10YRS	45(28.7)	21(23.9)	30(25.9)	28(27.7)	124 (26.8)
>10YRS	27(17.2)	19(21.6)	21(18.1)	19(18.8)	86 (18.6)

Distribution of categorical demographic covariates across the studies.

Covariate/ levels (p-value)[a]	Study N (%)				Total N (%)
	92-202	93-201	94-201	94-203	
# patients	157	88	116	101	462
Diabetes:					
NO	115(73.2)	72 (81.8)	87(74.0)	77(76.2)	351(75.9)
YES	42(26.8)	16(18.2)	29(25.0)	24(23.8)	111(24.0)
Myocardial infarction:					
NO	122(77.7)	78(88.6)	95(81.9)	80(79.2)	375(81.1)
YES	35(22.3)	10(11.4)	21(18.1)	21(20.8)	87 (18.8)
Cerebro-vascular event**(0.002):					
NO	148(94.2)	73(82.9)	92(79.3)	88(87.1)	401(86.8)
YES	9(5.73)	15(17.05)	24(20.69)	13(12.87)	61(13.2)

The following table shows the distribution of patients on concomitant medications.

Use of concomitant medications[b]

Concomitant medication or therapeutic subclass (p-value)[a]	Study N (%)				Total N (%)
	92-202	93-201	94-201	94-203	
Acetaminophen *** (0.0005)	46 (29.3)	14 (15.9)	41 (35.3)	15 (14.9)	116 (25.1)
Lovastatin *** (0.0000)	14 (8.9)	0 (0.0)	18 (15.5)	10 (9.9)	42(9.1)
Verapamil hydrochloride *** (0.0001)	21 (13.4)	1 (1.1)	2 (1.7)	4 (4.0)	28(6.1)
Gemfibrozil* (0.011)	9(5.7)	0(0.0)	8(6.9)	10(9.9)	27(5.8)
Ranitidine hydrochloride *** (0.0000)	16 (10.2)	0	12(10.3)	0	28(6.1)
Diclofenac sodium* (0.041)	9 (5.7)	4 (4.6)	11 (9.5)	1 (1.0)	25 (5.4)
Potassium chloride *** (0.0006)	8 (5.1)	5 (5.7)	17 (14.7)	1 (1.0)	31(6.7)
Diuretics *** (0.0007)	92 (58.6)	31 (35.2)	69 (59.5)	46 (45.5)	238 (51.5)
Sympathomimetic agents *** (0.0000)	37 (23.6)	0	43 (37.1)	24 (23.8)	104 (22.5)
hypotensive agents *** (0.0001)	20(12.7)	3 (3.4)	19 (16.4)	2 (2.0)	44 (9.5)
cathartics and laxative* (0.032)	17(10.8)	10(11.4)	27(23.3)	14 (13.9)	68 (14.7)

a) indications of significance: * $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

b) Only those concomitant medications/groups of medications that were significantly differently distributed between the studies

The following tables show the number and % of patients assigned to various exposure levels.

Number and percent of patients assigned to 'exposure levels'

Partition set	Value of smoothing parameter	Exposure levels: N (%)				
		1	2	3	4	Unclassified[a]
1	1	105 (22.7)	170 (36.8)	107 (23.2)	42 (9.1)	38 (8.2)
2	10	104 (22.5)	170 (36.8)	105 (22.7)	44 (9.5)	39 (8.4)
3	100	106 (22.9)	172 (37.2)	105 (22.7)	43 (9.3)	36 (7.8)

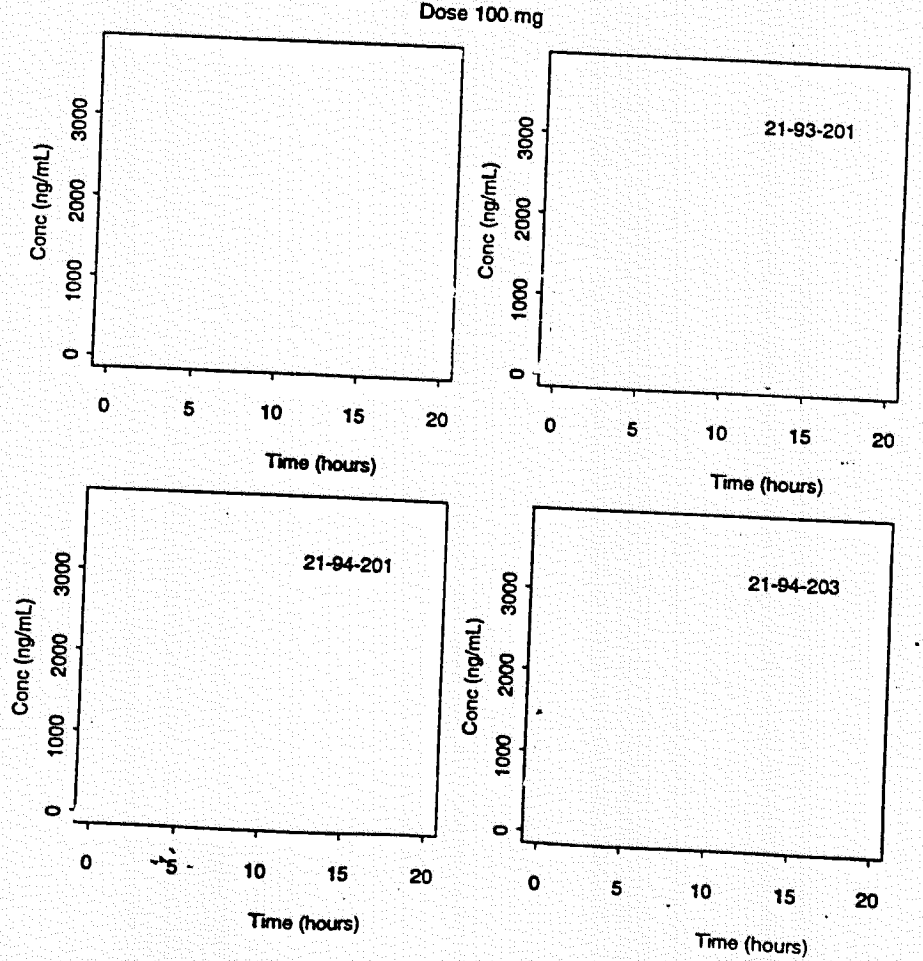
a) Concentrations span four observation levels

Numbers (percents) of patient types

Partition set	Patient type N (%)			
	All-in-one[a]	Two adjacent[b]	Three adjacent[c]	All four[d]
1	127 (27.5)	178 (38.5)	119 (25.8)	38 (8.2)
2	135 (29.2)	173 (37.5)	115 (24.9)	39 (8.4)
3	137 (29.7)	170 (36.8)	119 (25.8)	36 (7.8)

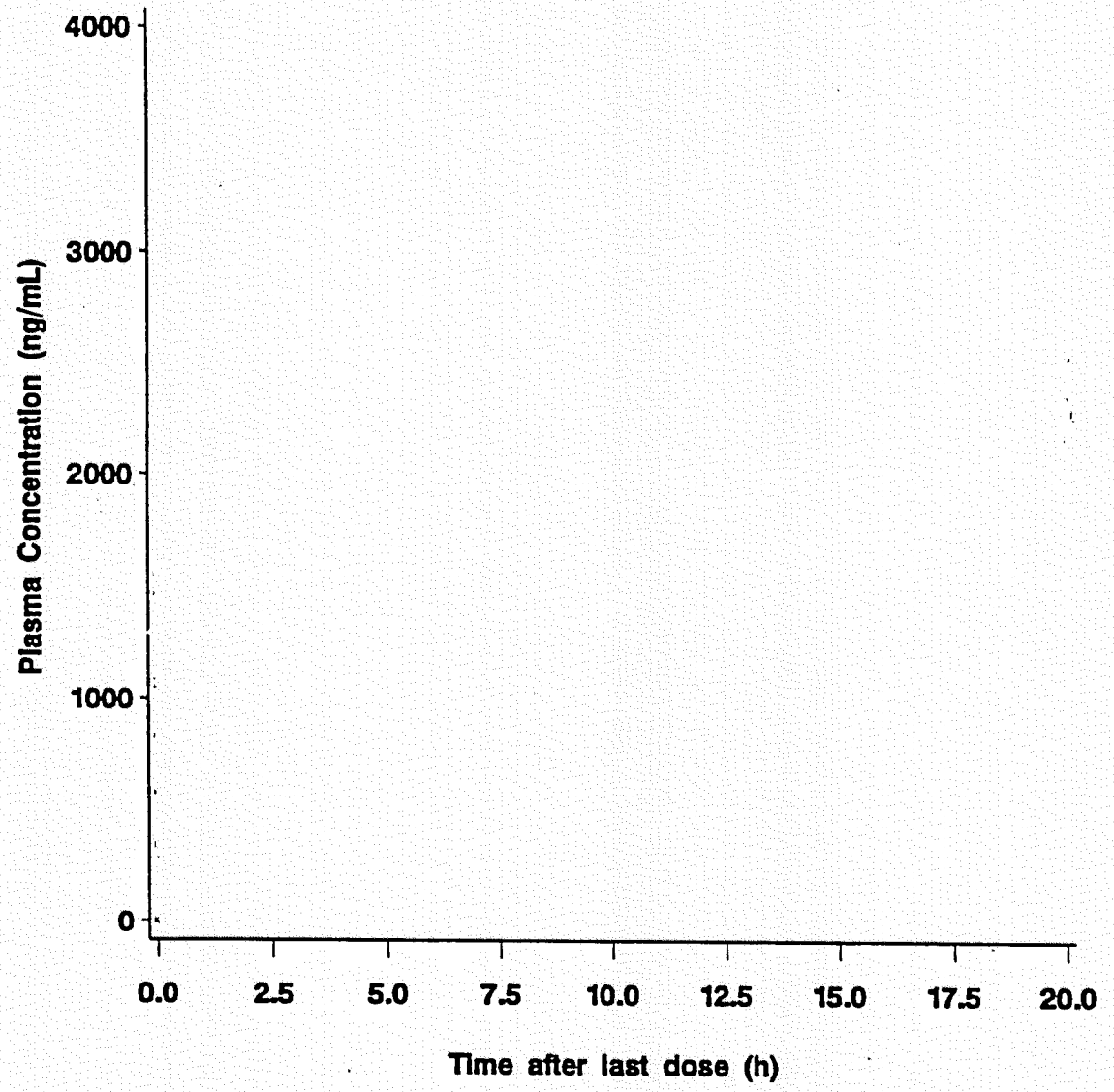
a) All concentrations in one observation level
b) All concentrations in two adjacent observation levels
c) All concentrations in three adjacent observation levels
d) Concentrations span four observation levels

The following figures are composed of scatter plots of blood concentrations for the 4 studies used in this analysis. Smooth curves were created by a smoothing algorithm that down weights outliers (Lowess regression).



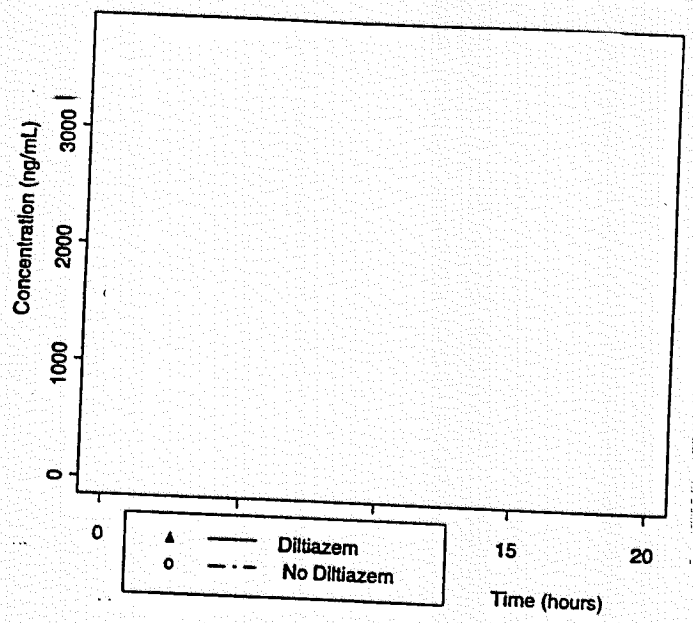
The following figure shows the 4 different observation levels (I, II, III, IV) that correspond to 25th, 50th, 75th percentiles.

Regions defining observation levels



Three smoothing splines fitted to the data correspond approximately to 25th, 50th, and 75th percentiles. They divide the region into four observation levels, denoted by Roman numerals

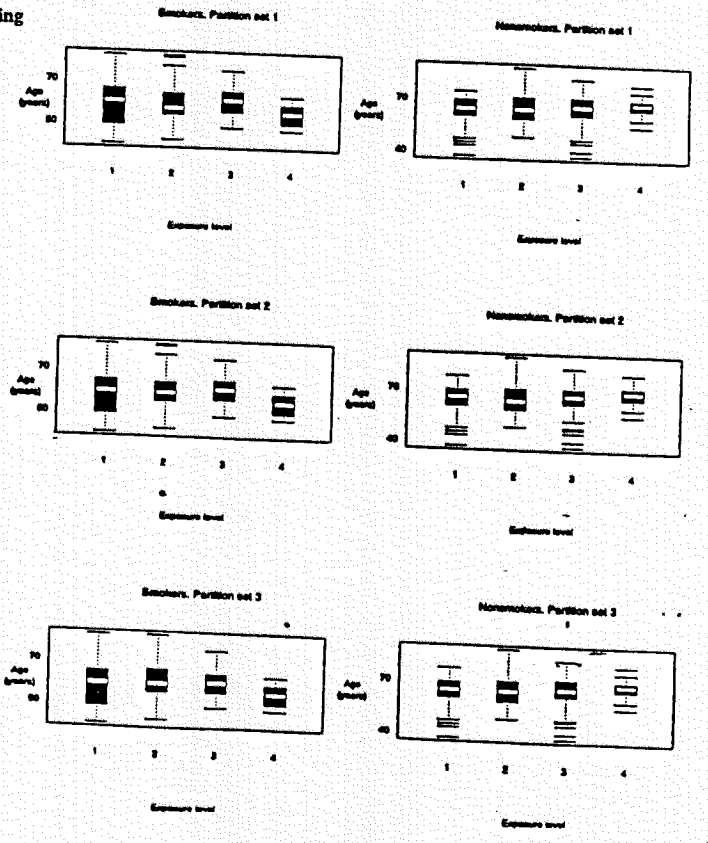
Concomitant use of cilostazol with diltiazem appeared to be the major covariate that significantly increases cilostazol levels by about 50%. The population smooth curves for patients with and without diltiazem are shown in the following graph. These results are expected as cilostazol is CYP3A4 substrate, and diltiazem is a CYP3A4 inhibitor.



Effect of smoking: Smoking decreased the exposure of cilostazol by 18% in those patients not taking diltiazem (smoking was correlated with diltiazem).

Correlation analysis showed that young patients smoked more than older patients (see figure below). The box plots failed to show that age has any effect on exposure. Patients not taking diltiazem or nitroglycerin smoked more than patients on these medications.

Age versus exposure level in smoking and nonsmoking patients not taking diltiazem



Comments & Conclusion

Data analysis can be prohibitively difficult depending on the nature of data (level and nature of variability, number of patients, samples collection design,.etc....). New approaches and methodologies are always received with much enthusiasm. However, this methodology is considered exploratory and not conclusive for the following reasons:

- Loss of information is a major drawback of this analysis.
- Loss of analysis validation. How sure are we that partitioning and level assignments are appropriate?
- This is not the first drug characterized with secondary peaks and high levels of variabilities. If the cause of secondary peak is established, modeling can accommodate and fit the data. Using the population approach, provided there are enough patients and data is obtained at different sampling times, the data could have been fit using the parametric approach. I couldn't find the NONMEM code for data analysis nor its table for model building and selection.
- Although the data analysis is considered exploratory, a positive interaction with diltiazem should be considered and mentioned in the label. This variable is strong enough that it would most probably show as significant covariate in traditional analysis. Smoking was also shown to be a positive covariate.
- We cannot conclude that all other covariates are not significant using this approach. A parametric analysis would be more definitive and conclusive in this regard.

APPENDIX II

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

27 pages
Draft Labeling

SEP 16 1998

Clinical Pharmacology and Biopharmaceutics Review

IND: 35,848 (BZ)
NDA: 20-863

Date: September 2nd, 1988

Drug: Cilostazol, Pletal, OPC-13013

Sponsor: Otsuka Pharmaceutical, Inc.

Reviewer: Nakissa Sadrieh, Ph.D.

Re: "A study to determine the effects of multiple-dose cilostazol tablets on single dose lovastatin pharmacokinetics in healthy volunteers". Study No. 21-98-208-01.

Background:

Cilostazol (OPC-13013) is an inhibitor of platelet aggregation and a peripheral vasodilator. It is indicated for the amelioration of symptoms in patients with intermittent claudication.

Cilostazol is extensively metabolized and its major metabolites are OPC-13015 (which is more active than the parent compound) and OPC-13213 (which is less active than the parent compound). The PK of cilostazol is linear between 50-200mg and recommended dose is 100 mg bid. Cilostazol's terminal half-life is 11 hours. Steady state is reached after 5 days of dosing and the accumulation ration is 1.7. A high fat meal increases the Cmax by 90% and the AUC by 25%.

In vitro metabolism studies using expressed cDNA P450, results have shown that cilostazol was a CYP3A4 inhibitor at concentrations approximatly 2 times the Cssmax. However in microsomal incubations, cilostazol inhibited CYP3A4 mediated reactions at a concentration that was 28 times the Cssmax. In vivo pharmacokinetics of R-warfarin (a CYP3A4 substrate) were not affected by 100 mg cilostazol bid for 7 days.

The objective of the present study was to determine the potential for cilostazol to affect the pharmacokinetics of lovastatin (a CYP3A4 substrate). Lovastatin is an HMG-Co-A reductase inhibitor and the recommended daily dose is between 10-80 mg. The Cmax and AUC of lovastatin is increased 20-fold by itroconazole and 12-15 fold by grapefruit juice. Lovastatin is metabolized to an active metabolite (ß-hydroxyacid-derivative).

Results:

There was a significant difference in cilostazol Cmax (p=0.041) and AUC (p=0.023) when cilostazol was co-administered with 80 mg of lovastatin, based on the comparison of day 7 (100 mg of cilostazol plus 80 mg of lovastatin) results with those of day 6 (100 mg cilostazol alone) (Table ST-16). The AUC and Cmax values were lower when cilostazol was administered with lovaststin (day 7). There was no significant change in the cilostazol metabolite upon coadministration of cilostazol with lovastatin.

Lovastatin and its ß-hydroxy metabolite plasma concentration time profiles are provided in figure 6.5.1. Additionally, the mean PK parameters for lovastatin and its metabolite are provided in the table above as well as in table 6.5.1.

The results show that the PK of lovastatin and that of its active metabolites were significantly different when administered alone and when administered with cilostazol. The mean AUC(t) and AUC (inf) increased by 56% and 72%, respectively, when comparing day 7 (cilostazol 100 mg plus lovastatin) to day 1 (lovastatin alone) and the same parameters were increased by 55 and 58% when comparing day 9 (cilostazol 150 mg plus lovastatin) with day 1 (lovastatin alone). Additionally, the Cmax of lovastatin increased by 58% when cilostazol dose was increased from 100 mg to 150 mg. The Cmax, AUC(t) and AUC(inf) values for the ß-hydroxymetabolite of lovastatin increased significantly when cilostazol was co-administered with lovastatin. However, these values did not rise further when the dose of cilostazol was increased to 150 mg. The increases ranged from 63% to 120% of the values from day 1 (lovastatin alone).

Reviewer's comments:

There are unacceptable differences between AUC(t) and AUC(inf) for lovastatin and its metabolite. The difference ranges

for lovastatin for its active ß-hydroxy metabolite. These large differences between AUC(t) and AUC(inf) are most likely due to the PK sampling time points which did not go out far enough until the drug plasma levels had declined by at least 3 half-lives. Consequently, the terminal phase rate constant and half-life values could not be accurately determined.

Discussion:

The sponsor concludes that although cilostazol is a potent inhibitor of CYP3A4, the 1.7-fold increase in the exposure to lovastatin is not likely to result in clinically relevant toxicities. Therefore, the sponsor concludes that a dose reduction of lovastatin is not recommended unless adverse events persist. In such an event, the dose of lovastatin is recommended to be decreased to 50 mg, from 80 mg per day. Similarly, the sponsor does not recommend a dose adjustment of cilostazol, even though the Cmax and AUC values tend to significantly decrease (15% and 20%, respectively) with lovastatin coadministration.

It should be noted that the validity of the data upon which the sponsor draws conclusions is in question. In table 6.5.1, the t ½ of lovastatin is said to range between 21.7-31 hours. However, the PK sampling time points only go as far as 24 hours after dosing. This is less than one half-life after dosing, and thus grossly inadequate. Additionally, the accuracy of the half-life determinations for lovastatin is in question, since the terminal phase rate constant could not have been accurately calculated, based on the poor study design. Since the PK sampling time points that were undertaken in this study were inadequate, they do not allow a precise evaluation of the results. Consequently, the difference between AUC(last) and AUC(inf) as reported in the summary table (in the results section of Appendix 1), show that the differences between these 2 parameters reaches 91%, whereas it is desirable that this difference not exceed 10 %.

Therefore, all conclusions that can be drawn from this study should be drawn and interpreted with a note of caution. The clinical relevance of the finding that cilostazol increases the exposure to lovastatin by 1.7 fold is beyond the scope of this review and will be determined by the medical reviewer. However, it is recommended that an advisory statement regarding the potential drug interaction between cilostazol and lovastatin be added in the package insert.

Comments:

The present study has certain shortcomings in its design which make the interpretation of the results tenuous at best. As the data stand now and based on the poor study design conducted, it would be hasty to draw conclusions on the clinical relevance of a cilostazol/lovastatin interaction. It can be however concluded that there appears to be a significant interaction between cilostazol and lovastatin, leading to a 1.7 fold increase in exposure to lovastatin, when coadministered with cilostazol at 100 mg bid. Similarly, there appears to be a significant increase in the plasma levels of ß-hydroxy metabolite of lovastatin, when lovastatin is coadministered with cilostazol. Since the ß-hydroxy metabolite is active, the relevance of the increase in exposure to this metabolite during concomitant therapy with lovastatin and cilostazol remains to be evaluated.

Recommendations:

Coadministration of lovastatin and cilostazol leads to a 1.7 fold increase in the exposure to lovastatin. Whether a 1.7-fold increase in the AUC of lovastatin will lead to blood levels of this drug that fall out of the tolerated range of exposure of lovastatin will need to be determined.

A similar 1.7 fold increase in the exposure to the active metabolite of lovastatin, ß-hydroxy-lovastatin, is also noted in the present study. When the dose of cilostazol is increased from 100 mg bid to a single dose of 150 mg, there appears to be an additional increase in both the Cmax (2.2 fold) and AUC (2 fold) of the ß-hydroxy metabolite of lovastatin. Since this metabolite is active, the clinical relevance of such an interaction needs to be determined.

The clinical relevance of these findings is beyond the scope of this review and will be deferred to the medical reviewer.

It is however recommended that an advisory statement be added to the package insert of cilastazol, regarding the interaction between cilostazol and lovastatin.

Ahmad EL-TAHTAWY Ph.D.

RD/FT Patrick Marroum, Ph.D.

9/16/98

Natasa Kolbah

9/16/98