8.5   Study 21-94-203:

5.1 @Design Summary   (study 21-94-203)

This concurrent placebo-controlled, double-blind, parallel-group, study randomized (in a 1:1 ratio) 239 subjects (peripheral atherosclerosis patients with moderate-to-severe, stable, intermittent claudication) to receive placebo, or cilostazol given as a fixed 200 mg/d dose in equally-divided twice-daily (100 mg bid) oral administrations for 16 weeks.   The primary objectives were to assess safety (although not including a mortality or cardiovascular morbidity endpoint), and change from baseline ACD, at trough, after 16 weeks of therapy.

The study was conducted from February 10, 1995 to November 27, 1995.

8.5.2 @Enrollment criteria.   (study 21-94-203)

Adult subjects (at least 40 years old) of both sexes were eligible for enrollment if they had atherosclerosis obliterans-induced intermittent claudication which was chronic (at least 6 months), stable (without significant improvement within the past 3 months), and not associated with lower extremity ischemic rest pain, ischemic ulceration, gangrene, or Buerger's Disease. To qualify for randomization, enrolled subjects had to meet additional qualifying criteria related to mptom severity, specificity, and invariability (see below discussion of subject qualification).

Additional bases for exclusion from enrollment were the following:

- female sex and childbearing potential (not recipient of bilateral tubal ligation, or hysterectomy, or not 1 year post-menopausal).
- any history of exercise-limiting cardiac disease (e.g., MI within 6 months or incomplete recovery from any MI, PTCA or CABG within 6 months, CHF, angina, symptomatic cardiac arrhythmias)
- >60% above ideal body weight
- >200 mmHg seated systolic BP or >100 mmHg seated diastolic BP.
- current malignancy with the exception of basal cell carcinoma, or in situ carcinoma of the cervix.
- sympathectomy, lower extremity arterial reparative surgery, Deep vein thrombosis (other than isolated calf vein thrombosis) within the previous 3 months.
- clinically significant bleeding tendencies (or recent surgeries, cerebral or dissecting aortic aneurysms, pericarditis, or pericardial effusions).
- platelet count less than 130,000 or hematocrit less than 30%
- greater than twice the upper limit of normal values for AST or ALT
   erum creatinine > 2.5 mg/dL.
- alcohol or other drug abuse.
- use of an investigational drug within the past 30 days.

- a requirement for the uninterrupted use of pentoxifylline, NSAIDs, the following antiplatelet meds (acetylsalicylic acid, sulfinpyrazone, dipyridamole, ticlopidine), or the following *icoagulants (warfarin, heparin, dicumarol).

8.5.3 @Qualifying criteria. (study 21-94-203)

After enrollment there was to be at least a 2 week lead-in period during which subjects were to be discontinued from prohibited medications. Subjects then qualified for randomization if the following pre-treatment observations were obtained during standardized treadmill testing (during which the treadmill incline increased from 0% by 3.5% every 3 minutes, and speed was fixed at 3.2 km/h):
- attainment of ICD ≤ 54 meters.
- attainment of ACD ≤ 805 meters, with no greater than 20% variance.
- test terminated for intermittent claudication only.
- Doppler supine ABI < 0.90 or evidence of ankle BP decreasing 10-20 mmHg by one minute following symptom-limited treadmill testing.

8.5.4 @Treatment regimen. (study 21-94-203)

Randomized subjects received either placebo, or cilostazol given as a fixed 200 mg/d dose in ially-divided twice-daily (b.i.d.) oral administrations for 16 weeks. Patients were instructed to ...ke their daily doses 30 minutes before breakfast and 30 minutes before dinner. Cilostazol was formulated as a 50 mg tablet (rather than the 100 mg tablet anticipated in the protocol). The lot number was 4C70PP1 for placebo tablets, and 4A81PB2 for cilostazol tablets.

8.5.5 @Endpoints. (study 21-94-203)

8.5.5.1 @Endpoint Descriptions (study 21-94-203)

The protocol-specified primary endpoint was an analysis of the effects of cilostazol on ICD and ACD using analysis of variance of the log of the ratio of the distance at week 16 to the pre-treatment distance, and employing the LOCF method of handling missing data. An amendment (dated June 23, 1995) made the ACD metric the sole primary endpoint, and relegated ICD to secondary endpoint status. Another amendment (dated November 21, 1994) added treadmill tests at presumed peak (3-4 hours after dosing), with the apparent intention for this to be a secondary endpoint.

The prespecified secondary outcome variables were:

    CD at presumed peak.
- ICD at presumed peak.
- trough ICD (at end of dosing interval).

- Subjective claudication improvement as per patient and physician.
- Doppler-measured limb pressures.
- Quality of Life questionnaires.

8.5.5.2 @Measurement methods (study 21-94-203)

The "delayed-incline" treadmill method was used wherein incline loading was delayed until the 3rd minute of walking, and then gradually increased by 3.5% increments every 3 minutes (with speed constant at 3.2 km/h (2 mph). Walking tests were only to be stopped for claudication of sufficient severity to cause the subject to be unable to continue walking. There was no prespecified provision for tests to stop for such reasons as reaching an arbitrarily long duration or distance of walking. Peak and trough tests were performed at weeks 8, and 16, with an additional trough test performed at week 12.

Quality of Life and disease-specific questionnaires (Medical Outcomes Scale Short Form-36 (SF36), the Walking Impairment Questionnaire (WIQ), and Physical Activity Recall (PAR) questionnaire) were administered at weeks 8 and 16.

Prior to treatment, and at weeks 2, 4, 8, 12, and 16 the patients were evaluated with assessment of adverse events and concomitant medications, as well as vital signs, serum chemistry, hematology, and EKG. Urinalysis was performed at weeks 2 and 16. Physical examination was performed at baseline, and week 16. Blood samples were drawn at weeks 2, 8, and 16 for an assessment of plasma concentration of cilostazol and two primary metabolites.

8.5.5.3 @Statistical analyses. (study 21-94-203)

The amended prospective primary endpoint was a comparision of 100 mg b.i.d cilostazol and placebo with respect to ACD at trough on week 16, using ANOVA of log(distance week 16/baseline) in an ITT/LOCF dataset.
Testing was to be two -sided at an alpha level of 0.05. The sponsor reports that there was no interim look for this study.

A secondary analysis was to employ a "completers" dataset of patients who had nonmissing treadmill data at baseline and at each follow-up visit.
- An exploratory analysis was to look at log(distance/baseline) over time employing repeated measures ANOVA, and the Wei-Lachin multivariate rank test using change from baseline.

The Wilcoxon test was used to compare treatments groups on quality-of-life parameters. Wei-Lachin will be used to assess change over time. Analysis will be performed on all existing data without the use of the LOCF method for handling of missing data. Baseline variables were compared using Wilcoxon rank sum test or Fisher's exact test.

The sample size of this study was based on the ACD endpoint, and entailed the following assumptions: an assumed raw percent change from pre-treatment ACD of 40% for cilostazol vs ˙% for placebo; an assumed ˍ ometric mean change from baseline (based on the log of (distance/baseline)) of 0.24 for cilostazol versus 0.08 for placebo. The sponsor reports that 100 patients per group were needed to provide greater than 80% power based on a two-sided, 5% significance level.

8.5.6 **Results other than Efficacy outcomes** (study 21-94-203):

8.5.6.1   @Code breaks: (study 21-94-203)

In study 21-94-203, the blind was reportedly broken for one patient (no. 219, unblinded 9/4/95) reportedly after the patient withdrew with an abnormally high serum alkaline phosphatase level.

8.5.6.2   @Covariates.   (study 21-94-203)

The reported imbalances in pre-treatment covariates were not of sufficient quality and/or quantity to plausibly influence outcome measures. Demographic and pre-treatment characteristics of subjects are shown in the table below.

Table: 17

@Demographic & Pre-treatment characteristics in study 21-94-203:
(dataset = all-randomized subjects)

	CLZ 100 mg bid	Placebo
	n= 119	n= 120
male	76%	75%
female	24%	25%
mean age	65	65
Caucasian	89%	85%
Black	8%	9%
other ethnic	3%	6%
wt mean (kg)	83	80
concomitant cigarette use	36%	40%
diabetes	25%	31%
resting ABI mean	0.64	0.68
SD	0.18	0.18

[source: table 7-1, pg 78, vol 160; & submission 7/6/98]

8.5.6.3   **@Disposition of subjects.**   (study 21-94-203)

Subject disposition was as follows:

- 239 subjects were randomized (evenly distributing among treatment groups as 119 cilostazole, 120 placebo).

- 219 subjects comprised the "efficacy" dataset (these were evenly distributed in the efficacy set as: 108 cilostazole, 111 placebo). These had at least one nonmissing pre-treatment ACD datum, and at least one nonmissing post-randomization ACD datum. No subjects were excluded because of missing pre-treatment walking test data.

The total rate of any dropout was roughly comparable in the two treatment groups. The attributed sons for all dropouts are shown in the following table.

Table: 18

Subject dropouts in study 21-94-203:
(all-randomized dataset)

	CLZ 100 mg bid	Placebo
# randomized	n = 119	n = 120
Total dropouts	15 (14%)	12 (11%)
Dropouts for any AE	12 (10%)	10 (8%)
All dropouts, by reason:		
nonfatal adverse event	12	9
death	0	1
lack of efficacy	0	1
noncompliance	2	0
other	1	1

[source: table 6-1, pg 72, vol 160]

The most frequent protocol deviations involved compliance deviations (21% in the cilostazol group, and 15% in the placebo group) and concomitant medication deviations (11% in the each group). An equivalent percent (71%) of cilostazol placebo patients received study drug from between 15 and 17 weeks. About half of the concomitant medication deviations involved pping prohibited medications less than 2 weeks prior to the study. No data were excluded as a result of protocol deviations.

8.5.7 @Efficacy Outcomes: (study 21-94-203)

5.7.1 @Tests stopped for nonspecific reasons: (study 21-94-203)

The stopping of final tests for nonspecific reasons (defined as reasons other than claudication) occurred in approximately 10% of clz-randomized subjects, and 9% of placebo-randomized subjects.

8.5.7.2 @Primary analyses: (study 21-94-203)

The baseline ACD data had a non-normal distribution.[1] At baseline in the efficacy dataset, the raw mean trough ACD was roughly comparable in the cilostazole vs placebo-randomized subjects, as was the mean trough ICD approximately similar in the two groups. These data are shown in the following table.

Table: 19

Baseline raw mean walking distances (in meters) in study 21-94-203:

| baseline metric	CLZ	Placebo
ACD	237	244
ICD	130	139

As shown in the figure below, the sponsor's results for the primary efficacy endpoint (the ratio of geometric mean trough ACD (cilostazol: placebo)) showed a 29% increase from pre-treatment at week 16 (95% CI = 17-41%; p=0.0001).

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

Figure: 10

Percent change from pre-treatment, in the ratio (clz:plac) of geometric mean walking distance at *TROUGH*

[study 21-94-203; log transformed data, ITT/LCOF]
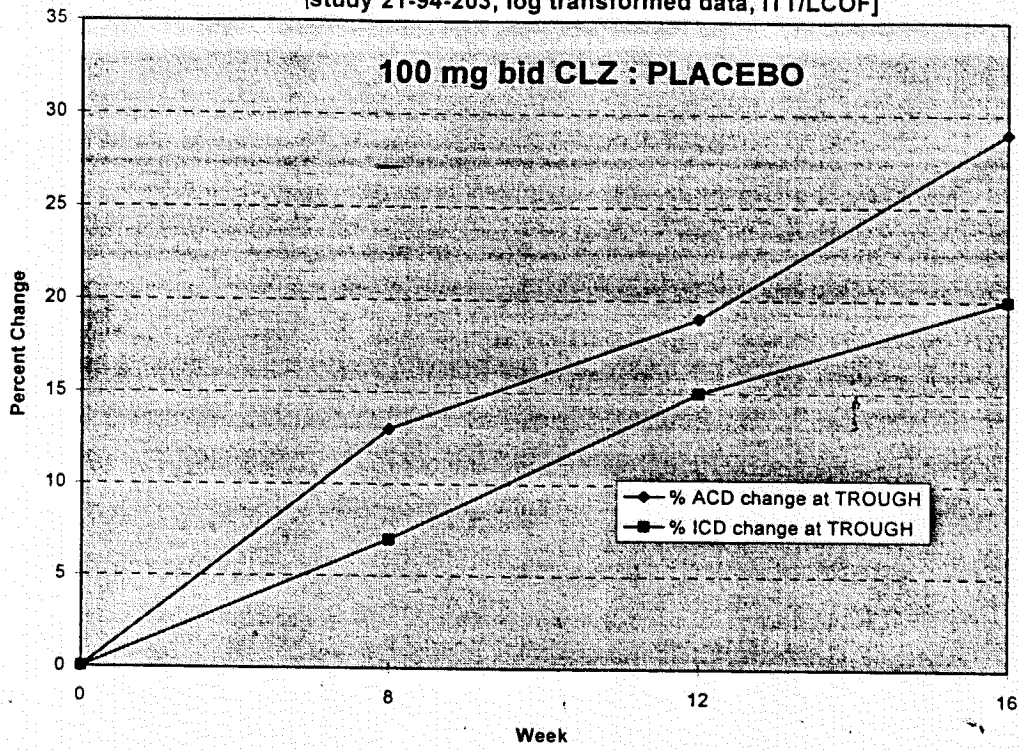
There was no treatment-by-center interaction nor any treatment-by-baseline interaction for either ACD or ICD.

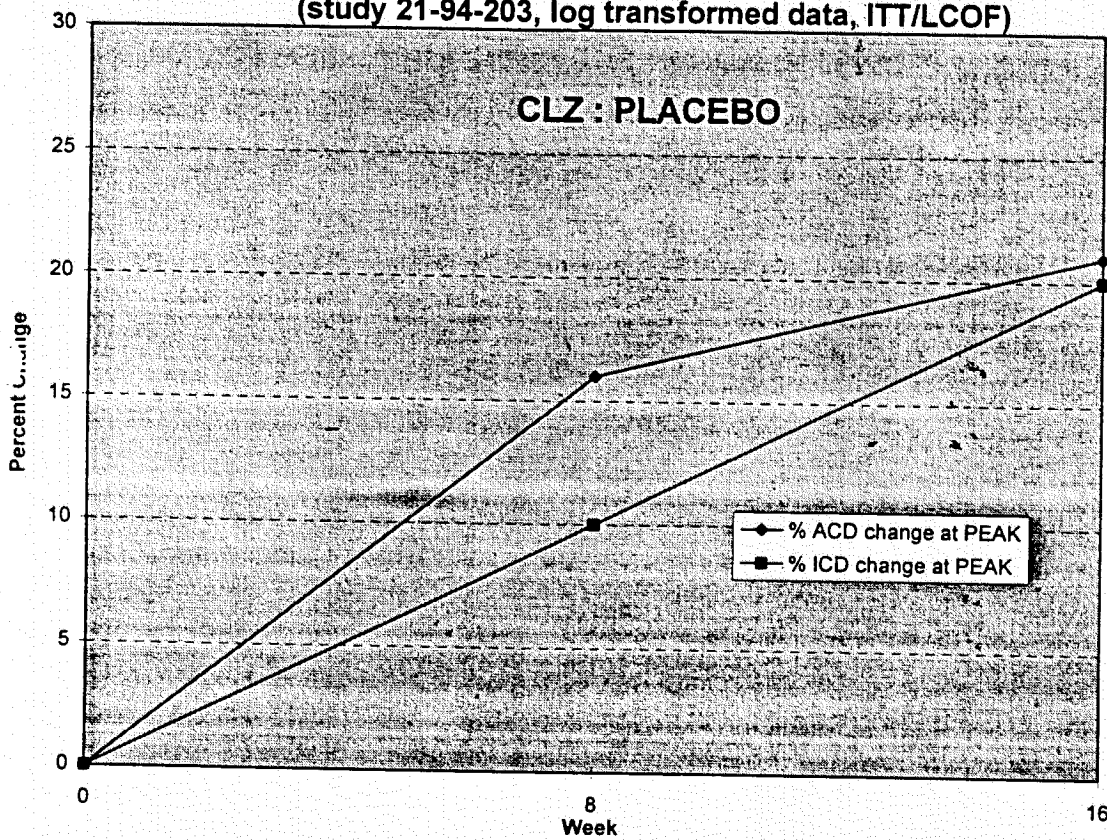...5.7.3   @Other efficacy analyses: (study 21-94-203)

The ratio of geometric mean changes at presumed *peak* are described in the figure below. These reached approximately 20% for ACD at week 16.

Figure: 11

Percent change from pre-treatment, in the ratio (clz:plac) of geometric mean walking distance, at *PEAK* (study 21-94-203, log transformed data, ITT/LCOF)

The raw data are shown in the two figures below. Note that the raw mean placebo-corrected change in trough ACD in the cilostazol 100 mg bid group was approximately 29 meters (at week 48 meters (at week 12), and 65 meters (at week 16). For ICD, the mean placebo-corrected change at trough was, in the cilostazol group, approximately 13 meters at week 8, 29 meters at week 12, and 29 meters at week 16.

At week 16 the point estimate of the trough/peak ratio was unexpectedly less than 1.0 for both ACD (0.64), and ICD (0.36).
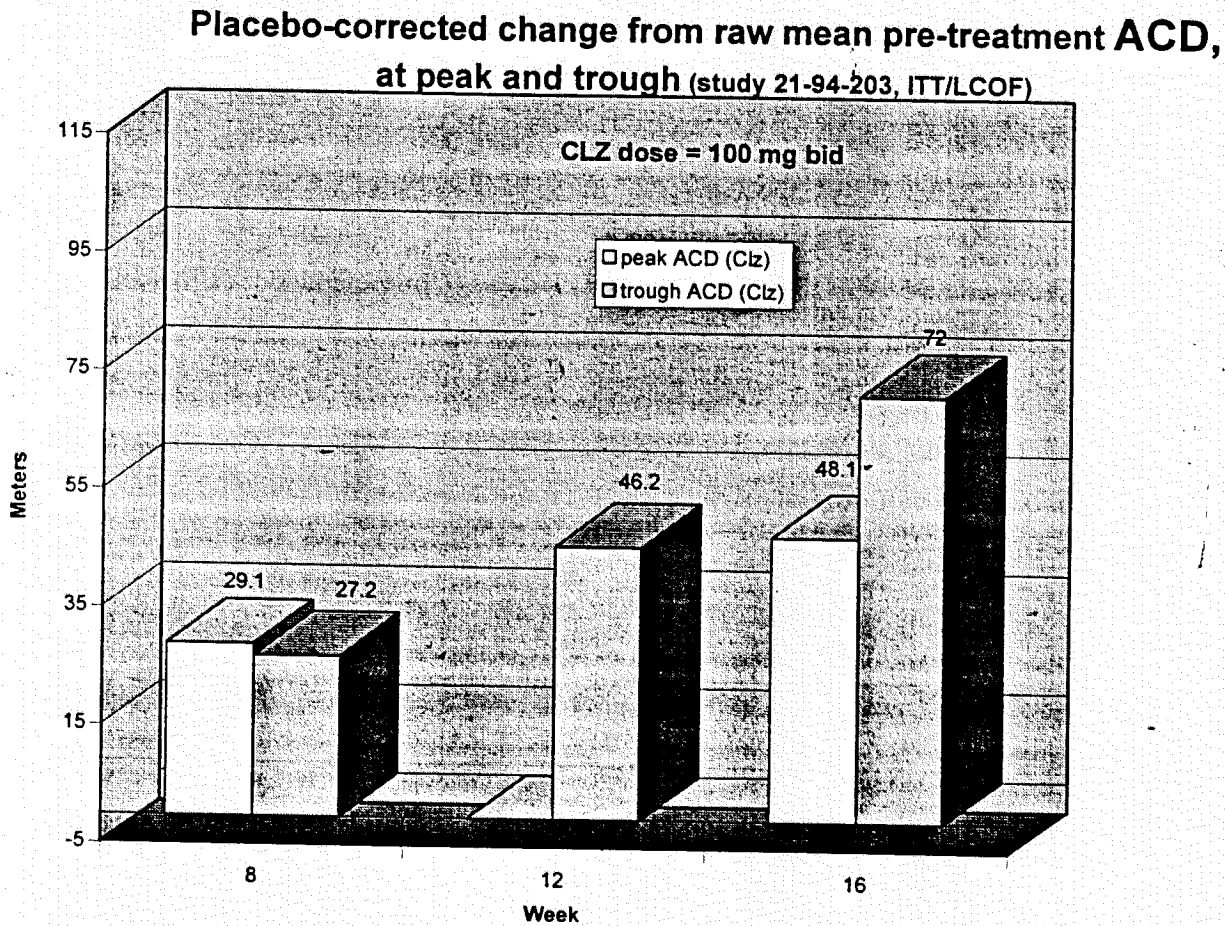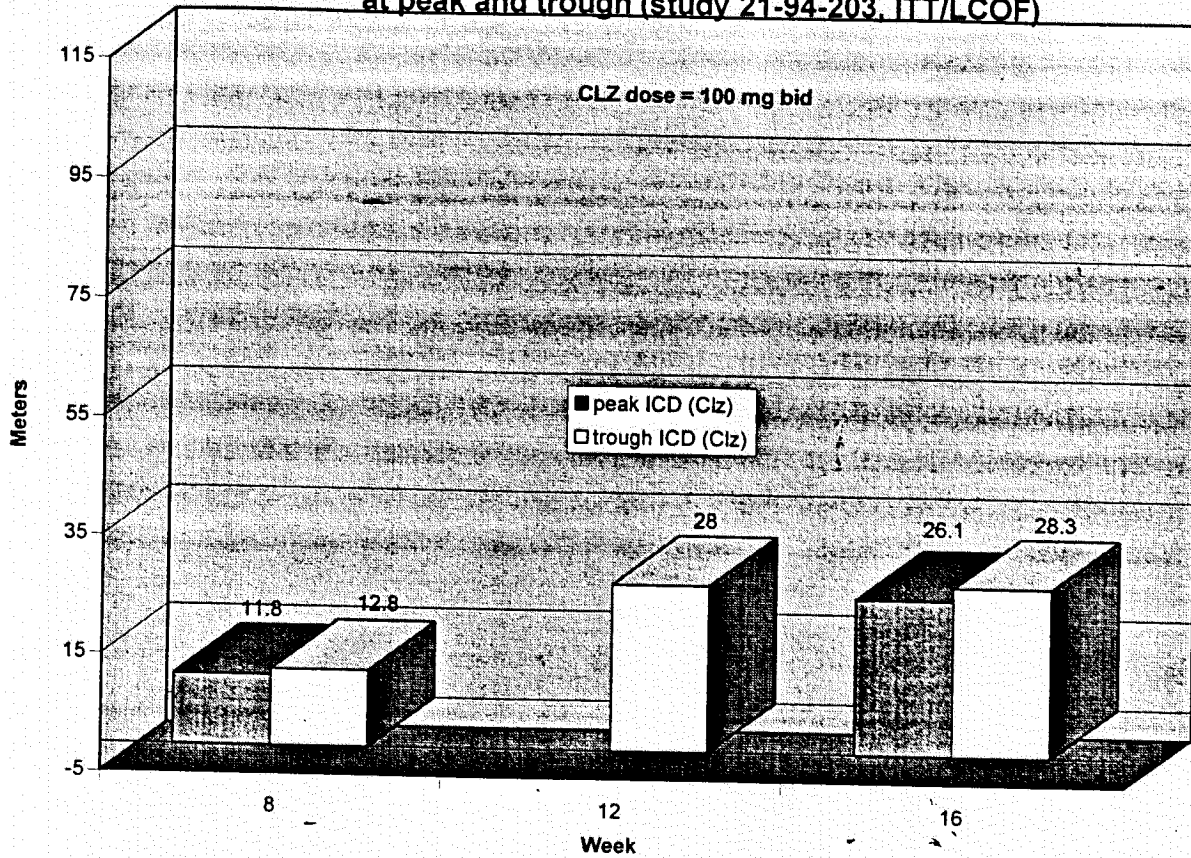
Figure: 12

Placebo-corrected change from raw mean pre-treatment ACD, at peak and trough (study 21-94-203, ITT/LCOF)

CLZ dose = 100 mg bid

Legend: □ peak ACD (Clz) □ trough ACD (Clz)

Values shown: Week 8: 29.1, 27.2; Week 12: 46.2; Week 16: 48.1, 72

Y-axis: Meters (-5, 15, 35, 55, 75, 95, 115)
X-axis: Week (8, 12, 16)

Figure: 13

Placebo-corrected change from raw mean pre-treatment ICD, at peak and trough (study 21-94-203, ITT/LCOF)

CLZ dose = 100 mg bid

Legend:
- peak ICD (Clz)
- trough ICD (Clz)

Values: 11.8, 12.8 (Week 8); 28 (Week 12); 26.1, 28.3 (Week 16)

Y-axis: Meters (-5, 15, 35, 55, 75, 95, 115)
X-axis: Week (8, 12, 16)

Quality of life measures reportedly showed the following: on Physical Function measures at week 16 the cilostazol group showed a mean change from baseline of 8.3 versus 2.3 in the placebo up, which was nominally significant (p<0.05). For the Bodily Pain measures and Role-physical measures there was a nonsignificant trend for the superiority of cilostazol group over placebo at week 16. For the Mental Health measures, Role-Emotional, General Health, Physical Activity Recall, and Social Functioning measures there were no statistically significant differences between treatment groups.

Therapeutic assessment by both investigators and patients reportedly showed nominally significantly more cilostazol patients than placebo patients having improvement in claudication symptoms. Investigators judged 49.6% of outcomes to be "better" or "much better" than pretreatment in the cilostazol group, compared to 33.6% in the placebeo group. Similarly, 57.4% of patients in the cilostazol group rated their own outcome as "better" or "much better" relative to pretreatment, compared to 35.9% in the placebo group.

Little differences in the response to treatment were noted between demographic subgroups.

8.5.8 @Commentary on the evidence   (study 21-94-203).

'he ratio of geometric mean increase from pre-treatment ACD (clz 100 mg bid: plac) was ,ortedly 29% at trough on week 16 (95% CI = 17-41%; p=0.0001).

b. in this study the effect of 100 mg bid CLZ at trough on week 16 was a raw mean placebo-corrected change from pre-treatment ACD of 72 m (the placebo-corrected median change was comparable, i.e. 61.5 m).

c. this study found that the mean clz effect on ACD at presumed peak (3-4 hours after dosing) was less than the effect at trough. The week 16 ratio (cilostazol: placebo) of geometric mean change from pre-treatment ACD was approximately 20% at presumed peak vs about 29% at trough; so too the raw median results reflected this apparent paradox (placebo-corrected median changes from pre-treatment ACD were 42 m at peak and 61.6 m at trough). The reason for this is unclear. Perhaps 3-4 hours post-dosing does not represent the actual pharmacodynamic peak.