Table: 38

Subject dropouts in study 21-87-101:

	CLZ 100 mg bid	Placebo
# randomized	n =10	n =9
Total dropouts	7 (70%)	4 (44.4%)
All dropouts, by reason:		
nonfatal adverse event	3	1
other	4	3

[source: addendum dated 5/15/98]

.7 @**Efficacy outcomes**: (study 21-87-101)

The raw mean pre-treatment ACD was about 30 m lesser in the cilostazole group than in the placebo group, and mean ICD was about 12 m lesser as well, as shown in the following table.

Table: 39

Baseline raw mean walking distances in study 21-87-101:

baseline metric	*CLZ 100 mg bid*	*Placebo*
ACD	116.6 m	148.0 m
ICD	61.2 m	73.2 m

Clz showed trends towards lesser efficacy than placebo. In the clz-randomized group the mean cebo-corrected raw change from pre-treatment at week 12 was -99.1 m for ACD and -92 m for ICD. The estimated clz treatment effect to change ACD (the ratio of geometric means clz:placebo) at week 12 was not statistically distinguishable from that of placebo (point estimate

0.83, 95% CI = 0.46-1.51; p=0.52); the effect on ICD had a similar quality (point estimate 0.69, 95% CI = 0.42-1.13; p=0.13).

5.3.8 @**Commentary on the evidence** (study 21-87-101)

a. While the results of this trial fail to confirm other trials (and showed trends towards lesser efficacy than placebo), the present study's conclusiveness is greatly limited by imbalances in baseline walking tolerance, small sample size, and it's reliance on single-center observations.

9.4 Study PUIC-2: !

· this study only an abstract was submitted, rather than a full study report.

9.4.1 @Design Summary (study PUIC-2)

This concurrent placebo-controlled, double-blind, parallel-group, study randomized (in a 1:1 ratio) 23 subjects (patients intermittent claudication) to receive (after a 2 week placebo run-in) placebo, or cilostazol given as a 200 mg/d oral dose[8] for 8 weeks. Patients had pre-treatment ICD < 200 m during 2.7 km/hr treadmill testing. Treadmill testing was performed pre-treatment, and at post-randomization weeks 4 weeks and 8. Neither the baseline comparability of the groups, nor the analysis methods were described. One patient from the clz group and two from the placebo group were excluded (apparently because of histories of recent acute arterial occlusions) from analyses.

The mean change from pre-treatment mean ICD (presumably at week 8) was reportedly 29.7 m in the clz group, and 13.2 m in the placebo group.
The mean change from pre-treatment ACD was reportedly 142.3 m in the clz group, and 38.5 m in the placebo group.

.2 @Commentary on the evidence (study PUIC-2)

a. The reported results of this trial are largely noncontributory.

[8] there was no description of whether this was fixed or titrated, or what the dosing interval was.

10 **Positive-controlled Study PUIC-1:**

reported results of this trial are noncontributory.

For this study only an abstract was submitted, rather than a full study report.
This positive-controlled, presumably parallel-group study randomized 21 subjects (peripheral artery disease patients with intermittent claudication) to receive oral pentoxifylline (300 mg), or oral cilostazol (100-200 mg) for 12 weeks. It is not clear whether these doses were repeated during a day (and if so, how often), or whether they represent total daily doses. Neither is it clear whether the study was blinded.

Subjects were to have demonstrated an ICD of <400 m prior to treatment (although it is not clear what treadmill protocol was used to obtain this measurement). The study was to exclude subjects with severe rest pain, severe systemic complications, as well as those who underwent vascular operation in the preceding 6 months, or who required the continued use of anti-platelet or anticoagulant agents.

The results section of the abstract is ambiguous in making any distinction between two analyses: within-group comparisons (post-treatment vs pre-treatment), and between-group comparisons (treated group vs an historical healthy control). Therefore I can provide no meaningful summary of the efficacy data.

11 Safety data

1 Overall exposure

The NDA submission (data cutoff date of 9/2/96, except for studies 21-94-301 and 21-96-202, which were reported in complete form on 5/29/98 and 6/1/98, respectively) describes in detail the placebo-controlled, double-blind drug adverse experience (AE) of 1441 patients who received clz (at 50-150 mg bid) in the 12 largest placebo-controlled intermittent claudication (IC) studies (i.e. the U.S. controlled trials)

With lesser detail the sponsor also describes other safety experience in this and other diseases, from a number of sources (controlled, uncontrolled, open-label, postmarket). Fifty five patients received clz in 4 small placebo-controlled IC studies, approximately 10,000 patients were exposed to cilostazol in worldwide pre-market studies, and an additional 735,000 are estimated to have been exposed post-market (usually at a dose of 100 mg bid). See the table below.

Table: 40

Distribution of overall cilostazol exposure

exposure setting	*n*
	ACTUAL NUMBERS:
12 large placebo studies in IC	1441
4 small placebo studies in IC	55
other premarket studies	1319
postmarket surveillance	3335
	ESTIMATES:
postmarket trials	5995
other postmarket	725,000
TOTAL	approximately 737,167

[source: pg 27, vol 265; submission 5/22/98]

11.2 Placebo-controlled safety data

2.1 @Exposure in placebo-controlled IC studies:

Initially, ten placebo-controlled claudication trials were reported (studies 21-92-202; 21-94-201; 21-94-203; 21-95-201; 21-93-201; 21-90-201; 21-86-101; 21-86-103; 21-87-101; and PUIC-2), and recently the data from two additional studies were submitted (studies 21-96-202 and 21-94-301).

From this total of 12 placebo-controlled trials, the sponsor pooled safety data from the 8 largest (these were the most adequately designed, conducted, and reported, i.e. studies 21-92-202, 21-96-202, 21-94-201, 21-94-301, 21-94-203, 21-95-201, 21-93-201, and 21-90-201). Where my review discusses integrated safety data, these generally derive from the pooling of these 8 trials[1].

These 8 trials randomized 1374 subjects to clz (representing 95.4% of the total such exposure in all placebo-controlled trials), and 973 subjects to placebo (representing 94.3% of the total such exposure in all placebo-controlled trials). Additional placebo-controlled exposure occurred in 4 small trials which are reviewed in unpooled form.

Drug exposure in the 8 largest (all of which were phase III studies) placebo-controlled IC trials s as follows:

Roughly half of the 303 subjects receiving 100 mg/d clz were exposed either for >12 to 24 weeks; the next most common duration was >24 to ≤ 34 weeks (occurring in 39%), and the mean exposure was 153 days (range 2-202 days). Patients receiving 200 mg/d clz (n=998) were most commonly exposed for either >12 to 24 weeks (49%) or for >24 to ≤34 weeks (26%), and had a mean exposure of 123 days (range 1-227 days). Infrequently (n=73), patients received 300 mg/d clz, most often for >8 to ≤ 24 weeks (66%); this overall group had a mean exposure of 62 d days (range 1-96 days). The patient exposure years were 127, 337, and 12 for the 100, 200, and 300 mg/d clz doses, respectively. The placebo group was most commonly exposed for either 12-24 weeks (54%) or for 24-34 weeks (29%), had a mean exposure of 134 days or 358 patient-exposure-years.

Subjects' demographic characteristics in the 8 largest of the intially submitted placebo-controlled IC trials were as follows: The groups were reasonably well matched with respect to pertinent covariates, as shown in the table below.

[1] exceptions will be noted as such.

Table: 41

emography, pre-treatment characteristics, and drug exposure of subjects in the 8 largest placebo-controlled IC studies

	Placebo	*CLZ 100 mg/d*	*CLZ 200 mg/d*	*CLZ 300 mg/d*
	n= 973	*n= 303*	*n= 998*	*n=73*
male	77%	76%	76%	81%
female	23%	24%	24%	19%
age (mean)	65	64	65	65
Caucasian	89%	85%	91%	84%
Non-Caucasian	11%	15%	9%	16%
wt mean (kg)	80	80	80	84
concomitant tobacco use	41%	41%	40%	33%
diabetes	25%	29%	25%	34%
history of ≥1 cardiovasc condition	38.1%	36.6%	36.9%	57.5%
prior MI	21.7%	25.4%	20.1%	27.4%
prior arrhythmia	11.0%	8.9%	12.4%	15.1%
prior stable angina	18.8%	12.2%	17.5%	24.7%
prior CHF	4.3%	1.7%	4.3%	9.6%
mean drug exposure	134 d	153 d	123 d	62 d

[source: pg 79, vol 264; pg 73, submission 7/6/98, "A"]

11.2.2 Deaths

2.1 All-cause deaths

Across the 12 pooled placebo-controlled studies, in only 1 clz-randomized subject (0.07%) and 1 placebo-randomized subject (0.10%) was there a failure to capture the post-randomization survival status, and all who were captured had their status determined no sooner than the last scheduled post-randomization visit. The Kaplan Meir method was used to handle these few censored data.

Pooling all 12 placebo-controlled IC studies, and counting all deaths occurring while on therapy or within 30 days of the study drug's discontinuation, among clz-exposed patients there were 12 deaths (crude all-cause mortality rate of 0.83%; 95% confidence interval (CI) = 0.43- 1.45%), as compared to 7 deaths (crude all-cause mortality rate of 0.68%; 95% CI = 0.27- 1.39%) in the placebo group. The point estimates for exposure-adjusted mortality rate were 2.47 vs 1.90 deaths per 100 patient-exposure-years (PEY) in the pooled clz vs pooled placebo groups, respectively. The number of PEY for pooled clz was 485.4 vs 368.4 for pooled placebo. See the table below for the 95% CI around these exposure-adjusted rates, and for all-cause mortality as a function of dose.

Table: 42

All-cause mortality rate, as a function of dose (pooling all 12 placebo-controlled IC studies)[a]

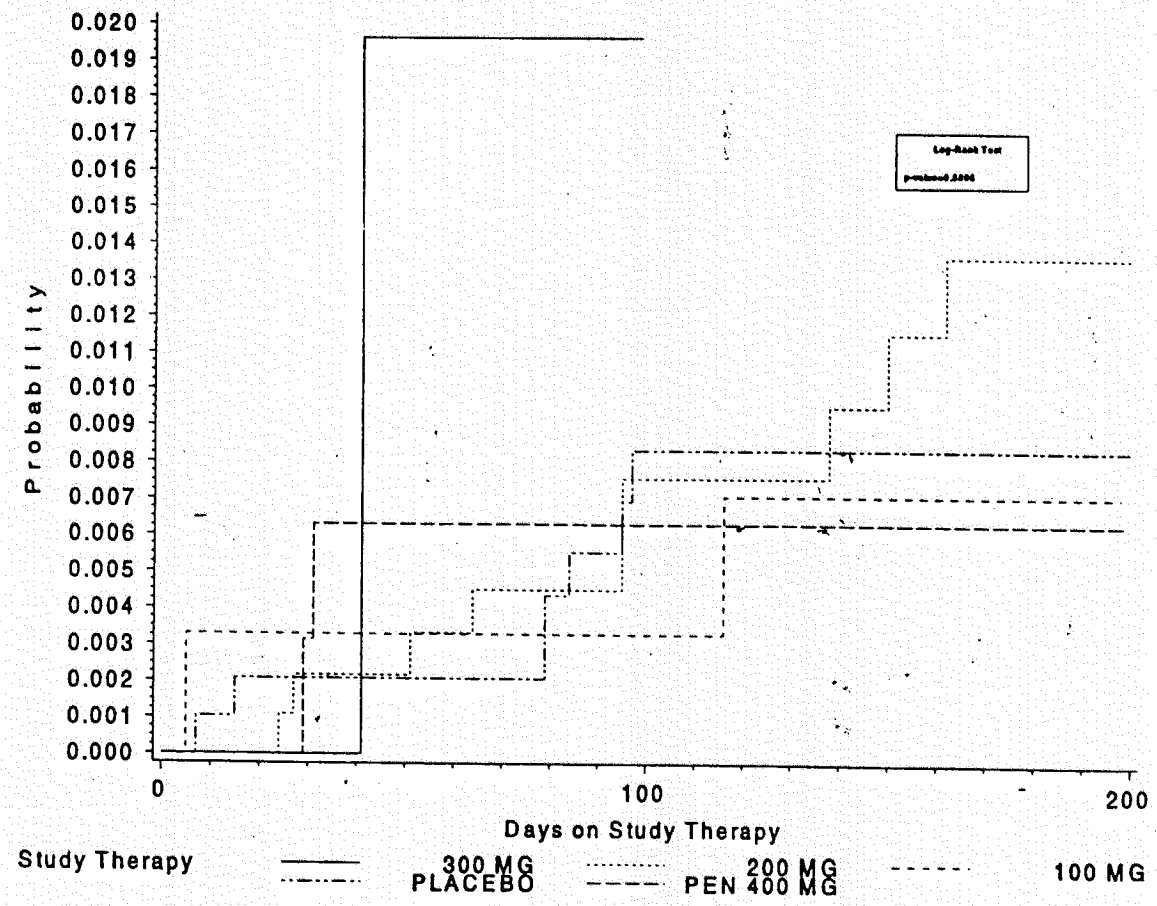
dose	*# deaths*	*crude rate (%)*	*exposure-adjusted rate (deaths per 100 PEY)*
placebo [n=1032]	7	0.68% (0.27 - 1.39%)	1.90 (0.77 - 3.90)
pooled clz [n=1441]	12	0.83% (0.43-1.45%)	2.47 (1.28-4.30)
clz 50 mg bid [n=303]	2	0.66% (0.08 - 2.36%)	1.58 (0.19 - 5.64)
clz 100 mg bid [n=1048]	9	0.86% (0.39 - 1.62%)	2.63 (1.20- 4.97)
clz 150 mg bid [n=90]	1	1.11% (0.03 - 6.04%)	6.30 (0.16 - 34.2)

[source: submission 35, dated 5/22/98]

[a] *Deaths shown are those occurring on-therapy or within 30 days post-treatment. Ninety-five percent confidence intervals are shown in parentheses.*

Figure: 20

Kaplan Meier estimate of cumulative probability of all-cause death
(pooling all 12 placebo-controlled IC studies)



[source: submission 6/9/98]

Deaths counted were those occurring on-therapy or within 30 days post-treatment.

Given the lack of validation of the process by which causes of death were classified one, as always, needs to be quite cautious in interpreting subsets of cause-specific mortality. Among clz-domized patients 10 of these 12 deaths were attributed to cardiovascular causes (predominantly ..ributed to MI). Although any number of these cardiovascular deaths could have plausibly been attributable to this PDE III inhibitor, for none is there much basis for excluding the possibility of non-cilostazol variables (e.g., pre-existing disease, severe toxic response plausibly attributable to another drug, motor vehicle accident) being the major or even sole causal factor. Among placebo-randomized patients 5 of these 7 deaths were attributed to cardiovascular causes.

Among CLZ-randomized subjects the reported deaths occurring on-therapy or within 30 days post-treatment had the following attributed causes and case narratives[2]:

- death C1: **Myocardial infarct** (MI):
study 21-92-202; Center 32; Patient 146. This 42 year-old black male with history of MI, was randomized to clz 50 mg bid. After exerting physically in the restraint of a psychiatric patient, this subject collapsed and died. Autopsy results revealed acute coronary thrombus.

- death C2: **MI**:
study 21-92-202; Center 11, Patient 0367; This 74 year-old caucasian male with a history of multiorgan arterial disease, was randomized to clz 100 mg bid. He developed worsening ..rtional angina, and had angiographic evidence of coronary stenoses. After refusing ..evascularization the investigator discontinued study medication. Within a month the the patient had an acute MI and died en route to the hospital.

- death C3: **MI**:
study 21-92-202; Center 16, Patient 484. This 64 year-old caucasian male (randomized to clz 50 mg bid) had a history of CAD, CABG, and diabetes. He had chest pain prior to randomization, and again shortly after randomization. Unrelieved by nitroglycerin, he was admitted to hospital and found to have an acute MI. This took an unstable course (AV block, rapid ventricular tachycardia) and ultimately resulted in death.

- death C4: **MI**:
study 21-94-203; Patient 144; Center 68. This 77 year old caucasian female (randomized on 4/19/95 to clz 100 mg bid) had a history of 65 pack-year cigarette use, hypertension, and hypothyroidism. About 2 months post-randomization she experienced chest pain, was diagnosed with acute MI, became hypotensive and then ultimately asystolic before eventual death.

- death C5: **MI** (presumed):
study 21-96-202; patient 9008; Center 091. This 67 year old black male (with a history of angina, ..CA, hypercholesterolemia, hypertension, and CHF) was randomized to the CLZ 100 mg bid.

[2] the numbering scheme (death #1, #2, etc) is my own arbitrary system.

He was reportedly found dead in his home on post-randomization day 24, having apparently died in his sleep. The cause of death was listed as an MI and CAD. No autopsy was performed.

-eath C6: **sudden death**:
study 21-94-201; patient 407; Center 43. This 70 year old caucasian male (randomized to clz 100 mg bid) had a history of CAD, CABG, and cardiomegaly. After a period of increased angina 6 months post-randomization, he had a witnessed sudden death.

- death C7[3]: **cardiorespiratory arrest →respiratory failure**:
study 21-95-201; Patient 266; Center 65. This 62 year old caucasian male (randomized to clz 150 mg bid) had a history of congestive heart failure (CHF), COPD, hypertension, and diabetes. About 5 weeks post-randomization the patient was hospitalized with severe dyspnea and thereupon suffered cardiorespiratory arrest. He was revived, but remained comatose and on ventilator support. Later that week the patient died of respiratory failure.

- death C8: **Ruptured aortic aneurysm**:
Patient 4708; Center 091; study 21-96-202. This 76 year old black male (with a history of prior abdominal aortic aneurysm repair, hypertension, arrhythmia, systolic murmur, palpitations, and hypercholesterolemia) was randomized to CLZ 100 mg bid. On post-randomization day 26 the patient experienced increasingly severe epigastric pain and was hospitalized with a ruptured racic aneurysm. He became hypotensive, and required emergency thoracotomy. A large quantity of blood was evacuated from the left chest. Repair of the large thoracic aortic aneurysm was attempted, but was complicated by a poor surgical exposure and hemorrhagic lung. By the next day the patient had developed serious neurologic damage and died. No autopsy was obtained.

- death C9: **CABG→fatal post-op complications**:
Patient 243; Center 6; study 21-92-202. This 81 year-old caucasian female with history of MI and three vessel CABG, was randomized to CLZ 100 mg bid. Three months post-randomization she was hospitalized with unstable angina, underwent bypass surgery, and died of complications following surgery.

- death C10: **CABG→fatal post-op complications**:
Patient 59; Center 39; study 21-93-201. This 70 year-old caucasian male (randomized to CLZ 100 mg bid) had a history of cigarette use, hypertension, and paroxysmal atrial tachycardia. About 3 months post-randomization he had a sudden onset of severe, intermittent angina. His medication was stopped, and he underwent CABG. After surgery, the patient went into ventricular fibrillation and died.

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[3] the sponsor reports that they did not list this case in their Advisory Committee briefing package's table 4.9-2 because the investigator-attributed reason for dropping out was not death, but respiratory failure.

- death C11: **Gastric cancer:**
patient 428; Center 20; study 21-94-301. This 68-year-old caucasian male (with history of atrial tachycardia and cigarette use) was randomized to CLZ 100 mg bid. One month post-randomization the patient had reportedly markedly abnormal elevations of alkaline phosphatase, AST, ALT, and bilirubin. The patient did not return to followup, and he eventually became known to have died of gastric carcinoma about 3 weeks subsequently.

- death C12: **motor vehicle accident:**
Patient 459; Center 75; study 21-94-201. This 67-year-old caucasian male, randomized to clz 100 mg bid, died in a motor vehicle accident. There was reportedly no evidence of loss of consciousness before the accident occurred (although it is not clear whether this assertion of the sponsor's is one of "absence of evidence" or one of "evidence of absence"). There was no information provided as to whether the patient was the passenger or the driver of the car.

These are the case narratives for the 7 placebo-randomized subjects reported to have died while on-therapy or within 30 days post-treatment:

- death P1: **sudden death**
Patient 0305; Center 6; study 21-92-202. This 75 year-old caucasian female (with history of hyperlipidemia) was randomized to placebo. She was last observed at post-randomization week Later a telephone inquiry found that the patient had died suddenly at about week 13. Death had been ascribed to atherosclerotic heart disease, although no autopsy was performed.

- death P2: **sudden death**
Patient 209[4], Center 02, Study 21-90-201. This 58 year old placebo-receiving male, with history of angina, was admitted to the hospital (at an unspecified time post-randomization) after experiencing crushing chest pain of unspecified duration. He was found to have CPK elevation to six times the upper limit of normal. The patient was discharged against medical advice, and had a sudden death one day later.

- death P3: **sudden death**
Patient 0200; Center 61; study 21-94-203. This 54 year old placebo-receiving caucasian male subject (with history of cigarette use, and hyperlipidemia). At about 11 weeks post-randomization he reported not feeling well, complaining of intestinal gas and difficulty going up stairs. He was found deceased the next day. No concomitant medications were taken at the time of his death.

- death P4: **ventricular fibrillation**
Patient 2316; Center 12; study 21-96-202. This was a 66 year old placebo-receiving caucasian male with history of prior MI, hypertension, hypercholesterolemia, angina, cerebrovascular

[4] supplemental details of this case were provided in the sponsor's addendum submission dated 4/13/98.

disease, and chronic obstructive pulmonary disease. On post-randomization day 93 he developed radiating chest pain. Two days later he had chest pain, dyspnea, diaphoresis, and lightheadedness. MI was diagnosed on the basis of 1-2mm EKG-ST depression, and reportedly positive CPK and MB fraction. Study drug was discontinued, and CABG was performed. Postoperatively, he developed compartment syndrome and underwent leg embolectomy and fasciotomy. He developed hyperkalemia (serum potassium of 7.8 mg/dL) and was dialyzed for renal failure. Less than a minute into dialysis, he had fatal ventricular fibrillation.

- death P5: **Cardiac Arrest**
Patient 0165; Center 21; study 21-94-301. This 65 year old, placebo-randomized, caucasian male had a history of hypertension, angina, hyperlipidemia, and cigarette use. At his week 2 visit he reported brief episodes of persistent angina which was relieved by nitrates. On post-randomization day 14 he underwent a treadmill walking test (stopped for limiting claudication after 1 minute 38 seconds) , and one hour later he experienced cardiac arrest. After unsuccessful rescusitation he died, of presumed ischemic arrhythmia. Autopsy revealed high grade coronary stenoses without evidence of acute MI or thrombosis.

- death P6: **pancreatic cancer**
Patient 0084; Center 80; study 21-95-201. This 69 year old, placebo-randomized, caucasian male had a history of MI, arrhythmia, hypertension, TIA, and diabetes. About 2 months after randomization he experienced dyspepsia, was discontinued from the study, and became hospitalized. He was diagnosed with pancreatic cancer, and died about 2 weeks later.

- death P7: **GI carcinoma**
Patient 0097; Center 81; study 21-95-201. This 50 year old placebo-randomized, caucasian female had a history of cigarette use. About 2 months post-randomization she was evaluated for severe nausea, vomiting, and abdominal pain. Exploratory surgery found widespread cancer of the liver, colon, and stomach. The patient withdrew from the study and died about 2 weeks later.

LATE DEATHS:

There were two additional deaths occurring beyond 30 days post-discontinuation of CLZ (and also 3 such late deaths among the placebo randomized). The late deaths among the CLZ exposed were as follows:

- late death #L-C1: **MI**:
study 21-95-201; Patient 60; Center 91. This patient died 77 days after discontinuing treatment. Fatal hemodynamic dysfunction was apparently closely temporally linked with the onset of prochlorperazine-induced extrapyramidal signs, suggesting the possiblity of a severe Neuroleptic Malignant Syndrome. This 71 year old caucasian female (randomized to clz 150 mg bid) had a history of congestive heart failure, hypercholesterolemia, diabetes, and lymphoma. After

administration of prochlorperazine for post-chemotherapy nausea, she developed a dystonic reaction and was transferred to the emergency room. She arrived in complete heart block, was otensive, and had enzyme evidence of acute MI. She remained dependent on pressors and pacing, and subsequently died.

- late death #L-C2: **cerebral hemorrhage**
study 21-92-202; Patient 40; Center 2. This 64 year-old caucasian male, was randomized to the CLZ 100 mg bid group, but withdrawn within days so as to be reinstated on aspirin therapy for stroke prevention. His medical history included cigarette use, diabetes, and hypertension. Four months later he developed symptomatic worsening of carotid stenosis, received carotid endarterectomy, and had a deteriorating postoperative course culminating in fatal intracerebral hemorrhage.

There were 4 additional deaths among pentoxifylline-randomized subjects in placebo-controlled trials. Two occurred within 30 days of exposure (a sudden death and a death from MI), and two occurred greater than 30 days following exposure (one was attributed to bladder carcinoma, and one to metastatic carcinoma).

11.2.2.1 @Comments (pooled deaths)

These studies excluded patients with diseases, like CHF, that symptomatically limited exercise tolerance for reasons other than claudication. This method was reasonable in that it served to support the validity of the claudication endpoint, however it was not without tradeoff. Whereas previous experience with PDE inhibitors strongly suggests that the excluded CHF population are potentially at risk of a cilostazol-mediated adverse survival effect, the current analysis of pooled deaths provides no basis for assessing that potential risk.

11.2.2 **@Dropouts:**

oled dropout rates and cumulative probabilities are shown in the following table and figure, spectively.

Table: 43

Crude mean rate of *all* dropouts
(pooling the 8 largest placebo-controlled studies):

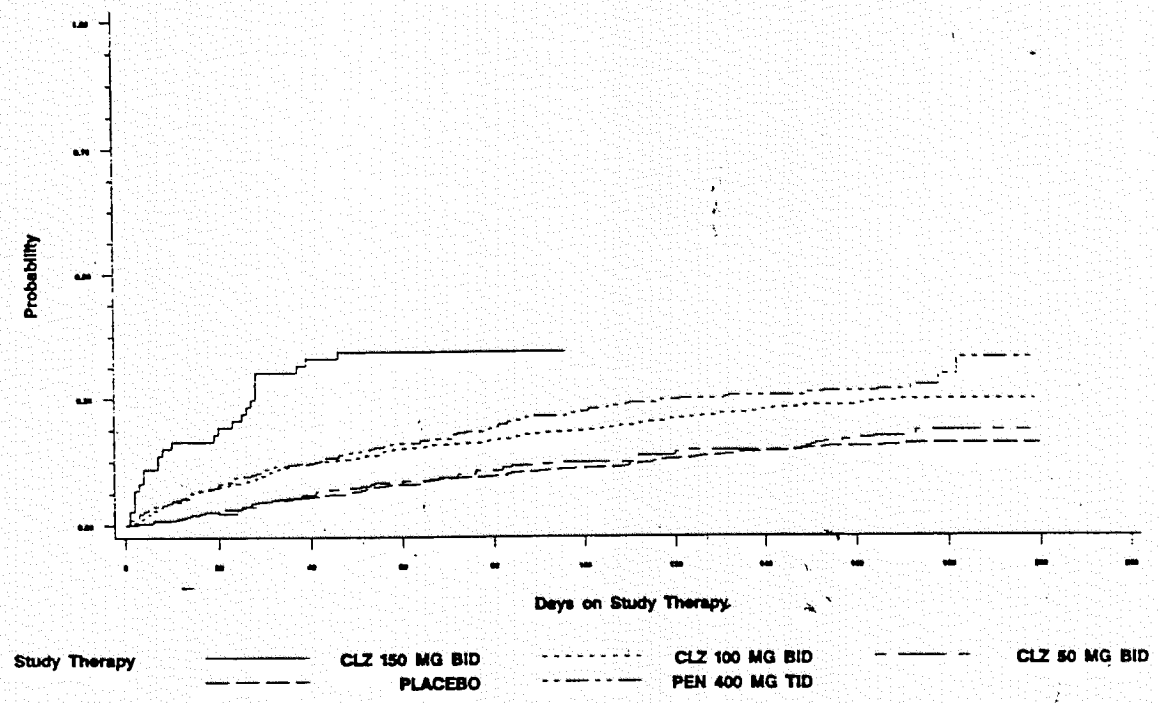
basis of dropout	*placebo* [n=973]	*clz 50 mg bid* [n=303]	*clz 100 mg bid* [n= 998]	*clz 150 mg bid* [n= 73]
any AE (fatal or nonfatal)	9.6%	13.9%	16.5%	32.9%
dropouts for other than AE:				
failed screening	0.1%	0%	0.6%	0%
inability to continue	0.9%	0.7%	1.1%	0%
non-compliance	0.7%	0.7%	0.9%	1.4%
non-response	0.4%	0.7%	0.2%	0%
other	1.7%	1.7%	2.1%	0%
total dropouts	14.2%	17.5%	22.3%	34.2%

[source: pg 15, submission 35, 5/22/98]
Each subject is counted only once in this analysis.

Figure: 21

Cumulative probability of dropping out for any reason

(Kaplan Meier estimate; pooling the 8 largest placebo-controlled studies):



[source: photocopy of pg 50, submission 7/6/98-"A"]