8.3.5.3 **@Adjudication** (study 21-94-201)

blinded Executive Committee, consisting of independent, expert reviewers, adjudicated the prespecified mortality and cardiovascular morbidity endpoints. All decisions by the committee were to be final.

8.3.5.4 **@Statistical analyses.** (study 21-94-201)

Two point comparisons using ANOVA were undertaken as the primary analysis. The pre-specified primary ANOVA analysis of the log of the ratio of the distance at week 24 to the pre-treatment distance calculated the ratio of geometric means (antilog of the difference in the mean of cilostazol change from pre-treatment minus the mean of placebo change from pre-treatment walking distance).

Statistical testing was two-sided. The primary prespecified comparisons were CLZ 100 mg bid versus placebo, and CLZ 50 mg bid versus placebo. The Dunn-Sidak multiple comparison correction was prespecified for the primary efficacy analysis. For these, the signficance level was considered to be $p < 0.025$.

Continuous efficacy measures were analyzed by analysis of variance, or (if nonnormal distributions) the Wilcoxon rank sum test. The independent variables included treatment assignment, center, baseline value of the response variable, center by treatment interaction, and baseline by treatment interaction.

For the secondary efficacy analyses, no adjustment was made for multiple comparisons. Time-to-event methods were to be used for comparing mortality and morbidity endpoints. An attempt was to be made to capture outcome in noncompleters by making telephone or other contact every 30 days up to 24 weeks postrandomization or until patient death. Reportedly there was no interim look for this study.

In a post-hoc analysis, dose-response was tested by using the linear and quadratic contrasts in an ANOVA assessment of log(ACD at week 24/ACD at pre-treatment).

Analyses were conducted according to the intent-to-treat principle. The "efficacy ITT" dataset consisted of randomized patients for which there was nonmissing ACD data at pre-treatment, and at one or more post-randomization timepoints. The prespecified means of handling missing data was the carry-foward (LOCF) method.

The prespecified "completer" dataset was comprised of patients who had nonmissin ACD data at pre-treatment and at each post-randomization follow-up. Safety analyses were based on an ITT dataset which excluded only those subjects who received no dose of study medication.
The study was powered for detection of anti-claudication effect, rather than

for discriminating a potential adverse effect on mortality/cardiovascular morbidity. The sponsor description of the power calculation is vague in that it omits discussion of the size of the detectable effect. They assert only that 125 subjects needed to be randomized to each of 3 groups in order to provide 90% power at a two-sided significance level of 5%.

8.3.6 @**Results other than Efficacy outcomes** (study 21-94-201)

8.3.6.1 @**Randomization code breaks:**

The blind was reportedly not broken during the course of the study.

8.3.6.2 @**Covariates:** (study 21-94-201)

Demographic and pre-treatment characteristics of subjects are shown in the table below. The distribution of these pre-treatment covariates was generally well balanced, with the exception of the mean pre-treatment ACD tending to be 3.3 m lesser in the high dose CLZ group, relative to the low dose group.

Table: 10

@Demographic and Pre-treatment characteristics of subjects
(study 21-94-201; efficacy LOCF/ITT dataset):

	Placebo	CLZ 50 mg bid	CLZ 100 mg bid
	n= 125	n= 128	n= 124
male	78%	75%	76%
female	22%	25%	24%
mean age (yr)	64.4	63.9	63.4
Caucasian	89%	79%	90%
non-Caucasian	11%	21%	10%
concomitant tobacco use	48%	47%	49%
diabetes	16%	28%	24%
PAD duration = 0.5-5 yr	67%	63%	58%
resting ABI			
mean	0.63	0.65	0.64
SD	0.15	0.16	0.16

[source: pg 93, vol 137; and submission 6/9/98 & 7/6/98]

8.3.6.3 **@Exposure to drugs:** (study 21-94-201)

There was an excess of concomitant lovastatin use in the drug-treated groups (16, 13, vs 4%, respectively in the CLZ high dose, CLZ low dose, vs placebo arms), however this was unlikely to have had important effect on the clinical outcome measures.

8.3.6.4 **@Disposition of subjects:** (study 21-94-201)

A total of 394 subjects were randomized (evenly distributing among treatment groups as 133 high dose, 132 low dose, 129 placebo). Their disposition was as follows:

- 377 subjects (evenly distributed as: 124 high dose CLZ, 128 low dose CLZ, 125 placebo) comprised the "efficacy" dataset. These had at least one nonmissing pre-treatment ACD datum, and at least one nonmissing post-randomization ACD datum at any timepoint in the study. No subjects were excluded because of missing pre-treatment walking test data.

- 316 subjects had a nonmissing pre-treatment ACD and a nonmissing 24 week ACD datum (distributed as: 97 high dose CLZ, 111 low dose CLZ, 108 placebo).

- 286 subjects had a nonmissing pre-treatment ACD datum, and a nonmissing ACD datum at each planned observation point (distributed as 89 high dose CLZ, 103 low dose CLZ, 94 placebo).

The total rate of subject dropouts was higher in the CLZ-treated groups than in the placebo group. The attributed reasons for all dropouts are shown in the following table. Reasons classified as "other" included the use of prohibited concomitant medications, loss to follow-up, or inevaluable data.

Table: 11

@Dropouts in study 21-94-201:
(all-randomized dataset)

	CLZ 100 mg bid	CLZ 50 mg bid	Placebo
# randomized	n = 133	n = 132	n = 129
Total dropouts	36 (29%)	21 (16%)	21 (17%)
Dropouts for any AE	29 (23%)	15 (12%)	11 (9%)
All dropouts, by reason:			
nonfatal adverse event	27	15	11
death	2	0	0
lack of efficacy	0	1	0
marked deterioration	0	1	2
noncompliance	1	1	3
lost to followup	0	0	2
required disallowed med	2	1	0
withdrew consent	1	1	0
inevaluable data	0	0	1
other	3	1	2

[source: table 6-1, pg 77-78, vol 137; & appendix V, submission 7/6/98-"A"]

The patients having a protocol deviation were evenly distributed among treatment groups. The majority of protocol deviations involved non-compliance, and yet only ten patients had mpliance ≤ 75% (5, 2, and 3 patients, respectively, in the CLZ 100 mg bid, CLZ 50 mg bid, and placebo groups). No data were excluded on the basis of protocol deviation.

8.3.7 @**Efficacy outcomes**: (study 21-94-201)

8.3.7.1 @**Tests stopped for nonspecific reasons** (study 21-94-201)

The stopping of final tests for nonspecific reasons (defined as reasons other than claudication) occurred in approximately 23% of CLZ 100 mg bid-randomized subjects, 14% of CLZ 50mg bid subjects, and 14% of placebo-randomized subjects.

8.3.7.2 @**Primary efficacy analyses**: (study 21-94-201)

The baseline ACD data had a non-normal distribution.[21] At baseline in the efficacy dataset, the raw mean trough ACD was comparable in all three treatment groups, as shown in the following table.

[21] as per FDA's Dr Kun Jin.

Table: 12

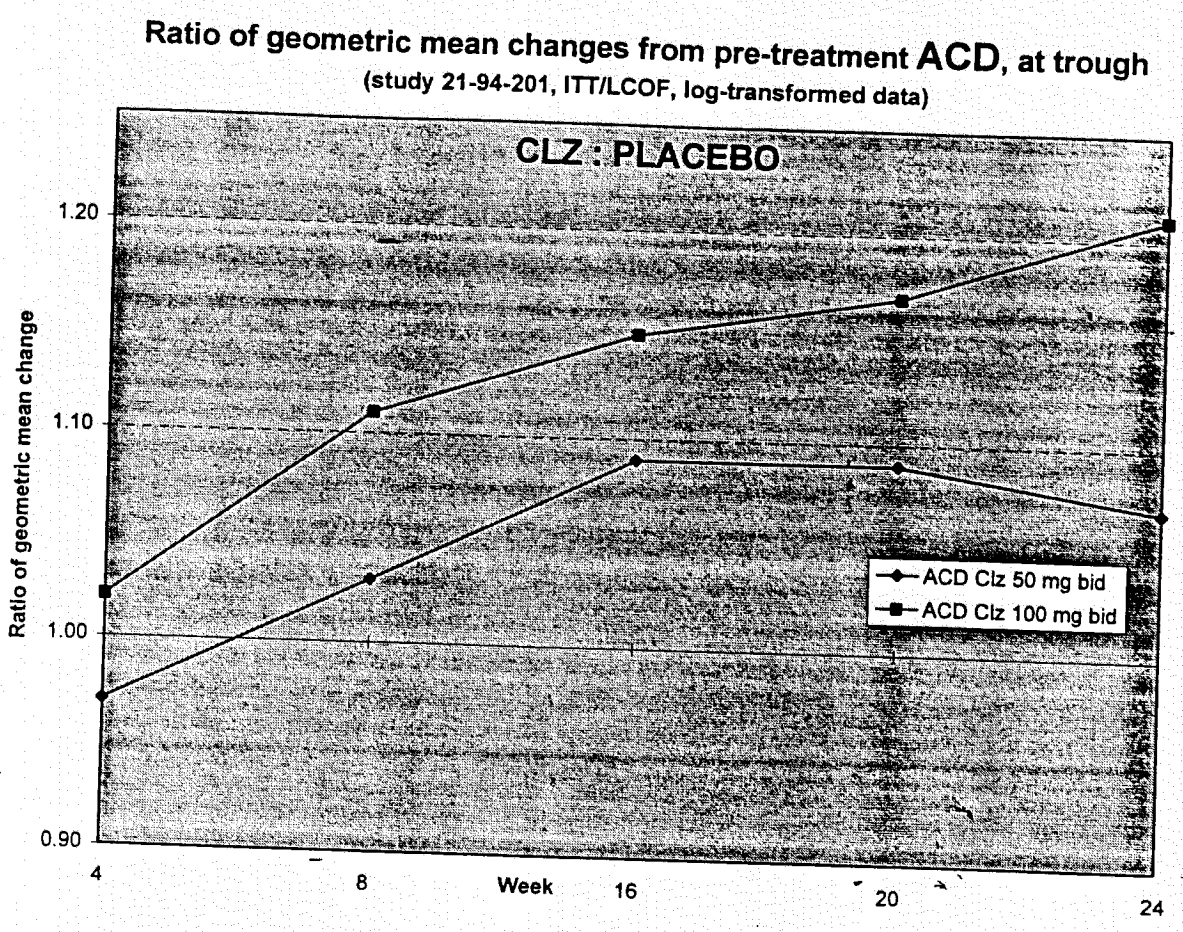
Baseline raw mean walking distances (in meters) in study 21-94-201:

baseline metric	*CLZ 100 mg bid*	*CLZ 50 mg bid*	*Placebo*
ICD	63 m	68 m	68 m
ACD	117 m	123 m	121 m

[source: submission dated 5/6/98]

As shown in the figure below, the sponsor's results for the primary analysis (log transform, week 24, ITT/LOCF) reportedly showed statistically distinguishable improvement from pre-treatment ACD for high dose CLZ, but not for low dose CLZ. The estimated treatment effect on trough ACD at week 24 (the ratio of geometric means CLZ:placebo) for CLZ 100 mg bid was reportedly 1.21 (95% CI = 1.09-1.35; p=0.0003); and for CLZ 50 mg bid was reportedly 1.07 (95% CI =0.97-1.19, p=0.18). Although not statistically distinguishable, there were directional trends towards drug effect with the 50 mg bid dose.

Figure: 6


Ratio of geometric mean changes from pre-treatment ACD, at trough
(study 21-94-201, ITT/LCOF, log-transformed data)
CLZ : PLACEBO
Ratio of geometric mean change
1.20
1.10
1.00
0.90
4
8
Week
16
20
24
ACD Clz 50 mg bid
ACD Clz 100 mg bid

For each CLZ group there was a statistically significant treatment-by-baseline interaction for baseline ACD at week 24, wherein the estimated magnitude of change in ACD was lesser in those with smaller pre-treatment ACD. Because of this, an unequal slopes model was used to assess treatment differences.

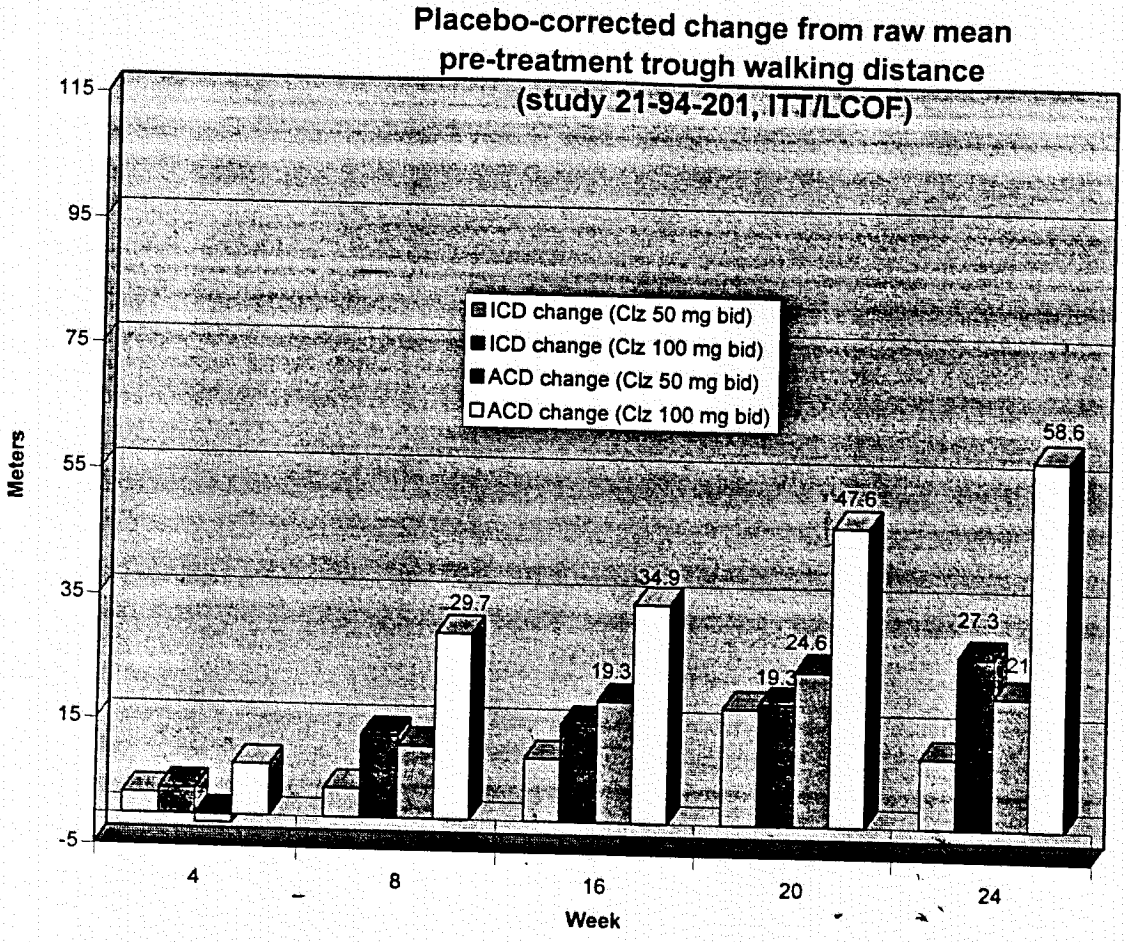
There was reportedly no significant treatment-by-center interaction for ACD.

8.3.7.3 **@Other efficacy analyses:** (study 21-94-201)

There were additional endpoints for which the reported analyses have not been protected against Type I error, because of retrospective defining of endpoints and/or because of multiplicity (e.g., the 2° endpoints, although prespecified, were several).

The raw (nontransformed) ACD and ICD data, expressed in meters, are shown in the figure below. This post-hoc examination of the data is presented for descriptive purposes. At trough, during week 24, the reported placebo-corrected mean changes from pretreatment ACD were 58.6 and 21.0 m for the CLZ 100 mg bid, and CLZ 50 mg bid groups, respectively, whereas the placebo-corrected mean changes from baseline ICD were 27.3 and 11.1 m for the high and low dose groups, respectively.

Figure: 7


Placebo-corrected change from raw mean
pre-treatment trough walking distance
(study 21-94-201, ITT/LCOF)
ICD change (Clz 50 mg bid)
ICD change (Clz 100 mg bid)
ACD change (Clz 50 mg bid)
ACD change (Clz 100 mg bid)
Meters
115
95
75
55
35
15
-5
29.7
19.3
34.9
19.3
24.6
47.6
27.3
21
58.6
4
8
16
20
24
Week

The prespecified secondary endpoint of ICD was also analyzed by the same log transform method as the primary endpoint (ITT/LOCF dataset). This reportedly showed a nominally statistically distinguishable ratio of geometric means (CLZ:placebo) of 1.22 with respect to trough ICD at week 24 in the 100 mg bid group. At earlier weeks this estimate ranged from 1.02-1.13. For the low dose group the estimated treatment effect on trough ICD at week 24 was 1.11 (and at earlier weeks this ranged from 1.02-1.08).

A post-hoc effort was made by the sponsor to describe the time of onset of appreciable trough ACD effect. For this the primary approach to analysis (log transform, ITT/LOCF dataset) was retrospectively extended to times prior to week 24. See the above figure for a descriptive sense of those data. Apparent trends towards ACD effect greater than placebo are suggested in the high dose group as early as week 8, but no convincing statement about onset of placebo-distinguishable trough effect can be made with adequate protection against Type I error.

Based on an analysis which was unprotected against Type I error, the sponsor's attempt at quantifying dose-response reports that a linear dose-response relationship was observed for ACD at week 24 (nominal $p = 0.0003$).

Subgroup analyses were reported by the sponsor as percent changes from baseline ACD at week 24 (nontransformed data, LOCF analyses from table 7-10, pg 104-5, vol 137). Those high dose subgroups divided according to diabetes status, and according to sex showed numerically comparable responses (e.g., 51.6 vs 57.7% ACD change in the diabetic vs nondiabetic subgroup, respectively; and 57.2 vs 53.1% ACD change in the male vs female subgroups, respectively). The CLZ 100 mg bid dose showed some numerical differences in response in association with age-group and smoking status (where subgroups entailed approximately 60 subjects). There was a 63.1 vs 49.3% ACD change in the below 65 year vs ≥65 year subgroup, respectively; and a 36.7 vs 75.1% ACD change in the smoking vs nonsmoking subgroup, respectively. With high dose CLZ there was also a numerical difference in response in association with race (where the non-caucasian sample comprised only 13 subjects), i.e. there was a 59.6 vs 24.6% ACD change in caucasian vs non-caucasian subjects, respectively. Because of small sample sizes and post-hoc assessments, the data are not adequate for inferring conclusively that response differed in any demographic subgroup.

Quality of life measures showed disparate results, reportedly as follows: Physical Function measures showed no drug effect, Bodily Pain measures were nominally statistically distinguishable for both dose groups, Role-Physical measures showed no differences, Role-Emotional measures favored the placebo group, and the Social Functioning measure did not differentiate treatment groups.

8.3.8 @**Commentary on the evidence** (study 21-94-201)

The estimated treatment effect on trough ACD at week 24 (the ratio of geometric means CLZ:placebo in the prespecified ITT/LOCF dataset) for CLZ 100 mg bid was reportedly 1.21 (95% CI = 1.09-1.35; p= 0.0003).

b. At trough on week 24 in the CLZ 100 mg bid group, the placebo-corrected raw *mean* change from pretreatment ACD was 58.6 meters, and the placebo-corrected raw *median* ACD change was 17.5 m.
In the CLZ 50 mg bid group at trough on week 24, the placebo-corrected raw change from pretreatment ACD was a *mean* of 21 meters vs a *median* of 7.5 m.

c. This study, although one of the "immediate-12.5% incline", and longer duration trials (16-24 week), showed a smaller trough effect of 100 mg bid CLZ on ACD than did the others (i.e. studies 21-92-202, and 21-90-201). The reason for this is not known with certainty, but possible explanatory factors have been considered in the conclusions section of this review.

8.4 Study 21-94-301 : !

4.1 @Design Summary (study 21-94-301)

This concurrent placebo-controlled, double-blind, parallel-group study randomized (in a 1:1 ratio) 247 subjects to either CLZ or placebo (and additionally randomized 123 other subjects to a parallel, positive-control (oxpentifylline[22]) arm). Subjects were atherosclerotic PAD patients with stable, moderate to severe intermittent claudication. They received oral administrations of placebo, cilostazol (given as a fixed 100 mg bid dose), or oxpentifylline (OXP, given as a fixed 400 mg tid dose) for 24 weeks. The objectives were to assess safety (by observing, for example, cardiovascular morbidity and all-cause mortality), and improvement in ICD and ACD, at trough, after 24 weeks of therapy.

The chronology of this study's execution was reportedly as follows:

[22] a British product (which for some reason goes by the slightly different generic name of oxpentifylline) was used. Otsuka asserts that the US and UK versions of Trental® are "clinically" identical.

Table: 13

@Chronology of the execution of study 21-94-301

Event Completed	Date
Original Protocol	11/23/94
1st Amendment	2/9/95
1st subject randomized	4/7/95
2nd Amendment	6/27/95
3rd Amendment	12/2/96
IND submission date	not submitted to IND
Last Subject's Final Follow-up	12/2/96
Final Analysis	5/27/98

[source: addendum submission dated 6/11/98]