Table 19.2 Platelet Aggregation Studies

Period →	A	B	C	D	E
ADP (2 uM)	31.3 ± 27.0	17.2 ± 21.0	35.1 ± 30.9	23.8 ± 22.1	20.8 ± 14.2
ADP (5 uM)	64.7 ± 25.4	44.0 ± 32.5**	60.1 ± 32.6	42.8 ± 32.5**	50.0 ± 25.3
Collagen 0.5 ug/ml	21.4 ± 21.8	8.4 ± 12.8**	17.9 ± 26.2	8.5 ± 18.8**	11.3 ± 15.8
Collagen 1.0 ug/ml	68.7 ± 21.5	25.0 ± 29.3*	42.0 ± 35.2	26.3 ± 31.7*	40.3 ± 31.8**
Collagen 2.0 ug/ml	84.8 ± 12.8	68.2 ± 38.0	81.6 ± 15.1	61.9 ± 30.7	69.7 ± 25.1
cAMP	6.87 ± 2.25	7.54 ± 2.10	8.23 ± 1.66	8.54 ± 3.10	9.84 ± 4.59**

* $p < 0.01$ ** $p < 0.05$ Relative to A

Headache was frequent during periods ADE (between 3-7/group).

Reference 20.

Title of Study: Abstract: The Effects of Anti-Platelet Drugs on the Platelet Aggregation Function in Patients with Ischemic Heart Disease.
Investigator and Sites: Fukata, M.; Wakaida, Y.; Kakihana, M.; Iwa, T.; Miautani, K.; Kobayashi, T.; Aichi Medical University, Aichi, Japan

Study Summary. This was an abstract from some unstated meeting. This was a study of 28 day treatment of four different antiplatelet drugs (one of which was cilostazol) in ten patients with ischemic heart disease. Cilostazol, at a dose of 200 ug/day, did not inhibit maximum platelt aggregation. "[D]e-aggregation, however, was provocated (sic) by ADP, Co[llagen], ADP and Epi[nephrine].

Reference 21:

Title of Study. Neutrophils, Augment Anti-Platelet Action of A Phosphodiesterase Inhibitor, Cilostazol.
Investigator and Sites: Hoshido, S.; Kuzuya, T.; Yamashita, N.; Fuji, H.; Oe, H.; Kitabatake, A.; Tada, M.; Kamada, T.;
Osaka University School of Medicine , Osaka, Japan

The study suggests that the anti-aggregatory effects of cilostazol (200 mg/day) on platelets after 28 days of treatment were increased by the concurrent inclusion of neutrophils to the platelet rich plasma samples.

Reference 22:

Title of Study: Phosphodiesterase Inhibitors as Antiplatelet Agents in Vascular Surgery.
Investigator and Sites:Kamabyashi, J.; Watase, M.; Kawasaki, T.; Shiba, E.; Sakon, M,.;

Mori, T.; And Kimura, K.; Kamada, T.
Advances in second Messages and Phosphodiesterase Research , vol 25, Ed by S.J. Strada and H. Hidaka, Raven Press, Ltd. New York, 1992.

This report consists of two studies.

The first study was an animal model of short term (5 hours) treatment of cilostazol (doses of 0, 0.5, 1, and 2 mg/kg/hr) in rabbits who had Textron graft replacement of a segment of their inferior vena cava. At the end of the infusion, the animals were sacrificed and the graft site examined both for patency and for structure. The amount of dried thrombi at the graft site was apparently diminished in the presence of higher doses of cilostazol. Ultrastructure studies of the graft site showed that the platelet aggregates and fibrin plugs which occurred in the placebo treated group, diminished in cilostazol (> 1 mg/kg/hr) treated rabbits. **(Note the usual dose proposed for patients is approximately 3 mg/kg/day or approximately 0.125 mg/kg/hr. The dose here was 1-2 orders of magnitude above the doses planned.)**

The second study consists of outcomes of 30 aorto-iliac bypass patients who were treated as follows: Group A (n=10) had knitted dacron grafts and were treated with ticlopidine. Group B (N=10) had Gore-Tex grafts and were treated with ticlopidine (300 mg). Group C (N=10) had Gore-Tex grafts and were treated with cilostazol (200 mg/day, orally). The duration of cilostazol treatment was only 6 months. None of the patients in either of the three treatment groups had graft occlusions within 6 months.

Reference 23:

Title of Study: Pharmacological Evaluation of Cilostazol by Thermograms of Patients Chronic Arterial Occlusive Disease.
Investigator and Sites: Kitani, Y,; Tomita, Y.; Ishizki, k.; and Fujita, F.;
Gurma University School of Medicine; Showa-machi Maebashi, Gurma, Japan

Study summary. This was an abstract presented at the ACC meeting (what year?) Single doses of either cilostazol (100 ug???) or ticlopidine (1000 ug??) were given to 13 patients with chronic pain secondary to arterial occlusive disease. Skin temperature was measured by thermography. Both cilostazol and ticlopidine increased skin temperature.

Reference 24:

Title of Study: Antiplatelet Therapy in Patients with Cerebral Thrombosis at the Chronic Phase-Assessment of its effect on Coagulation and Fibrinolytic Parameters.
Investigator and Sites: Kohiryama, T.; Tanaka, E.; Katayama, S.; Yamamura, Y.; and Nakamura, S.; Hiroshima University School of Medicine; Hiroshima, Japan.
Publication: Clin Neurol: 34: 771-776, (1994)

Study Summary: The submitted abstract was in English and the publication in Japanese.

18 patients with cerebral thrombosis were treated with cilostazol (200 mg/day), 21 patients were treated with ticlopidine (200 mg) and 9 patients were treated with 100 mg ticlopidine and 60-150 mg of acetylsalicylic acid. The duration of follow up was 8.4 ± 3.0 months. One patient (in which group?) had a recurrent stroke. The sponsor claims a decrease in platelet aggregation as induced by ADP. Platelet factor 4, beta thromboglobulin, coagulation factor VIII, vWF, thrombin-antithrombin III complex and alpha 2-plasmin inhibitor-plasmin complex were decreased in all groups on therapy.

Reference 25.

Title of Paper: Clinical; Studies of Phosphodiesterase Inhibitors for Cardiovascular Disease
Investigator and Sites: Numanao, F.; Kishi, Y.; Ashikaga, T.;
Tokyo Medical and Dental University, Tokyo, Japan.
Advances in Second Messenger and Phosphodiesterase Research vol 25 edited by S. J. Strada and H. Hidaka; Raven Press Ltd. New York 1992

A total of 26 patients with peripheral artery disease were treated with 200 mg of cilostazol daily for three months or more. The specific diagnosis was Takayasu's arteritis (14 patients), Buerger's disease (seven patients) and arteriosclerosis obliterans (five patients). Five of these patients discontinued for adverse events such as palpitation, headache or dizziness.

Only anecdotal data is given the outcomes of those followed.

Reference 26:

This is a duplicate of the abstract cited as Reference 22.

Reference 27.

Title of Study: Hemodynamic Effects of Cilostazol on Peripheral Artery in Patients with Diabetic Neuropathy.
Investigator and Sites:Okuda, Y.; Mizutani, M.; Ikegama, T.; Ueno, E.; Yamashita, K.;
Publication: Arzneim-Forsch/Drug Res. 42 (II); 540-542 (1995).

Study Summary. Thirty patients with non-insulin dependent diabetes received a single dose of 100 mg cilostazol. Measurements included real-time two-dimensional Doppler Echocardiography.

Reference 28.

Title of Study: Effects of Forskolin and Cilostazol on Clot Retraction
Investigator and Sites: Sannomiya, Y.; Tatsumi,N.; Okuda, K.;
Publication: Biochemistry International ; 17 (60) 1059-1070 (1988).

Study Summary: This study contains *in vitro* information using platelet enriched plasma, which suggests that cilostazol at concentrations ranging from 10 to 100 uM inhibited ADP-induced (10 uM) platelet aggregation. Platelet aggregation was inhibited by cilostazol when it was included prior to the inducing stimulus or even at the point of maximal aggregation. Clot retraction was also decreased by cilostazol in a dose-related manner.

Reference 29:

Title of Study: Clinical Usefulness of Cilostazol (Pletal®) on Diabetic Neuropathy and Serum Lipid Levels
Investigator and Sites: Sekiguchi, M.; Morikawa, A.; Nakajima, K.; Ito, H.; and Takahjashi, M. Anishikawa Medical College

Study Summary. Abstract was in English, Publication was in Japanese.
Thirteen diabetic patients were treated with cilostazol at a dose of 100 mg/day, the article claims improvement in diabetic symptoms and increase in nerve conduction.

Reference 30:

Title of Study: Clinical Study of Some Platelet Anti-aggregation Agents on Healthy Volunteers
Investigator and Sites: Shimodaira, H.; Shibuya, H.; Kuchida, K.; Matsumoto, Y.; Uchida, Y.; and Kudo, T.; Hachoji
Pharmaceutical Center , Hachioji, Japan and Hachioji Medical Center of Tokyo Medical College
Publication: Jpn J Clin Pharmacol There; 21 (3); 605-612 (1990).

Study Summary. Abstract in English, the complete publication was in Japanese. Ten normal subjects were treated with either dipyridamole (300 mg/day), limaprost (30 ug/day) or cilostazol (200 mg/day), *ex-vivo* platelet function was measured.

Reference 31

Title of Study: A study of the Effects of Cilostazol on Platelet Function and Serum Lipids in Patient with Diabetes Mellitus
Investigator and Sites: Suehiro, A.; Sugimoto, Y.; Masuda, H.; and Karishita, E.; Hyogo College of Medicine; Hyogo, Japan.

Publication: Current Therapeutic Research; 54; 553-561 (1993).

Study Summary. This is an open label study of platelet function in diabetics. Subjects were treated for four weeks with 50 mg BID of cilostazol and then for an additional 4 weeks with 100 mg BID of cilostazol. *Ex vivo* platelet functions were measured.

Reference 32.

Title of Study: Effects of Cilostazol (Pletaal®) on Serum Lipid Levels in Diabetic Patients.
Investigator and Sites:Takazakura, E.; Oshawa, K.; Hamamatsu, K.;
Kurobi Municipal Hospital, Japan
Publication: The article, including the Title was written in Japanese; 17; 6; 341-345.

The abstract describes the effects of cilostazol in 23 diabetic patients at a dose of 200 mg/day for a mean of 12 ± 3 weeks.

Reference 33.

Title of Study: Reduction of Low Density Lipoprotein by Cilostazol in The Non-insulin Dependent Diabetic Patients
Investigator and Sites:Tamai, T.; Shimada, A.; Maeda, H.; Takahashi, S.; Oida, K.; Nakai, T.; and Miyabo, S.; Fuaui Medical School.
Publication: Jpn pharmacol There. 20 (12); 241-248 (1992).

Study Summary: Abstract in English. This was an open label study of the effect of cilostazol on lipoprotein metabolism in 14 non-insulin dependent diabetics who were treated from between 4-8 weeks.

Reference 34.

Title of Study:" Effects of Acetyl Salicylic Acid and Cilostazol Administration on Serum Thrombomodulin Concentration in Diabetic Patients".
Investigator and Sites:Tani, N.; Hada, K.; Kitami, A.; Nakano, M.; Takahashi, H.; Ito, Seiko, Sato, I.; Shibata, A.; Nilgata University school of Medicine,
Nanbugou General Hospital and Mitsubisho Gas Chemical Co, All of Nilgata, Japan.
Publication: Thrombosis Research 69: 153-158, (1993).

Summary: Thirteen patients with non-insulin dependent were treated with cilostazol at a dose of 100 mg once daily, an additional thirteen patients were give aspirin at a dose of 81 mg daily. Both groups were treated for 4 weeks. Four of the cilostazol treated patients discontinued. The reasons were: headache (2 patients), fatigue (1 patient) and nausea (1 patient). According to the report, the serum thrombomodulin (a marker for endothelial cell damage) decreased from baseline for both groups. For the cilostazol

group the thrombomodulin decreased from 28.1 ± 7.1 ng/ml to 23.7 ± 5.4 ng/ml. For aspirin group the decrease was from 30.7 ± 10.9 to 27.9 ± 11.6 ng/ml.

Reference 35.

Title of Study: "Effects of the Anti-Platelet Agent Cilostazol on Peripheral Vascular Disease in Patients With Diabetes Mellitus.
Investigator and Sites: Uchikawa, T.; Murakami, T.; and Furukawa, H.; Tokyo Metropolitan Komagome Hospital; Tokyo, Japan.
Publication: Arzneim-Forsch/Drug Res; 42 (I) nr; 3; (1992).

Summary: Five diabetic patients with peripheral vascular disease were treated with cilostazol at a dose of 200 mg/day (100 mg BID). Three of the patients had the dose increased to 300 mg/day (100 mg TID). Skin temperatures were reported to have increased in both finger and toes (3.3 and 4.4 degrees, respectively).

Reference 36 :

Title of Study: Effects of Cilostazol, A Phosphodiesterase Inhibitor, on Urinary Excretion of Albumin and Prostaglandins in Non-Insulin Diabetic Patients;
Investigator and Sites:Watanabe, J.; Sako, Y.; Umeda, F.; and Nawata, H.; Fukoka Medical Association Hospital and Kyushu University Fukoka, Japan.
Publication: Diabetes Research and Clinical Practice; 22; 53-59; (1993).

Summary: Thirteen patients with non-insulin dependent diabetes mellitus were treated with 100 mg of cilostazol for three months. Compared to baseline, there was a decrease in the albumin/creatinine ratio while on cilostazol. Urinary thromboxane B2 was decreased after the start of cilostazol treatment.

Reference 37:

Tab labeled as Watanabe, no had no document included.

Reference 38:

Title of Study: Increased External Carotid Artery Blood Flow in Headache Patients Induced by Cilostazol.
Investigator and Sites:Yamashita, K.; Kobayashi, S.; Okada, K.; Tsunematsu, T. Shimane Medical University Izumo, Japan.
Publication: Arzneim-Forsch./Drug Res; 40 (I) nr 5; 587-588; (1990).

Study Summary: A total of 12 patients who had a history of cerebral infraction were categorized based on those who had headache while on cilostazol and those that did not (nine patients did not have headaches and three had headaches). The systolic peak

frequency of the common and external carotid arteries were examined both before and after cilostazol at a dose of 100 mg BID. After cilostazol, among those without headache, the peak systolic measurement was increased in the common carotid artery but not in the external carotid arteries. In those who had headache, conversely, the peak frequency for the common carotid artery did not show a difference and the peak systolic frequency increased in the external carotid artery.

Reference 39 Report No 002832 and 002923

Title of Study: Inhibitory Effect of Cilostazol on Human Platelet Aggregation and Its Dispersing Effect on Human Platelet Aggregate (in Vitro).
Investigator and Sites:Tani, T.; Kimuri, Y.; Tokushima Research Institute.

Study Summary: The inhibitory effect on *Ex vivo* platelet aggregation in platelet rich fractions of cilostazol was compared to that of trapidil. According to the report, cilostazol produced dose related inhibition of platelet aggregation, when aggregation was induced by ADP (5 uM), epinephrine (1 ug/ml), collagen (2 ug/ml) or arachidonic acid (200 ug/ml). According to the sponsor, cilostazol was 26 to 79 fold more potent than trapidil, depending on the specific inducer. The IC50 for cilostazol ranged from 2.5 to 16 uM.

In addition to aggregation studies, de-aggregation studies were also performed. The index drug was added at 1, 2 and 3 minutes after the addition of the inducing agent. Cilostazol also dispersed aggregating platelets, but the concentrations of cilostazol which was needed was one to two orders of magnitude greater than the concentrations required to inhibit *de novo* aggregation.

Concentration of 1 uM inhibited the activity of cAMP-phosphodiesterase isolated from human platelets.

Reference 40. Study 007167

Title of Study: Effects of Cilostazol on Release Reaction in Human Platelet: An in *vitro* Study"
Investigator and Sites:Tani, T.; Tokushima Research Institute.

Study Summary: Cilostazol was added to platelet rich plasma, with platelet aggregation stimulated by collagen (1 ug/ml). At cilostazol concentrations at 3 uM and below, there was no observable effect on platelet aggregation. At concentrations of 10 and 30 uM, platelet aggregation was inhibited by 50 % or more. PDGF and platelet factor 4 was also inhibited by more than 50 % only at those concentrations of cilostazol which inhibited platelet aggregation.

Cilostazol was also added to a washed platelet fraction (this is the platelet rich fraction that was washed in Tris-Tyrode's buffer and CaCl2 and MgCl2 were added at a final concentration of 1 and 8 mM, respectively) to which thrombin (0.05 U/ml) was the inducing agent. Platelet aggregation at cilostazol concentrations of >3 uM induced both > 50% platelet aggregation and also inhibited by more than 50% the PDGF and platelet factor 4 which was released.

Reference 41: Report No 009117.

Title of Study: Cilostazol: Mechanism of Action in Human Vascular Tissue.
Investigator and Sites: C. T. Harker Oregon Health Science University; Portland OR.

Study Summary: This was an *ex vivo* studies in which subcutaneous resistance vessels (OD 280.5 ± 15.3 uM; n=45) were dissected from human groin (freshly harvested at the time of surgery). These vessels included those with intact endothelium and those whose endothelium was denuded by running a human hair through the lumen of the vessels. To determine if the endothelium was intact, acetylcholine (1 uM) was infused; intact endothelium promptly relaxed, denuded endothelium did not respond to acetyl choline.

Prior to OPC-13013 exposure, each artery was exposed to a dose range of NE, and a dose response curve for NE-induced contraction was constructed. NE produced a dose related contraction in arteries, both with intact and denuded endothelium. NE's EC50 for the intact endothelium was (mean ± SEM?) 0.29 ± 0.06 uM and for the denuded endothelium was 0.15 ± 0.04.

Arteries that were then exposed to concentrations of epinephrine which induced somewhere between 30 to 50% maximal contractions. OPC-13013 (or other compounds) were then cumulatively added at half log increments. The EC50 for reversing the NE induced contraction for OPC-13013 (n=7) was 3.1 ± 0.7 uM for arteries with intact endothelium and 3.3 ± 0.7 for those with denuded endothelium.

Conclusion: This study would suggest that the effect of cilostazol does not require an intact endothelium.

Reference 42: Rep 10529

Title of Study: Effect of Cilostazol on Shear Stress-Induced Platelet Aggregation *In Vitro*
Investigator and Sites: Nisikawa, M.; Edobashi Tsu,
Mie Prefecture, Japan.

Study Summary: *Ex vivo* platelet aggregation (with human platelet rich plasma fractions) was induced by shear stress (approximately 100 dynes/cm3) in the presence and absence of cilostazol. Platelet aggregation that was induced by shear stress was

inhibited by cilostazol at concentrations of 10 uM and higher. Platelet aggregation induced by PGE1 required cilostazol of 1 uM or higher.

Reference 43:

Title of Study: Effect of Cilostazol on Platelet Aggregation and Experimental Thrombosis;
Investigator and Sites Kimura, Y.; Tani, T.; Kanbe, T.; and Watanabe, K.; Tokushima Research Institute, Otsuka Pharmaceutical Co. Ltd. Tokushima (Japan).
Publication: Arzneim-Forsch/Drug Res. 35 (II) Nr 7a; 1144-1149 (1985).

Study Summary: This publication consisted of five separate experiments.

Experiment 1. The *ex vivo* effect of cilostazol in humans on platelet aggregation induced by ADP (2 uM); collagen (2 ug/ml); epinephrine (1 ug/ml) and arachidonic Acid (200 ug/ml).

The study was carried out *Ex vivo* in a human platelet enriched plasma fractions. The IC_{50} of cilostazol and other agents to inhibit platelet aggregation are shown in Table 43.1.

Table 43.1 IC50 (in uMol/l) of inhibitors of platelet aggregation. (Values in parenthesis are 95% confidence intervals).

Aggregating Agent	ADP (2 uMol/l)	Collagen (2 ug/ml)	Epinephrine (1 ug/ml)	Arachidonic Acid (200 ug/ml)
Cilostazol	12.8 (19.7- 8.52)	3.86 (5.45 - 11.5)	11.5 (17.9-7.53)	3.56 (4.97-2.57)
Aspirin	> 1000 (.>1000)	148 (234-98.6)	83 (135-48.9)	98.6 (158-61)
Pentoxyfylline	> 1000 (.>1000)	> 1000 (.>1000)	> 1000 (.>1000)	986 (7650-387)
Bencyclane	153 (212-114)	96.4 (149-61.8)	58.7 (101-29.5)	241 (477-145)
Ifenprodil	> 100 (.>100)	49.3 (175-24.1)	10.9 (21.7-5.61)	> 1000 (.>100)

Cilostazol demonstrated platelet inhibition at concentrations ranging which is at least a half-log to log unit more potent than the other anti-platelet drugs.

Experiment 2. The effect of cilostazol in inhibiting aggregation in dogs, rabbits, rat and mouse, when the aggregation was induced by ADP or collagen.

This was an *ex-vivo* study using platelet rich plasma from different species. The results are shown in Table 43.2

Table 43.2 IC50 (in uMol/l) in Different Species of Platelet Aggregation. (95% Confidence Intervals).

Species	Cilostazol			Aspirin		
	ADP (7.5 uMol/l)	Collagen (20 ug/ml)	Arachidonic Acid (20 ug/ml)	ADP (7.5 uMol/l)	Collagen (20 ug/ml)	Arachidonic Acid 20 ug/ml)
Dog (n=3)	17.9 (12.5-27.3)	8.87 (5.1-18.6)	____	1065 (413-8394)	163 (100-294)	____

Rabbit (n=3)	19.8 (14-29)	11.8 (8.0-18)	14.5 (11-21)	> 1000 (> 1000)	421 (160-4900)	4516 (270-2400)
Rat (n=3)	.>100 (> 100)	26.2 (15-61	____	____	____	____
Mouse (?)	39.8	18.2	____	____	____	____

____= No data

The concentrations of the inducers of aggregation in these animal studies differed for those used in studies of aggregation in humans. Cilostazol was consistently able to inhibit aggregation in PRP from all four species, when aggregation was induced by collagen. With the exception of rat, cilostazol inhibited aggregation when the inducer was ADP.

Experiment 3. *Ex vivo* platelet aggregation in dogs following oral cilostazol at dose of 3 mg/kg and 30 mg/kg, for up to 4 hours after cilostazol.

Ex vivo inhibition of platelet rich plasma derived from dogs after oral administration of cilostazol is shown in Table 43.3

Table 43.3 Time Course of Percent Inhibition in Beagle Dogs

	Time(hr)	Cilostazol 3 mg/kg (n=7)	Control (n=7)	Cilostazol 30 mg/kg (n=4)	Control (n=3)
ADP	0.5	50.8 ± 18.4	8.4 ± 28.4	48.6 ± 6.3	12.8 ± 38.0
	1	48.0 ± 31.4	22.4 ± 12.4	28.0 ± 55.0	4.7 ± 12.6
	2	46.1 ± 22.8	22.5 ± 20.6	44.9 ± 46.0	44.9 ± 46.0
	4	17.4 ± 25.9	5.4 ± 16.3	17.4 ± 11.9	17.4 ± 11.9
Collagen	0.5	29.3 ± 34.1	-1.2 ± 13.1	100	13.8 ± 18.4
	1	44.1 ± 39.8	3.8 ± 13.3	100	4.4 ± 7.3
	2	44.9 ± 42.0	4.6 ± 8.4	100	41.2 ± 45.1
	4	29.1 ± 45.3	-4.6 ± 9.3	100	10.2 ± 5.3

Experiment 4. The effect of cilostazol on platelet dispersion.

Cilostazol at a concentration 0, 10 and 100 uM was added, at several time points, to platelet rich plasma (derived from a single subject), after aggregation was induced by either ADP (2 uM); collagen (2 ug/ml); epinephrine (1 ug/ml) or arachidonic acid (200 ug/ml). Cilostazol was more effective in reversing platelet aggregation when it was co-incubated at 1 minute after the inducer was added. There was only minimal reversal of aggregation when cilostazol was co-incubated at 4 minutes after the inducer was added.

Experiment 5. *Ex vivo* thrombosis induced mortality in mice.

This was a study of an animal model of thrombosis. Each treatment group

contained 30-60 mice. Active drug (at the dose listed below) was (injected ? It is unclear as to the route of administration) into mice. Thirty minutes later either ADP (400 mg/kg) or collagen (10 mg/kg) was injected into the same mice and mortality over the next hour is shown in Table 43.4.

Table 43.4 . Mortality in In vivo thrombosis Animal Model.

	ADP-Induced Thrombotic Death (Died/total)			Collagen Induced thrombotic Death (Died/Total		
Drug: Dose (mg/kg)	Control	Treated	% Inhibition	Control	Treated	% Inhibition
Cilostazol: 1	-/-	-/-	-	18/30	16/29	8
3	27/37	20/29	5	38/58	16/59	59**
10	46/64	28/55	29**	18/30	0/19	100**
30	46/64	18/54	54**	20/28	0/30	100**
100	19/27	9/25	49**	-/-	-/-	-
ASA: 100	21/30	25/29	-23	35/38	11/30	60**
300	-/-	-/-	-	35/38	5/26	79**
Bencyclane: 100	24/30	20/27	6	21/30	13/21	13
300	24/30	20/24	-3	21/30	13/27	32
Pentoxyfylline: 100	18/29	17/18	2	-/-	-/-	-
300	18/29	17/23	-19	20/29	20/29	5
Dilazep: 30	-/-	-/-	-	23/30	23/29	-3
100	19/25	24/29	-9	23/30	23/30	0
300	19/25	23/30	-1	23/30	25/29	-12
Ifenprodil: 1	-/-	-/-	-	20/30	20/30	0
3	19/25	23/28	-8	20/30	17/30	15
10	19/25	24/30	-5	23/30	5/30	78**
30	19/25	16/29	28	23/30	8/30	65**
100	19/25	11/29	50**	23/30	5/29	78**

In this animal model, there was a decided inhibition of thrombotic-stimulated death at doses of cilostazol of 10 mg/kg for ADP-induced thrombosis and at 3 mg/kg for collagen-induced thrombosis (note: no pathology was supplied and a thrombotic cause of death was presumed based on the inducing stimuli). Aspirin at 100 or 300 mg/kg inhibited collagen-induced death. Ifendopril inhibited ADP-induced death at 100 mg/kg and collagen induced death at doses greater than 10 mg/kg.

Appendix A
SUMMARY OF STUDIES

Study #	# PTs	In Vitro Study	In Vivo Study	PK?	Other	Daily Dose	Divided	Duration	POPULATION
1	6		Yes			50-300	QD	1 DOSE	NORMALS
2		Yes							
3			Yes	Yes		50-300	QD-TID	UP TO 4 DAYS	NORMALS
4	10		Yes			100-200	BID	2 WEEKS	CEREBRO VASC DIS
5	15		Yes			75-300	TID	2 WEEKS	CEREBRO VASC DIS
6	52		Yes			150-300	TID	1-2 WEEKS	CEREBRO VASC DIS
7	9		Yes				QD?	1 WEEK	CEREBRO VASC DIS
8	24		Yes	Yes		50-200	BID	4 WEEKS	CEREBRO VASC DIS
9	10		Yes			100	BID	4 WEEKS	CEREBRO VASC DIS
10	6		Yes			100	BID	2 WEEKS	CEREBRO VASC DIS
11	13		Yes			200	BID	2-6 WEEKS	8 CEREBRO VASC DIS 5 ABD AORTIC ANEURISMS
12	14				Cerebral Blood Flow	200	BID		CVA
13	12				Blood Hemodynamics	200-300	TID	2 WEEKS	CVA
14	9				Blood Hemodynamics	150	TID	2 WEEKS	PERIPH VASC DIS
15	4				Blood Hemodynamics	200	BID	4 WEEKS	ASTERIOSCLER HEART DIS
16	10				Skin Temp	100-200		4-6 WEEKS	PERIPHERAL VASC DIS
17	16				Headaches	50-100		1 DOSE-	N
18	8				Pulnmonary Function	200		1 DOSE	N
19	12		Yes			200		12 DAYS	N
20	10		Yes			200		4 WEEKS	ASTERIOSCLER HEART DIS
21	?		Yes			200		4 WEEKS	
22	10					100		6 MONTHS	AORTIC GRAFTS
23	13					100		1 DOSE -	PERIPHE VASC DIS
24	18		Yes			200		8.4 ± 3 MONTHS	CEREBRO VASC DIS

25	26					200		> 3 MONTHS	PERIPHE VASC DIS
26									
27	30				ECHO	100		1 DOSE	NIDDM
28		Y							
29	13				Nerve Concudtion	100			
30	10		Yes			200			N
31	10		Yes			100	BID	4 WEEKS	N
32	23				Lipids	200		12 ± 3 WEEK	DM
33	14							4 -8 WEEKS	NIDDM
34	13		Yes		Skin Temp	100	QD	4 WEEKS	NIDDM
35	5					200-300	BID	> 1 MONTH	PERIPHE VASC DIS
36	13		Yes			100		3 MONTHS	NIDDM
37	?								
38	12				Headache	200	BID		CEREBRO VASC DIS
39		Yes							
40		Yes							
41		Yes							
42		Yes							
43		Yes							