The AE-associated dropouts in the 8 largest placebo-controlled studies were as shown in the next table. The mean rate of dropouts for nonfatal treatment emergent AE was higher in the clz-treated groups (ranging from 12.5-23.3%) than in the placebo group (8.1%), and the rate of dropouts for any nonfatal AE showed a monotonic relationship to dose. These findings are based on an analysis in which only up to one AE is counted for each subject. Investigators were reportedly asked to list one AE as the cause of withdrawal in cases were more than one was present.

Table: 44

Crude mean rate of those nonfatal *AE-associated* dropouts which showed a monotonic dose-relationship

(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 nonfatal AE	8.1%	12.5%	13.2%	23.3%
Headache	0.3%	1.3%	2.6%	6.8%
Syncope	0%	0%	0.1%	1.4%
Diarrhea	0.2%	0.3%	0.5%	4.1%
Anxiety	0%	0%	0.1%	1.4%

[source: pg 30, submission 7/6/98-A

For certain of the discrete AE (i.e., headache, diarrhea, and palpitation) the rates of dropping out were dose-related. Headache-associated dropout occurred at rates of 1.3%, 3.7%, and 6.8%, respectively in the low, medium and high dose cilostazol groups, while at a 0.3% rate in the placebo group. Diarrhea-associated dropout occurred at rates of 0.3%, 0.8, and 6.8% respectively in the low, medium and high dose cilostazol groups, while at a 0.4% rate in the placebo group. Palpitation-associated dropout occurred at rates of 1.0, 1.0, and 2.7%, respectively in the low, medium and high dose cilostazol groups, while at a 0.1% rate in the placebo group. Tachycardia-associated dropout was relatively uncommon (there was one case each in every one of the treatment groups, including placebo). Arrhythmia reportedly did not result in the dropping out of any cilostazol-randomized subject.

Only rarely (n=1 CLZ subject and 2 placebo patients) was there a dropout which was not classified among the treatment emergent cases. This happened when discontinuation was for an AE that

received the same severity classification as a previous occurrence of this AE (and for that reason was not captured among the "treatment emergent").

.2.3 Serious adverse events other than MIs

This section discusses the reported rates of serious treatment-emergent AE other than myocardial infarctions (MIs), irrespective of whether resulting in dropout. MIs will be described separately in a subsequent section of this report because of the need to additionally qualify methodologic and interpretive aspects.

Pooling the 8 largest placebo-controlled studies, the sponsor provided a descriptive analysis of serious AE according to the following method: when more than one serious event occurred in a given patient each such event was counted, irrespective of whether the subject ultimately died or not (i.e. no temporal or event-severity hierarchies were applied). Below I present salient results:

Table: 45

erious treatment-emergent events (other than MIs) for which the placebo crude rate was exceeded in any clz group

(pooling the 8 largest placebo-controlled studies)

Event	CLZ 100 mg/d [n=303]		CLZ 200 mg/d [n=998]		CLZ 300 mg/d [n=73]		**Placebo** [n=973]	
	#	crude mean rate	#	crude mean rate	#	crude mean rate	#	crude mean rate
Chest pain	3	1.0%	10	1.0%	2	2.7%	8	0.8%
Peripheral vascular disorder	7	2.3%	12	1.2%	0	0%	12	1.2%
Ventricular tachycardia	0	0%	3	0.3%	1	1.4%	2	0.2%
Syncope	0	0%	2	0.2%	1	1.4%	3	0.3%
Atrial fibrillation	0	0%	6	0.6%	1	1.4%	2	0.2%
Angina	4	1.3%	9	0.9%	1	1.4%	7	0.7%
Dyspnea	3	1.0%	5	0.5%	1	1.4%	4	0.4%
Pyelonephritis	2	0.7%	0	0%	0	0%	0	0%
CHF	1	0.3%	6	0.6%	0	0%	5	0.5%
Pneumonia	1	0.3%	6	0.6%	0	0%	2	0.2%
Dizziness	1	0.3%	2	0.2%	0	0%	2	0.2%
skin cancer	3	1.0%	3	0.3%	0	0%	1	0.1%
Urinary tract infection	1	0.3%	1	0.1%	0	0%	0	0%

[source: pg 16, submission 35, 5/22/98]

When more than one serious event occurred in a given patient, each such event was counted, irrespective of whether the subject ultimately died or not.

The placebo crude mean rate of ventricular fibrillation (0.2%) was not exceeded by the rate in any clz group (these rates being 0%, 0.1%, and 0%, in the CLZ 100 mg/d, CLZ 200 mg/d, and CLZ

300 mg/d, respectively). Neither was the placebo crude mean rate of stroke (0.5 %) exceeded by the rate in any clz group (these rates being 0.3%, 0.5%, and 0% in the CLZ 100 mg/d, CLZ 200 'd, and CLZ 300 mg/d, respectively).

As for the apparent treatment group differences shown in the above table, for some the sponsor submitted results of statistical testing. These showed that with respect to ventricular tachycardia, CHF[5], and syncope[6] the trends towards adverse drug effect were not statistically certain. Ninety-five percent confidence intervals around the estimated rates were overlapping, even after adjusting for patient-exposure-years[7].

This is not to say that a causal relationship between clz exposure and the development of some of these serious AE is not plausible (e.g., its sympathomimetic effect could clearly contribute to such things as angina, atrial or ventricular arrhythmia, etc), but simply that the play of chance cannot be ruled out as the source of the apparent differences between drug and placebo in this sample of modest size.

The individual case accounts of AE among clz-exposed subjects provided useful qualifying information, as follows:

- the one case of ventricular fibrillation was plausibly caused by factors other than drug (i.e. occurring in the immediate post-CABG setting).
- the 4 reported cases of ventricular tachycardia (VT), 2 were documented to be nonsustained, one was documented to be just minimally sustained, and the 4th case has not been described with adequate detail to exclude sustained VT.
- I have evaluated the 3 cases of reported syncope[8], and find little objective basis for either implicating or ruling out an underlying ventricular arrhythmia in 2 of those cases. The third case (Patient 003, study 21-92-202, Center 038) was plausibly atributable to underlying sinus node disease (in a 75 year-old male with past history of syncope, and eventual need for permanent pacemaker insertion).

These are the salient case narratives for the potentially more serious AEs among clz-treated subjects:

event: *Ventricular fibrillation*

This was a case of post-CABG ventricular fibrillation. Study 21-93-201, Patient 59; Center 39. This 70 year-old caucasian male (with history of cigarette use, hypertension, and paroxysmal atrial tachycardia) was randomized to CLZ 100 mg bid.. About 3 months post-

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[5] these were cases of CHF which required hospitalization.

cused on here because of the possibility of being a symptom of ventricular proarrhythmia.

per the submission dated 4/14/98.

[8] these being: Patient 003, study 21-92-202, Center 038; Patient 083, Study 21-92-202, Center 16; and Patient 122, Study 21-95-201, Center 68.

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.

event: *nonsustained ventricular tachycardia*

study 21-92-202, Patient 450, Center 6. This 75 year-old caucasian male (with history of occasional PVCs and CAD) was randomized to CLZ 100 mg bid. About 5 months after randomization he was hospitalized with nonsustained ventricular tachycardia (VT) which was apparently largely asymptomatic. He discontinued study drug[9], and his usual amiodarone dose was increased. The nonsustained VT resolved in association with the altering of these drug variables.

event: *nonsustained ventricular tachycardia*

study 21-95-201, Patient 116, Center 75. This 76 year-old caucasian male (with history of arrhythmia, palpitation, CHF, CAD, MI, PTCA, hypertension, and diabetes) was randomized to CLZ 150 mg bid. About 2 weeks post-randomization a Holter monitor showed 373 runs of non-sustained ventricular tachycardia (VT), while the pre-treatment Holter showed only one 4-beat run of VT. The patient was thus withdrawn from the study. Four days after discontinuation of clz a provocative electrophysiologic (EPS) study showed EPS-provocable AV nodal reentry tachycardia and monomorphic VT. The patient was initiated on sotalol, but remained EPS-provocable upon retesting. An implantable cardioverter/defibrillator was implanted.

event: *nonsustained ventricular tachycardia*

study 21-94-203, Patient 227, Center 21. This 77 year-old Caucasian male (with history of MI, CABG, and hypertension) was randomized to cilostazol 100 mg b.i.d. The patient was hospitalized about 2 months post-randomization with a two-week history of dizziness not associated with postion or excessive exertion. He was discovered to have nonsustained ventricular tachycardia, and was discharged with plans to follow up with electrophysiologic assessments. Study medication was not interrupted, and he completed the study.

Event: *unspecified ventricular tachycardia*

study 21-94-201, Patient 230, Center 43. This 67-year-old caucasian male (with history of hypertension, angina, carotid stenosis, and renal artery bypass) was randomized to CLZ 100 mg bid. After 97 days on study drug he was admitted hospital in acute CHF and study drug was discontinued. Three days after the last dose, an unspecified ventricular tachycardia was revealed on Holter monitor. The record makes no mention of arrhythmic instability or need for cardioversion. He was started on amiodarone afterwhich he improved and was discharged to home. He was known to be alive at the 6 month post-randomization followup.

[9] this dropout was incorrectly classified by the sponsor as a completer.

Event: *severe supraventricular tachycardia*

dy 21-94-301, Patient 0641, Center 004. This 66 year old caucasian female was randomized to CLZ 100 mg bid. Her history included palpitations, hypertension, hypercholesterolemia, and cigarette use. On day 4 the patient had a sudden onset of severe palpitations. Ambulatory 24-hour EKG findings were negative and the patient continued on study. About 3 months post-randomization she collapsed during another prolonged attack of severe palpitations, and paroxysmal atrial fibrillation was diagnosed at hospitalization, at which time study drug was discontinued.

She was then found to have hyperthyroidism, and received medical therapy for SVT and for hyperthyroidism. Medical records do not report any subsequent symptomatic reccurrence (although Holters have revealed asymptomatic atrial fibrillation).

Other infrequent, but nonetheless serious AE (not described in the table above) are noted in the below narratives[10].

There were 4 reports of serious AE that involved bleeding phenomena. One was the death already cited above (and re-iterated here for the convenience of the reader). These cases were as follows.

bleeding event B1[11]: **Fatal 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 was hospitalized with a ruptured thoracic aneurysm. He became hypotensive, and required emergency thoracotomy. A large quantity of blood was evacuated from the left chest. Aneurysm repair 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.

bleeding event B2: **GI hemorrhage**

study 21-92-202, Patient 438, Center 3. This 56 year-old caucasian male (with history of daily alcohol use, cholecystectomy, hemorrhoidectomy, diabetes, and hypertension), was randomized to the CLZ 100 mg bid group. About 3 months after randomization he was hospitalization with lower gastrointestinal hemorrhage in the setting of diagnosed diverticulosis. He reportedly recovered with no treatment, and was known to be alive 6 months post-randomization.

[10] here I have culled data from all placebo trials, not just the largest 8 such trials.
[11] this was described above as death C10.

bleeding event B3: **Post-catheterization retroperitoneal bleed**

study 21-94-201, Patient 362, Center 78. This 60 year old black male (with history of CAD and peripheral arterial revascularizations) was randomized to CLZ 50 mg bid. After 151 days on study drug he developed severe pain in the right foot, and an iliac artery thrombus was found at catheterization. CLZ was discontinued, whereupon warfarin, urokinase, and aspirin were administered. Two days after discontinuation of CLZ, the patient experienced a retroperitoneal bleed. He was last known to be alive at 7 months post-randomization.

bleeding event B4: **Hematuria**

study 21-96-202; patient 2907; Center 006. This 66 year old caucasian female (randomized to CLZ 100 mg bid) had a history of adenocarcinoma of the endocervical canal, hypertension, hypercholesterolemia, pulmonary hypertension, and emphysema. Since receiving radiation therapy for endocervical carcinoma she reportedly has had a history of episodic hematuria. About 4 months post-randomization she was admitted to the hospital with hematuria, and withdrawn from clz. Cystoscopy noted marked telangiectasia and edema of the bladder, considered evidence of hemorrhagic cystitis. About 2 weeks later, reportedly non-serious microscopic hematuria was noted. The patient recovered with treatment.

Other infrequent, serious AE were:

event: *Leukopenia*

study 21-94-201, Patient 186, Center 11. This 51-year-old caucasian male (with history of Wegener's granulomatosis and secondary chronic renal insufficiency) was randomized to CLZ 100 mg bid. After approximately 56 days of drug exposure his white blood cell count (the normal range of which was 3,800 to 10,800/μL) reportedly decreased from a pre-treatment level of 7,600/μL to 2,000/μL in association with increased cough, nausea, and vomiting. He reportedly recovered, and completed the study (although there was an intervening period in which he stopped the study medication because of nausea and vomiting).

event: *Allergic reaction*

study 21-86-103, patient 12. After 3 days of cilostazol exposure this male patient developed generalized edema, tachycardia, shivering and dyspnea. This was diagnosed (on the basis of unspecified criteria) to be an allergic reaction. His condition returned to normal 2 hours after the administration of cortisol. No additional details were submitted about this case.

Hospitalization rates are shown in the following table.

Table: 46

Crude mean rate of hospitalization, according to body system
(pooling the 8 largest placebo-controlled studies)

body system	*Placebo [n=973]*	*CLZ 50 mg bid [n=303]*	*CLZ 100 mg bid [n=998]*	*CLZ 150 mg bid [n=73]*
any	13.6%	18.2%	14.3%	16.5%
whole body	2.5%	2.3%	1.7%	4.1%
cardiovascular	7.3%	8.9%	8.0%	9.6%
digestive	1.5%	0.67%	0.4%	0%
hem/lymphatic	0%	0.33%	0.1%	0%
metabolic/nutrit	0.5%	0.67%	0.7%	0%
musculoskeletal	0.1%	0%	0.2%	0%
nervous	0.4%	0.99%	0.3%	1.4%
respiratory	0.8%	2.3%	1.2%	1.4%
skin/appendages	0.2%	0%	0.3%	0%
special senses	0%	0%	0.3%	0%
urogenital	0.3%	2.0%	1.1%	0%

[source: table 17, appendix IX, submission 7/6/98-"A"]

11.2.4 Myocardial Infarctions

2.4.1 Background summary

Pooling the 8 largest placebo-controlled studies, the sponsor generated an analysis of MI rates in all placebo-controlled IC studies. Note that in only 3 of these (21-92-2020, 21-94-201, 21-94-301) did the MI event classification method involve standardized diagnostic criteria, and that in only 2 of these (21-92-202, 21-94-201) was the endpoint centrally adjudicated.

In the additional 4 small placebo-controlled studies (21-87-101, 21-86-103, 21-86-101, and PUIC-2) no events were attributed as MI or "heart attack" (in the context of trial designs which did not employ standardized diagnostic criteria or centralized endpoint adjudication).

11.2.4.2 Classification schema:

In studies 21-92-202 and 21-94-201, although the protocols specified no precise definition for MI, the Executive Committee ultimately such diagnostic criteria (reportedly while blinded, and prior to any analysis (even a blinded one)). Their schema intended to capture both acute MIs, and non-acute or asymptomatic MIs. Unfortunately, because of the absence of protocol prespecification of this intention, the necessary diagnostic information was at times not obtained by investigators.

In studies 21-92-202, 21-94-201, and 21-94-301 acute MIs were defined as cases in which evidence obtained of at least 2 of the following 3 conditions[12]:

- central chest discomfort of ≥ 30 minutes.
- ST elevation ≥0.1 mv in ≥2 contiguous leads.
- total CPK ≥150% of the upper limit of normal (ULN) accompanied by ≥3% CK-MB).

Non-acute MIs (marked by the presence of "pathologic Q waves") were defined differently in studies 21-92-202 than in the other 2 studies in which criteria were prespecified:

- in study 21-92-202 these were classified according to the judgement of the principal investigator without reference to any operational guideline, and without any subsequent endpoint adjudication[13].

[12] these criteria for acute MI, although not unreasonable, are limited by their dependence on subjects surviving their event long enough to obtain clinical diagnostic data (EKGs, circulating enzymes, etc); this approach would be expected to be insensitive at detecting rapidly fatal MIs.

[13] This is potentially problematic, given the nonspecificity of EKG Q waves.

- In studies 21-94-201 and 21-94-301 "pathologic Q waves" were defined as those present in ≥2 contiguous leads, having new onset, and meeting the following detailed criteria: Leads I, II, aVF: ≥0.04 seconds in duration, > 0.2 mv amplitude and > 25% of the amplitude of the succeeding R wave; Lead aVL: ≥0.04 seconds in duration, > 0.2 mv amplitude and > 15% of succeeding R wave; Leads V4-V6: ≥0.04 seconds in duration, > 0.2 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.

11.2.4.3 **Events investigator-attributed to MI:**

For the cases investigator-attributed as MI, the quality of the objective diagnostic evidence ranges from debatable to convincing. There were instances in which the individual case record data compelled me to either a more or less conservative interpretation than the reporting investigator.

Pooling the 8 phase III placebo-controlled claudication trials, the MI-attributed cases which I find to have convincing or suggestive objective evidence supporting the diagnosis (and which occurred while on therapy or within 30 days of the study drug's discontinuation) numbered as follow: among clz-exposed patients there were 9 such events as compared to 6 in the placebo group. This represented a crude rate in the pooled clz groups of 0.66% vs 0.62% in the placebo group. There was no evidence of a monotonic relationship between dose and rate of such events.

The following are all the events attributed as MI (irrespective of whether convincingly diagnosed) in the 8 phase III placebo-controlled IC trials.
In my assessment of the strength of objective evidence for infarct I use the term "debatable" broadly to imply debatable or lesser strength of evidence.

First are presented the narratives for the placebo-randomized cases:

placebo MI-attributed case P1[14]:

strength of objective evidence for MI: *Convincing*

Patient 0339, study 21-92-202, Center 43. This 59 year old, placebo-receiving caucasian female (with history of cigarette use, and transient ischemic attack). About 2 months post-randomization she presented to the emergency room with chest pressure, dyspnea, and diaphoresis. There was reportedly both EKG and enzymatic evidence of acute MI (with ST elevation, CK level of 5927 IU/L (upper limit of normal 200 IU/L), and CK-MB fraction of 602 ng/mL (upper limit of normal 5 ng/mL)). She was started on TPA, heparin, and aspirin, and dropped out of the study. The patient was known to be alive at 5.5 months post-randomization.

[14]this numbering system is arbitrary, and my own invention, used simply for convenience.

placebo MI-attributed case P2:

strength of objective evidence for MI: *Convincing*

.ient 2316, Center 012; study 21-96-202. This was a 66 year old placebo-receiving caucasian male with history of prior MI, hypertension, hypercholesterolemia, angina, cerebrovascular 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, a positive CPK (459), and a positive MB fraction (36)[15]. 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 about 3 months post randomization.

placebo MI-attributed case P3:

strength of objective evidence for MI: *Convincing*

Patient 5346 Center 081; study 21-96-202. This 51 year old placebo-receiving caucasian male had a history of CAD, prior MI, hypertension, hypercholesterolemia, and cigarette use. On post-randomization day 25 the patient was admitted to the hospital with chest pain of more than 3 ırs' duration, CPK of 616, MB fraction of 18, and EKG-ST segment elevations. Study drug .as discontinued, and he received thrombolytic, nitroglycerin and heparin. His hospital course was complicated by non-sustained VT, and mild pulmonary edema. He was alive at six months post-randomization.

placebo MI-attributed case P4:

strength of objective evidence for MI: *Convincing*

Patient 6217, Center 099; study 21-96-202. This 77 year old placebo-receiving caucasian female had a history CAD, angina, aortic insufficiency and stenosis, hypercholesterolemia, hypertension, chronic obstructive lung disease, and cigarette use. On post-randomization day 94 she was admitted to the hospital with chest discomfort and diaphoresis of more than six hours duration. There was reportedly an elevated CPK (876 U), positive MB (10.4%), and EKG-ST segment depression. A non-Q wave myocardial infarction was diagnosed and study drug was discontinued. She was alive at six months post-randomization.

[15] units were not described by the sponsor for either of these measures.

placebo MI-attributed case P5:

strength of objective evidence for MI: *Convincing*

Patient 7682 Center 012; study 21-96-202. This 75 year old placebo-receiving caucasian female had a history of CABG, angina, hypertension, and diabetes. On post-randomization day 33 she was hospitalized for surgical repair of hip fracture, and study drug was discontinued. Two days later she experienced post-operative chest heaviness of 3-4 hours duration, with non-specific EKG-ST changes, CPK of 750 U, and a 3.1% MB fraction. She was alive at six months post-randomization.

placebo MI-attributed case P6:

strength of MI evidence: *Suggestive* objective evidence

Patient 209[16], 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). He had experienced crushing chest pain of unspecified duration, and CPK peaked at 1206 (reportedly 6 times the ULN). These findings are clearly suggestive of MI, but MB bands were vaguely described only as "positive", and EKG showed unspecified ST changes. The patient was discharged against medical advice, and had a sudden death one day later.

cebo MI-attributed case P7:

strength of objective evidence for MI: *Debatable*

Patient 0199, study 21-95-201, Center 84. This 62 year-old placebo-receiving black female had a history of hypertension, hypercholesterolemia, and diabetes. About 2 months later the patient was admitted and she received the diagnosis of acute subendocardial MI. The duration of chest pain was not specified, no ST elevation was noted (prior to CABG); total CPK was not noted, and MB bands were 3% of an unknown total CPK. EKG was said to be "consistent with acute subendocardial MI". She underwent an emergency CABG that day. She dropped out of the study, was discharged home, and was alive at the end of the study period.

placebo MI-attributed case P8:

strength of objective evidence for MI: *Debatable*

Patient 403[17], Center 43, Study 21-94-201. This event in a placebo-receiving subject was attributed as MI on the basis of a patient report that a "heart scan" performed shortly after randomization showed evidence for a previous MI. There was no evidence of MI by EKG; none of the prespecified criteria for MI were met. There is no basis for assuming the scintigraphy findings to be specific for MI, even if assumed to be accurately reported. The Executive

[16] this case was cited in the sponsor's addendum submission dated 4/13/98.
[17] this case was cited in the sponsor's addendum submission dated 4/13/98.

Committee, which was to adjudicate putative MI events in this study, did not adjudicate this event (apparently because only events of a clinically serious nature triggered the administrative process presention to the Committee). The patient was known to be alive 6 months post-randomization.

placebo MI-attributed case P9:

strength of objective evidence for MI: *Debatable*

Patient 0130, study 21-92-202, Center 15. This 66 year-old placebo-receiving caucasian male (with history of cigarette use, hypercholesterolemia, and hypertension). During a routine visit, the patient's ECG showed a possible inferior-wall MI. This was reportedly different from any prior ECG test finding. The patient reported having had some chest "tingling" over the previous few months. The patient's complaint was not clearly that of chest pain, CPK data were not obtained, EKG data were not submitted, and he was never admitted to the hospital. Repeat EKG and a stress test were reportedly consistent with prior silent MI. The patient was withdrawn from the study after about 5 months, and was alive at the end of the study period.

placebo MI-attributed case P10:

strength of objective evidence for MI: *Debatable*

Patient 0334, Center 008; study 21-94-301. This 67 year old placebo-receiving caucasian female d an extensive history of cigarette use. On post-randomization day 31 she experienced radiating chest pain of increasing severity over 2 hours, which was associated with vomiting. Study drug was discontinued, she was hospitalized. A diagnosis of MI was reportedly based on EKG findings, but the actual data supporting the diagnosis were not submitted. She was treated with heparin and aspirin, and was known to be alive 9 months post-randomization.

placebo MI-attributed case P11:

strength of objective evidence for MI: *Debatable*

Patient 134, center 71, study 21-94-201. The Executive Committee determined this case to have not met the diagnostic criteria for MI, although this placebo-receiving subject had received a clinical diagnosis of "heart attack" and underwent emergency CABG. The patient was alive at the end of the study period.

placebo MI-attributed case P12:

strength of objective evidence for MI: *Debatable*

Patient 0402, Center; study 21-94-301. This 61-year-old placebo-receiving caucasian male had a history of prior MI, CABG, angina, diabetes, and cigarette use. On study day 104 he was spitalized with a diagnosis of inferior MI. The objective basis for this event attribution has not

been reported. The patient was withdrawn from the study, and underwent coronary angiography and thrombolysis. He was discharged and known to be alive 5.5 months post-randomization.

These are the case narratives for the CLZ patients:

clz MI-attributed case C1[18]:

strength of objective evidence for MI: *Convincing*

Patient 322, Center 12, Study 21-94-201. This 49 year-old caucasian male (with history of hypertension, hyperlipidemia, and cigarette smoking) was randomized to CLZ 100 mg bid. After 130 days on study drug the patient experienced an event which met the Executive Committee's criteria for MI (reportedly involving 120 minutes of chest pain, a CPK level that was 1.5 times the upper limit of normal, and 10.5% MB bands). Study drug therapy was discontinued, and angioplasty was attempted. He was known to be alive 8.5 months post-randomization.

clz MI-attributed case C2:

strength of objective evidence for MI: *Convincing*

Patient 452, study 21-94-201, Center 65. This 48-year-old caucasian male (with history of hyperlipidemia, angina, and cigarette smoking) was randomized to CLZ 100 mg bid. After 99 days on study drug he developed chest pain that was unrelieved by sublingual nitroglycerin. This event met the Executive Committee's definition of MI, on the basis of adequate duration of chest pain (> 30 minutes), extent of CPK elevation (644), and extent of CK-MB elevation (11.8%). Treatment with study medication was interrupted, and CABG was performed. He was alive at six months post-randomization.

clz MI-attributed case C3:

strength of objective evidence for MI: *Convincing*

Patient 545, study 21-92-202, Center 40. This 59 year-old caucasian male (with history of cigarette use, and borderline hypertension) was randomized to CLZ 100 mg bid. In the first few days of exposure he dropped out because of headache and weakness-fatigue. About 1.5 weeks after his final dose he experienced a sudden onset of severe chest pain which lasted for >30 minutes. CPK was 340% of the ULN (peaking at 866), and MB fraction was abnormal at 4.6%. These enzyme levels are potentially confounded by the fact that emergency PTCA was initiated prior to the first blood draw for CPK. Unspecified EKG findings were also reportedly consistent with an acute MI (the EKGs are said to be unavailable). The emergent PTCA was undertaken for near total occlusion of the right coronary artery (it is not clear whether fresh thrombus was

[18] this numbering system is arbitrary, and my own invention, used simply for convenience.