STUDY 21-93-205: RELATIVE BIOAVAILABILITY AND BIOEQUIVALENCE STUDY

AN OPEN-LABEL, SINGLE CENTER STUDY OF THE RELATIVE BIOEQUIVALENCE OF FOUR FORMULATIONS OF CILOSTAZOL

Reference: Volume 1.55 to 1.58
Investigator:
Study Location:
Objective:

To determine the relative bioequivalence of three tablet formulations of cilostazol, manufactured at two production factories, with that of a formulation of cilostazol when administered to healthy males under fasting conditions.

Drug Dosage Forms:

Cilostazol 50 mg tablet, lot #4A81PB2
Cilostazol 100 mg tablet, lot #1G86-100
Cilostazol 100 mg lot #3B78K-2,

Cilostazol 100 mg tablet, as reference, lot #4A93PA1.

Study Design:

This study was an open-label, single-dose, randomized, incomplete block design, three period, four treatment crossover trial conducted at a single center. Twenty four healthy male volunteers of age 18 to 40 years participated in this study (23 completed treatment). Subjects were randomized to one of the four treatment sequences as shown below:

Sequence	Treatment period I	Treatment period 2	Treatment period 3
A	2 x 50 mg tablet	100 mg tablet	100 mg (pilot) tablet
B	100 mg tablet	100 mg tablet	100 mg suspension
C	100 mg tablet	100 mg suspension	2 x 50 mg tablet
D	100 mg suspension	2 x 50 mg tablet	100 mg tablet

There was a one week washout between each dosing period. Each dose was taken with 180 ml of water. Subjects fasted for 10 hours prior to study drug administration. After dosing, subjects refrained from eating lunch and dinner until 4 and 10 hours after dosing. Subjects receiving the suspension formulation (100 mg powder) drank the suspension directly out of the dosing container. In addition, these subjects received 10 ml of water rinsing from the preparation syringe, directly out of the dosing container, followed by 170 ml of water.

Blood samples for the analysis of cilostazol and its metabolites (OPC-13015 and OPC-13213) were drawn in each treatment period at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 24, 36, 48, 72, 96 and 120 hours after dosing.

PK parameters for cilostazol and its major metabolites were determined by noncompartmental methods. The natural logarithms of PK parameters were analyzed with an ANOVA for an incomplete block design with subject, treatment, and period as factors, using PROC GLM of SAS. 90% confidence intervals were then calculated using the two one-sided tests procedure. Since the incomplete block design was not balanced, the ANOVA for a repeated measures design was also performed.

Results:

ASSAY PERFORMANCE:

CILOSTAZOL (OPC-13013):
Method used:
Range:
Linearity: Linear within the range.
QC samples:

Precision:
Accuracy:

Specificity:

OPC-13015:
Method used:
Range:
Linearity: Linear within the range.
QC samples:

Precision:
Accuracy:

Specificity:

OPC-13213:
Method used:
Range:
Linearity: Linear within the range,
QC samples:

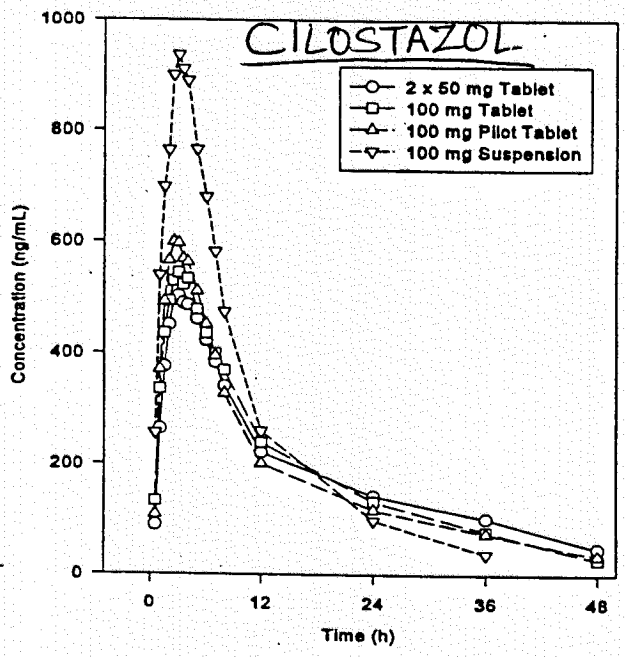
Precision:
Accuracy:

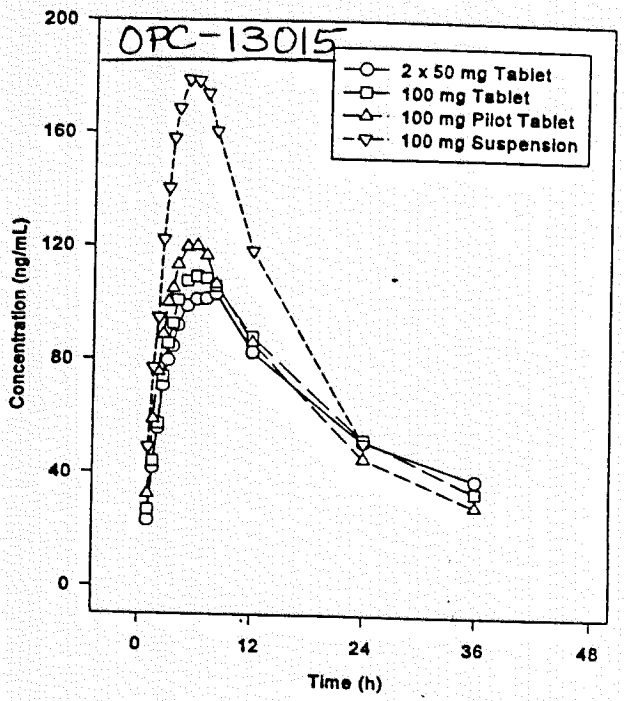
Specificity:

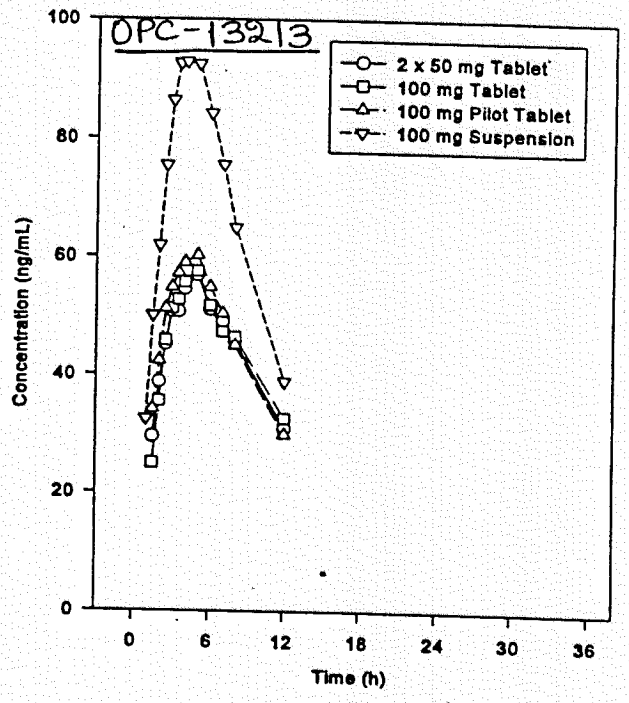
ole.

Assays were found to be acceptable (see comment 1 below for calibration curve).

Plot of mean plasma concentrations of cilostazol, OPC-13015 and OPC-13213 following administrations of various formulations is provided in the following figures.







Mean (and standard deviation) pharmacokinetic parameters of cilostazol after administration of each formulation are given in the table below.

Cilostazol pharmacokinetic parameters following oral administration of cilostazol as 2 x 50 mg tablets, 100 mg reference tablet, 100 mg pilot tablet and 100 mg suspension

Treatment		T_{max} (h)	C_{max} (ng/mL)	$t_{1/2z}$ (h)	AUCt (ng.h/mL)	AUC (ng.h/mL)	CL/F (mL/h/kg)	Vz/F (mL/kg)
2 x 50 mg Tablet	MEAN	3.68	568.65	20.19	8744	10494	136.5	3533
	S.D.	1.74	141.9	13.46	2701	3381	49.3	1601
	N	17	17	17	17	17	17	17
	GEOM. MEAN	3.36	552.89	17.66	8373	9991	128.8	3285
	LOWER C.L.							
	UPPER C.L.							
100 mg Reference Tablet	MEAN	3.38	665	15.53	8483	9571	144.3	3226
	S.D.	1.62	209.79	5.95	2643	2791	40.5	1447
	N	17	17	17	17	17	17	17
	GEOM. MEAN	3.11	636.9	14.64	8101	9190	138.8	2933
	LOWER C.L.							
	UPPER C.L.							
100 mg Pilot Tablet	MEAN	3.5	686.65	17.88	8271	9388	142.2	3548
	S.D.	2.44	189.24	7.63	1939	1883	38.2	1366
	N	17	17	17	17	17	17	17
	GEOM. MEAN	3.02	667.28	16.33	8049	9191	138	3250
	LOWER C.L.							
	UPPER C.L.							
100 mg Suspension Suspension	MEAN	2.89	1024.17	9.35	9611	10514	129	1742
	S.D.	0.88	264.71	3.09	2691	2446	29.9	751
	N	18	18	17	18	17	17	17
	GEOM. MEAN	2.76	993.07	8.88	9284	10270	125.5	1607
	LOWER C.L.							
	UPPER C.L.							

Mean (and standard deviation) pharmacokinetic parameters of OPC-13015 after administration of each formulation are given in the table below.

OPC-13015 pharmacokinetic parameters following oral administration of cilostazol as 2 x 50 mg tablets, 100 mg reference tablet, 100 mg pilot tablet and 100 mg suspension

Treatment		T_{max} (h)	C_{max} (ng/mL)	$t_{1/2z}$ (h)	AUCt (ng.h/mL)	AUC (ng.h/mL)	CL/F (mL/h/kg)	Vz/F (mL/kg)
2 x 50 mg	MEAN	6.18	112.39	22.56	2582	3591	406.8	12119
Tablet	S.D.	1.42	31.02	9.9	1066	1405	143.5	3668
	N	17	17	17	17	17	17	17
	GEOM.	6.02	108.82	21.08	2406	3369	382.4	11634
	LOWER C.L.							
	UPPER C.L.							
100 mg Reference	MEAN	6.41	125.01	22.62	2473	3555	392.4	11893
Tablet	S.D.	2.48	32.41	15.62	922	1275	108.8	5676
	N	17	17	17	17	17	17	17
	GEOM.	6.02	121.57	19.55	2339	3378	377.3	10640
	LOWER C.L.							
	UPPER C.L.							
100 mg Pilot	MEAN	5.76	132.19	18.96	2398	3229	415.6	10860
Tablet	S.D.	2.14	28.64	7.18	640	757	112.7	3409
	N	17	17	17	17	17	17	17
	GEOM.	5.44	129.34	17.7	2319	3146	403.1	10295
	LOWER C.L.							
	UPPER C.L.							
100 mg Suspension	MEAN	5.25	189.17	11.2	2898	3557	400.1	6163
Suspension	S.D.	1.2	46.79	4.07	1167	1305	125.9	2290
	N*	18	18	17	18	17	17	17
	GEOM.	5.12	183.59	10.57	2726	3381	381.1	5807
	LOWER C.L.							
	UPPER C.L.							

* The Ns are different for the 4 treatments since one subject did not complete the study and did not receive the three tablet treatments.

Mean (and standard deviation) pharmacokinetic parameters of OPC-13213 after administration of each formulation are given in the table below.

OPC-13213 pharmacokinetic parameters following oral administration of cilostazol as 2 x 50 mg tablets, 100 mg reference tablet, 100 mg pilot tablet and 100 mg suspension

Treatment		T_{max}	C_{max}	$AUC_{0\text{-}12hh}$
2 x 50 mg	MEAN	5.03	62.26	485
Tablet	S.D.	1.62	14.8	121
	N	17	17	17
	GEOM. MEAN	4.8	60.87	469
	LOWER C.L.			
	UPPER C.L.			
100 mg Reference	MEAN	4.74	64.65	491
Tablet	S.D.	2.19	22.19	180
	N	17	17	17
	GEOM. MEAN	4.4	61.14	453
	LOWER C.L.			
	UPPER C.L.			
100 mg Pilot	MEAN	4.68	66.46	504
Tablet	S.D.	2.18	21.38	161
	N	17	17	17
	GEOM. MEAN	4.34	63.43	476
	LOWER C.L.			
	UPPER C.L.			
100 mg Suspension	MEAN	4.17	99.86	759
Suspension	S.D.	0.92	25.01	203
	N	18	18	18
	GEOM. MEAN	4.07	96.64	727
	LOWER C.L.			
	UPPER C.L.			

Geometric mean ratios and 90% confidence intervals of PK parameters for each formulation in comparison to the 100 mg factory XI tablet as reference are provided in the following 3 tables.

Comparison of 2 x 50 mg tablet to 100 mg reference tablet: Geometric mean ratios and 90% confidence intervals of pharmacokinetic parameters for cilostazol, OPC-13015 and OPC-13213

Parameter	Analyte	Ratio (%)	90% C.I. (%)
C_{max}	Cilostazol	88	79,98
	OPC-13015	92	84,100
	OPC-13213	99	90,108
AUC_t	Cilostazol	103	95,111
	OPC-13015	101	93,110
AUC_{0-12h}	OPC-13213	99	91,108
AUC	Cilostazol	106	96,118
	OPC-13015	96	86,107

Comparison of 100 mg suspension to 100 mg reference tablet: Geometric mean ratios and 90% confidence intervals of pharmacokinetic parameters for cilostazol, OPC-13015 and OPC-13213

Parameter	Analyte	Ratio (%)	90% C.I. (%)
C_{max}	Cilostazol	152	137, 168
	OPC-13015	151	138, 164
	OPC-13213	153	140, 168
AUC_t	Cilostazol	112	104, 121
	OPC-13015	112	103, 122
AUC_{0-12h}	OPC-13213	156	143, 171
AUC	Cilostazol	104	95, 116
	OPC-13015	93	84, 104

Comparison of 100 mg pilot tablet to 100 mg reference tablet: Geometric mean ratios and 90% confidence intervals of pharmacokinetic parameters for cilostazol, OPC-13015 and OPC-13213

Parameter	Analyte	Ratio (%)	90% C.I. (%)
C_{max}	Cilostazol	104	93,115
	OPC-13015	106	97,116
	OPC-13213	110	100,121
AUC_t	Cilostazol	102	94,110
	OPC-13015	98	90,106
AUC_{0-12h}	OPC-13213	112	102,122
AUC	Cilostazol	100	90,110
	OPC-13015	92	82,102

CONCLUSION:

The data of interest for this NDA are the 2 x 50 mg tablet, 100 mg reference tablet and the Results indicate that the relative bioavailability of cilostazol in comparison to as reference is almost 100% based on cilostazol and OPC-13015 (based on AUC). However, the rate of absorption with oral suspension is faster than the tablet. Further, the 90% confidence intervals for the 2 x 50 mg tablet in comparison to the 100 mg factory tablet as reference, indicate that the confidence intervals for AUC for cilostazol and its metabolites meet the 80 - 125% criteria. However, the Cmax of cilostazol fails to meet the criteria with a confidence interval of 79 - 98%. The geometric mean ratio for Cmax of cilostazol is 88%. This suggests that the 50 mg tablet may have a slower absorption than the 100 mg tablet. These two strengths are bioequivalent based, however, on the metabolite data.

COMMENT:

1. The calibration curves, provided for cilostazol assay, plot the concentration of analytes on Y-axis and the peak height ratios on X-axis. This is not acceptable. In future, the sponsor should plot the independent variable (drug concentration) on the X-axis.
2. Comparison to suspension data is important since, in this NDA, study to determine absolute bioavailability has not been carried out due to solubility constraints of the drug. Since we do not have any I.V. data or oral solution data, the next alternative to get some indication of oral bioavailability of the cilostazol tablet dosage form is comparing it to the suspension.

STUDY 21-93-206 (STUDY IN RENALLY IMPAIRED PATIENTS)

AN OPEN LABEL STUDY OF THE SAFETY AND PHARMACOKINETICS OF CILOSTAZOL IN SUBJECTS WITH RENAL INSUFFICIENCY

Volumes: 80 to 83
Investigators: Dr. William Smith
Clinical Site: New Orleans Center for Clinical Research, New Orleans, LA.
Objective:

To determine the effects of varying degrees of renal insufficiency on the safety and pharmacokinetics of cilostazol under single dose and steady state concentrations.

Drug Dosage Forms: Cilostazol 50 mg tablets, lot # 4K77PB1.

Study Design:

This study was an open-label, parallel, multiple dose trial conducted in one study center. Four groups of subjects were enrolled in this study: six subjects with normal renal function (creatinine clearance > 90 ml/min), six subjects with mild renal impairment (CrCl between 50 - 89 ml/min), five subjects with moderate renal impairment (CrCl between 26 - 49 ml/min), and six subjects with severe renal impairment (CrCl between 5 - 25 ml/min). The subjects with renal impairment were matched by sex, age and ideal body weight with subjects with normal renal function. Totally 23 male and female subjects (of age 18 years and older) were enrolled in the study. Subjects with renal insufficiency were not permitted to be undergoing dialysis.

All subjects received a single 50 mg dose of cilostazol on day 1 and multiple dosing (50 mg bid) on days 2 to 8. The cilostazol tablets were administered orally every 12 hours with 240 ml of water 15 minutes after breakfast (fed state administration of drug).

In all subjects, the PK evaluation was conducted on days 1 and 8. Venous blood samples were collected for determination of cilostazol, OPC-13015 and OPC-13213 concentrations on day 1 at 0, 1, 2, 3, 4, 5, 6, 8, 12 and 16 hours post-dose, at pre-am dose on days 2, 3, 4, 5, 6 and 7 and at pre-pm dose on days 2 and 7 and at 0, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144 and 168 hours post dose on day 8. An additional sample was collected on day 0 for determination of cilostazol protein binding. Urine was collected on day 1 at 0 and 0 - 24 hours post-dose and on day 8 at 0 - 12 hours post-dose.

Plasma and urine samples were analyzed using validated analytical methods. Plasma protein binding was determined using an ultrafiltration method.

Pharmacokinetic parameters of cilostazol and its metabolites were estimated by non-compartmental methods. Effect of stages of renal impairment on PK profile of cilostazol and its metabolites was examined using one-way analysis of variance. If the test was significant, the least significant difference test was used to compare the least square means for each pair of renal function groups. Linear regression was used to assess the relationship between creatinine clearance and selected PK parameters.

Results:

ASSAY PERFORMANCE (plasma and urine assays):

1. For cilostazol:
Method used:
Range:
Linearity: Linear within the range,
QC sample levels:
Accuracy:
Precision:
Specificity:

2. For OPC-13015:
Method used:
Range:
Linearity: Linear within the range,
QC sample levels:
Accuracy:
Precision:
Specificity:

3. For OPC-13013:
Method used:
Range:
Linearity: Linear within the range,
QC sample levels:
Accuracy:
Precision:
Specificity:

Assays for cilostazol and its metabolites were found to be acceptable.

ASSAYS FOR DETERMINATION OF CILOSTAZOL, OPC-13015 AND OPC-13013 IN URINE: Analysis conducted

1. For cilostazol:
Method used:
Range:
Linearity: Linear within the range.
QC sample levels:

Accuracy:
Precision:
Specificity:

2. For OPC-13015:
Method used:
Range:
Linearity: Linear within the range,
QC sample levels:
Accuracy:
Precision:
Specificity:

3. For OPC-13213:
Method used:
Range:
Linearity: Linear within the range,
QC sample levels:
Accuracy:
Precision:
Specificity:

The pharmacokinetic parameters of cilostazol, OPC-13015 and OPC-13213 for each group of subjects are shown in the 3 tables below.

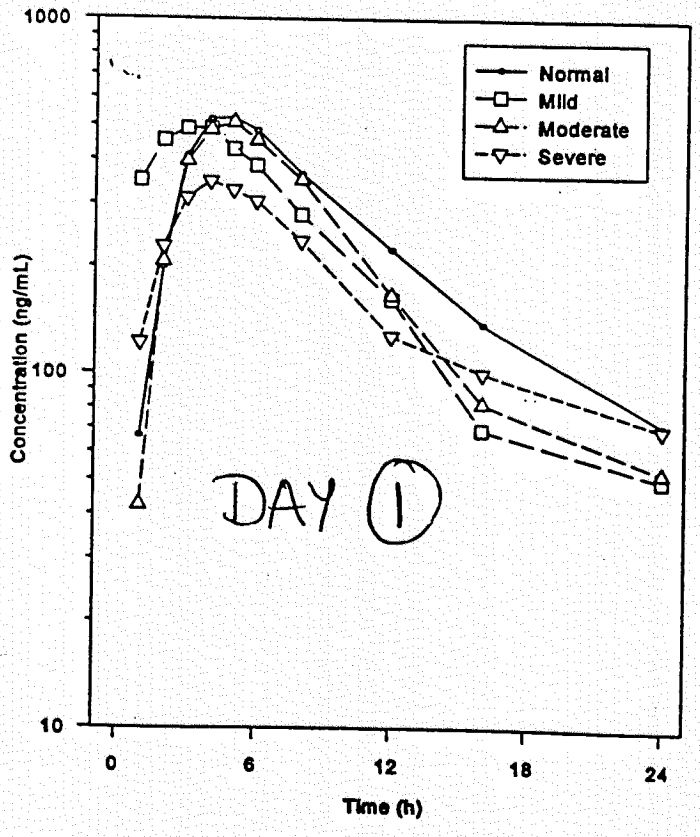
Cilostazol Mean ± SD Pharmacokinetic Parameters After Morning Dose of 50mg cilostazol on Day 8

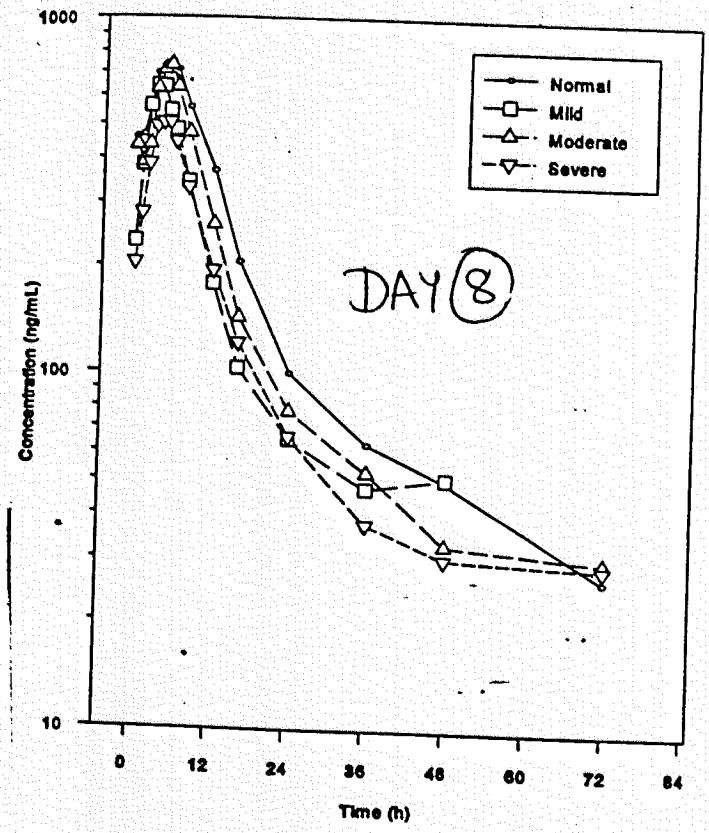
Group	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-12} (ng•h/ml)	$Cl/F_{unbound}$ (ml/hr/kg)	$t_{1/2}$ (hr)
Normal	799.8 ± 245.1	4.3 ± 2.0	5856 ± 2299	2801 ± 1204	11.97 ± 10.54
Mild	708.2 ± 181.7	2.7 ± 0.8	4621 ± 1004	4178 ± 1513	11.47 ± 6.64
Moderate	749.0 ± 331.7	4.4 ± 0.9	5533 ± 2692	3661 ± 1882	13.80 ± 7.91
Severe	569.0 ± 224.8	3.8 ± 1.0	3548 ± 1430	4444 ± 2815	16.33 ± 8.14

OPC-13015 Mean ± SD Pharmacokinetic Parameters After Morning Dose of 50 mg cilostazol on Day 8				
	C_{max} (ng/ml)	T_{max} (hr)	AUC_{0-12} (ng•h/ml)	$t_{1/2}$ (hr)
Normal	231.8 ± 41.3	4.5 ± 2.5	2099 ± 471	13.44 ± 7.09
Mild	190.3 ± 50.5	4.0 ± 1.3	1740 ± 412	10.08 ± 3.79
Moderate	190.0 ± 67.6	4.2 ± 2.4	1789 ± 649	11.80 ± 1.61
Severe	137.5 ± 26.3	5.2 ± 1.0	1103 ± 209	9.64 ± 2.77

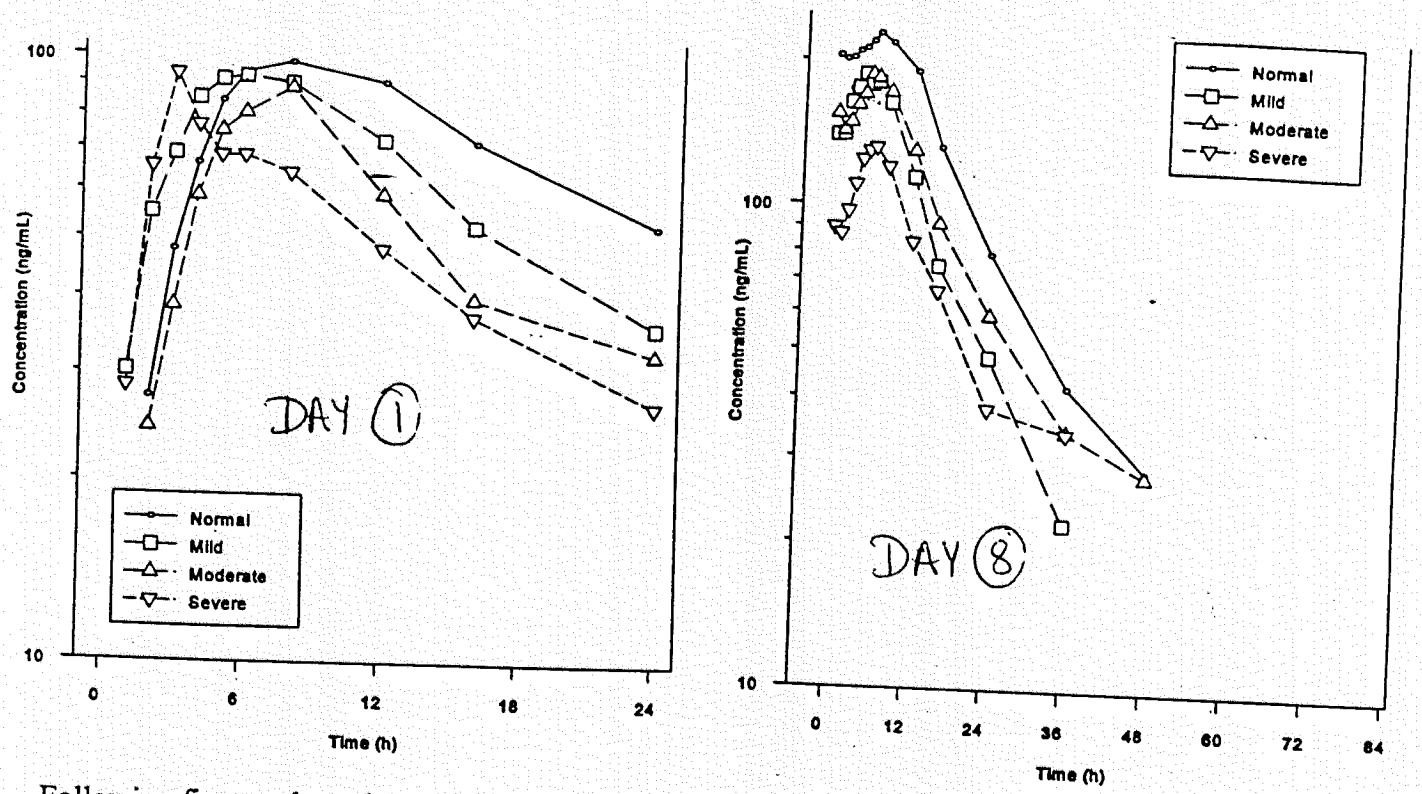
OPC-13213 Mean ± SD Pharmacokinetic Parameters After Morning Dose of 50mg cilostazol on Day 8 (* Not Determinable)						
	Cmax (ng/ml)	Tmax (hr)	AUC_{0-12} (ng•h/ml)	$t_{1/2}$ (hr)	Renal Clr (ml/min)	Cl/F_{total} (ml/hr/kg)
Normal	80.1 ± 26.7	5.5 ± 1.4	614 ± 249	ND*	250 ± 113	901.0 ± 141.2
Mild	96.6 ± 21.9	4.2 ± 0.8	756 ± 179	ND*	273 ± 43	879.8 ± 214.4
Moderate	169.0 ± 52.4	4.2 ± 2.4	1498 ± 448	ND*	84 ± 37	454.0 ± 208.3
Severe	219.0 ± 49.8	5.5 ± 2.1	1902 ± 457	ND*	36 ± 19	300.6 ± 87.0

Following figures show the mean plasma concentration-time profiles of cilostazol on days 1 and 8 in the 4 groups of subjects.

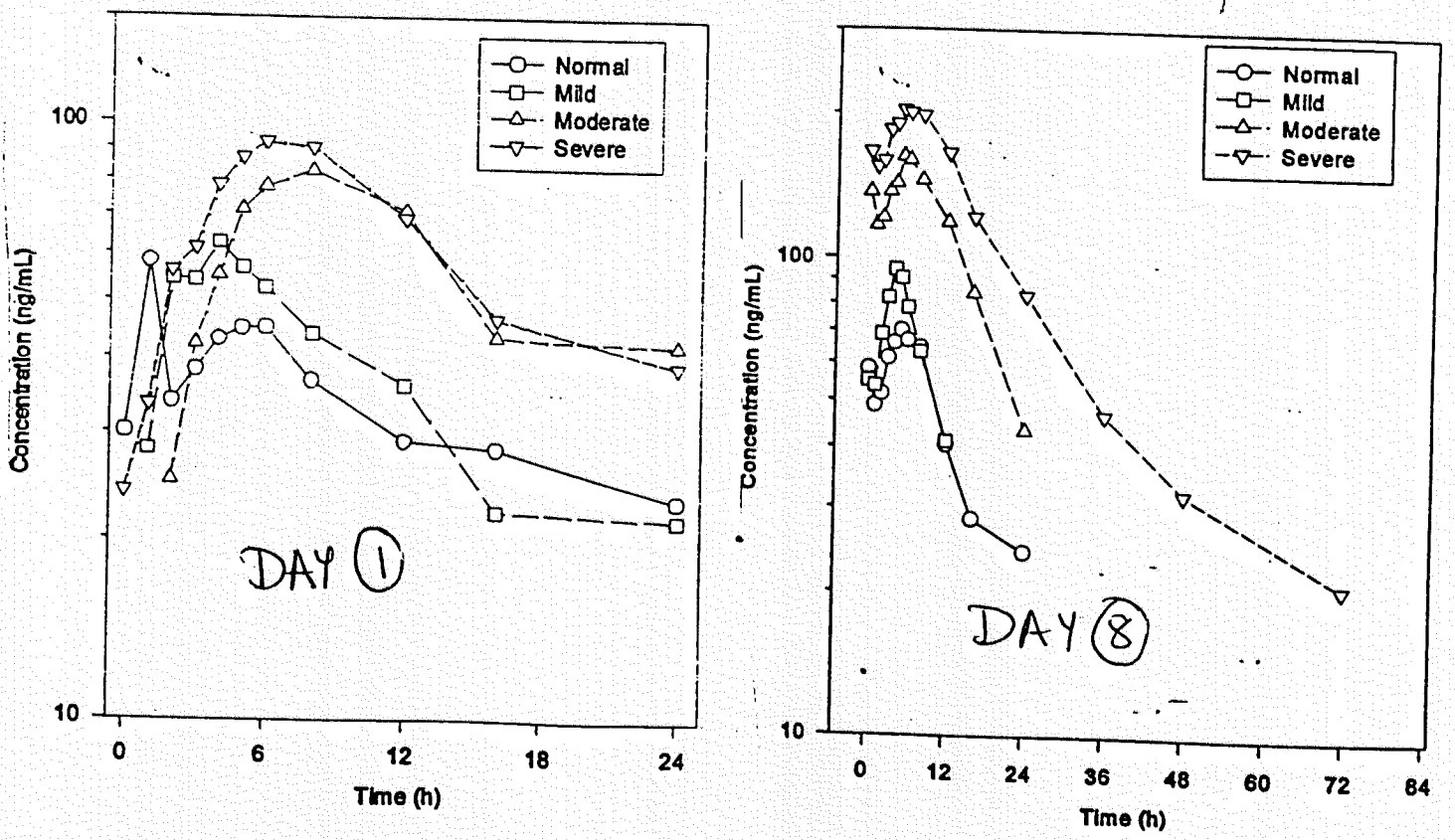




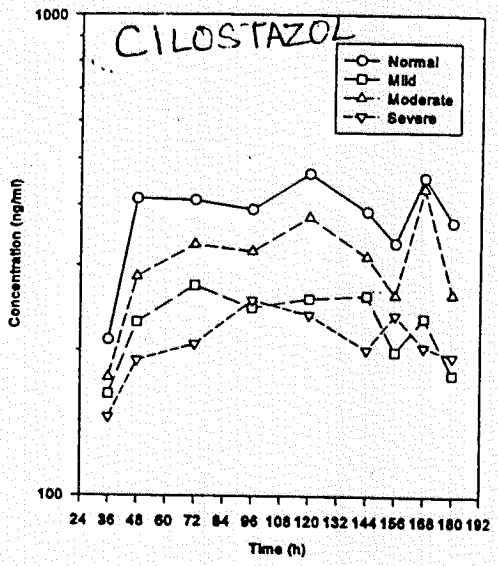
Following figures show the mean plasma concentration-time profiles of OPC-13015 on days 1 and 8 in the 4 groups of subjects.

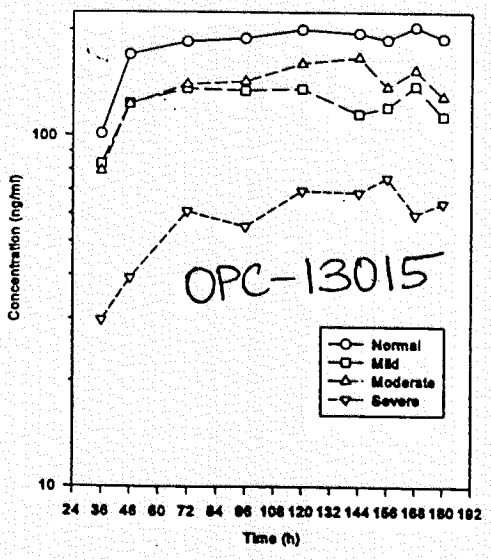


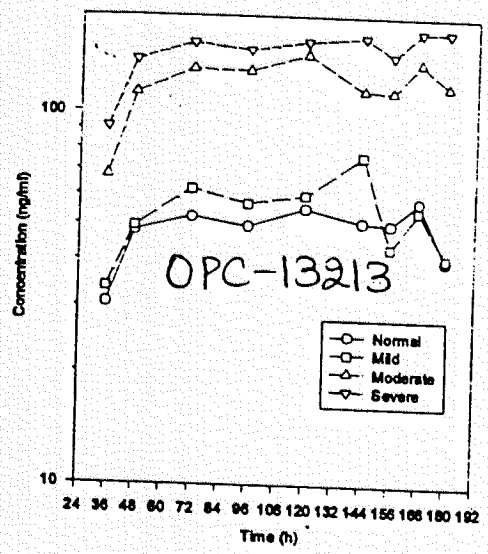
Following figures show the mean plasma concentration-time profiles of OPC-13213 on days 1 and 8 in the 4 groups of subjects.



Following three figures show the trough cilostazol and its metabolite plasma concentrations vs. time. This indicates that steady state is achieved by about 72 to 96 hours.

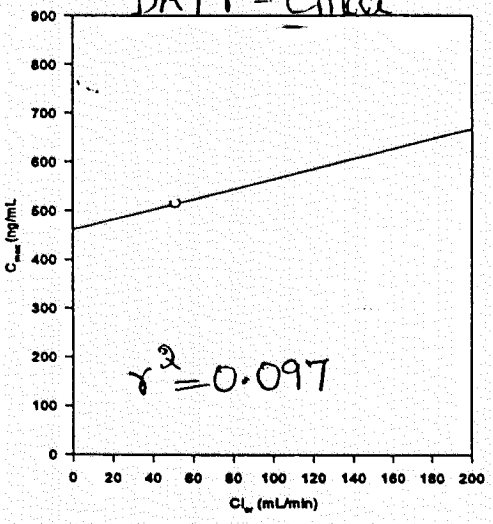




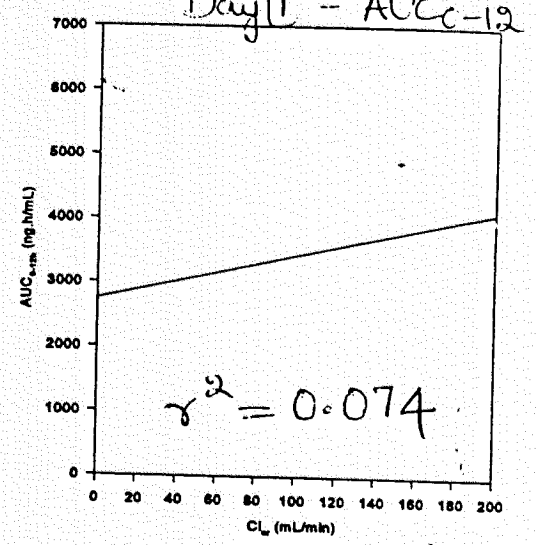


Plots of the relationship between PK parameters of cilostazol vs. creatinine clearance are shown in the following 4 figures:

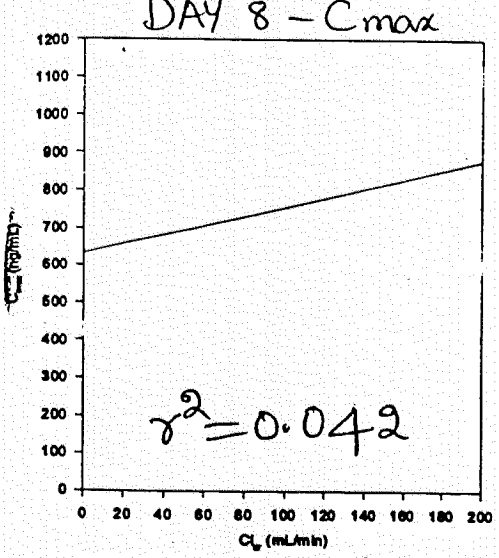
DAY 1 - Cmax



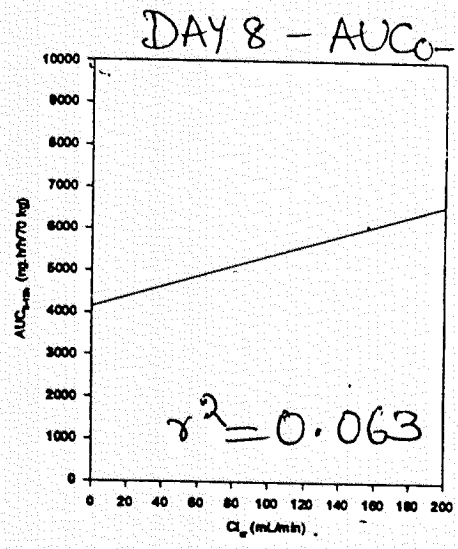
Day 1 - AUC0-12



DAY 8 - Cmax

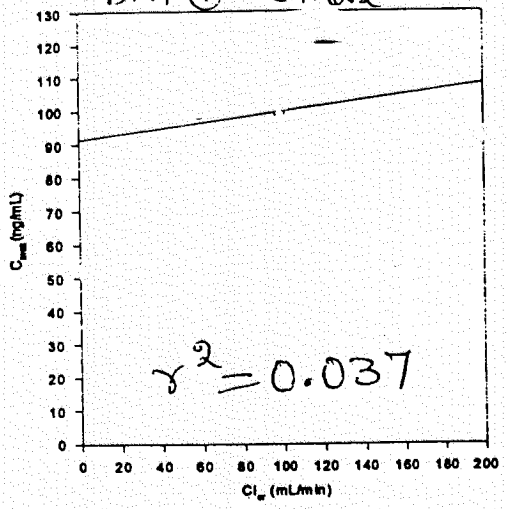


DAY 8 - AUC0-12

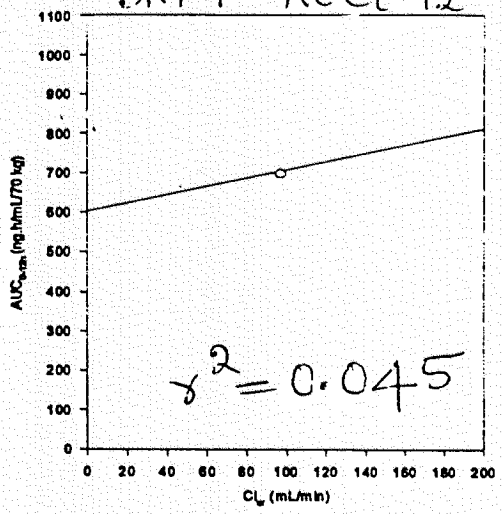


Plots of the relationship between PK parameters of OPC-13015 vs. creatinine clearance are shown in the following 4 figures:

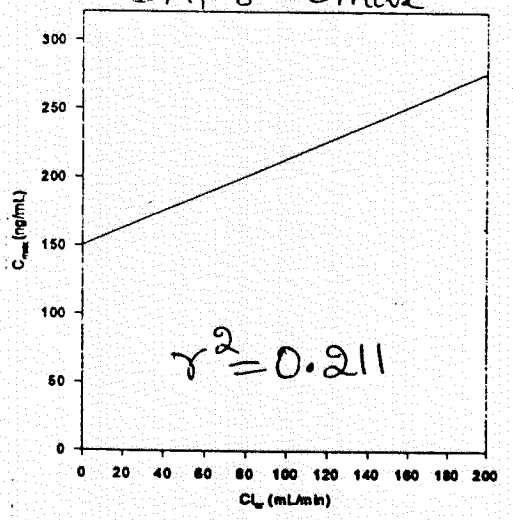
DAY ① - Cmax



DAY 1 - AUCτ-12



DAY 8 - Cmax



DAY 8 - AUCτ-12