**@Demographic and pre-treatment characteristics of all randomized subjects in study 21-93-201:**

(all-randomized dataset)

| | CLZ 100 mg bid | Placebo |
|---|---|---|
| | n= 95 | n= 94 |
| male | 87% | 81% |
| female | 13% | 19% |
| age (mean) | 67 | 66 |
| age <65 yr | 39% | 45% |
| Caucasian | 88% | 82% |
| Black | 12% | 15% |
| other ethnic | 0% | 3% |
| wt mean (kg) | 82 | 81 |
| concomitant cigarette use | 39% | 45% |
| diabetes | 19% | 20% |
| resting ABI mean | 0.66 | 0.65 |
| SD | 0.17 | 0.16 |

*[source: pg 80, vol 170]*

8.7.6.3 **@Disposition of subjects.** (study 21-93-201)

Subject disposition was as follows:

- 189 subjects were randomized (evenly distributing among treatment groups as 95 cilostazole, 94 placebo).

75 subjects (evenly distributing as 86 in the clz group, and 89 in the placebo group) 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.

The total rate of any dropout was higher in the clz-treated group than in the placebo group. The ibuted reasons for all dropouts are shown in the following table.

**Table: 24**

**Subject dropouts in study 21-93-201:**
(all-randomized dataset)

| | CLZ 100 mg bid | Placebo |
|---|---|---|
| | n = 95 | n = 94 |
| Total dropouts | 13 (14%) | 6 (6%) |
| Dropout for any AE | 12 (13%) | 5 (5%) |
| All dropouts, by reason: | | |
| general inability to continue | 0 | 1 |
| noncompliance | 1 | 0 |
| adverse event | 12 | 5 |

*[source: pg 73, vol 170]*

The patients having a protocol deviation were generally roughly comparably distributed by treatment group; the majority involved compliance and nonadherance to the window for conducting peak treadmill tests. No data were excluded as a result of protocol violations.

8.7.7 @**Efficacy outcomes:** (study 21-93-201)

.7.1 @**Tests stopped for nonspecific reasons:** (study 21-93-201)

The stopping of final tests for nonspecific reasons (defined as reasons other than claudication) occurred in approximately 11% of clz-randomized subjects, and 10% of placebo-randomized subjects.

8.7.7.2 @**Primary analyses:** (study 21-93-201)

The baseline ACD data had a non-normal distribution.[3] Considering the raw mean data, it was reported that at baseline in the all-randomized dataset all measures of walking distances (i.e., ACD and ICD, at both trough and presumed peak) showed lower pre-treatment exercise tolerance in the cilostazole group than in the placebo group. These data are provided in the table below.

**Table: 25**

**Baseline raw mean walking distances (in meters) in study 21-93-201:**

| *metric* | *CLZ 100 mg bid* | *Placebo* |
|---|---|---|
| trough ACD | 258 | 300 |
| peak ACD | 262 | 278 |
| trough ICD | 134 | 145 |
| peak ICD | 122 | 142 |

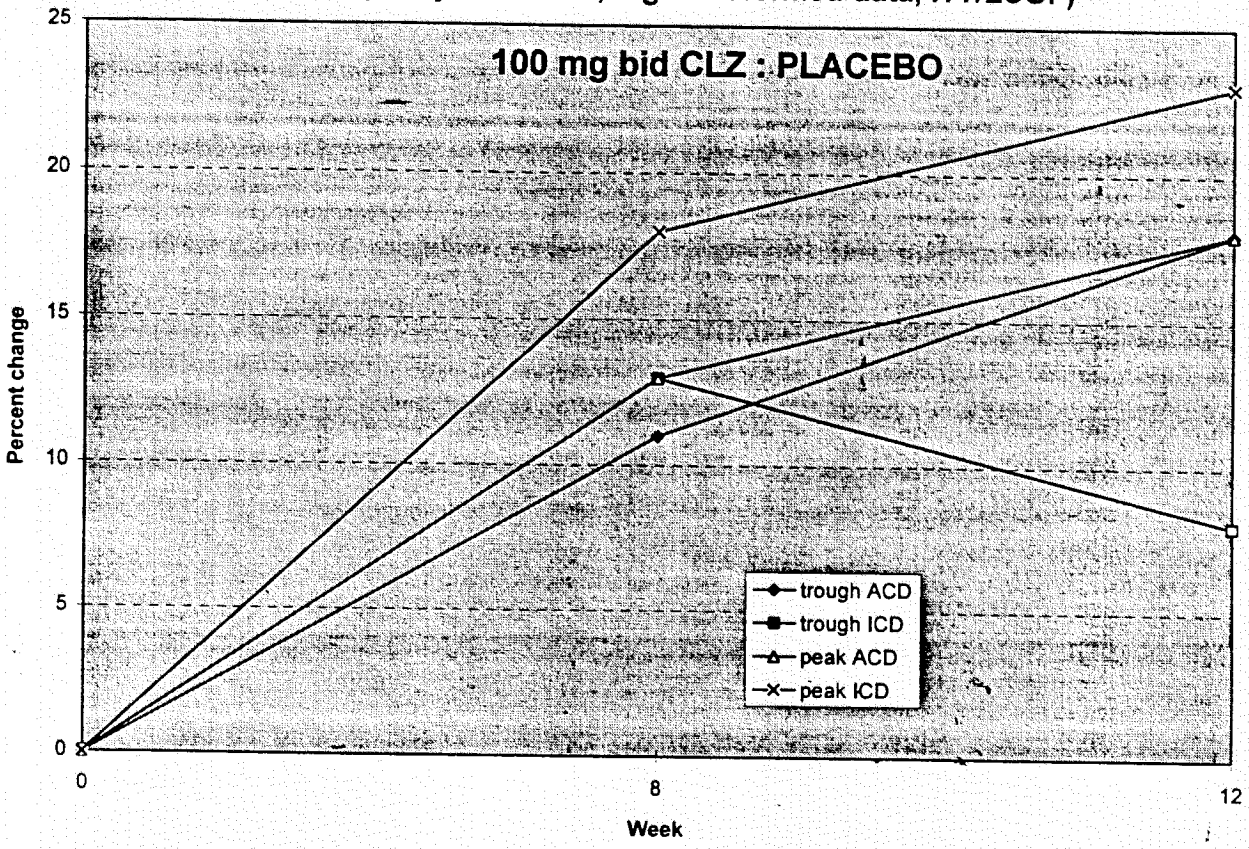
As shown in the below figure depicting the results of the sponsor's analyses, at week 12 the cilostazole group's trough ACD results showed a nominally significant[4] 13% change from the baseline ratio (clz:placebo) of geometric mean ACD (95% CI = 1-26%; uncorrected p= .035), while this group's trough ICD results were nonsignificant (8% mean change; 95% CI = -8 to +27%).

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

[4] but not expected to remain significant after multiplicity correction for what I count to be 6 primary endpoints.

## Figure: 16

**Percent change from pre-treatment in the ratio (clz:plac) of geometric mean walking distances**
**(study 21-93-201; log transformed data, ITT/LCOF)**




At week 12, the cilostazole group's ACD results at presumed peak showed a nominally significant 18% change (95% CI = 4-33%; uncorrected p= 0.008), as did this group's peak ICD results (23% mean change; 95% CI = 5-43%; uncorrected p= 0.009).

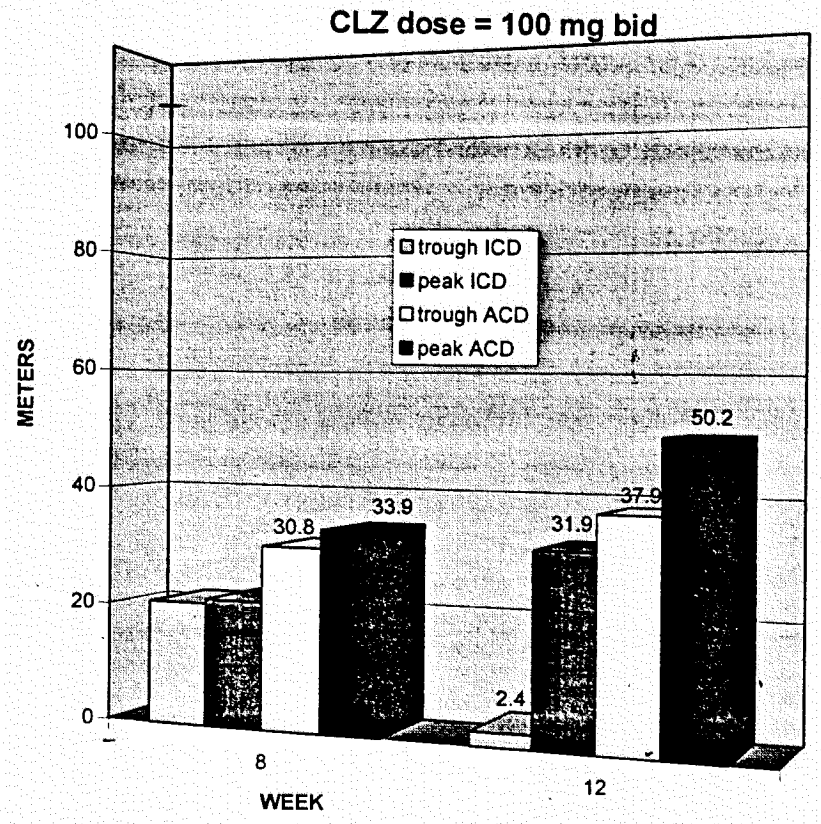
There was no significant treatment-by-center interaction and there significant treatment-by-baseline interaction for either ACD or ICD.

8.7.7.3 **@Other efficacy analyses:** (study 21-93-201)

As shown in the figure below, at week 12 the raw data showed an approximately 38 meter placebo-corrected increase from baseline mean ACD in the cilostazole group at trough, but essentially no improvement in trough ICD. At presumed peak on week 12 in the cilostazole group there was an approximately 50 meter placebo-corrected increase from baseline raw mean ACD, and an approximately 32 meter increase in peak ICD.

# Figure: 17

**Placebo-corrected change from pre-treatment raw mean walking distances, at peak and trough (study 21-93-201, ITT/LCOF)**



Quality of life measures: For most of the quality of life questionnaires (e.g. Bodily Pain measures, 'e-Physical measures, Mental Health measures) drug reportedly could not be distinguished .ın placebo, and for some (e.g. Physical Function measures) there was purportedly a finding of the clz group showing a larger than placebo improvement.

Investigators judged 48% of outcomes to be "better" or "much better" relative to pretreatment in the CLZ group, compared to 31.9% in the placebo group. More patients in the cilostazol group than in the placebo group (51 vs 34%, respectively) rated their own degree of improvement from baseline as outcome as "better" or "much better".

## 8.7.8 @Commentary on the evidence (study 21-93-201)

CLZ (100 mg bid) showed, at trough on week 12, a nominally significant 13% (95% CI = 1-
%) change from the pre-treatment ratio (clz:placebo) of geometric mean ACD. The uncorrected p value (p=.035) would not be expected to remain significant after multiplicity correction for what were 6 primary endpoints[5]. With respect to trough ICD, there was not even a nominally significant change.

b. CLZ (100 mg bid) increased pretreatment ACD, at trough on week 12, by a raw mean of 38 meters (the median change was 30.5 m).

c. peak:trough effect ratio- at presumed peak on week 12 the clz group showed a 12 meter larger raw mean placebo-corrected increase in ACD, relative to that observed at trough.

[5] three metrics (trough ACD, trough ICD and serum HDL) were analyzed by each of 2 methods (Wei-Lachin and log(distance/baseline)).

## 8.8 Study 21-90-201: !

### 1 @Design Summary (study 21-90-201)

This placebo-controlled, double-blind, parallel-group study randomized (in a 1:1 ratio) 81 subjects (peripheral atherosclerosis patients with moderate-ly severe, stable, intermittent claudication) to receive placebo, or cilostazol given as a fixed 100 mg bid oral dose for 16 weeks. Subjects were randomized 2:1 to cilostazol vs placebo. The primary objectives were to assess change from baseline ACD, change from baseline ICD, and change in a quality of life scale.

**Table: 26**

**@Chronology of the execution of study 21-90-201**

| Event Completed | Date |
|---|---|
| Original Protocol | 11/30/90 |
| 1st Amendment | 3/22/91 |
| 1st subject randomized | 7/14/91 |
| IND submission of 1st Amendment | 4/25/91 |
| Last Subject's Final Follow-up | 9/15/92 |
| Final Analysis | 6/23/97 |

[source: addendum submission dated 5/13/98]

### 8.8.2 @Enrollment criteria. (study 21-90-201)

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, severe ulceration, or gangrene. To qualify for randomization, enrolled subjects had to meet additional qualifying criteria related to symptom specificity, and invariability (see below discussion of subject qualification).

Additional bases for exclusion from enrollment were the following:

- female of childbearing potential.
- sympathectomy or lower extremity arterial reparative surgery, including endovascular procedures, within the previous 3 months.
- greater than 60% above ideal body weight.
- treated sitting arterial BP >200 mmHg systolic or >100 mmHg diastolic.
- deep vein thrombosis within the past 3 months, other than isolated calf vein thrombosis.

- non-vascular disease causing inability to perform a treadmill walking test.
- a requirement for the uninterrupted use of pentoxifylline, NSAIDs (except acetaminophen and, when clinically necessary for pain, diclofenac sodium), the following antiplatelet meds (acetylsalicylic acid, sulfinpyrazone, dipyridamole, clofibrate), the following anticoagulants (warfarin, heparin), or the following vasoactive agents (papaverine, isoxsuprine, nylidrin, cyclandelate, or niacin derivatives). Nitroglycerin was allowed used used "occasionally" (undefined) on a once or twice daily basis.
- current alcohol or other drug abuse, or use of an investigational drug within the past 30 days.

8.8.3 @**Qualifying criteria.** (study 21-90-201)

After enrollment there was to be at least a 2-4 week lead-in period during which subjects were to be discontinued from prohibited medications. Subjects then qualified for randomization if the following observations were obtained during standardized treadmill testing conducted prior to to study treatment:

- attainment of 30-200 meter ICD (with treadmill conditions of: 12.5% incline, and 3.2 km/h speed), with no greater than 35% intra-patient variation between tests.
- test terminated for intermittent claudication only.

.4 @**Treatment regimen.** (study 21-90-201)

Subjects were randomized (2:1, cilostazol versus placebo) to receive placebo, or cilostazol given as a fixed 100 mg bid oral dose for 12 weeks.
Patients were to take study drug 30 minutes prior to eating. Randomization was stratified by whether or not subjects took calcium channel blockers. Cilostazol was formulated as 100 mg tablets, from lot number 0H89-100P.

8.8.5 @**Endpoints.** (study 21-90-201)

8.8.5.1 @**Endpoint Descriptions** (study 21-90-201)

The primary efficacy endpoints were prespecified as log (ACD on treatment/ACD at pre-treatment baseline), log (ICD on treatment/ICD at pre-treatment baseline), and a quality-of-life assessment. This description was vague insofar as no discrete on-treatment week(s) was declared for use in the primary analysis. The data were reportedly obtained only at trough. The prespecified quality-of-life scale was the Sickness Impact Profile, but a second instrument (Claudication Outcome Measures (COM) was also pursued. Subjective claudication improvement, as per patient and physician, was assessed as a secondary outcome variable.

8.8.5.2 @**Measurement methods** (study 21-90-201)

The "immediate-incline" treadmill method was used wherein the incline load started immediately 12.5% (and remained constant), with speed also 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. Treadmill tests were performed pre-treatment, and at weeks 4, 6, 8, 12, and 16.

Quality of Life questionnaires (Sickness Impact Profile, and Claudication Outcome Measures), and urinalysis were performed pre-treatment, and at weeks 4, 8, 12, and 16. Prior to treatment, and at weeks 4, 6, 8, 12, and 16 the patients were evaluated with assessment of adverse events and concomitant medications, as well as EKG, vital signs, serum chemistry, and hematology. Blood samples were drawn at pre-treatment, and weeks 4, 6, 8, 12, and 16 for central lab assessment of plasma concentration of cilostazol and its two main metabolites (OPC-13213 and OPC-13015). Physical examination was performed at baseline, and week 16.

8.8.5.3 @**Statistical analyses.** (study 21-90-201)

Analyses were prespecified to be conducted on the all-randomized/LOCF dataset, according to the intent-to-treat principle. Comparisons of treatments were to be based on the extended Mantel-Haenszel procedure and the Fisher procedure. Comparisons of treatments were to be based on the extended Mantel-Haenszel procedure and the Fisher procedure. The sponsor reports that there was no interim look. The sample size was only briefly (and somewhat vaguely) described as being based on the "ICD and/or ACD" endpoint, a power of 90%, a two-sided significance level of 0.05, with a detection threshold of 40% difference from placebo.

8.8.6 @**Results other than Efficacy outcomes** (study 21-90-201)

After the reportedly pre-specified goal of 60 randomized patients was met, enrollment was extended and then stopped arbitrarily when 81 patients had been randomized.

8.8.6.1 @**Covariates.** (study 21-90-201)

Demographic and pre-treatment characteristics of subjects are shown in the table below. There was a somewhat higher percentage of males, tobacco users, and non-diabetics in the placebo group.

## Table: 27

**@Demographic & Pre-treatment characteristics of subjects in study 21-90-201:**
(all-randomized dataset)

| | Placebo | CLZ 100 mg bid |
|---|---|---|
| | n= 27 | n= 54 |
| male | 89% | 70% |
| female | 11% | 30% |
| age (mean) | 67 | 66 |
| Caucasian | 100% | 98% |
| Black | 0% | 2% |
| wt mean (kg) | 84 | 79 |
| concomitant tobacco use | 56 | 41 |
| diabetes | 15 | 26 |
| resting ABI mean | 0.59 | 0.55 |
| SD | 0.18 | 0.14 |

*[source: pg 50, vol 194; & submission 7/6/98]*

8.8.6.2 **@Disposition of subjects.** (study 21-90-201)

Subject disposition was as follows:

- 81 subjects were randomized (distributing as 54 to the cilostazole group, and 27 to placebo).

The fraction of patients who dropped out because of an AE was higher in the clz-treated group (9%) than in the placebo group (4%). The attributed reasons for all dropouts are shown in the following table.

## Table: 28

**Subject dropouts in study 21-90-201:**
(all-randomized dataset)

| | Placebo | CLZ 100 mg bid |
|---|---|---|
| | n = 27 | n = 54 |
| Total dropouts | 5 (19%) | 10 (19%) |
| Dropouts for any AE | 1 (4%) | 5 (9%) |
| All dropouts, by reason: | | |
| adverse event | 1 | 5 |
| clinical deterioration | 1 | 3 |
| failed screening | 1 | 2 |
| other, | 2 | 0 |

*[source: pg 49, vol 194]*

8.8.7 @**Efficacy outcomes**: (study 21-90-201)

8.8.7.1 @**Tests stopped for nonspecific reasons**: (study 21-90-201)

The stopping of final tests for nonspecific reasons (defined as reasons other than claudication) occurred in approximately 15% of clz-randomized subjects, and in 11% of placebo-randomized subjects[6].

[6] as per addendum submission dated 6/9/98.

8.8.7.2 @**Primary analyses:** (study 21-90-201)

e baseline ACD data had a non-normal distribution.[7] At baseline in the efficacy dataset, the mean trough ACD was about 13 meters lower in the cilostazole group, relative to the placebo group. These data are shown in the following table.

**Table: 29**

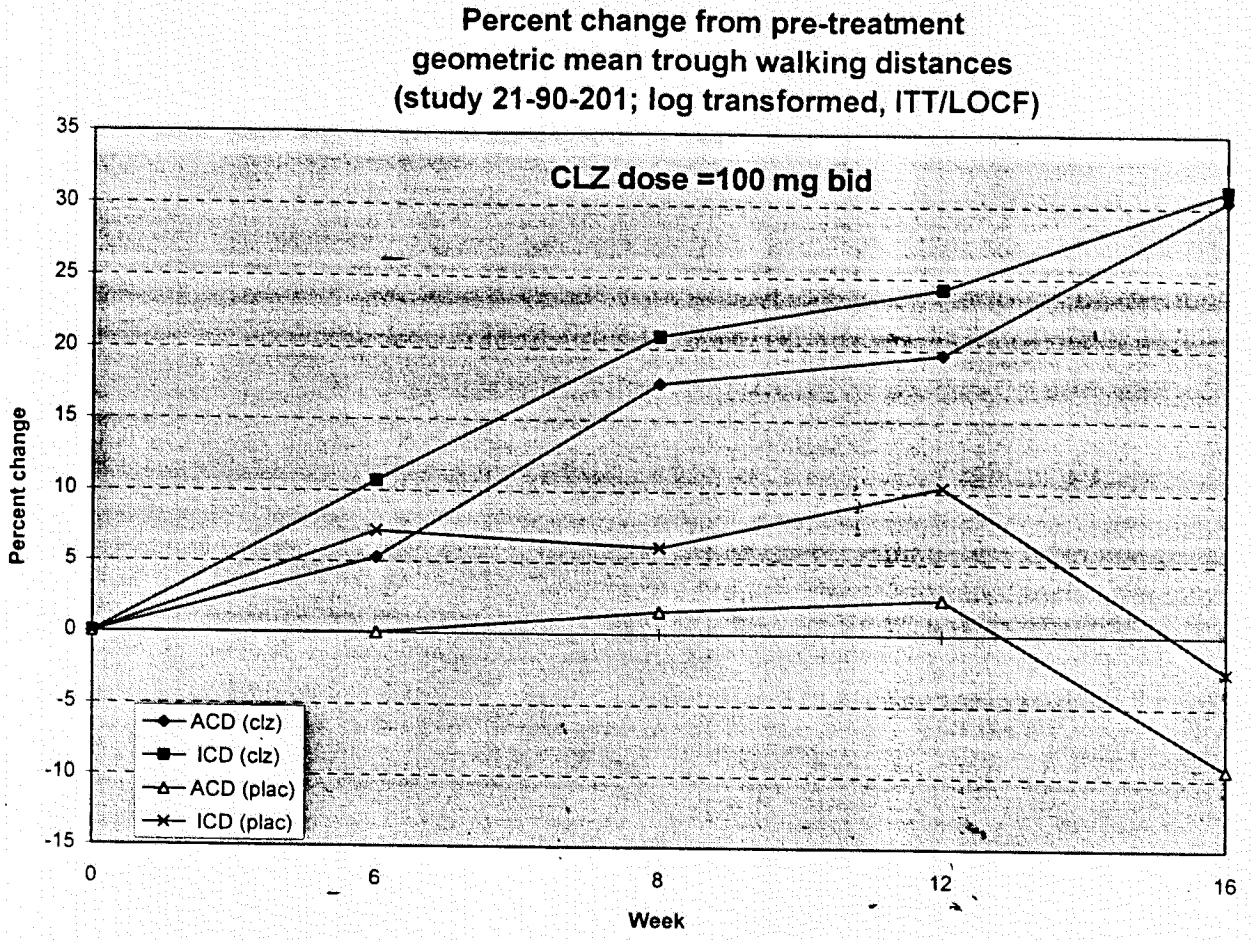
**Baseline raw mean walking distances (in meters) in study 21-90-201:**

| *baseline metric* | *Placebo* | *CLZ 100 mg bid* |
|---|---|---|
| trough ICD | 76 m | 70 m |
| trough ACD | 163 m | 140 m |

In the sponsor's analyses, at trough on week 16 the clz group manifested a nominally statistically significant 30.5% increase from pre-treatment geometric mean ACD (uncorrected p value = 01) while the placebo group showed about a 9.3% decrease from pre-treatment geometric mean ACD. A comparable and also nominally statistically significant (uncorrected p value = 0.015) week 16 clz effect was reported with respect to ICD. These results are shown in the figure below.

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

# Figure: 18


Percent change from pre-treatment
geometric mean trough walking distances
(study 21-90-201; log transformed, ITT/LOCF)
CLZ dose =100 mg bid
Percent change
35
30
25
20
15
10
5
0
-5
-10
-15
ACD (clz)
ICD (clz)
ACD (plac)
ICD (plac)
0
6
8
12
16
Week

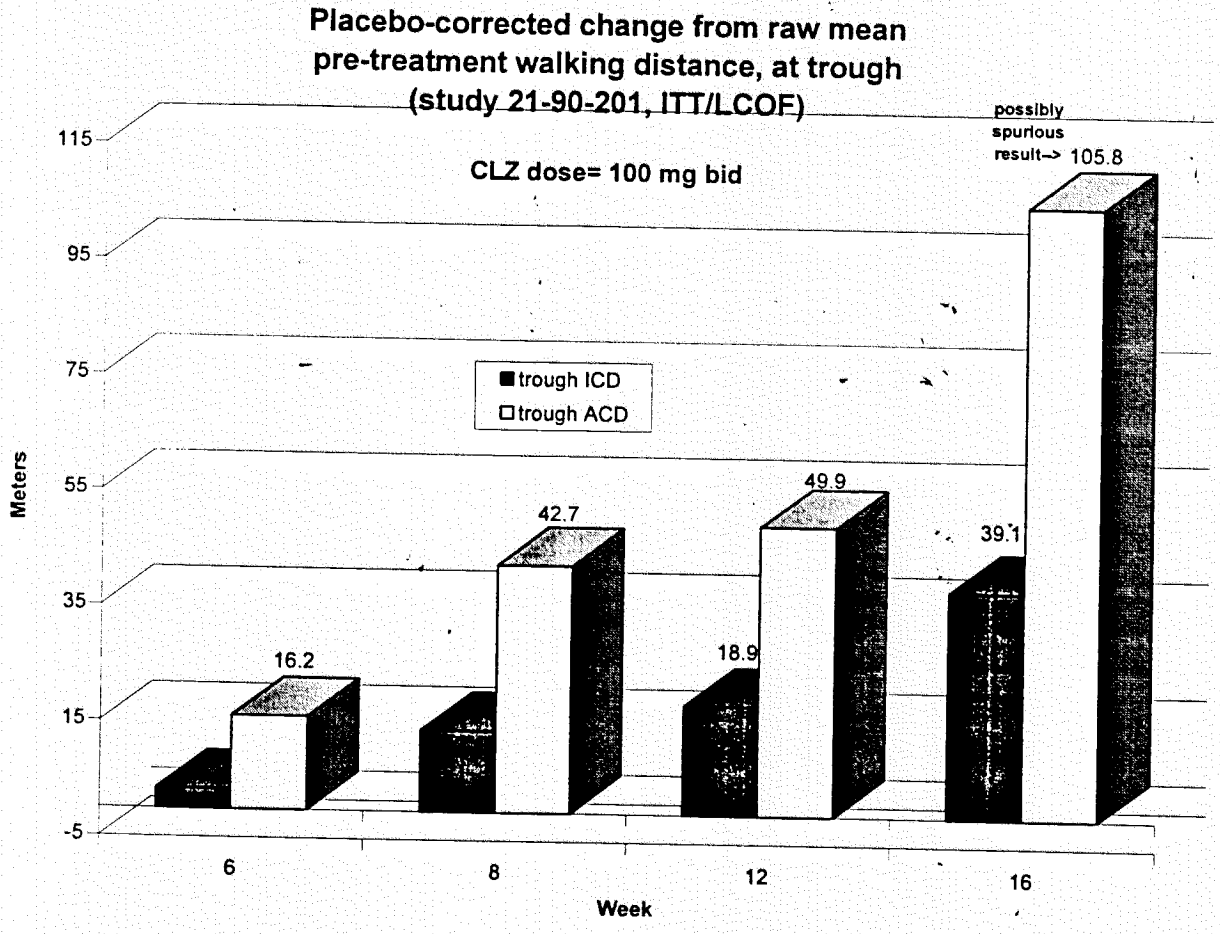
In the 100 mg bid clz group there was reportedly a statistically significant treatment-by-baseline interaction for baseline ACD wherein the estimated magnitude of effect on ACD was lesser in those with smaller pre-treatment ACD.

There was no significant treatment-by-center interaction for either ACD or ICD.

8.8.7.3 @**Other efficacy analyses:** (study 21-90-201)

The raw data are shown below. Here the mean placebo-corrected change from pre-treatment at 16 weeks was 31.9m for ICD and 105.8m for ACD (a result influenced by deterioration in the placebo group at week 16).

**Figure: 19**



Subjective claudication improvement as per patient and physician showed patients in the ostazol group to be more frequently rated as better or much better at the end of the study. Fifty cent of the cilostazol-treated patients felt the study drug helped their claudication compared to only 19% of the placebo-treated patients. No patients receiving cilostazol felt the drug made their claudication worse. Forty-eight percent of the physicians felt that the cilostazol-treated patients' claudication was improved compared to only 22% for the placebo-treated patients.