activity in humans and canines were generally in the 0.07-0.7 uM range. Cilostazol increases tissue cAMP (*ex vivo*) in dog (femoral arteries after forskolin treatment[9]), human (platelets)[6] and rat (aortic cultured smooth muscle cells)[10] tissues. The bath concentrations of cilostazol needed to double cAMP were generally 10 uM or greater, The bath concentrations are substantially greater than those needed to inhibit PDE III activity.

In either *ex vivo* preparations or intact animals, cilostazol induced vascular (both arterial and venous) relaxation. The effect of cilosatazol was not homogenous across all vascular beds. In *ex vivo* dog preparations, cilostazol was more potent in relaxing femoral than basilar or cerebellar arteries, when the arteries were contracted either by prostaglandin F2α or KCl[11]. Cilostazol was also capable of relaxing femoral veins when contraction was stimulated by prostaglandin F2α[12]. Cilostazol was able to relax norepinephrine stimulated contraction of isolated canine pulmonary arteries and veins *ex vivo*.[13] Cilostazol was slightly more potent in inhibiting contraction when the endothelium was removed[14]. Endothelial derived factors are, therefore, not necessary for cilostazol's ability to relax vasculature.

Intraarterial infusion[15] of cilostazol at doses of 1-100 ug directly into individual arterial beds of anesthetized dogs, caused relaxation of the femoral> vertebral, > internal carotid> common carotid > superior mesenteric artery. Renal arteries, were not dilated even at the highest dose.

Cilostazol also has a marked effect on cardiac tissue. The effect of intra-arterial

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[9] Forskolin inhibits cAMP production and cilostazol excessively increases cAMP concentrations by inhibiting its normal degradation. Study # 012138

[10] Study # 007672.

[11] Study #003946

[12] Study # 007257

[13] Study # 009658

[14] Study # 012233

[15] Study # 214365-1419; It is hard to estimate the concentration of cilostazol in these studies since the rate of infusion is not stated.

infusion of cilostazol, at a dose of 1 to 100 ug[16], into perfused *ex vivo* canine hearts[17] is reproduced as Table 1. The effect of cilostazol on isolated heart preparations is consistent with that of a PDE-III inhibitor: sinus rate, contractile force, coronary blood flow and ventricular automaticity (a measure of ectopic activity) are all increased and A-V conduction time is decreased.

Table 1- Intra-arterial Injection of Cilostazol into Canine Hearts (Adapted from Dr. Koerner's Review)

	Percent Change From Baseline				
	1 ug	3 ug	10 ug	30 ug	100 ug
Sinus Rate	0.6± 1.3	3.3 ± 2.0	10.7 ± 1.6	15.0 ± 2.3	19.3 ± 1.7
Ventricular Automaticity	0	0.3 ±0.3	2.6 ± 0.6	4.7 ± 0.9	7.1 ± 2.3
Myocardial Contractile Force (Right Papillary Muscle with Strain Gauge)	0.6 ± 0.2	4.4 ± 1.3	12.8 ± 4.3	33.0 ± 5.8	67.3 ± 12.9
AV Conduction Time	-3.7 ± 1.3	-9.1 ± 7.2	-19.0 ± 3.6	-26.1 ± 3.5	-23.8 ± 6.6
Coronary Blood Flow	21.4 ± 6.0	34.8 ± 4.2	49.1 ± 6.1	60.7 ± 5.8	60.1 4.2
Coronary Blood Flow LAD Injection Placebo	6.7 ± 1.7 1.5 ± 1.5	18.9 ± 6.0 1.5 ± 1.5	25.6 ± 7.0 0	45.0 ± 12.5 5.8 ± 2.6	51.5 ± 9.7 9.3 ± 3.5

The concentration of cilostazol at two hours among conscious dogs[18] who received single oral dose of 100 mg/kg, was equivalent to those of humans after doses of 100 mg bid. At 100 mg/kg of cilostazol, dogs had heart rate increased ($p < 0.05$), mean blood pressure decreased ($p = 0.05$) and left ventricular dp/dt (max) increased ($p < 0.01$).

Qualitatively similar effects on myocardial and vascular performance were also observed in anesthetized[19] and conscious[20] dogs who received intravenous boluses of cilostazol and in cynomolgus monkeys[21] infused (at some unstated rate) with doses of cilostazol at a dose 30-1000 ug/kg.

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[16] The infusion rate is not stated and, therefore, the concentration of cilostazol in the coronary arteries can only be guessed at.

[17] Study # 005994.

[18] Study 003117

[19] Study # 00617

[20] Study # 003117

[21] study # 006241

In vitro, several of the metabolites of cilostazol have substantial PDE inhibitory activity (most likely PDE-III, but an action on other PDEs cannot be ruled in or out)[22]. As a PDE inhibitor, OPC-13015 is approximately four to seven times more potent than cilostazol; OPC-13217 and OPC-13366 are equivalently potent and OPC-13213 is substantially less potent than cilostazol. Of these metabolites, OPC-13015 and OPC-13213 were routinely measured in clinical and pharmacokinetic studies.

Table 2. PDE Inhibition (Not Necessarily PDE-III, as per Dr. Koerner) and The Effect on Platelet Aggregation of Various OPC metabolites [95%-Confidence Limits]

Compound	Phosphodiesterase Inhibition IC50 (x 10^{-8}M)	Platelet Aggregation IC50 (uM)	
		ADP-Induced Aggregation	Collagen-Induced Aggregation
Cilostazol	7.58 [3.06-19.0]	13.3 [11.2-16.0]	10.1 [7.14-14.4]
OPC-13015	1.06 [0.83-1.34]	3.43 [3.07-3.83]	2.61 [1.88-3.56]
OPC-13213	38.9 [30.4-49.5]	31.4 [27.1-36.4]	26.2 [18.7-35.1]
OPC-13217	6.96 [1.85-26.2]	11.7 [10.1-13.7]	8.64 [6.27-11.8]
OPC-13366	15.4 [1.85-19.0]	10.3[8.92-11.8]	7.68 [5.44-10.6]

In summary, the effect of cilostazol on cardiac and hemodynamic function is perfectly consistent with that of a PDE III inhibitor. Cilostazol produces vasodilation, heart rate increase, inotropy and increased cardiac irritability. The major metabolites of cilostazol are also PDE inhibitors and these metabolites would likely have similar effects on cardiac function.

Biopharmaceutics:
ADME:

Otsuka proposes that cilostazol be dosed at either 50 or 100 mg BID for the treatment of intermittent claudication. There is also modest exposure to doses of cilostazol up to 150 mg BID.

Ten healthy males received a single 50 mg ^{14}[C]-cilostazol dose, as an oral solution [23] and the mass balance of radioactivity was determined. Seventy four percent of the dose was recovered in urine and 21% in feces. No parent drug was identified in urine and only approximately 1% of the administered dose was recovered unchanged in feces. Approximately 60% of the radioactive dose was recovered as identified metabolites within 24 hours, and 76% after 144 hours. OPC-13213 (see Figure 2) accounted for approximately 30% of the administered dose,

[22]Study # 002925 and study # 002923

[23]Study 21-96-201

Figure 2. Metabolic Transformatio Pathway of Cilostazol (Taken from Dr. Uppoor's Review

(cumulative recovery up to 144 hours post dose). Fifty six percent of the radioactivity in plasma was due to cilostazol (based on $AUC_{cilostazol}/AUC_{radioactivity}$). These results suggest that a respectable amount of the administered dose can be accounted for by the identified metabolites.

When, however, ^{14}[C]-cilostazol was administered as a oral capsule[26], the profile of radioactivity differed from when ^{14}[C]-cilostazol was administered as an oral solution. After the capsule, nearly 60% of the dose was recovered in the feces (versus 21% for the oral solution) and 26% of the dose was recovered in urine (versus 74% after the solution).

Absolute Bioavailability: There was no human intravenous studies of this drug, so the AUC_{iv} versus AUC_{po} was not studied and consequently, the absolute bioavailability of cilostazol is unknown. Although a large fraction of the dose of ^{14}-C-labeled cilostazol is eventually absorbed, the parent drug accounts for only a small fraction of the recovered material. It is, therefore, unclear if cilostazol is pre-systemically cleared and metabolized, with subsequent absorption of the resultant degraded products or whether a substantial fraction of the dose is absorbed and only after gaining access to the circulation is cilostazol metabolized and then excreted.

There is only limited additional information about cilostazol's absolute bioavailability from animal data. When dogs, were administered a 30 mg/kg dose of cilostazol intravenously, the concentration at two hours (2613 ng/ml)[27] were more than three-fold higher than dogs who received an oral dose of 30 mg/kg (734 ng/ml)[28]. This is sketchy information and would suggest that the absolute bioavailability of cilostazol in dogs is less than 30%.

Absorption: Cilostazol is rapidly absorbed by healthy individuals at doses of up to 200 mg as a single dose or divided BID. Peak effects are generally seen at approximately 3-4 hours post dose, but may be delayed to 4-5 hours with food or

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24 These include OPC-13215, OPC-13211, OPC-13388, OPC-13366, OPC-13371, OPC-13217 and OPC-13213. Note OPC-13269; OPC-13211; OPC-13388 are formed both by quinolinone and cyclohexyl ring oxidation.

25 OPC-13326, OPC-13015. Note OPC-13269; OPC-13211; OPC-13388 are formed both by quinolinone and cyclohexyl ring oxidation. Note OPC-1533 is 6-HQ on the metabolic scheme.

26 Study # 21-94-303, what dose?

27 Report no. 011115. Study number was not supplied

28 Study # 004659

after erythromycin. C_{max} values for single cilostazol dose of 100 mg (fasting) are approximately 600 to 750 ng/ml (approximately 1.5- 2 uM). After single doses of 100 mg BID cilostazol, the concentration of OPC-13015 is approximately 100-150 ng/ml (approximately 0.3 uM) and that of OPC-13213 approximately 60-100 ng/ml (approximately 0.2 uM). After multiple doses, peak concentration of cilostazol are approximately 1250 ng/ml (3.2 uM) that of OPC-13015 approximately 400 ng/ml (1.1 uM) and OPC-13213 at approximately 120 ng/ml (0.3 uM)[29].

The sponsor also provided population pharmacokinetic data (analyzed by Dr. El Tahtawy). Kinetic samples were collected from four large clinical studies (# 21-92-202; #21-93-201;#21-94-201 and #21-94-203), each study contributed between 88 and 157 subjects. In all four studies, kinetic samples were collected at trough, with mulitple samples from each subject corresponding to different weeks of treatment. In two studies, samples were also collected at a time corresponding to peak drug levels. There were a total of 2166 samples analyzed from 462 subjects. Concentrations at 2.5 hours post dose were approximately 1200 ng/ml; concentration at 12 hours post dose were approximately 800 ng/ml. Approximately 1% of the measurments were > 2700 ng/ml.

Neither the Division nor Otsuka has analyzed the collected population pharmacokinetic samples for the other metabolties of cilostazol (i.e. OPC-13213 and OPC-13015).

Distribution: Since no intravenous formulation was studied in humans there is no estimate of volume of distribution of either cilostazol or its active metabolites.

Enterohepatic recirculation. In her review, Dr. Uppoor suggests that a secondry small peak seen in some patients during pharmacokinetic studies may indicate that cilostazol is enterohepatically recirculated.

Metabolism/Excretion: The half-life of cilostazol is approximately 11 hours in healthy individuals. The two frequently co-measured metabolites OPC-13015 and OPC-13213 have terminal half lives of approximately 11 and 14 hours, respectively.

Cilostazol's metabolism was studied through several *in vitro* systems: 1) cloned human AHH-1 TK+/- cells expressing CYP450 [30]; 2) cloned and expressed B-

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[29] Study 21-93-202

[30] Studies #010514, # 011114 and 012060 :
CYP: 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4

lymphoblastoid cell line expressing human CYP450[31] and 3) a panel of nine human liver microsmes[32].

Several methodologies were used in conjunction with the above systems to define the CYP450 enzymes responsible for the metabolic transformation of cilostazol. These methods include: 1) analysis of the resultant metabolites after incubating cilostazol with the test systems [33]; 2) cilostazol's ability to inhibit the transformation of several CYP 450-specific model substrates [34]; 3) CYP450-specific model substrates ability to inhibit of cilostazol's degradation[35] , and 4) correlating the metabolism of CYP450 model substrates by a panel of human microsomes with the production of the various cilostazol metabolites [36].

The conclusions derived from these studies are somewhat dependent on the type of study which was performed. Oxidation of the quinolinone ring which accounts for the majority of isolated metabolites, appears to be largely carried out by CYP3A4 with some contribution of CYP2D6 and a lesser effect of CYP1A4[37]. Complete inhibiton of quinolinone oxidation by 1 uM ketoconazole (a potent CYP3A4 inhibitor) in human microsomes is consistent with the important role of CYP3A4[38]. The same study, however, showed no inhibitory effect of cilostazol on a CYP3A substrate (Dextromethorphan and its transformation to 3-methoxymorphinan; at concentrations of substate between 10-75 uM), this last observation is the "fly in the ointment" since it is not consistent with cilostazol as a substrate for CYP3A4.

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[31]Study # 012542: CYP 2C9, 2C19, 3A4

[32]Study #11083

[33]Study # 010514, 011114, #11083

[34]Study # 010514, # 02160, #012542 and #11083

[35]Study #11083

[36]Study #11083

[37]Study #11114

[38]Study # 11083

Binding constants or estimates of the concentration of cilostazol needed to inhibit CYP3A4 is highly variable. Ki for the inhibition of testerosne 6B- hydroxylase ranged from 6.4-19.4 uM[39], 50% inhibition of testosterone oxidation occurred at approximately 5 uM[40]). The Km for cilostazol metabolism was estimated at 100.6 uM[41]. The concentration and free concentration of cilostazol in the liver is unknown. The ability of cilostazol to inhibit the metabolic transformation of CYP3A4 sensitive drugs has not been extensively studied.

Oxidation of the cyclohexyl group appears to be a result of the action of CYP3A4 with some contribution of CYP2D6, CYP2C19 and CYP2B6.

There appears to be little information as to the process by which OPC-13015 is degraded or removed. This metabolite appears to be responsible for a substantial portion of PDE inhibition (see below).

Drug-Drug Interaction:

Cilostazol[42] was administered to sixteen healthy males both prior to, and during, treatment with erythromycin[43] . Erythromycin, a substrate for as well as an inhibitor of CYP3A4 was also continued for the next 5 days, during which blood samples were collected for pharmacokinetic measurments of cilostazol and two of its metabolites. With respect to cilostazol, both C_{max} and AUC were increased 43% and 88%, respectively. Clearance decreased by 40%. One subject, however, had an approximately three fold increase in the AUC of cilostazol following erythromycin treatment. It is, therefore, quite likely that some patients would have substantial alterations in cilostazol concentrations when treated with potent CYP3A4 inhibitors.

With respect to the cilostazol's metabolites, there was a 28% increase in the

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[39]Study #012542 and #10572

[40]Study #012060

[41]Study #11083. The calculation was made from the rate of appearance of metabolites. This rate, however, does not appear to be first order with respect to time, presumably because the metabolites undergo further degradation. Optimally, the kinetics should have been made before subsequent degradation, that is when the rates of formation of the metabolites were truly linear with time. Under the circumstances of the study the Km for cilostazol is likely over-estimated.

[42]Study #21-95-202

[43] Ery-Tab enteric coated; at a dose of 500 mg Q8 hours after one week.

C_{max} and a 119% increase in AUC for OPC-13213 (oxidation of the cyclohexyl ring - a CYP2B6 substrate). There was, however, 26% decrease in the C_{max} and a 6% increase in AUC for OPC-13015.

Omeprazole is a substrate for CYP3A4 as well as for CYP 2C19. Concomitant administration of omeprazole 40 mg/day with cilostazol produced similar effects as erythromycin on the kinetics of cilostazol[44], The C_{max} for OPC-13213, however,was not increased but diminished by approximately 25%[45]. This study would suggest that OPC-13213 is produced by the action CYP2C19 on cilostazol. The *in vitro* data of study #01114, however, did not show that AHH-1 TK+/- cells expressing CYP2C19, produced OPC-13213 from cilostazol. Again, these two pieces of data are not consistent. The *in vitro* studies suggest that OPC-13213 is produced by CYP2B6. The omeprazole study, however, suggests that a CYP2C19 substrate can modify OPC-13213's production.

Quinidine is an inhibitor of CYP2D6 and also a substrate for CYP3A4. Cilostazol's kinetics were measured both before and after quinidine (200 mg two doses) treatment. Quinidine has a small effect (<20%) on C_{max}, and AUC of cilostazol as well as on the AUC and C_{max} of the two metabolites, OPC-13015 and OPC-13213.

Population pharamacokinetic analyses indicated that cilostazol's concentration is increased when patients were also treated with diltiazem, a CYP3A4 substrate (see Dr. El Tahtawy's review). Data on the other metabolites of cilostazol was not measured or if measured were not analyzed and presented.

There was no pharmacokinetic interaction study with ketoconazole (a potent CYP3A4 inhibitor).

Warfarin: Cilostazol (100 mg BID) did not alter the kinetics of either of the two optical isomers of warfarin (25 mg single dose). Warfarin is a substrate for several different CYP450 such as CYP1A2; CYP2C9 (specific for S-isomer) and CYP3A4.

Dose Proportionality: As per Dr. Uppoor's review, there were deviations from dose proportionality after single doses of cilostazol, ranging from 50 -200 mg (single dose). The C_{max} and $AUC_{0-\infty}$ of cilostazol, OPC-13015 and OPC-13213 were less than proportionally increased as the dose increased[46].

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[44]Study# 21-96-203

[45] It is unclear why this metabolite is diminished. The in vitro data suggest this metabolite is produced by CYP2B6.

[46]Study# 21-93-204

Food Effects: After a single 100 mg dose of cilostazol, a high fat meal[47] substantially increased the C_{max} of cilostazol, OPC-13015 and OPC-13213 (95%, 79% and 91%, respectively); but had a lesser effect on $AUC_{0-\infty}$ (16%; 8% and 34%, respectively). The T1/2 for cilostazol and its metabolites is decreased (by 64%, 49% and 36%, respectively).

A second study [48], with an unstated meal, showed that this meal had a substantial effect on a single 50 mg dose of cilostazol. The C_{max} for cilostazol, OPC-13015 and OPC-13213 increased 126%, 76% and 45 % respectively; the $AUC_{0-\infty}$ increased (37%, 21%, and 22%, respectively).

Protein Binding: Cilostazol is largely protein bound (~ 92-95%), at concentrations of cilostazol ranging from 0.25 to 5 ug/mL. Binding is predominantly to human serum albumin [49]. Other studies have shown the bound fraction at approximately 98% (free fraction ~ 2%) [50] . OPC- 13015 is approximately 96-97% protein bound (free fraction ~ 3-4%) and OPC-13213 is 66-67% protein bound (free fraction ~33-34%)[51]. The free fraction for metabolites other than OPC-13015 and 13123 is not stated.

Estimate of Contribution to Effect of Cilostazol/Metabolites. Below is a "back of the envelope" calculation to estimate the contribution to PDE inhibition of cilostazol and the two measured metabolites, taking into account concentrations, free fraction and PDE binding constants.

Some additional assumptions that are made to perform this calculation include: 1) the free concentration in serum are reflective of the free concentrations at the site of PDE activity; 2) there are no differences in protein binding intracellularly of cilostazol and its metabolites; 3) the nature of binding i.e. competitive or uncompetitive is the same for all PDE inhibitors; 4) the majority of inhibition that is observed in studies reflect inhibition of the same PDE (not all studies sort out PDE-III inhibition from PDE-inhibition in general).

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[47] Study# 21-93-204

[48] Study # 011808

[49] Study 003630

[50] Study # 21-91-201

[51] Study # 21-93-206

This calculation suggest that OPC-13015 is as important, if not the most important moiety, in inhibiting PDE.

Table 3. Calculation of Relative Importance of Molecular Entities For PDE Inhibition
[Concentrations From Normals-Study #21-93-206=Study 1] {Concentrations From Study 21-93-202=Study 2}

	C_{max} Steady state conc (ng/ml) [study 1] {study 2}		uM [study 1]	{study 2}	Free Fraction	Estimated Free Conc (x 10-8M) [study 1]	{study 2}	PDE* ED 50 x 10-8M	Ratio Estimate free/ED50 [study 1]	{study 2}
Cilostazol	[799.8]	{1229}	[2.1]	{3.3}	0.04	[8.4]	{13.2}	7.58	[1.11]	{1.74}
OPC-13213	[80.1]	{126}	[0.21]	{.0.33}	0.33	[6.93]	{10.9}	38.9	[0.18]	{0.28}
OPC-13015	[231.8]	{409}	[0.63]	{1.11}	0.04	[2.52]	{4.44}	1.06	[2.4]	{4.19}

* See table 2 above.

Special Populations:

Effect of Gender and Age: A total of 42 subjects, all greater than 50 years old, consisting of both males and females were enrolled into a pharmacokinetic study[52]. Although neither cilostazol nor the two metabolites OPC-13015 and OPC-13213 statistically differed across gender or age ranges (50-59; 60-69 and ≥ 70 years), there was a trend to higher concentrations among females (was this a weight effect?).

Renal Failure: Progressive renal dysfunction has only modest effects on the pharmacokinetic parameters of cilostazol and two of its metabolites OPC-13015 and OPC-13213, both acutely and after eight days of treatment. In this study, those patients with severe renal dysfunction generally had creatinine clearances between 10 and 20 ml/min. After multiple doses of cilostazol, those with severe renal dysfunction had lowered C_{max} and $AUC_{(0-12)}$ for cilostazol and OPC-13015. However, C_{max} for OPC-13213 was higher among those with severe renal dysfunction. Protein binding was less among those with severe renal dysfunction. Dr. Uppoor's review suggests that the overall effects i.e. the lower protein binding, in conjunction with slightly increased concentration of a less active metabolite, would only modestly alter the totality of PDE inhibition in patients with renal dysfunction.

Hepatic Dysfunction: There was minimal effect on cilostazol's pharmacokinetics among a cirrhotic population who were predominantly mildly impaired.

Pharmacodynamic Interaction:

Aspirin(ASA). A single study[53] explored the interaction between cilostazol (100 mg BID) and ASA (325 mg/day). The kinetic sampling was too sparse, so that no conclusion about kinetic interactions can be drawn. There was no apparent dynamic

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52 Study #21-93-202)

53 Study #21-95-3010

interaction between ASA and cilostazol on bleeding time, PTT or PTT. *Ex vivo* platelet aggregation (using AUC of aggregation), however, was inhibited by cilostazol when the inducing agent was either ADP (2 uM) or arachidonic acid (500 ug/ml). When the inducer of aggregation was ADP (4 uM) there was no effect on platelet aggregation by cilostazol alone (? this appears to be an outlier). There was a significant effect, however, in inhibiting platelet aggregation when aspirin was superimposed on cilostazol (when compared to aspirin superimposed on placebo) when the aggregating inducer was either 2 or 4 uM ADP or 500 ug/ml arachidonic acid).

Some Summary points:

- The absolute bioavailability of cilostazol as an oral preparation is unknown.

- Approximately 24% of the labeled dose when taken an oral solution is not identified.

- *In vitro* data does not entirely form a consistent story. Most, but not all, of the in vitro data suggest that CYP3A4 is pivotal in the metabolic degradation of cilostazol, and is responsible for the formation of the quinolinone hydroxylation and some of the oxidation of the cyclohexyl ring (see Figure 2 which was copied from Dr. Uppoor's review). Although there is some indication from *in vitro* metabolic transformations that CYP2D6 is contributory to the to quinolinone oxidation, concurrent treatment of cilostazol with quinidine (a potent CYP2D6 inhibitor) had only minimal effect on cilostazol or OPC-13213 or OPC-13015.

- No *in vivo* studies were done with ketoconazole. Ketoconazole is a particularly potent inhibitor of CYP3A4.

- OPC-13015 and cilostazol are account for the majority of PDE inhibition .

- The metabolic pathway and the enzymes which are responsible for degrading OPC-13015 are unknown.

4. Clinical Pharmacology:

The effect of cilostazol on either muscle energetics or blood flow in patients with peripheral vascular disease is poorly defined in the submission. All studies in patients with peripheral vascular disease were small, open-labeled and baseline controlled. None of these studies adequately define either the time course or dose range of any such effect (Reference # 14, 15, 16 and 23 of Dr. Karkowsky's review).

In vitro, cilostazol at concentrations of > 10 uM, altered human platelet aggregation when the inducing stimulus was ADP. Lesser concentrations (> 3 uM) of

cilostazol were capable of modifying aggregation when thrombin was the aggregating stimulus (study #10524).

There were a large number of studies in both normals or subjects either with cerebrovascular disease or diabetes which examined the effect of oral cilostazol on *ex vivo* platelet aggregation. Most of these studies were small, open-labeled and baseline controlled. Although most (but not all) studies, showed some inhibitory effect of cilostazol on platelet aggregation, when aggregation was induced by any of several stimuli (at different concentrations of inducers), it is difficult to describe the time course or dose-range of the effect of cilostalzol's action in inhibiting platelet aggregation.

Clinical Efficacy:
Study Design:

There were a total of 12 placebo controlled studies within the data base. Eight of these studies were relatively large, four were modest in size. I have tabulated the broad description of all the placebo controlled clinical studies in Table 4. Most studies explored a modest dose range of cilostazol 50-100 mg BID daily, with one relatively short term study (12 week) exploring a dose of 150 mg BID (study # 21-95-201). Two studies #21-96-202 and #21-94-301 included pentoxifylline (or oxpentifylline) as a positive control. Exercise performance were generally evaluated at interdosing interval, with two studies collecting performance also at approximately 3 hours post dose (peak). Drugs were usually administered 30 minutes or 2 hours after a meal. There are similarities and difference in the design of the 12 placebo-controlled studies.

To summarize the similarities, patients were enrolled if they had stable atherosclerosis obliterans as evidenced by exercise-induced claudication, not associated with pain at rest, ischemic ulceration or gangrene. In addition, these subject are to have reproducible onset of pain with exercise (ICD=initial claudication distance or the walking distance at claudication onset) and also have evidence of diminished blood flow to the compromised extremity as measure by an ABI (an ankle: brachial ratio , that is, a compromised ankle blood pressure when normalized to brachial blood pressure). Indeed, based on the degree of diminished blood pressure to the extremity during rest, those enrolled had substantial obstruction of free blood flow to the involved extremity.

Patients with conditions which might otherwise limit exercise performance such as CHF, angina pectoris, concomitant symptomatic arrhythmias or recent MI were excluded from the study. Patients with these conditions, whose exercise at baseline was limited by claudication, however, were eligible to enroll. Prohibited medication included anticoagulants, vasoactive drugs (except occasional NTG or isosorbide dinitrate) hemorheologic drugs and anti platelet drugs (including aspirin, from some but not all studies).