observed). The subject recovered well, and was known to be alive at 5.5 months post-randomization.

MI-attributed case C4:

strength of objective evidence for MI: *Convincing*

Patient 121, study 21-94-201, Center 79. This 65-year-old caucasian male (with history of hypertension and cigarette smoking) was randomized to CLZ 100 mg bid. After 106 days on study drug the patient experienced chest discomfort and was admitted to the hospital. Total CPK was 226 U/l, CK-MB was 13.0 ng/mL, and ruptured coronary plaque was found at angiography. Study medication was discontinued and his clinical course was uneventful. He was known to be alive at 8 months post-randomization.

clz MI-attributed case C5:

strength of objective evidence for MI: *Convincing*

Patient 484, study 21-92-202; Center 16. This 64 year-old caucasian male (randomized to clz 50 mg bid) had a history of CAD, CABG, and diabetes. Two days after randomization he had chest pain which was unrelieved by nitroglycerin, and was admitted to hospital where he was dyspneic and extremely diaphoretic. The EKG showed 3 mm ST elevation in leads 2 and V6, and markedly upright T waves in the anterior leads. CK levels rose to >2,000 u/L. Diagnosed with MI, his EKG the next day showed persistent elevated ST-T changes, and his course became unstable (including episodes of rapid ventricular tachycardia, and asystole), ultimately leading to death.

clz MI-attributed case C6:

strength of objective evidence for MI: *Convincing*

Patient 413, Center 43, study 21-94-201. This apparently 100 year old male had a history of CHF. The MI-attributed event occurred 23 days after he discontinued placebo-controlled exposure to CLZ in study 21-94-201.
This subject went on to continue CLZ use after that trial by enrolling in open-label study 21-91-201, and the MI-attributed event actually occurred during this subsequent open-label CLZ exposure[19]. Presenting with angina unrelieved by nitroglycerin, diaphoresis and dyspnea, he reportedly had a CPK of 300 and CK-MB of 30. There was no report of diagnostic EKG findings. He received open-label cilostazol (200-300 mg bid) over a span of 190 days. About 6 months after this MI he was reported (on the basis of unspecified criteria) to have another MI in the absence of EKG Q waves, and expired in CHF.

[19] he had the same identification code and center numbers in open-label study 21-91-201.

clz MI-attributed case C7:

strength of objective evidence for MI: *Convincing*

Patient 564, study 21-92-202, Center 12. This 68 year-old caucasian male (with history of angina, CABG, and pacemaker) was randomized to CLZ 50 mg bid. One month after randomization he was hospitalized with chest pain, and discontinued study medication. One day following catheterization (which detected multivessel CAD) he had an acute MI with electromechanical dissociation. Peak CK levels were 2200 U/L, with corresponding CK-MB level of 199 U/L. He was discharged and known to be alive at 7 months post-randomization.

clz MI-attributed case C8:

strength of objective evidence for MI: *Convincing*

Patient 245, study 21-94-201, Center 36. This 74-year-old caucasian male (with history of angina, PTCA, chronic atrial fibrillation, and hypertension) was randomized to the CLZ 100 mg bid group. After 66 days on study drug the patient presented to the emergency room with fever, chills and diarrhea. He had an irregular heart rate with atrial fibrillation. His initial CPK was 373 U/liter, and CK MB fraction was 17.7 ng/mL, with a CK isoenzyme index of 4.7%. Subsequent CPKs were not reported. He was admitted to the intensive care unit, and study drug was temporarily interrupted while he received anticoagulants. After improving he was discharged, and completed the study.

clz MI-attributed case C9:

strength of objective evidence for MI: *Suggestive* (conservatively)

Patient 146, study 21-92-202; Center 32;. 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.

Depending on one's assumptions this evidence can be considered suggestive of acute MI (as I have deemed it, in the interest of high sensitivity capture of all possibly drug-associated toxicity). Alternatively, the diagnosis could be considered debatable on the theoretical grounds that the clot might have been: i) productive of fatal electrical instability, in the absence of infarct.
ii) causally unrelated to the patient outcome (despite occurring pre-mortem).
ii) a post-mortem artefact.

clz MI-attributed case C10:

strength of objective evidence for MI: *Debatable*

Patient 359, study 21-92-202, Center 6. This 70 year-old caucasian male, was randomized to the CLZ 50 mg bid group. His medical history included CABG, angina, and hypertension. About 6

weeks post-randomization study medication was discontinued because of the following event: he experienced chest pain unrelieved by nitroglycerin, and had unspecified EKG changes and specified enzyme changes. These were apparently considered "indicative" of MI, but the objective basis for this determination is not clear. His course included transient asystole, and congestive heart failure. The patient was alive at the 6 month post-randomization observation.

clz MI-attributed case C11:

strength of objective evidence for MI: *Debatable*

Patient 241, study 21-92-202, Center 6. This year-old caucasian male was randomized to CLZ 100 mg bid. His past medical history included diabetes, and angina. Six weeks after randomization he presented to the hospital with persisting chest pain, and study medication was discontinued. The diagnosis of MI was based on an unspecified degree of persistence of chest pain, and a total CK elevation to 216 U/L. No information has been provided about the exact duration of chest pain, the nature of ST changes (although unspecified changes were reported), or MB fractions. He received a CABG and was discharged from the hospital. He was alive at the 6 month post-randomization followup.

clz MI-attributed case C12:

strength of objective evidence for MI: *Debatable*

Patient 0367, study 21-92-202; Center 11. This 74 year-old caucasian male with a history of multiorgan arterial disease, was randomized to clz 100 mg bid. He developed worsening exertional angina, and had angiographic evidence of coronary stenoses. After refusing revascularization the investigator discontinued study medication. Within a month the patient awoke one early morning with dyspnea, urinated and defecated in his bed, and died en route to the hospital. The objective basis for a diagnosis of MI is not clear.

clz MI-attributed case C13:

strength of objective evidence for MI: *Debatable*

Patient 144, study 21-94-203; Center 68. This 77 year old caucasian female (randomized on 4/19/95 to clz 100 mg bid) had a history of cigarette use, hypertension, and hypothyroidism. About 2 months post-randomization she experienced chest pain and received a diagnosis of acute MI. The objective basis for this diagnosis was not described. She was given thrombolytic therapy, and became hypotensive, and asystolic, and died.

clz MI-attributed case C14:

strength of objective evidence for MI: *Debatable*

Patient 0014, study 21-95-201, Center 81. This 51 year-old caucasian female (with history of cigarette use, and hypertension) was randomized to CLZ 150 mg bid. The day after randomization she was hospitalized for chest pain and received a diagnosis of acute MI (by unspecified criteria). Catheterization showed an occluded right coronary artery (it is not clear whether fresh thrombus was observed). She dropped out of the study about 2 weeks post-randomization. She was known to be alive 6 months post-randomization.

clz MI-attributed case C15:

strength of objective evidence for MI: *Debatable*

Patient 224, Center 2, Study 21-90-201. This 62 year old white male (with history of smoking, TIA, and hypertension) was randomized to clz 100 mg bid. He was admitted to hospital about one month post-randomization. The EKG reportedly showed a "suggestion of questionable small Q waves" in leads II, III, and AVF. At one point the investigator apparently attributed these findings to an MI, but the attending physician apparently indicated on the medical record that the patient had not experienced an MI. The patient was withdrawn from the study. He was known to be alive at the end of the study period.

clz MI-attributed case C16:

strength of objective evidence for MI: *Debatable*

Patient 487, Center 28, Study 21-92-202. This 67 year-old caucasian male (with history of angina, MIs, CABG, hypertension, and hyper-cholesterolemia), was randomized to CLZ 50 mg bid. Four days after randomization he experienced intermittent chest pain unrelieved by nitroglycerin. EKG showed some transient "accentuation" of ST depression in antero-lateral leads. His CPK level peaked at 359 U/L. CK-MB fraction was not reported. He received a diagnosis of non-Q wave anterior MI. Study drug was temporarily discontinued. The patient completed the study.

clz MI-attributed case C17:

strength of objective evidence for MI: *Debatable*

Patient 433, study 21-94-201, Center 81. The only datum supportive of the diagnosis was a CPK level of 775 (the CK-MB band fraction was not specified, no ST elevation was noted, no description of any EKG Q waves was made (the EKG is reportedly unavailable), and the duration of chest pain was not specified). By the Executive Committee's definition, this event failed to meet the criteria for classification as MI. For unclear reasons, the Executive Committee did classify this case as MI.

The further details of this case are as follows: this 45-year-old caucasian male (with history of hyperlipidemia, and cigarette smoking) was randomized to CLZ 100 mg bid. After 204 days on study drug the patient experienced an event which was considered an MI by the investigator. Study drug therapy was discontinued while he was admitted to hospital. He underwent PTCA with placement of stents, and was known to be alive at 7 months post-randomization.

clz MI-attributed case C18:

strength of objective evidence for MI: *Debatable*

Patient 0039, study 21-95-201, Center 87. This 53 year-old caucasian male (with history of (stable angina, and cigarette use) was randomized to CLZ 150 mg bid group. A routine EKG was diagnosed (on unspecified grounds) as new MI compared to one obtained two weeks prior. The patient denied any chest pain or shortness of breath. He reported that since starting the study drug he experienced a rapid heart beat, but that this had become less pronounced. The patient was discontinued from the study because of this event. A cardiologist subsequently suspected that the EKG finding was an artefact based on reversal of arm leads. He was known to be alive at the end of the study period.

clz MI-attributed case C19:

strength of objective evidence for MI: *Debatable*

Patient 261, study 21-94-201, Center 34. The event attributed as an MI by the investigators was deemed not an MI by the adjudicating Executive Committee because it failed to meet any of the criteria for duration of chest pain, ST elevation, total CPK level, or fraction of MB bands. This 61-year-old caucasian male (with history of hypertension, hypercholesterolemia, and smoking tobacco) was randomized to the CLZ 100 mg bid group. After 6 days on study drug the patient was admitted to the hospital with complaints of chest pain, diaphoresis, and dizziness. The investigator's impression was that of a non-Q wave myocardial infarction. Study drug therapy was discontinued, and angiography revealed severe aortic stenosis and single vessel CAD. He successfully underwent aortic valve replacement and CABG, and was discharged to home in stable condition. He was known to be alive at about 6 months post-randomization.

clz MI-attributed case C20:

strength of objective evidence for MI: *Debatable*

Patient 0503, center 2, study 21-94-301. This 58-year-old caucasian male (with history of MI, angina, CHF, atrial fibrillation, and diabetes) was randomized to CLZ 100 mg bid. Three weeks post-randomization he was hospitalized with a diagnosis of severe acute MI. The diagnosis was reportedly based on EKG and cardiac enzyme findings, but the actual data supporting the diagnosis were not submitted. Study drug was discontinued, and he was discharged about 10 days later, and known to be alive at 5.5 months post-randomization.

clz MI-attributed case C21:

strength of objective evidence for MI: *Debatable*

Patient 0544, center 12, study 21-94-301. This 59-year-old caucasian male (with history of MI, aortic aneurysm, and diabetes) was randomized to CLZ 100 mg bid. About 10 weeks post-randomization he was hospitalized and diagnosed with myocardial infarct. The objective basis of the diagnosis is reportedly currently unavailable to the sponsor. He dropped out of the study, received streptokinase and aspirin and was discharged from hospital. He was known to be alive at 6 months post-randomization.

clz MI-attributed case C22:

strength of objective evidence for MI: *Debatable*

Patient 7879, Center 006; study 21-96-202. This 85 year old caucasian male (with history of prior MI, and hypertension) was randomized to CLZ 100 mg bid. On post-randomization day 103 the patient was withdrawn from the study drug and hospitalized after a 5 day history of dyspnea and possible CHF. He was reportedly diagnosed with an MI the following day. The objective basis for this diagnosis is reportedly not available. He was known to be alive 6 months post-randomization.

clz MI-attributed case C23:

strength of objective evidence for MI: *Debatable*

Patient 9008, Center 091; study 21-96-202. This 67 year old black male (with a history of PTCA, angina, CHF, hypertension, hypercholesterolemia, and diabetes) was randomized to CLZ 100 mg bid. On post-randomization day 24 he was found dead in home, apparently having died while sleeping. No autopsy was performed. Death was attributed to MI (although the objective basis for this was not described) and CAD. He was known to be alive 6 months post-randomization.

LATE MIs: In both the CLZ and placebo groups there was one additional acute MI occurring late, i.e. beyond 30 days post-discontinuation of drug.
The placebo case of late MI was as follows: Patient 0486, Center 22; study 21-94-301. This 77-year-old placebo-receiving caucasian male had a history of hypertension, transient ischemic attack, and cigarette use. Three weeks after randomization he withdrew because of groin pain. About 3 months later he experienced a fatal event that was putatively an MI. The objective basis for this event attribution has not been reported.

CLZ case of late MI was as follows: study 21-95-201; Patient 60; Center 91. This 71 year old caucasian female (with history of CHF, hypercholesterolemia, diabetes, and lymphoma) was

randomized to clz 150 mg bid). Three days after randomization she discontinued study medication because of epistaxis. About 10 weeks after randomization, in close temporal ociation with administration of prochlorperazine for post-chemotherapy nausea, she developed ...iat was believed to be a dystonic reaction. On arrival at the emergency room she was hypotensive and in complete heart block. Troponin and CK levels reportedly suggested significant acute MI. The MB fraction was 4.4%. She remained dependent on pressors and pacing, and subsequently died 77 days after discontinuing treatment.

11.2.5 Pooled Composite morbidity/mortality endpoint

2.5.1 Summary background

Pooling the 2 submitted placebo studies which prespecified both this combined endpoint and the adjudication thereof (21-92-202 and 21-94-201), the sponsor reported the following results. They excluded study 21-94-301 from this pooling because those data were not adjudicated (the unpooled results of the combined endpoint in 21-94-301 are separately presented below). The subjects observed in this two study subset comprise 44.5 and 30.7% of the total sample of cilostazol and placebo subjects, respectively, in all 8 placebo-controlled phase III studies.

For the convenience of the reader, the principal design features of these two studies (described elsewhere in the efficacy section of this report) will be re-iterated here:

11.2.5.2 Pertinent elements of study 21-92-202 design

This was a concurrent placebo-controlled, double-blind, parallel-group study which randomized 516 subjects (atherosclerotic PAD patients with moderately severe, stable, intermittent claudication) to receive placebo, or cilostazol given as a fixed 100 vs 200 mg/d dose in equally-divided twice-daily oral administrations for 24 weeks.

Pertinent exclusions from enrollment were subjects with history or current evidence of concomitant exercise-limiting disease other than intermittent claudication. The sponsor specified that for example, there was to be exclusion of such conditions as congestive heart failure (CHF), myocardial infarction (MI) within 6 months or incomplete recovery from an MI which occurred > 6 months previously, symptomatic cardiac arrhythmias, angina pectoris, and orthopedic conditions.

The prespecified primary safety endpoint was the assessment of a combined morbidity/mortality endpoint using standard life table analyses, with adjustment for covariates using the proportional hazards model. The analysis employed a temporal hierarchy when counting events; first events were the only ones included, irrespective of the seriousness of the event (relative to that of any subsequent event).

The components of the composite endpoint were:

- all-cause death
- myocardial infarct (MI): the definition of MI was just as described above in subsection of this Safety section, entitled "MIs: Classification Schema". For convenience thise re-iterated here:

Though the protocol specified no precise definition for MI, the Executive Committee ultimately generated diagnostic criteria (reportedly while blinded, and prior to any analysis (even a blinded

one)). The schema intended to capture both acute MIs, and non-acute or asymptomatic MIs. MIs were to be counted, irrespective of whether acute, remote, or silent: An event was to be classified acute MI when the subject manifested at least 2 of the following 3 criteria: central chest discomfort for 30 minutes; ≥0.1 mv ST segment elevation in at least 2 contiguous leads; total CPK ≥150% of the ULN with ≥3% MB CPK. An event was to be classified as silent or remote MI when pathologic Q waves were evident in at least 2 contiguous leads. Q waves were to be considered pathologic if they meet the following criteria: Leads I, II, aVF: .04 seconds in duration, > .2 mv amplitude and > 25% of the amplitude of the succeeding R wave; Lead aVL: .04 seconds in duration, > .2 mv amplitude and > 15% of succeeding R wave; Leads V4-V6: .04 seconds in duration, > .2 mv amplitude and > 15% of succeeding R wave; Lead III: similar to Lead I criteria, but only important if leads II and aVF are also abnormal.
- stroke: defined as neurological deficit ≥ 24 hours and confirmed by angiography, computed tomography, or magnetic resonance imaging.
- revascularization of a central or peripheral artery.
- amputation for worsening arterial status.

11.2.5.3 Pertinent elements of study 21-94-201 design

This was a concurrent placebo-controlled, double-blind, parallel-group study which randomized 394 subjects (peripheral atherosclerosis patients with moderately severe, stable, intermittent claudication) to receive placebo, or cilostazol given as a fixed 100 vs 200 mg/d dose in equally-divided twice-daily oral administrations for 24 weeks.

Pertinent exclusions from enrollment were subjects with exercise-limiting cardiac disease. The sponsor specified that for example, there was to be exclusion of such conditions as recent (within 6 months) MI or PTCA or CABG or hospitalization for angina, symptomatic cardiac arrhythmias, exercise-limiting CHF, current exercise-limiting angina pectoris, or angina at rest.

Among the prespecified secondary outcome variables was a composite endpoint including:
- all-cause mortality;
- MI
- stroke
- arterial revascularization
- amputation

For the composite mortality/cardiovascular morbidity endpoint, the Executive Committee reportedly recorded up to three events for each patient, classified by onset as first, second, and third events. Kaplan Meier estimates were based on the time to the first occurrence of one of these events. The protocol provided no definitions for the individual components of the cardiovascular morbidity endpoint. The Executive Committee defined these (reportedly while blinded, and prior to any analysis, even a blinded one) as follows:

- MIs were to be counted, irrespective of whether acute, remote, or silent. The criteria used for ssification of events as MI (and the post-protocol generation of these criteria by the Executive ommittee) were the same as described above for study 21-92-202.
- Stroke: defined as any cerebral vascular infarct that causes at least transient symptoms.
- Arterial revascularization: defined as any undertaken on a peripheral or central artery (including endarterectomy, and stent placements, with the exception of lower extremity stents).
- Amputation: for reason other than trauma or tumor.

The following were the methods of capturing morbidity/mortality outcomes 24 week post-randomization in subjects who dropped out: In study 21-92-202 the CRF contained a page (called "post termination contact") in which the survival status was to be recorded, along with the dates of serial contact with the subject (intended to be every 30 days post-termination, until 24 weeks post-randomization or death occurred). This form did not elicit the recording of any of the specified nonfatal morbid events (MI, stroke, arterial revascularization, or amputation). Another form (called "unscheduled vital signs") served to elicit the description of intervening adverse events. In study 21-94-201 the CRF combined into one form (called "post termination contact") the functionality of these two forms used in study 21-92-202.

11.2.5.4 Results of pooled composite endpoint analysis

The mean exposure duration was 127.8, 126.9, and 122.1 PEY in the placebo, CLZ 50 mg bid, and CLZ 100 mg bid groups, respectively.

There were small imbalances in the numbers of dropouts among treatment groups. The mean rate of all dropouts was 16.7%, 17.5%, and 23.7% in the placebo, CLZ 50 mg bid, and CLZ 100 mg bid groups, respectively. The mean rate of dropouts for AE was 10.7%, 13.5%, and 17.9% in the placebo, CLZ 50 mg bid, and CLZ 100 mg bid groups, respectively.

There was incomplete followup for the composite mortality/morbidity endpoint (recall that the protocol's intention was to capture immediately at the end of post-randomization week 24 the mortality/morbidity status of those subjects who dropped out prior to week 24). In study 21-92-202 there was one clz-randomized subject (assigned to 100 mg/d)[20] and zero placebo-randomized subjects in whom the final mortality/morbidity status was not captured; an additional 3 (0.9%) clz-randomized and 4 (2.4%) placebo-randomized subjects had their last known mortality/morbidity status captured prior to the intended final followup (which was supposed to be at post-randomization week 24). In study 21-94-201 reportedly all subjects had their final survival status captured.

[20] this was subject 451.

Considering all deaths occurring up to 30 days after cessation of treatment, irrespective of whether death was the first event, in these 2 studies there were reported among clz-randomized jects a total of 9 deaths (crude rate of 0.9%). This point estimate is comparable to that obtained in placebo-treated patients (0.8%). After correction for duration of exposure, the adjusted mortality was 2.4 deaths per 100 patient exposure years in the placebo group, 1.6 in the clz 100 mg/d group, 3.0 in the clz 200 mg/d group, and 8.1 deaths per 100 patient exposure years in the cilostazol 300 mg/d group.[21]

Beyond 30 days post-treatment, two additional deaths occurred in the placebo group and two additional deaths were reported among cilostazol-treated subjects. One of the clz deaths occurred at 139 days due to cerebral hemorrhage in a patient who had received 200 mg/d (patient 40/study 92-202), and the other (at 79 days post-treatment) was attributed to MI in a patient who had received clz 300 mg/d (patient 60/study 95-201).

Results of a pooled analysis of only first events (death or cardiovascular morbidity, irrespective of the morbid event's contribution to subsequent mortality[22]) are shown in the table below. The log-rank test on the composite endpoint reportedly showed no statistically distinguishable differences among the treatment groups (p=0.86). Considering component endpoints, there was a statistically nonsignificant tendency towards a dose-related increase in number of MIs (p=0.17).

Because of the relatively small sample size (n= 73) and brief exposure duration (12.4 patient exposure years) the nt estimate in the highest dose group is not a compelling basis of inference.

[22] with this analysis only deaths unpreceded by any cardiovascular morbid event were counted as deaths, whereas deaths preceded at any time by cardiovascular morbid events were counted as morbid events.

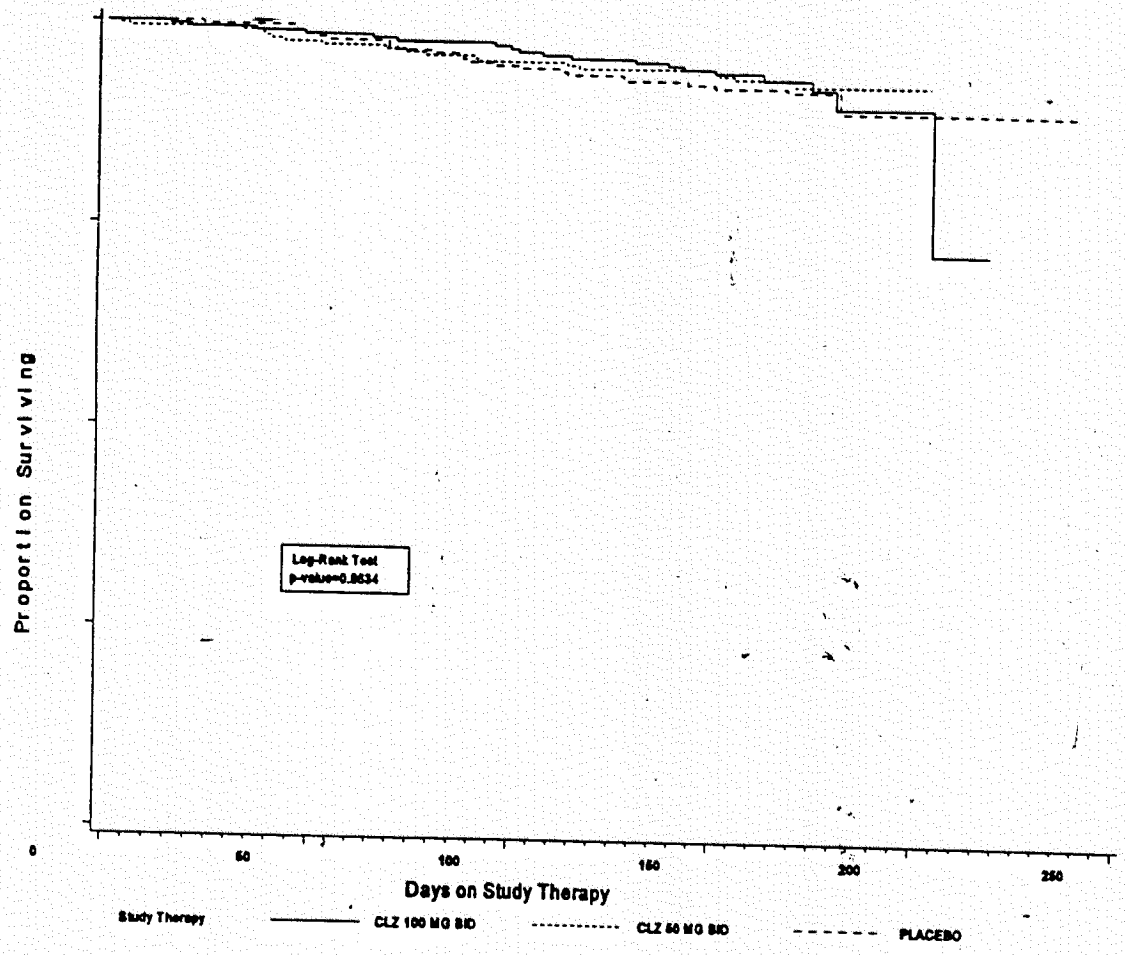
Table: 47

Reported number and crude rate of first events
(pooling studies 21-92-202 and 21-94-201)

event	*Placebo* n= 299		*CLZ 50 mg bid* n= 303		*CLZ 100 mg bid* n= 308	
all-cause Death	2	0.67%	1	0.33%	4	1.30%
MI	2	0.67%	4	1.32%	6	1.94%
Stroke	4	1.3%	2	0.66%	3	0.97%
Arterial revascularizations	14	4.7%	12	4.0%	7	2.3%
Amputation	1	0.33%	0	0%	0	0%
ANY FIRST EVENT	23	7.69%	19	6.27%	20	6.49%

[source: pg 146, vol 264]

Figure: 22
Kaplan-Meier estimate of Cumulative probability of cardiovascular morbidity/all-cause mortality
(pooling studies 21-92-202 and 21-94-201)



[source: original ISS, vol 264, pg 148]

11.2.5.5 @Comments (pooled composite endpoint analysis):

There are analyses of both deaths and MIs, presented earlier in this review, which are more informative than the present one. Those pool, not just the 2 trials pooled here, but 8-12 placebo-controlled studies. With respect to the analysis of deaths, there is an additional advantage to the earlier presented analysis of deaths (other than that related to power). The earlier analysis, unlike the present one, is not subject to the filtering that can (and did[23]) occur, i.e. the filtering of fatal events that are non-first events.

b. The present 2 study pooling found, within the limits of its power, no statistically distinguishable adverse drug effect on the composite endpoint in an essentially CHF-free population. With this 2 study pooling, after conservatively imputing a death for the 1 clz case lost to followup in study 21-92-202,[24] the crude mean all-cause death rate is 1.0% in the pooled clz groups vs 0.67% in the placebo group. There is also a numerically larger crude mean rate of MIs in both clz groups, relative to placebo.

c. At its nominal level of power this analysis overestimates the pragmatically important level of power. Assuming that there is no compelling basis for hypothesizing drug effect on the rate of arterial revascularizations[25], and given that the component endpoint which contributed the most events to the composite was arterial revascularizations, one would be concerned that the advertent result of including this component was a sort of "power padding".

d. The nominal power of this analysis was not clearly described, but there is reason to be concerned with the potential for underpowering. Study 21-94-201 was designed without powering it for discrimination of adverse effect on mortality/cardiovascular morbidity; it was powered for detection of anti-claudication effect. Secondarily, in study 21-92-202 it is not clear what power calculation assumptions were made about the rate of subject attrition; the known assumptions were a 10% composite event rate in placebo patients over 24 weeks, 80% power, detection of a doubling of event rate, two-sided alpha level of 0.05.

e. These studies excluded patients with cardiovascular disease that symptomatically limited exercise tolerance for reasons other than claudication. Although a reasonable strategy (insofar as it supported the claudication endpoint's validity), an important information vacuum has resulted. Risk in cardiac disease populations is not described, whereas previous experience with PDE inhibitors suggests that among the excluded population (CHF patients in particular) are groups plausibly at risk of cilostazol-mediated morbidity/mortality.

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[23] Two of the eventual deaths were classified, not as death, but rather as morbid events (i.e. a stroke in patient 40, an MI in patient 484).

The possibility that additional cases failed to have final outcome captured is still under evaluation.

[25] an assumption supported by the absence of convincing demonstration (to my knowledge) of drug effect on this endpoint in appreciable prior experience with PDE inhibitors.