11.3.5 Longterm uncontrolled study 21-91-201

3.5.1 Design Summary

This is an ongoing, uncontrolled, open-label study of the safety[32] of long term cilostazol exposure in subjects who completed phase III studies. Subjects are administered an oral starting dose of cilostazole 100 mg bid, with optional uptitration to 150 mg bid or downtitration to 50 mg bid . Drug is supplied as a 50 mg tab (lots 3K94PB1 and 4A81PB2), and a 100 mg tab (lots 0H89-100, 1G86-100, 3K98PA1, 4K79PA1, and 6C73PA1). Patients are to undergo clinical and laboratory safety evaluations every 2-12 weeks.

The study was submitted to the IND on July 30, 1991 and the first patient visit was on August 29, 1991. The presently reviewed interim report has a data cutoff date of September 2, 1996.

11.3.5.2 Enrollment criteria. (study 21-91-201)

Patients are to be eligible for enrollment if they were randomized in a previous cilostazol study, and had been exposed to no investigational drug other than clz. Patients are to be excluded if they had exhibited poor compliance during their previous protocol, or for "sound" (undefined) medical reasons.

11.3.5.3 Treatment regimen. (study 21-91-201)

Subjects are to be administered an open-label, oral starting dose of cilostazole 100 mg bid, with optional uptitration to 150 mg bid or downtitration to 50 mg bid.

Disallowed concomitant medications are to be the following anticoagulants (warfarin, heparin), antiplatelet agents (sulfinpyrazone, dipyridamole, clofibrate, ticlopidine)[33], vasoactive agents (papaverine, isoxsuprine, nylidrin, cyclandelate, niacin derivatives), pentoxifylline, or NSAIDs (except acetaminophen or diclofenac sodium; aspirin is to be allowed (by protocol amendment) up to a maximum daily dose of 325 mg).

11.3.5.4 Endpoints (study 21-91-201)

The protocol-specified primary analysis was an assessment of safety and uncontrolled walking distance data, but the efficacy endpoints were later abandoned by protocol amendment.

Prior to treatment, and again at weeks 2, 4, 6, 8, 12, 16, 28, 40, 52, and yearly thereafter there are to be measurements of vital signs, serum chemistry, hematology, plasma drug levels (cilostazol,

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[32] additional plans to obtain uncontrolled walking distance data were later aborted by protocol amendment.
[33] aspirin use is not disallowed.

and its two primary metabolites), and 12-lead EKG. Urinalysis is to be performed prior to treatment, and again at weeks 4, 8, 12, 16, and at the time of termination. Physical examination is to be performed prior to treatment, and again at the time of termination.

11.3.5.5 **Interim Safety Results** (study 21-91-201):

11.3.5.5.1 **Exposure** (study 21-91-201):

The interim report described the results in 1105 subjects[34]. The majority (73%) were treated at an average dose between 100 and 200 mg/d. The mean daily dose was 203 mg/d. The mean number of days on treatment was 260 days in the ≤100 mg/d group, 345 days in the 100-200 mg/d group, 411 days in the 200-300 mg/d group, and 675 days in the >300 mg/d group. The total number of patient exposure years was 1085 years.

11.3.5.5.2 **Demographics** (study 21-91-201)

As shown in the table below, the patients were primarily Caucasian and male.

[34] 3 additional patients were excluded reportedly because of missing dosing records.

Table: 51

Demographic & Pre-treatment characteristics of subjects thusfar enrolled in study 21-91-201:

	100-200 mg/d CLZ	*200-300 mg/d CLZ*
	n= 803	*n= 259*
male	78%	82%
female	22%	18%
age (mean)	65	63
Caucasian	87%	92%
non-Caucasian	13%	8%
wt mean (kg)	80	81

[source: interim report, pg 66, vol 203]

11.3.5.5.3 **Disposition** (study 21-91-201)

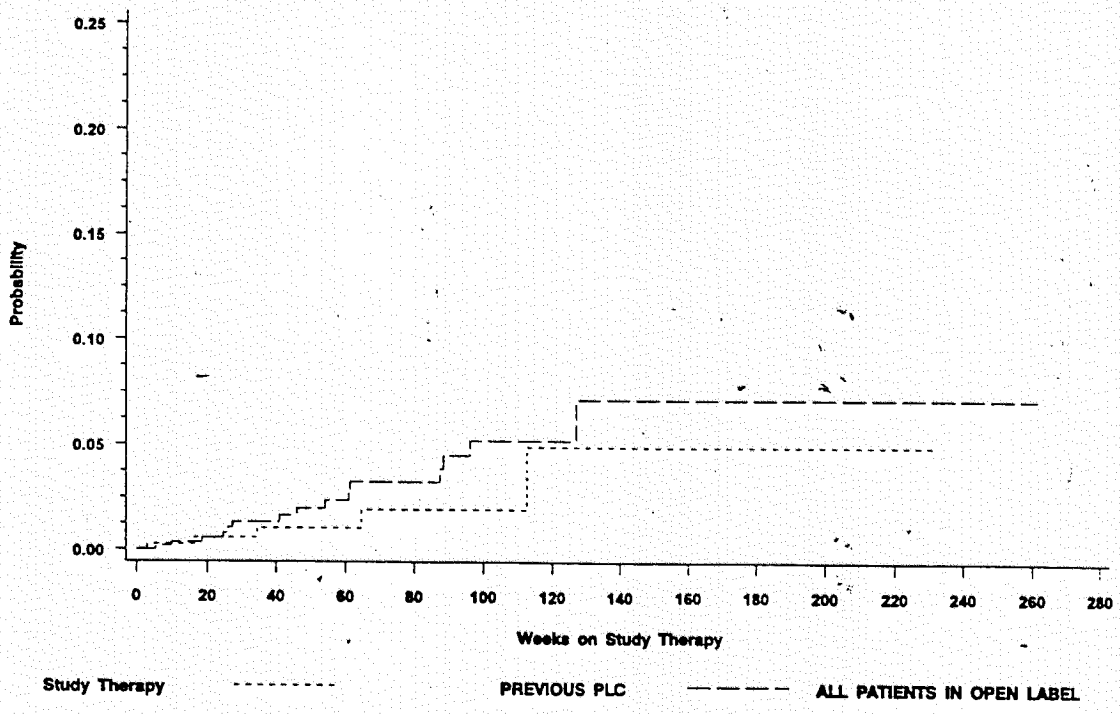
Three patients have been lost to follow-up: Patients #084, #550, #145, and #124.

11.3.5.5.4 **Deaths** (study 21-91-201)

ere were 27 deaths reported, 14 occurring while on drug, and 13 occurring 1-157 days after ..ug discontinuation. The following table shows the survival analysis for all patients, and for those previously randomized to placebo.

Table: 52

Kaplan-Meier estimate of cumulative probability of death within 30 days of stopping study medication (study 21-91-201)



[source: pg 38 of submission 7/6/98]

The following were the reported cases narratives:

death #1: **Sudden Death** Patient 216, Center 002. This 78-year-old caucasian male, with history of peripheral arterial bypass and multiple myeloma, received CLZ at a final dose of 50 mg bid. He dropped out on day 702 due to an unspecified AE, and was hospitalized 2 weeks later with recurrence of multiple myeloma, and again one month later with acute renal failure. The patient collapsed at home about one month later with a probable myocardial infarction.

- death #2: **Stroke** Patient 223, Center 2. This 65-year-old caucasian female received clz at a final dose of 100 mg bid. Her history included bilateral internal carotid artery stenosis, and she was noted to be hypertensive at baseline. The patient experienced an episode of amaurosis fugax, and shortly thereafter dropped out after 443 days on drug. Three days later the patient experienced a fatal stroke.

- death #3: **hypotensive death, with multisystem dysfunction**
Patient 228, Center 2. This 70-year-old caucasian male received clz at a final dose of 150 mg bid. His history included COPD, hypertension, and carotid endarterectomy. Reportedly in preparation for in-patient treatment of COPD, he dropped out on day 197. He was later admitted to the hospital with odynophagia, became progressively anorectic, and had increasing pulmonary ltrates. He developed a hepatitis of unclear etiology (presumed by his clinicians to be either toxic or ischemic). The patient ultimately died primarily a hypotensive death, with reportedly no significant event occurring in the prior several days. The discharge diagnosis was COPD with progressive pulmonary infiltrates of undetermined etiology, exacerbated by CHF and vascular disease. Other presumed contributory factors were malnutrition and hepatic dysfunction.

- death #4: **presumed Myocardial Infarct** Patient ID: 302, Center: 3. This 80-year-old caucasian male had a history of angina pectoris, diabetes mellitus, and cigarette use. His final clz dosage was 100 mg bid. On study day 209 the patient was admitted to a hospital with hemoptysis, and was diagnosed with metastatic carcinoma of the lungs. Thirty two days later he was found unconscious in his car and was pronounced dead of a presumed myocardial infarction. No further details of this adverse event are available.

- death #5: **Myocardial Infarct** Patient 3, Center 3. This 51-year-old caucasian female received clz at a final dose of 100 mg bid. Her history was that of CAD and cigarette use. On study day 889 the patient had an acute MI complicated by cardiogenic shock. She received TPA, was found to have a left main coronary artery stenosis, arrested and died.

- death #6: **Arteriosclerosis** Patient 34, Center 2. This 66-year-old caucasian male was eiving CLZ at a final dose of 100 mg bid. His history included previous cardiomyopathy, hypertension cigarette use, and hyperlipidemia. The patient was found unresponsive on study day

69. Death was attributed to advanced atherosclerosis complicated by coronary artery thrombus, healing myocardial infarctions, nephrosclerosis, and cardiomegaly.

death #7: **Arrhythmia** Patient 440, Center 3. This 65-year-old caucasian female received clz at a final dose of 100 mg bid. Her history included CAD, MI, and hypertension. On study day 427 the patient was admitted to hospital in CHF. Two days later the patient collapsed and was pronounced dead secondary to primary cardiac arrhythmia.

- death #8: **Sudden Death** Patient 73, Center 4. This 71-year-old caucasian male received clz at a final dose of 100 mg bid. His history included angina, hyperlipidemia, hypertension, and diabetes. He visited his doctor with complaints of chest pain, and on study day 21 was found dead at home. Further details have not been provided.

- death #9: **Respiratory Arrest** Patient 88, Center 4
This 44-year-old caucasian male received clz at a final dose of 100 mg bid. His history included current cigarette use and PAD. He dropped out for unspecified reasons after 214 days. About 4 months later the patient underwent aortofemoral bypass surgery, and he died of respiratory arrest reportedly as a complication of surgery.

- death #10: **Ventricular Fibrillation** Patient 17, Center 6. This 61-year-old caucasian male received clz at a final dose of 100 mg bid. His history included angina and multiple coronary revascularizations. The patient died suddenly on day 327, reportedly due to Vfib.

- death #11: **Sudden Death** Patient 358, Center 6. This 77-year-old caucasian male received clz at a final dose of 100 mg bid. His history included hypertension, cigarette use, and renal insufficiency. On study day 792 he experienced sudden death. Contributing conditions were felt to be coronary and systemic atherosclerosis.

- death #12: **Stroke** Patient 402, Center 6. This 76-year-old caucasian male received clz at a final dose of 100 mg bid. This patient's medical history included cigarette use, MI, and CABG. He discontinued drug after 294 days, in preparation for planned removal of pleural sarcoma. On study day 314 the patient collapsed and was diagnosed with stroke which took a rapidly fatal course.

- death #13: **Sudden Death** Patient 273, Center 10
This 64-year-old caucasion male received clz at a final dose of 50 mg bid.
The patient's medical history included current cigarette use and PAD.
It was reported that the patient died in his sleep on study day 193. The death certificate ascribed this to cardiopulmonary failure secondary to arteriosclerotic heart disease.

- death #14: **Cardiopulmonary Arrest** Patient 349, Center 12. This 67-year-old caucasian female received clz at a final dose of 150 mg bid. Her history included previous arette use, hypothyroidism, hypertension, and carotid artery disease. On study day 405 she as admitted to hospital with chest pain. Drug was stopped, and she received CABG and PTCA interventions. Her recovery was complicated by renal failure requiring dialysis, and multi-organ system failure. She died of cardiopulmonary arrest.

- death #15: **Myocardial Infarct** Patient 21, Center 20. This 73-year-old black male received clz at a final dose of 100 mg bid. His history included cigarette use, hypertension, and diabetes. After not making a scheduled appointment, the investigator was informed that the patient had died of a myocardial infarction. Reportedly, no additional information is available.

- death #16: **Cardiac arrest post MI** Patient 361, Center 24. This 65-year-old caucasian male received clz at a final dose of 100 mg bid. Past history included three prior MIs, CABG, and hypertension. On study day 14 the patient had a large MI and went into a coma, whereupon study drug was discontinued. Later, he suddenly became asystolic and died.

- death #17: **Sudden Death** Patient 173, Center 38. This 68-year-old caucasian male received clz at a final dose of 100 mg bid. His history included CAD, CHF, mitral regurgitation, ertension, diabetes, and renal insufficiency. The patient died on study day 193. He was ound, after mowing his lawn, sitting in a chair with his hand to his chest.

- death #18: **Postop bowel infarct** Patient 547, Center 41. This 68-year-old caucasian male received clz at a final dose of 100 mg bid. This patient's medical history included abdominal aortic aneurysm, previous cigarette use, hypertension, transient ischemic attack, and emphysema. In preparation for elective surgery on abdominal aortic aneurysm the patient discontinued drug on day 612. During surgery hemostasis was said to be somewhat more difficult to establish than is usually the case. The postop course was complicated by small bowel infarction believed to be mechanical and related to the surgical approach. There was reportedly no evidence of a clinical hyperthrombotic state. He underwent emergency bowel resection, and died 3 days later.

- death #19: **CAD** Patient 548, Center 41. This 59-year-old black male received clz at a final dose of 100 mg bid. His history included MI, angina, and CABG. This patient was found dead at home on study day 673. The death certificate stated that the cause of death was coronary artery disease, while the investigator thought it a probable MI.

- death #20: **Death during sleep** Patient 176, Center 61. This 84-year-old caucasian le received clz at a final dose of 100 mg bid.

His history included CAD, arrhythmia, CABG, and MI. The patient reportedly died in his sleep on study day 453, after a reportedly uneventful day.

death #21: **Myocardial Infarct** Patient 22, Center 62.
This 46-year-old caucasian male received clz at a final dose of 100 mg bid.
His history included cigarette use, and hyperlipidemia. On study day 379 this patient was found dead, with acute myocardial infarction being the attributed cause.

- death #22: **Death** Patient 189, Center 6. This 83-year-old caucasian male received clz at a final dose of 100 mg bid. His history included prior MI, and diabetes. On study day 130 he was admitted to a hospital with acute MI and pulmonary edema, at which time drug was discontinued. About a month later the patient, while at home, died a death whose cause was reportedly not defined. The previous MI was considered plausibly contributory.

- death #23: **Colon carcinoma** Patient 208, Center 21. This 51-year-old caucasian female received clz at a final dose of 100 mg bid.
Her history included cigarette use, and hyperlipidemia. The patient began experiencing severe nausea, vomiting, and diarrhea and drug was ultimately discontinued. She was diagnosed with obstructive metastatic carcinoma of the colon, and died as a result of this pathology on study day 251.

- death #24: **Myocardial Infarct** Patient 88, Center 43. This 68-year-old caucasian male received clz at a final dose of 100 mg bid. His history included CABG, cigarette use, diabetes, and hypothyroidism. On study day 29 he was admitted to the hospital with acute MI. The patient withdrew his consent to participate in the study and discontinued the drug on day 46. The following week he had another acute MI. About 2 months later he had unstable angina, and was found to have severe left main disease. He refused heart transplantation, ultimately went into cardiopulmonary arrest and died in cardiogenic shock secondary to myocardial infarction.

- death #25: **Cardiac arrest** Patient 39, Center 65. This 52-year-old caucasian male received clz at a final dose of 100 mg bid. His history included MI, hypertension, diabetes, and hypothyroidism. On study day 367 he presented at an emergency room with dyspnea. He developed respiratory arrest, was unsuccessfully rescuscitated, and had an unstable course before dying the next day. The cause of death was thought to be cardiac arrest secondary to acute MI, CHF, and arrhythmia.

- death #26: **Death, possibly sudden** Patient 163, Center 65.
This 67-year-old black male received clz at a final dose of 100 mg bid.
His history included CAD, angina, and hypertension. The patient was found dead in his auto on study day 171. Reportedly no further details are available.

- death #27: **Intracranial Bleed after thrombolysis for presumed MI**

Patient 169, Center 67. This 78-year-old caucasian male received clz at a final dose of 150 mg

This patient's medical history included multiple MIs, CAD, CHF, CABG, hypertension, and diabetes. On study day 115 the patient presented at the emergency room with chest pain. He was diagnosed with possible MI, and thrombolysis was performed. Later that day the patient experienced sudden intracranial hemorrhage and died.

11.3.5.5.5 **Dropouts in longterm study 21-91-201**

Table: 53

Subject dropouts thusfar reported in study 21-91-201, according to average total daily dose:

	≤100 mg/d CLZ	*100-200 mg/d CLZ*	*200-300 mg/d CLZ*	*>300 mg/d CLZ*
	n = 39	n = 803	n = 259	n = 4
Total dropouts	13 (33%)	286 (36%)	91 (35%)	4 (25%)
All dropouts, by reason:				
adverse event	7	148	37	0
lack of efficacy	2	36	26	0
noncompliance	0	16	6	1
general inability to continue	1	11	2	0
withdrew consent	0	6	6	0
failed screening	0	4	0	0
other	3	65	14	0

[source: interim analysis, pg 56, vol 203]

11.3.5.5.6 **Serious AE** (study 21-91-201)

ious treatment-emergent AE reported by ≥1% of patients were
ipheral vascular disorder (3%), MI (3%), vascular disorder (2%), angina (2%), CHF (2%), pain (1%), pneumonia (1%), chest pain (1%), and hernia (1%).

11.3.5.5.7 **Common AE in study 21-91-201**

Headache, pain, abnormal stools, diarrhea, and pharyngitis were each reported at a rate ≥ 10% in the total population, and showed tendencies to be related to dose.

11.3.5.5.8 **@Comments** (study 21-91-201)

a. The causal role of drug (if any) in the deaths observed in this study is generally ambiguous, given the absence of a controll, and the presence in this elderly population of potentially life-threatening (albeit drug-independent) factors.

b. In this longterm study the types of AE were similar to those observed in short-term trials.

c. Comparison of short and long-term studies for increase in frequency or severity with increased ation suggests that pain and pharyngitis were each common (rate ≥ 10%) only in the longterm ıal. Given the absence of a placebo control, the interpretability of this observation is limited.

11.4 Safety in studies of Heart Disease:

Limited safety data (limited in number, quality, and availability) are available from uncontrolled, open-label studies in patients with various types of heart disease. These are summarized below, and then discussed in some detail.

Table: 54

Summary of studies of Heart Disease

study #	*population*	*# enrolled*	*design*	*clz dose and duration*
21-89-002	NYHA class II-III CHF	60	uncontrolled, open-label	50 or 100 mg bid, 4 wk
21-89-008	CAD	43	uncontrolled, open-label	100 mg bid, ≥ 3 months.
21-89-010	CAD	8	uncontrolled, open-label	single 200 mg dose
21-90-001	CAD	10	uncontrolled, open-label	200 mg bid for 4 weeks
21-90-002-1	CAD	13	uncontrolled, open-label	50 mg bid for 4 weeks
21-90-002-2	stable angina and remote MI	10	uncontrolled, open-label	50 mg bid for 4 weeks
21-90-002-3	stable angina	17	uncontrolled, open-label	100 mg bid for ≥ 8 weeks
21-90-002-4	angina	10	uncontrolled, open-label	100 mg bid for 4 weeks
21-90-003	CAD	37	placebo-controlled, double-blind	50 mg bid for ≥ 3 months
21-90-004	CAD	46	positive-controlled, open-label	100 mg bid for ≥ 3 months

11.4.1 Heart Failure study 21-89-002

ese are the reported safety data in CHF patients[35] (albeit short-term, uncontrolled, and few in mber).

In this uncontrolled, open-label study cilostazol (50 or 100 mg bid) was administered to 60 patients with stable, mild to moderate CHF (NYHA class II-III) for 4 weeks. AE rates were assessed, as were changes from baseline NYHA class and systemic BP (compared via the signed rank test).

HR reportedly increased a mean of 8 bpm in the high dose group at week 4, but was without change from baseline in the low dose group. Reportedly, NYHA classification was improved in both groups in assocation with 4 weeks of drug exposure, while no significant changes were seen in systemic arterial BP.

In the low dose group, 7 AE were reported, as opposed to 25 AE in the high dose group. The drug-associated AE were described only qualitatively, as follows: headache, palpitation, increase in ventricular premature contractions, anemia, decreased BP, edema, subcutaneous bleeding, decreased WBC count, increase in LDH. There were reportedly no deaths.

4.2 Safety in CAD patients

11.4.2.1 CAD study 21-89-008

The reported results of this study are non-contributory to the assessment of this NDA. Safety information is reportedly unknown on the basis of no AE information being recorded on case report forms.

In this uncontrolled, open-label study 43 CAD patients undergoing PTCA were treated with cilostazole 100 mg bid for at least 3 months. Safety information is reportedly unknown on the basis of no AE information being recorded on case report forms. The restenosis rate was reportedly lower than the historical (40%) rate at the institution.

11.4.2.2 CAD study 21-89-010

This open-label, uncontrolled study treated 8 angina patients with a single 200 mg dose of cilostazol while measuring AE rates, central and peripheral hemodynamics (before and 30, 60 and 120-180 minutes after drug), and angiographic coronary luminal diameters.

[35] a population for which there is a plausible risk of adverse survival effect of this drug.

There were reportedly no AE. This dose was reportedly associated with coronary dilatation (after 2 hours) as well as quantitatively unspecified "marked" (not defined either) changes in pulmonary ›illary wedge pressure, stroke work index, systolic BP, and mean BP.

11.4.2.3 CAD study 21-90-001

The reported results of this study are non-contributory to the safety assessment for this NDA. Safety information is reportedly unknown on the basis of no AE information being recorded on case report forms.

In this uncontrolled, open-label study 10 CAD patients were treated with oral cilostazol 200 mg bid for 4 weeks. Ex-vivo platelet anti-aggregatory effects were measured. The study (reported in abstract form only) was said to demonstrate drug-associated inhibition of platelet aggregation.

11.4.2.4 CAD study 21-90-002-1

In this uncontrolled, open-label study 13 CAD patients with stable effort angina were treated with oral cilostazol 50 mg bid for 4 weeks. AE rates were assessed. In addition, the baseline and post-treatment (2 and 4 weeks) anginal attack and nitrate usage rates were captured by patient diaries. Treadmill exercise testing was performed at baseline and at 4 weeks post-treatment, with the lowing measurements obtained and analyzed by signed rank test: angina-limited exercise uuration, ST-segment depression, cardiac rhythm, and peripheral hemodynamics. The study was reported in abstract form only.

Headache and head numbness occurred in 1 patient each, but each resolved spontaneously.

Drug was reportedly associated with neither a worsening nor an improvement in angina-limited exercise tolerance (with respect to total exercise time, time to angina onset, or time to 1-mm ST-segment depression). The mean number of anginal episodes reportedly tended to decrease in association with drug exposure (from 5.1 times in the first week to 3.7 times in the fourth week), as did mean consumption of nitrates (from 2.2 tablets in the first week to 1.7 tablets in the fourth week). Resting heart rate (HR) and the product of BP and HR were reportedly significantly increased in association with treatment. There was no effect on HR at maximum work load. The product of BP and HR reportedly remained significantly increased at the time of maximum ST-segment depression, and at identical durations of exercise.

11.4.2.5 CAD study 21-90-002-2

In this uncontrolled, open-label study, 10 patients with stable angina and remote MI were treated ;h oral cilostazol 50 mg bid for 4 weeks. AE rates were assessed. In addition, treadmill exercise testing was performed at baseline and at unspecified time post-treatment, with the

following measurements obtained and analyzed by signed rank test: angina-limited exercise duration, ST-segment depression, cardiac rhythm, and peripheral hemodynamics. The study was ported in abstract form only.

One patient showed an increase in fasting blood sugar level, and the other 1 patient showed an increase in SGOT level. Reportedly, in association with treatment, resting heart rate tended to increase, as did total exercise time.

11.4.2.6 CAD study 21-90-002-3

In this uncontrolled, open-label study 17 patients with stable effort angina were treated with oral cilostazol 100 mg bid for at least 8 weeks (with a 22 week average duration of treatment). Six patients reportedly either dropped out or were removed because of protocol violations, and 11 were included in analyses. AE rates were assessed. In addition, treadmill exercise testing was performed at baseline and at unspecified times post-treatment, with the following measurements obtained and analyzed by signed rank test: angina-limited exercise duration, ST-segment depression, cardiac rhythm, and peripheral hemodynamics. The study was reported in abstract form only.

Eight AE were reported: headache, bleeding, chills, chest discomfort, heartburn, and shoulder ffness. In three subjects drug was discontinued for AE (headache, chill, or chest discomfort) at which time the events resolved. Resting heart rate tended to increase. Total angina-limited exercise duration did not change in association with treatment.

11.4.2.7 CAD study 21-90-002-4

In this uncontrolled, open-label study 10 patients with angina were treated with oral cilostazol 100 mg bid for 4 weeks. AE rates were assessed. In addition, treadmill exercise testing was performed at baseline and at unspecified times post-treatment, with the following measurements obtained and analyzed by signed rank test: angina-limited exercise duration, ST-segment depression, cardiac rhythm, and peripheral hemodynamics. The study was reported in abstract form only.

There were 3 AE reported (headache, leg edema, and mild constipation) in association with drug. During treatment, resting heart rate was higher than at baseline, but total angina-limited exercise duration did not change appreciably from baseline.

11.4.2.8 CAD study 21-90-003

The reported results of this study are non-contributory to the assessment of this NDA. Safety information is reportedly unknown on the basis of no AE information being recorded on case report forms.

For completeness, the following is noted:

This was a placebo-controlled, double-blind study in which 37 patients with coronary artery disease (CAD) patients received cilostazole 50 mg bid for a least 3 months in the pre- and post-PTCA setting. Coronary restenosis rates were reportedly comparable between groups.

11.4.2.9 CAD study 21-90-004

In this positive-controlled, open-label study 46 CAD patients undergoing PTCA were treated with oral cilostazol 100 mg bid for 3 or more months. AE rates and restenosis rates were assessed.

Among cilostazol-treated patients there were reportedly three who had palpitation, but without need for drug discontinuation. There was also a report of "slight" (undefined) decrease in WBC count and "slight" (undefined) increase in SGPT, neither of which required drug discontinuation. The cilostazol-treated patient had severe angina in the setting of restenosis. There was no apparent cilostazol effect on coronary re-stenosis rate.

11.5 Safety in Collagen vascular disease

Note that the laboratory data from subjects enrolled in several of the Japanese non-PVD studies present interpretive problems. Several such studies were conducted between 1982 and 1985, reportedly before the Japanese GCP had been established. The lab values were not measured centrally, rather the values at each site were classified with respect to normalcy by the attending investigator. The sponsor has not quality-controlled the accuracy of those classifications (relative to the local laboratory's normal range), and in some cases normal ranges have not been made available.

11.5.1 Collagen vascular disease study 21-90-901

In this placebo-controlled, double-blind study 167 subjects (patients with with cutaneous ulcers secondary to various collagen vascular diseases) received clz 50-100 mg bid, or placebo for 6 weeks. An abstract of the study describes that four patients were excluded from the safety analysis, for unidentified reasons. Headache, nausea and palpitation were reported. A 72.7% overall AE rate was observed in the 200-mg/d group; this was significantly higher than the rate for the other groups.