Study #	Doses	Duration (wks)	Tread-mill Protocol#	Peak (P) Trough (T)	Primary End Point (s)	Secondary End points	# Enrolled	# With Efficacy (At least one baseline and one on-therapy measurement)
21-92-202	PBO BID Cilost. 50 mg BID Cilost 100 mg BID	24	A	(T)	1. Log (ACD wk 24/ACD bl) 2. Log (ICD wk 24/ICD bl) 3. Median ACD 4. Median ICD Measured at trough	1. Kruskal Wallis tests log (ACD wk 24/ACD bl) 2. Categorical Analysis ACD at each time point : i.e. <0% incr; 1-50% incr; 51-100 % incr; > 100 % incr 3. Categorical Analysis ICD at each time point t i.e.<0% incr; 1-50% incr; 51-100 % inc;r > 100 % incr 4.ANOVA of log (ACD wk 24/ACDbl) 5. Log rank score using the extended Mantel-Haenszel procedure	N= 516 PBO= 170 Cilost 50 BID= 171 Cilost 100 BID= 175	N= 419 PBO= 140 Cilost 50 mg = 139 Cilost 100 mg= 140
21-96-202	PBO BID Cilost 100 mg BID Pentox 400 mg TID	24	B	(T)	1.Log (ACD wk 24/ACD bl) pentox to Cilost	1. Log (ACD wk x/ACD bl)pentox to Cilost weeks = 2,4,8,12,16, 20 and 24 2. Examination of per protocol data set 3. Walking Impairment Questionnaire 4. Medical Outcome Scale Short Form 36	N=699 PBO=239 Cilost 100 BID=228 Pentoxy 400 TID= 232	N=643 PBO=226 Cilost 100 BID=205 Pentoxy 400 TID=212
21-94-201	PBO BID Cilost 50 mg BID Cilost 100 mg BID	24	A	(T)	1. Log (ACD wk 24/ACD bl) ANOVA Measured at Trough	1 Log (ICD wk 24/ICD bl) Measured at trough 2. Doppler limb pressures at rest 1, 5 and 9 min post exercise 3. QOL 4. Subjective Improvement categorical scale	N=394 PBO=129 Cilost 50 BID= 132 Cilost 100 BID= 133	N=377 PBO=125 Cilost 50 BID= 128 Cilost 100 BID= 124
21-94-301	PBO BID Cilost 100 mg BID Pentox 400 mg TID	24	C	(T)	1. Log Change ACD Cilost-vs PBO ITT 2, Log Change ACD cilost vs PBO Efficacy subgroup 3. Log change ACD Pentox vs Cilost ITT 4. Log Change ACD Pentox vs Cilost Efficacy Measured at Trough	1.Log change(ICD wk 24/ICD bl) ITT Cilost vs PBO 2. Log change(ICD wk 24/ICD bl) "efficacy" Cilost vs PBO 3. Log change(ICD wk 24/ICD bl) ITT Cilost vs OXP 4.Log change(ICD wk 24/ICD bl) "efficacy" Cilost vs OXP	N=370 PBO BID= 124 Cilost 100 BID=123 Pentox 400 TID=123	N=363 PBO BID= 122 Cilost 100 BID=123 Pentox 400 TID=118

21-94-203	PBO cilost 100 mg BID	16	B	(T) (P)	1.Trough Log (ACD wk16 /ACD bl) cilost vs PBO	1. Trough ICD 2. Peak ICD 3. Peak ACD 4. Subjective Assessment 5.Doppler -Measured limb Pressure 6. QOL	N=239 PBO= 119 Cilost 100 BID= 120	N=219 PBO=111 Cilost 100 BID=108
21-95-201	PBO BID Cilost 100 mg BID Cilost 150 mg BID	12	A	(T)	1. Log ACD (week 12/baseline). Dose for comparison not specified methodology by ANOVA if normality assumption holds else Cochran Mantel-Haenszel	Trough Log(ACDwk 8/ACD bl) Log(ACDwk 4/ACD bl) Trough Log(ICDwk 12/ICD bl) Log(ICDwk 8/ICD bl) Log(ICDwk 4/ACD bl) Subjective claudication per physician and patient	N=215 PBO BID=70 Cilost 100 BID=72 Cilost 150 BID=73	N=179 PBO BID=66 Cilost 100 BID=60 Cilost 150 BID =53
21-93-201	PBO BID Cilost 100 mg BID	12	B	(T) (P)	1. Trough Log ACD (wk 12/BL) 2. Trough Log ICD (wk 12/BL) 3. HDL	1. Subjective Claudication improvement per patient and physician 2. Doppler-Measured limb Pressures 3. QOL questionnaires 4. Walking distance at peak	N= 189 PBO BID=94 Cilost 100 BID= 95	N=175 PBO BID= 89 Cilost 100 BID =86
21-90-201#	PBO BID Cilost 100 mg BID	16	A	(T)	1.Trough Log ACD(wk12/Bl) 2. Trough Log IC D (wk12/bl) 3.QOL-Sickness Impact Profile	Claudication Outcome Measures	N=81 PBO=27 Cilost BID= 54	N=77 PBO BID=25 Cilost BID= 52
Small Studies								
21-86-101	PBO BID Cilost 100 mg BID	6	D	(T)	1..ICD baseline/ICD on wk 6	1.Subjective claudication symptoms per patient 2.Doppler measured limb pressures	N=53 PBO=24 Cilost 100 BID= 28	N=49 PBO=24 Cilost 100 BID= 25
21-86-103	PBO BID Cilost 150 mg BID	6	D	(T)	1. Change in ACD from baseline 2. Change in ICD from Baseline	1. Subjective claudication improvement 2. Palpitation of arterial pulses 3. Doppler -measured limb pressure 4. Sitting arm blood pressure	N=33 PBO=17 Cilost BID= 16	N=32 PBO=16 Cilost N=16
21-87-201	PBO BID Cilost 100 mg BID	12	D	?	Change in ACD at wk 12 from baseline Change in ICD at wk 12 from baseline	?	N=19 PBO BID=9 Cilost 100 BID=10	N=19 PBO BID=9 Cilost 100 BID=10
PUIC-2	PBO BID Cilost	8	E	?	?	?	N=23 PBO=? Cilost 100 BID= ?	N?

*ICD initial claudication distance ACD-Absolute claudication distance) Cilost=Cilostazol Pentox=Pentoxifylline=OXP QOL=quality of Life bl=baseline PBO=placebo
#Treadmill Protocols:
A. 3.2 km/h, fixed 12.5%(~7°) incline B 3.2 km/h, initial 0° incline increasing 3.5° every 3 minutes C: 3.2 km/h within 30 sec of start , 10 % incline.
D. 3.5 km/h,10% incline. E. 2.7 km/h, no incline stated.
study stopped prematurely for administrative reasons

Two sets of data, the ICD as well as the ACD (ACD=absolute claudication distance or the maximal-symptom limited walking distance at claudication) were collected for each study. Based on discussions with this Division, the pre-specified primary end point for each study was to be the ACD.

In the analyses of the eight larger studies, the increase in walking distance for a given treatment, when compared to baseline, was log transformed [equation 1]. The process of log transformation requires the multiplication of all the on-therapy values for the "n" patients in a treatment group and taking the n^{th} root of this product, which is then divided by the same process for the patient's corresponding baseline values. This metric was compared across treatments either by examining the percent change [equation 2] or by forming a ratio [equation 3]. This log transformed parameter, was prospectively defined as the primary metric for analysis of exercise performance. The distribution of the log transformed data satisfied normality assumptions, in fact better than the raw untransformed data (See Dr. Kun Jin's review for a discussion of the use of log transformed data).

Equation 1: Transformation $$(\prod_{I=1}^{n}(\text{distance})_i)^{(1/n)} \;/\; (\prod_{I=1}^{n}(\text{baseline})_i)^{(1/n)}$$

Equation 2: Percent Change $$[(\prod_{i=1}^{n}(\text{distance})_i)^{(1/n)} \;/\; (\prod_{i=1}^{n}(\text{baseline})_i)^{(1/n)} - 1] * 100$$

Equation 3: Ratios $$\left[(\prod_{i=1}^{n}(\text{distance})_i)^{(1/n)} \;/\; (\prod_{i=1}^{n}(\text{baseline})_i)^{(1/n)} \right]_{\text{treatment}}$$

$$\div$$

$$\left[(\prod_{i=1}^{n}(\text{distance})_i)^{(1/n)} \;/\; (\prod_{i=1}^{n}(\text{baseline})_i)^{(1/n)} \right]_{\text{placebo}}$$

Although several statistical methodologies were described in the sponsor's protocol, Dr. Kun Jin routinely analyzed the log transformed data by ANOVA or if the assumptions underlying the ANOVA were not satisfied, a Kruskal-Wallis procedure. Since the interpretation of log transformed data is not conceptually intuitive, the median change from baseline was also tabulated for each of the treatments.

For those who discontinued early, a last observation carried forth analysis was performed (LOCF), again, this was prospectively stated as the primary method of data analysis. For those who did not have a first on-treatment observation, the protocols did not specify how such subjects were to be treated in the analysis and

these subjects were generally censored[54]. The results of the primary analysis of the effect of cilostazol versus placebo on ACD (the absolute claudication distance) are tabulated in Table 6 (adapted from Dr. Kun Jin's Tables 5 and 6). Table 7 below contains the cilostazol-pentoxifylline comparisons (as analyzed by Drs Mahjoob and Cui).

There are some notable design differences which confound any across-study analyses. First, the protocols differed in the duration of observations. The larger studies generally enrolled subjects for between 12- 24 weeks. The smaller studies generally enrolled patients for anywhere between 6-12 weeks.

Exercise treadmill testing differed between protocols. Although the eight large studies held the speed of the treadmill to 3.2 km/hour (or 2 mile/hour), the protocols differed in the angle of incline of the treadmill. In some studies (arbitrarily labeled as A in Tables 4, 5, 8 and 9), exercise was performed on a fixed incline (usually 12.5% or 7°). Other studies, labeled as B (in the same tables), had an incline imposed only after walking on level ground for 3 minutes, with the incline then increased at 3 minute intervals (at a rate of 3.5°/3 min). In those studies with variable slope, a distance of 320 meters had to be walked before the slope approached the 7° incline of the fixed slope protocols labeled as A.

Table 5 contains the baseline ACD grouped by the treadmill protocols. Within similar treadmill protocols, the walking distance at baseline for ACD (and ICD, data not shown) were fairly consistent.

Table 5

Study #	Treadmill Test	Baseline Measurements of ACD				
		PBO	50 mg	100 mg	150 mg	Pentoxifylline
21-92-202	A	147.2	131.5	129.7		
21-94-201	A	117.3	123.2	120.9		
21-95-201	A	124.6		122.7	120..3	
21-90-201	A	168.6		141.9		
21-93-201	B	305.2		279.13		
21-94-203	B	249.7		236.3		
21-96-202	B	235		243		243
21-94-301	C	128		128		135

A. 3.2 km/h, fixed 12.5%(~7°) incline B 3.2 km/h, initial 0° incline increasing 3.5° every 3 minutes
C: 3.2 km/h within 30 sec of start, 10 % incline.

[54]Dr. Kun Jin analyzed the largest of the submitted studies by non-parametric methodology, with all those treated with active drug who discontinued prior to the first on-treatment exercise study as having the worst outcome. The results of this analysis did not markedly modify the conclusions derived from censoring those who discontinued prior to any exercise tests.

The fractional change in walking distance is very dependent on baseline walking distance. An increase in walking distance of 50 meters superimposed on a baseline distance of 100 meters is a 50 % increase. The same increase superimposed on a walking distance of 250 meters is only a 20% increase. It is, therefore, not possible to simply compare the increases in fractional changes across studies which employed different treadmill protocols.

For subjects enrolled into protocol B, at the median stopping point, these subjects were walking up a slope of 3.5°. Among those enrolled into treadmill protocol A, the slope at the median stopping point was the fixed slope of 7°. It is therefore, not surprising that the added walking distance among those enrolled in treadmill protocol B, given the more gentle initial slope, was substantially greater than those subjects who were exercised by treadmill protocol A.

There were eight substantial placebo-controlled studies. Of these studies, six (#21-92-202; #21-94-201; #21-94-203; #21-90-201;# 21-93-201; #21-96-202) showed an overall statistical significance in increasing ACD distances. In one of these studies, study # 21-90-201, enrollment was truncated early. The reason for prematurely discontinuing the study was not completely explained. As such, less weight should be given to the results of this study. In general, the effect of cilostazol on ICD seems to mirror its effect of ACD.

The 100 mg-BID dose was superior to placebo in the same six studies. In two studies, however, there was no statistical differences between placebo and the 100 mg BID dose. As noted above, the median added distance walked on cilostazol was dependent on the slope of the treadmill. Among those who were enrolled into studies using Treadmill protocol A, the median increase in ACD was approximately 20 meters (Table 8). Among those enrolled into studies that used protocol B the increase in ACD walking distance, at trough, was approximately 20 to 35 meters with one study demonstrating an increase of 65 meters (Table 8). The change in ICD was slightly less than that of the ACD, with the 100 mg dose having a median increase of approximately 12 Meters for the Treadmill protocol A and approximately 24 Meters for treadmill protocol B (Table 9).

There were two studies in which the 50 mg BID cilostazol was compared to placebo #21-92-202 and #21-94-201. In one of the studies, 50 mg cilostazol was statistically superior to placebo (see Table 6). In the other study, the effect of 50 mg BID cilostazol only trended in the appropriate direction (p=0.141). The median increase in ACD walking distance (both used treadmill protocol A), was approximately 10-15 meters (Table 9). The median increase in ICD walking distances were similar to the ACD values.

Only one study explored the 150 mg BID dose (#21-95-201). The overall p-value for the study was not quite significant. A two-point comparison against

placebo was marginally significant (p=0.04). The median increase in walking distance (protocol treadmill A) was approximately 20 meters (Table 8). The median increase in ICD was approximately 14 Meters (Table 9).

With respect to the adequacy of the BID dosing regimen, two studies (# 21-94-203 and #21-93-201) examined the exercise performance both 3-4 hours post dose (peak) as well as at the interdosing intervals (trough). The ratios show relatively consistent effect both at peak when compared to trough.

There two studies in which cilostazol, at a dose of 100 mg, was compared to pentoxifylline. In the largest of the two studies (# 21-96-202) there was a statistically significant (p=0.0002) improvement in exercise performance among those treated with cilostazol relative to those treated with placebo. In the second study (# 21-94-301), a study of reasonable size, there was no differences between pentoxifylline and cilostazol 100 mg.

Table 6 ACD differences- Based on Dr. Kun Jin's Analysis

Study #	Sponsor's Analysis of Effect							p-values					
	Percent				Ratio								
	PBO	50 mg	100 mg	150 mg	50 mg /PBO	100 mg /PBO	150 mg /PBO	Overall	50 mg/ PBO	100 mg/ PBO	150 mg/ PBO	100 mg/ 50 mg	150 mg /100 mg
21-92-202	15%	38%	51%	___	1.20	1.32		0.0002	0.001	0.0002	____	0.147	
21-94-201	12%	21%	37%	___	1.08	1.22	___	0.0001	0.141	0.0003		0.0.036	
21-94-203	5%	___	38%	___	____	1.31	____	2.8 e-07		2.8 e-07			
21-94-203 peak	15%	___	42%	____	____	1.24	____	0.0002		0.0002			
21-90-201#	-3%	___	40%	____	___	1.45	____	0.0008		0.0008			
21-93-201		___			___	1.16	____	0.011		0.011			
21-93-201 peak	6%	___	27%	___	___	1.20	___	0.004		0.004			
21-95-201	22%	___	23%	42%	____	1.01	1.17	0.07		0.910	0.04		0.065
21-96-202	19%	___	38%	___	____	1.14	____	0.0006					
21-94-301	31%	____	38%	___	____	1.05	____	NS		NS			

This study was prematurely discontinued for reasons that are unclear.

Table 7. ACD for Cilostazol compared to Pentoxifylline.

Study #	Percent			p-values	
	Pentoxifylline	Cilostazol 100 mg BID	Ratio	Overall	100 mg/Pent
21-94-301	40%	38%	0.99	NS	NS
21-96-202	19%	38%	1.13	0.0006	0.0002

Table 8 ACD -Median Changes in Meters (Parenthesis Represent Number of Subjects with Efficacy Numbers).

Study	Treadmill Protocol	week	PBO	50 mg BID	100 mg BID	150 mg BID	Pentox 400 TID	PBO Subtraction Cilost Dose BID Pentox Dose TID				Pentox Subtr
								50 mg Cilost	100 mg Cilost	150 mg Cilost	Pentox	100 mg Cilost
21-92-202	A	24	9 (n=140)	27 (n=139)	34.5(n=140)			18	25.5			
21-94-201	A	24	10 (n=125)	17.5 (n=128)	27.5 (n=124)			7.5	17.5			
21-90-201	A	16	-2 (n=25)		24.5 (n=52)				26.5			
21-95-201	A	12	23 (n=66)		16.5 (n=60)	37 (n=53)			-6.5	19.5		
21-96-202	B	24	39 (n=226		63 (n=205)		31 (n=212)		24		-8	32
21-94-203	B	16	9 (n=111)		70.5 (n=108)				61.5			
21-94-203 peak	B	16	42 (n=111)		104 (n=108)				62			
21-93-201	B	12	28(n=89)		58.5 (n=86)				30.5			
21-93-201 peak	B	12	-4 (n=88)		45 (n=86)				49			
21-94-301	C	24	23 (n=122)		31 (n=123)		29 (n=118)		8		6	2

A. 3.2 km/h, fixed 12.5%(~7°) incline B 3.2 km/h, initial 0° incline increasing 3.5° every 3 minutes
C: 3.2 km/h within 30 sec of start , 10 % incline.

Table 9 ICD-Median Changes in Meters (Parenthesis Represent Number of Subjects with Efficacy Numbers).

Study	Treadmill Protocol	week	PBO	50 mg BID	100 mg BID	150 mg BID	Pentox 400 TID	PBO Subtraction Cilost Dose BID Pentox Dose TID				Pentox Subtr
								50 mg Cilost	100 mg Cilost	150 mg Cilost	Pentox	100 mg Cilost
21-92-202	A	24	7 (n=140)	22 (n=139)	20(n=140)			15	13			
21-94-201	A	24	12 (n=125)	20 (n=128)	23 (n=124)			8	11			
21-90-201	A	16	2 (n=25)		22 (n=52)				20			
21-95-201	A	12	14 (n=66)		19 (n=60)	28 (n=53)			5	14		
21-96-202	B	24	35 (n=226)		58 (n=205)		45 (n=212)		23		10	13
21-94-203	B	16	21(n=111)		50 (n=108)				29			
21-94-203 peak	B	16	32 (n=111)		66(n=108)				34			
21-93-201	B	12	23(n=89)		48 (n=86)				25			
21-93-201 peak	B	12	23 (n=89)		41 (n=86)				18			
21-94-301	C	24	23 (n=122)		25 (n=123)		23 (n=118)		2		0	2

A. 3.2 km/h, fixed 12.5%(~7°) incline B 3.2 km/h, initial 0° incline increasing 3.5° every 3 minutes
C: 3.2 km/h within 30 sec of start , 10 % incline.

In neither study was there an estimate of the peak effect of cilostazol relative to that of pentoxifylline. There is, therefore, no information with respect to superiority of cilostazol relative to pentoxifylline over the entire dosing interval.

Ankle Brachial ratios: A subnormal ankle:brachial ratio reflects a diminished blood pressure and, therefore, blood flow into the involved extremity and was a required entry criteria into all studies. In general, subjects had ankle/brachial ratios of approximately 0.60 to 0.65 at entry, suggesting substantial compromise to extremity blood flow. These ABI measurements were performed resting at baseline, and in selected protocols resting and also after the performance of exercise while subjects were on-treatment. Neither the primary review nor the statistician's review analyzed the effect of treatment on ABIs in all studies.

Time to Reach Effect: Most, but not all, of the studies, based on group mean effects or ratio of effects, suggest a gradual widening of the effect relative to placebo over the duration of the study. If there is any flattening of effect, it occurs after 12-16 weeks of treatment (I've requested a graph of median changes of ACD at the various weeks of treatment for various protocols from the sponsor). It is unclear to this reviewer if this reflects a true widening of exercise effect or an artifact of the imputed measurements among those who prematurely discontinued.

Quality of Life Issues/Physician's Assessment/Patient's Assessment: There were a large number of individual quality of life parameters including Patient Assessment, Physician Assessment, Medical Outcome Scale (SF-36), Walking Impairment Questionnaire, Claudication Outcome Measurements and Listing of Physical Activity. These parameters were performed several times during the study and , several of the measurements contained multiple subscales.

Dr. Kun Jin's review makes it clear that, given the large number of secondary end points, the large number of individual items contained within each of the quality of life questionnaires, the multiplicities of treatments and the multiplicity of times in which the questionnaire were administered, none of the quality of life measurements/patient's or physicians assessments can be considered as statistically significant.

The sponsor, however, makes an argument that the intent of the QOL metric, particularly the (SF-36) questionnaire is not to show an overall effect on QOL. There are portions of the questionnaire reflecting for example, mental health, which are not likely to be modified by cilostazol. Unfortunately, the sponsor did not prespecify this eminently logical analytic approach. None of the sponsor's analyses, however, correct for the multiple other prespecified secondary end points.

The sponsor analyzed the Quality of Life Assessment (in particular the SF-36) only for those who completed therapy. Those who prematurely discontinued were censored. Since those who discontinued for adverse event(s) had their QOL sufficiently negatively changed that they chose to discontinue their medication despite any gain in exercise

performance, the censoring of such patients paints an overly rosy picture of QOL. Given the larger number of subjects who discontinued for adverse events, partcularly in the active treatment groups, censoring discontinuations for adverse events creates a bias and overestimates any QOL effect of each treatment cohort. An analysis, of the QOL treating those who prematurely discontinued as though they were the worse outcomes has been requested, but not yet submitted.

Safety:

Several different data bases were used to describe the safety of the population exposed to cilostazol. Most of the sponsor's analyses reflects the outcome of the eight large placebo controlled studies. Dr Rodin, however, often requested the pooling of all 12 placebo-controlled studies. At times in the following sections the outcome from the 12 studies is reported. For most of the other sections the results of the eight large studies is reported. In describing adverse events which led to discontinuation only seven studies were pooled.

Demographics: The closest demographic data that has been tabulated is that of the largest eight placebo-controlled studies. I have reproduced the data from Dr. Rodin's Table 42 with some information also derived from sponsor's Table 4.9-4 of the Advisory Committee Briefing Package.

Since those who were enrolled into the cilostazol treatment data base were to have exercise limited by their peripheral vascular disease, any concurrent CHF, angina or arrhythmia was likely mild and did not represent the extremes of these conditions

Table 10. Demographics in the Eight Large Controlled Studies

	Cilostazol				PBO N=973	Pentox N=355
	Total (N=1374)	50 mg BID N=303	100 mg BID N=998	150 mg BID N=73		
Gender: Male (%) /Female (%)	1043 (76%) /331 (24%)	230 (76%) /73 (24%)	758 (76%) /240 (24%)	59 (81%) /14 (19%)	745 (77%) /228 (23%)	270 (76%) /85 (24%)
Age mean ± SD (range)	65 ± 9.2 (40-91)	64	65	65	65.4 ± 9.2 (40-88)	66.4 ± 8.8 (40-87)
Race Caucasian/Other	1225 (89%) /149 (11%)	85%	91%	84%	866 (89%) /107 (11%)	328 (93%) /27 (7%)
Weight (kg) ± SD	79.8 ± 16 (36-178)	80	80	84	79.5 ± 15 (41-149)	78.6 ± 14 (44-131)
Diabetes	26%	29%	25%	34%	25%	22%
Smoking	40%				41%	33%
Cardiovascular Baseline Condition						
Past MI	298 (22%)	77 (25%)	201 (20%)	20 (27%)	211(22%)	88 (25%)
Past CHF	162 (12%)	27 (8.9%)	124 (12%)	11 (15%)	42 (4.3%)	28 (7.9%)
Past Angina	230 (17%)	18 (25%)	175 (18%)	37(12%)	183 (9%)	74 (21%)
Past ventricular arrhythmia	?	?	?	?	?	?

Supraventricular Arrhythmia	?	?	?	?	?	?
Duration of Exposure	127 days	153 days	123 days	62 days	134 days	139 days

? Still waiting for this data.

Discontinuations:

Table 11 contains the outcomes among those who were enrolled in the eight large placebo controlled studies (this table is adapted from sponsor's Table 4.9-2 of the Advisory Committee Briefing Package). I've appended as Appendix A the listing of the adverse events leading to discontinuations (derived from sponsor's Table A-18 of the 5 June 1998 submission)[55].

Since a subject could have more than one event which led to discontinuation, the sum of the events in the appended table are greater than the number of subjects who discontinued. The number of events per subject (again, this number is slightly different than the number of subjects with events which led to discontinuation), was 12.9% in the placebo group, and 20.6% in the overall cilostazol group. For the individual doses of cilostazol the event rates were 16% in the 50 mg BID dose group, 21% in the 100 mg dose group and 34% in the 150 mg dose group. Since the duration of exposure was substantially shorter in the 150 mg dose group than either of the other two cilostazol groups or placebo, the adverse event profile leading to discontinuation is even more impressive for the 150 mg BID cilostazol group.

Table 11. Patient Accounting Eight Placebo-Controlled Studies.

	Cilostazol				PBO	Pentox
	Total	50 mg BID	100 mg BID	150 mg BID		
Randomized	1374	303	998	73	973	355
Completed	1073 (78%)	250 (83%)	775 (78%)	48 (66%)	835 (86%)	258 (73%)
Days Exposure (days)	127	153	123	62	134	139
Withdrawn	301(22%))	53 (18%)	223 (22%)	48 (34%)	138 (14)	97 (27%)
Reason:						
Failed Screen	6 (0.4%)	0	6 (0.6%)	0	1(0.1%)	0
Inability to Continue	13 (0.9%)	2 (0.7%)	11 (1.1%)	0	9(0.9%)	3 (0.8%)
Non-Compliance	12 (0.9%)	2 (0.7%)	9 (0.9%)	1 (1.4%)	7 (0.7%)	3 (0.8%)
Deterioration	5(0.4%)	1 (0.3%)	4 (0.4%)	0	6 (0.6%)	0
Lack of Response	4(0.3%)	2 (0.7%)	2 (0.2%)	0	4 (0.4%)	0
Death	8 (0.6%)	2 (0.7%)	6 (0.6%)	0	4(0.4%)	2 (0.6%)
Other	29(2.1%)	5 (1.7%)	24 (2.4%)	0	19 (2.0%)	13 (3.7%)
Adverse Experience	224 (16.3%)	39 (13%)	161 (16%)	24 (33%)	88 (9.0%)	76 (21%)

[55]Appendix A only contains the information in seven of the eight large studies. Study 21-90-201 was excluded because the sponsor claims the CRFs differed from the other studies.