11.2.6 Unpooled composite endpoint (study 21-94-301)

2.6.1 Design summary

In study 21-94-301, although there was prespecification of a combined mortality/morbidity endpoint similar to that of studies 21-92-202 and 21-94-201, reportedly no central adjudication of those data was undertaken.

For morbidity/mortality outcomes, all dropouts were to have been contacted every 30 days until day 168 post-randomization, with information captured on the Post-Termination Contact page of the CRF.

11.2.6.2 Results of unpooled composite endpoint analysis

The mean exposure duration was 47.3, 45.7, and 52.2 PEY in the CLZ, OXP, and placebo groups, respectively.

The mean rate of all dropouts was 27.6%, 30.1%, and 15.3% in the CLZ, OXP, and placebo groups, respectively. The mean rate of dropouts for AE was 25.2%, 26.8%, and 12.1% in the CLZ, OXP, and placebo groups, respectively.

Reportedly 1.6% and 0.8% of clz-randomized vs placebo-randomized subjects, respectively, had their final outcome captured only prior to post-randomization week 24, but subsequent efforts reportedly established survival status in all subjects at post-randomization week 24.

The composite endpoint results were reportedly as follows:

Table: 48

Reported number and crude rate of FIRST events in study 21-94-301
(all-randomized dataset)

event	*CLZ 100 mg bid* (n=123)		*Placebo* (n=124)	
all-cause Death	1	0.8%	2	1.6%
MI	2	1.6%	3	2.4%
Stroke	2	1.6%	0	0%
Arterial revascularizations	3	2.4%	1	0.8%
Amputation	0	0%	0	%
ANY FIRST EVENT	8	6.5%	6	4.8%

[source: pg 21, submission 35, 5/22/98]

11.2.6.3 @**Comments** (unpooled composite endpoint analysis): ^

definitive signals regarding drug toxicity were generated by the relatively small number of events observed in this unpooled sample.

11.2.7 **Pooled EKG findings**:

The sponsor pooled the 8 largest placebo-controlled IC trials, read EKGs (either automatically or, in the case of studies 21-94-301 and 21-90-201, by hand), and had a certified cardiologist over-read them. Rate correction of QT intervals was undertaken by the Bazett (QTc_B), (Fredericia (QTc_F), and Framingham Linear Regression (QTc_{LR}) methods.

Non-ambulatory trough EKG results were as follows[26]: Mean QTc_B increased from pre-treatment in clz-treated subjects, in a dose-related (and reportedly heart-rate dependent) manner. The sponsor reports that at the end of treatment (excluding dropouts) the mean QTc_B increases were 3.05 (SD= 20.3), 5.70 (SD= 24.0), and 8.21 (SD= 23.9) ms for the 100 mg/d, 200 mg/d, and 300 mg/d groups, respectively, whereas in the placebo group the change was 0.12 ms. In an attempt to achieve better heart-rate correction the same dataset was queried using the Framingham Linear Regression (QTc_{LR}) method; this resulted in a mean change in QTc_{LR} of -0.49 (SD= 17.3), 0.62 (SD= 20.0)and 0.95 (SD= 17.0) ms for increasing doses of cilostazol, respectively, and a change 0.29 ms for placebo. The Fredericia method found a mean change in QTc_F of -2.01 (SD= 18.7), -1.39 (SD= 21.3)and -2.22 (SD= 17.8) ms for the low, medium, and high dose clz groups, respectively, compared to a change of -0.33 (SD= 25.2) ms for placebo.

Using the QTc_B method among dropouts who had pre-treatment $QTc_B < 500$ ms, at the final observation (within 14 days of termination) there were no cases of $QTc_B \geq 500$ ms in 973 placebo subjects, while the rate of this finding was 0%, 0.1%, and 1.4% in the clz 100 mg/d, clz 200 mg/d, and clz 300 mg/d groups, respectively. The nonzero point estimates are a limited basis for inference insofar as they are based on just one observation each.

Among completers who had pre-treatment $QTc_B < 500$ ms, at the end of treatment the rate of occurrence of $QTc_B \geq 500$ ms was 0.8% in the placebo group, vs. 0.3%, 0.6%, and 1.4% in the clz 100 mg/d, clz 200 mg/d, and clz 300 mg/d groups, respectively. Again, the point estimates for the lowest and highest dose of cilostazol need be recognized as each deriving from just 1 observed event.

At the end of treatment (excluding dropouts) the rates of patients, from among those with pre-treatment $QTc_F < 500$ ms, who developed a $QTc_F \geq 500$ ms were 0, 0.3, and 0% in the low, medium, and high dose clz groups, respectively, compared to 0.6% in the placebo group.

[26] between weeks 17 and 24 the number of nonambulatory EKGs obtained were approximately 740, 1380, 130, and 1520 in the CLZ 100 mg/d, 200 mg/d, 300 mg/d, and placebo groups, respectively.

At the end of treatment (excluding dropouts) the rates of patients, from among those with pre-atment $QTc_{LR} < 500$ ms) who developed a $QTc_{LR} \geq 500$ ms were 0, 0.2, and 0% in the low, medium, and high dose clz groups, respectively, compared to 0.5% in the placebo group.

Ambulatory EKG (Holter monitoring) results were obtained (in limited quantity) at pre-treatment baseline, and at post-randomization weeks 2, 8, 12, and 16. These evaluations were performed in a portion of centers in study 21-92-202, and at all centers in study 21-95-201. The subjects undergoing these measures numbered 84, 18, 94, and 70 in the placebo, CLZ 100 mg/d, 200 mg/d, and 300 mg/ groups, respectively. At the time of Holters the dropout rate had reached 4.2%, 1.2%, 7.3%, and 34.3% in the placebo, CLZ 100 mg/d, 200 mg/d, and 300 mg/ groups, respectively. Holter data capture was less than 24 hours in a discrete fraction of subjects, i.e. in 24%, 23%, and 34% of the placebo, 200 mg/d, and 300 mg/ groups, respectively at week 8. The CLZ 100 mg/d group had its post-randomization Holters captured at week 12, and at that time 11% failed to provide a full 24 hours of data.

In one of the sponsor's analyses the number of VT events/hr (which defined "VT event" as the occurrence of ≥3 successive ventricular beats having an average rate of ≥150 beats/min, with each ≥3 beat run was classified as a distinct event) at the end of therapy the mean change from pre-treatment number of ventricular tachycardia (VT) events/hr was reportedly -0.02 in the placebo group vs -0.03, 0.04, and zero in the clz 100 mg/d, clz 200 mg/d, and clz 300 mg/d groups, respectively. The mean change from pre-treatment number of ventricular premature beats (VPB) per hour was -32.9, 17.6, and 10.3 for 100 mg/d, clz 200 mg/d, and clz 300 mg/d clz, respectively. For placebo treated patients the change was -2.7 VPB/hr.

Applying Morganroth pro-arrhythmic criteria, the sponsor found one sustained VT event each in the CLZ group (at 150 mg/d) and placebo group, an increase in VPB frequency in 4.4% of CLZ patients vs 1.2% of placebo patients[27], an increase in non-sustained ventricular tachycardia beats (NSVT) in 9.4% of CLZ patients vs 7.1% in the placebo group, and a 10 fold increase in NSVT beats (among those with NSVT ≥ beats prior to treatment) in 3.3% of CLZ patients vs none of the patients on placebo.

[27] counting events meeting one or more Morganroth criteria.

11.2.8 Hemodynamics

›ling the 8 largest (phase III) placebo IC trials, the following trough hemodynamic findings ..ere reported[28]:

Mean resting heartrate in the cilostazol treatment groups increased, relative to pre-treatment, in a dose-dependent manner. In the placebo-controlled trials, EKGs showed that cilostazol increased the mean ventricular rate in a dose-related manner (the placebo-corrected increases were approximately 5, 7, and 10 bpm in the 100 mg/d, 200 mg/d, and 300 mg/d groups, respectively.

Small mean changes from pre-treatment resting systolic blood pressure were also observed; the placebo-corrected changes were 0.9, -2.0, and -0.9 mmHg in the 100 mg/d, 200 mg/d, and 300 mg/d groups, respectively.

[28] as updated by the sponsor in submission #35 of 5/22/98.

11.2.9 Common AE

Pooling the 8 largest placebo IC trials, the reported rates of all treatment-emergent AE (serious or otherwise, common or rare) were comparable across the clz groups (ranging from 89-92%), and in each case higher than the placebo rate of 80%. These data were as follows: placebo (80%); 100 mg/d cilostazol (89%); 200 mg/d cilostazol (88%); 300 mg/d cilostazol (92%).

The common (≥ 1%) treatment-emergent AE that showed a statistically significant difference ($p<0.05$) between the 100 mg bid cilostazol group and the placebo group were reportedly: headache, diarrhea/abnormal stools,
palpitation, tachycardia, arrhythmia, peripheral vascular disorder, dizziness, and eye disorder. Those that showed a dose-relationship were headache, diarrhea/abnormal stools, palpitation, and tachycardia.

Headache was the most common treatment-emergent AE. The rate of headache was 33.4% among 100 mg bid clz users vs 13.1% in placebo group.

Diarrhea was the second most common treatment-emergent AE. It occurred at a 18.5% rate in the 100 mg bid cilostazol group vs 6.7% in the placebo group. Most commonly it was of mild to moderate severity, and its onset was variable.

Palpitation occurred in 9.6% of the 100 mg bid cilostazol group vs 1.0% of the placebo group. It was predominately of mild to moderate severity.

Tachycardia occurred in 4.3% of the 100 mg bid cilostazol group versus 0.7% of the placebo group, and was largely of mild to moderate severity.

Arrhythmia occurred at a rate of 0.9% in the 100 mg bid cilostazol group versus 0.1% in the placebo group. Predominately of mild to moderate severity (with no case of severity sufficient, among the clz or placebo groups, to cause discontinuation from the study), this AE had variable onset, and no statistically distinguishable relationship to dose.

Dizziness (undefined) occurred at a rate of 9.8% in the 100 mg bid cilostazol group versus 6.2% in the placebo group. Predominately of mild to moderate severity, this AE had variable onset, and no statistically distinguishable relationship to dose.

11.2.10 Laboratory findings:

Pooling the 8 largest placebo-controlled IC trials, treatment-emergent laboratory abnormalities are shown in the table below. Note that the point estimates for the clz 300 mg/d group are based on a small sample size and are thus limited bases for inference.

What is evident is that with the exception of SGOT, the point estimated rates of occurrence of any ree of abnormal elevation of liver function tests were higher in one or another CLZ group than in the placebo group. However, these findings did not show a monotonic relationship to dose. For total bilirubin and LDH it was only the CLZ 300 mg/d group which showed a higher point estimated abnormality rate. For GGPT, all but the low dose CLZ group had an excess rate of abnormality. In the 100 mg/d CLZ group the mean rate of SGPT elevation >120 U/L was higher than control (1.0 vs 0.36%, respectively), as was the rate of SGOT > 100 U/L[29] (0.33 vs 0.12%, respectively). For neither measurement, however, was there a monotonic relationship between dose and prevalence of abnormalities of this extent.

Elevated mean BUN was, in the two highest dose CLZ groups, more prevalent than control. The occurrence of any degree of abnormally elevated serum creatinine was, in each drug group, more prevalent than control, and the relationship to dose was monotonic. In the two dose groups for which point estimates are a reasonable basis for inference (i.e. 100 and 200 mg/d), the mean rates of creatinine elevation > 2.5 mg/dL (0.67 and 0.24%, respectively) were less than in the placebo group (0.72%), whereas the 300 mg/d group had a 2.8% mean rate of this finding.
There were no pooled CPK levels reported with which one could assess the possibility of myolysis contributing to the elevated creatinines.

vated mean serum urate was, only in the two highest dose CLZ groups, more prevalent than control, thus there was no monotonic relationship to dose. The mean rate of urate elevation ≥13 mg/dL was, in each of the high dose groups, higher (ranging from 0.32-1.41%) than in the placebo group (were there were no occurrences of this degree of abnormality).

Elevated mean serum sodium was more prevalent than control in each CLZ group, and the relationship to dose was monotonic. In contrast, without a monotonic relationship to dose were the higher than control prevalences of elevated mean serum chloride, and mean serum potassium. Reduced serum sodium was slightly more prevalent than control in the clz 100 and 200 mg/d groups, but not so for the highest dose group.

There was also a higher than control prevalence of elevated mean serum glucose, but without monotonic relationship to dose.

[29] the severity thresholds discussed here were prespecified, albeit arbitrary.

Table: 49

Blood Chemistries: mean percentage of subjects showing treatment-emergent shifts outside of reference range
(pooling the 8 largest placebo-controlled IC studies)

measure- ment	Direction of shift from Reference range	mean percentage who changed			
		Placebo [n= 529-819]	Clz 100 mg/d [n=250]	Clz 200 mg/d [n= 519-762]	Clz 300 mg/d [n= 48]
sodium	high	0.3%	0.4%	0.8%	2.1%
	low	1.9%	2.4%	2.0%	0%
potassium	low	0.7%	1.2%	1.3%	0%
chloride	high	0.5%	0.8%	0.8%	2.1%
BUN	high	3.4%	1.2%	3.5%	4.2%
creatinine	high	3.2%	4.0%	5.4%	18.8%
glucose	high	7.8%	7.6%	8.3%	12.5%
urate	high	1.5%	1.2%	1.9%	4.2%
Alk phosph	high	3.5%	2.0%	3.9%	2.1%
SGPT	high	2.0%	3.6%	1.7%	0%
GGPT	high	3.1%	1.2%	4.6%	4.2%
total bilirubin	high	0.9%	0.4%	0.8%	2.1%
LDH	high	1.2%	0.4%	1.1%	2.1%

[source = submission 6/12/98]

Shown are shifts, among completers, from pre-treatment to end of the study.

Hematology shifts are shown below. Note again that the point estimated rates shown for the clz 300 mg/d group are based on a relatively small sample size. Hematology findings showing at least numerically greater mean prevalence of abnormality in one or another CLZ dose group (relative to placebo), but no monotonic relationship to dose, were low hematocrit, and low erythrocyte count. Low hemoglobin, leukopenia, and thrombocytosis also showed at least numerically greater mean prevalence of abnormality in one or another CLZ dose group, and also manifested an apparent dose response.

The problem of statistical multiplicity is appreciable if one were to attempt to go beyond descriptive analyses of these data; results of statistical significance testing were not submitted.

Table: 50

Hematology Measures: mean percentage of subjects showing treatment-emergent shifts outside of reference range
(pooling the 8 largest placebo-controlled IC studies)

Measurement	Direction of shift from Reference range	mean percentage who shifted			
		Placebo [n= 827-829]	Clz 100 mg/d [n= 249-250]	Clz 200 mg/d [n= 761-767]	Clz 300 mg/d [n= 47-48]
Hemoglobin	low	2.4%	2.8%	3.1%	8.5%
Hematocrit	low	1.5%	2.8%	2.9%	0%
Erythrocyte count	low	1.5%	0.40%	1.56%	6.4%
Leukocyte count	low	0.48%	0.80%	1.9%	2.1%
platelet count	high	0.7%	1.6%	2.0%	2.1%

[source = submission 6/12/98]

Shown are shifts, among completers, from pre-treatment to end of the study.

11.2.11 Drug interactions:

2.11.1 Drug-demographic interactions

Pooling the 8 largest placebo-controlled trials, the headache rate (pooled across clz doses) was higher in subjects <65 years (37%) than in those ≥65 years (28%), and at both levels of age this was more frequent than the placebo rate of 12-15%. Diarrhea (pooled across clz doses) showed a somewhat higher rate in subjects ≥65 years (18%) than in those <65 years (11%), and at both levels of age was higher than the placebo rate of 4-5%.

Although point estimates are a limited basis for drawing inferences when sample sizes are relatively small (as they were in the case of female or non-caucasian subjects), it is noted that the peripheral edema rate (pooled across clz doses) tended to be higher in females than in males (12 vs 6%, respectively), and at both levels exceeded the placebo rate of 4%. Similarly, reports of pain of any kind tended to be be higher in Non-caucasians than Caucasians (20 vs 12%, respectively), and only in Non-caucasians did this exceed the placebo rate (which was 13% in that group).

11.2.11.2 Drug-disease interactions:

e the Biopharmaceutical review for discussion of drug-disease interaction studies 21-93-206 (renal impairment), 21-94-304 (hepatic impairment), and 21-91-201F (kinetics in intermittent claudication patients vs healthy subjects).

11.2.11.3 Drug-drug interactions:

See the biopharmaceutical and secondary Medical reviews for analyses of the most useful drug-drug interaction data. Briefly, it is noted that cilostazole's metabolism is reportedly CYP 3A4-dependent.

It is plausible that the frequency of concentration-dependent adverse effects of cilostazol would be increased by the co-administration of CYP 3A4 inhibitors like ketoconazole. The efficacy trial data were interrogated for CLZ-ketoconazole interaction by the sponsor, but the analysis was greatly limited by the infrequent co-administration of ketoconazole.[30] They pooled the 8 largest placebo-controlled intermittent claudication trials, and (using dose as a surrogate for concentration at active sites) retrospectively surveyed the AE rates. In describing those results I will focus on the comparative rates (in co-users vs non-users of ketoconazole) of those AE which across the entire placebo dataset demonstrated a dose-relationship (i.e. headache, diarrhea/abnormal stools, palpitation, and tachycardia).

[30] this was co-administered in only two clz-randomized and two of placebo-randomized subjects.

Point estimates of the observed rates (a crude basis of estimation, but the only one provided) were reported to be as follows: 100% of the 2 ketoconazole co-exposed subjects experienced headache during clz use, while 25% reported this while receiving clz alone; 0% of the 2 ketoconazole co-exposed subjects experienced tachycardia during clz use, while 3.7% reported this while on clz alone; 50% of the 2 ketoconazole co-exposed subjects experienced abnormal stool during clz use, while 12% reported this while on clz alone; 50% of the 2 ketoconazole co-exposed subjects experienced diarrhea during clz use, while 11% reported this while on clz alone; 50% of the 2 ketoconazole co-exposed subjects experienced palpitation during clz use, while 4.7 % reported this while on clz alone.

11.2.13 Study PUIC-2

In placebo-controlled study PUIC-2 there were reportedly no deaths. No other safety results were presented in the abstract submitted for this study.

11.3 Other short-term Peripheral Vascular Disease data

11.3.1 Study PUIC-1

In positive-controlled study PUIC-1 there were reportedly no deaths. No other safety results were presented in the abstract submitted for this study.

11.3.2 Study G-22

In this uncontrolled, open-label study 42 subjects (patients with ischemic ulceration of an extremity, on the basis of either Buerger's disease (n=26), arteriosclerosis (n=15), or Raynaud's disease (n=1)) were treated with oral cilostazol at doses of either 50 mg bid, 100 mg bid, or 100 mg tid for at least 6 weeks. AE rates were assessed.

There were 9 reports of headache (with a tendency towards dose-relatedness), and 1 report each of gastric discomfort and sleepiness. One patient developed elevated liver function tests (levels of SGOT, SGPT, and LDH at up to twice the upper limit of normal) at week 6, however this person reportedly had a history of pre-treatment liver dysfunction. Three patients dropped out for AE, and 4 dropped out for other reasons.

11.3.3 Study G-23

In this uncontrolled, double-blind study 96 subjects (patients with ischemic ulceration of an extremity on the basis of either Buerger's disease (63 patients) or arteriosclerosis (33 patients)) were treated with oral cilostazol 100, 150, 200 mg/d for 6 weeks. AE rates were assessed, and ulcer healing rates were also observed.

Reported AE, and their number of reports were as follows: headache (4), facial flush (1), upper abdominal pain (2), and 1 case each of gastric discomfort, diarrhea, chest pain, and "glittering" (undefined) vision. Headache rates showed a tendency towards dose-relatedness. There were 3 dropouts for AE, whereupon the AE reportedly resolved.

One 74 year old male had a mild, treatment-associated anemia (Hct 28.9), and one 52 year old male had an isolated treatment-associated increase in SGOT to 1.75 times the upper limit of normal that was without other evidence of liver function abnormality.

11.3.4 **Study G-24**

In this positive-controlled, randomized, double-blind study 176 subjects (patients with ischemic ulceration of an extremity, on the basis of either Buerger's disease[31] or arteriosclerosis) were treated with oral cilostazol 100 mg bid or ticlopidine 500 mg/d for 6 weeks. AE rates were assessed, and ulcer healing rates were also observed.

Among clz-exposed subjects the reported AE, and their number of reports were as follows: headache (5); two cases each of vomiting, rash, and unspecified other AE (2); and 1 case each of dizziness, sleepiness, palpitation, and gastric pain. There were reportedly abnormal laboratory values in 27% of the cilostazol-treated patients, but the clinical significance of these is difficult to judge given that only the frequencies of an abnormal result were described rather than individual levels of laboratory tests prior to and after exposure.

[31] the majority had Buerger's disease.