Table: 2

@Demographic & Pre-treatment characteristics of subjects
in study 21-92-202:
(efficacy dataset)

	CLZ 100 mg bid	CLZ 50 mg bid	Placebo
	n= 140	n= 139	n= 140
male	74%	75%	78%
female	26%	25%	22%
age (mean)	65	64	65
age <65 yr	46%	45%	43%
Caucasian	88%	89%	87%
Black	9%	10%	10%
other ethnic	3%	1%	3%
wt mean (kg)	79	80	78
concomitant tobacco use	34%	36%	42%
diabetes	28%	30%	29%
resting ABI			
mean	0.63	0.60	0.63
SD	0.18	0.16	0.17

[source: table 4, pg 6-7, vol 120; and submissions 6/9/98 & 7/6/98]

8.1.7.3 @Exposure to drugs: (study 21-92-202)

Neither the reported deviations from the intended exposure to randomized drug, the deviations from intended avoidance of nonrandomized drugs, or the distribution of allowed concomitant medication use were such as to plausibly distort outcome assessments. Although there was somewhat greater use of acetaminophen in the CLZ 100 mg bid versus placebo patients (45 vs 32%, respectively), to my knowledge this analgesic has no demonstrated effect on claudication pain. Certain of the concomitant meds had the potential to reduce cardiovascular morbidity

and/or mortality (enalapril, lisonopril, lovastatin), but the distributions of these exposures were comparable across the groups.

.1.7.4   @**Disposition of subjects**:   (study 21-92-202)

It must be considered that not all randomized subjects were randomized to receive walking tests. Some were, by protocol revision, randomized solely to the morbidity/mortality assessment in order to increase the sample size for those safety endpoints. Thus some subjects contributed no postrandomization walking data, but nonetheless were study completers in the sense that their morbidity/mortality outcomes were observed for 24 weeks post-randomization. Although a relatively large number (i.e., 97) had no postrandomization walking data, this was in large part by design. In summary:

- 516 subjects were randomized (evenly distributing among treatment groups as 175 high dose, 171 low dose, 170 placebo).

- 419 subjects (evenly distributed as: 140 high dose CLZ, 139 low dose CLZ, 140 placebo) comprised the "efficacy" dataset. These had at least one nonmissing pre-treatment walking test datum, and at least one nonmissing post-randomization walking test datum at any timepoint in the study. No subjects were excluded because of missing pre-treatment walking test data.

- 316 subjects had at least one nonmissing pre-treatment walking test datum, and at least one nonmissing walking distance datum at each planned observation point (evenly distributed as: 106 high dose, 108 low dose, 102 placebo)

The rate of total dropouts was somewhat higher in CLZ-treated groups than in the placebo group. The attributed reasons for dropouts are shown in the following table.

Table: 3

Subject dropouts in study 21-92-202:
(all randomized dataset)

	CLZ 100 mg bid	CLZ 50 mg bid	Placebo
# randomized	n = 175	n = 171	n = 170
Total dropouts	37 (26%)	32 (23%)	29 (21%)
Dropouts for any AE	26 (18.6%)	26 (18.7%)	21 (15%)
All dropouts, by reason:			
nonfatal adverse event	25	24	20
death	1	2	1
lack of efficacy	2	1	2
clinical deterioration	0	0	3
failed screening	2	0	0
noncompliance	2	1	1
other	5	4	2

[source: pg 89-90, vol 119]

The patients having a protocol deviation were evenly distributed by treatment group; the majority involved non-compliance. No data were excluded as a result of these.

-8.1.8 @**Efficacy outcomes:** (study 21-92-202)

1.8.1 @**Tests stopped for nonspecific reasons** (study 21-92-202)

The stopping of final tests for nonspecific reasons other than claudication occurred in approximately 16% of CLZ-randomized subjects, and 15% of placebo-randomized subjects.

8.1.8.2 @**Primary efficacy analyses:** (study 21-92-202)

The baseline ACD data had a non-normal distribution[8]. At pre-treatment baseline in the efficacy dataset, the raw mean trough ACD was comparable in the CLZ 100 mg bid vs CLZ 50 mg bid groups but 16-18 meters higher in placebo-randomized subjects. Raw mean trough ICD was roughly comparable across all treatment groups at baseline. These data are provided in the table below.

Table: 4

Baseline raw mean trough walking distances (in meters) in study 21-92-202:

baseline metric	CLZ 100 mg bid	CLZ 50 mg bid	Placebo
ACD	130	132	148
ICD	70	67	72

The sponsor's analysis showed a reportedly statistically distinguishable improvement from pre-treatment ACD and ICD at trough on week 24 (nominal p=0.001). The sponsor's pairwise comparisons of CLZ vs placebo reportedly showed uncorrected p values ≤ 0.0003 at each CLZ dose.

As shown in the two figures below, the week 24 increase from pre-treatment ACD, at trough (and not placebo-corrected), was 51% in the CLZ 100 mg bid group, 38% in the CLZ 50 mg bid group, and 15% in the placebo group. The increase from pre-treatment ICD, at trough (and not placebo-corrected), was 59% in the CLZ 100 mg bid group, 48% in the CLZ 50 mg bid group, nd 20% in the placebo group).

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

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Figure: 1

Geometric mean percent change from pre-treatment ACD, at trough
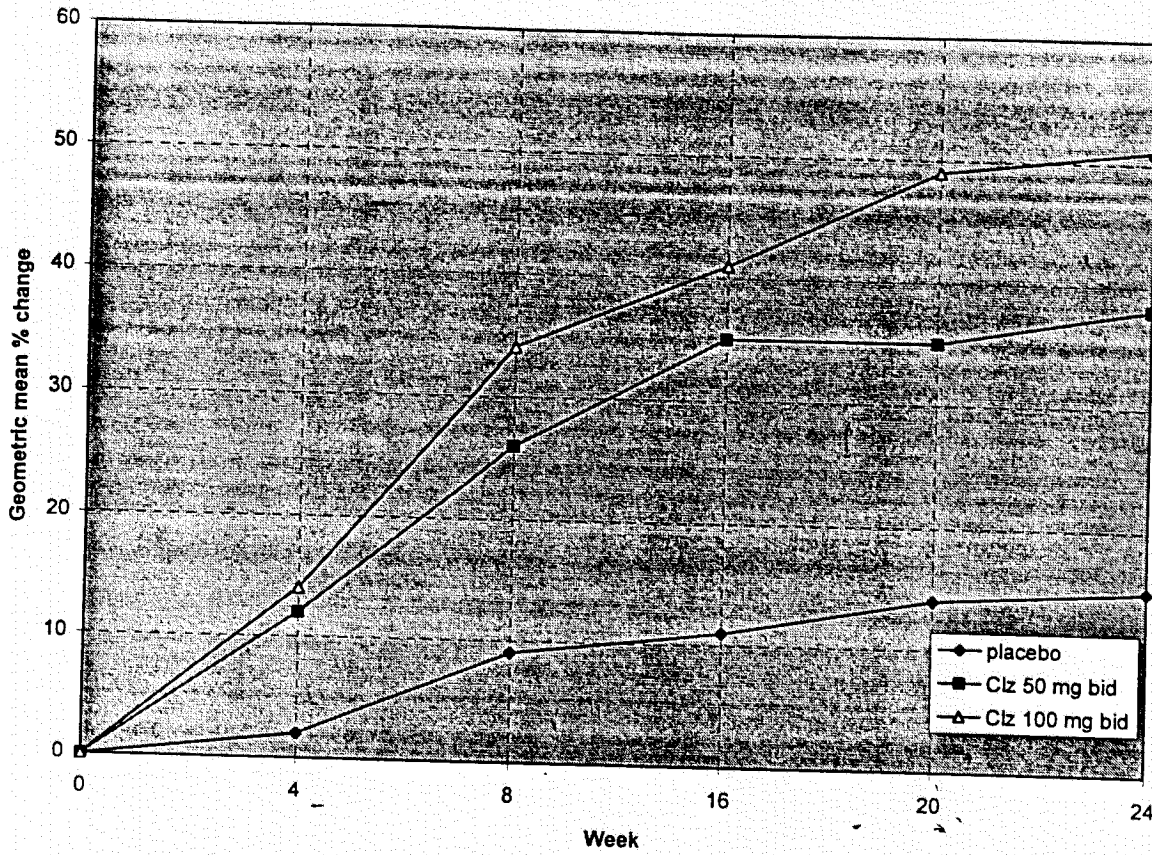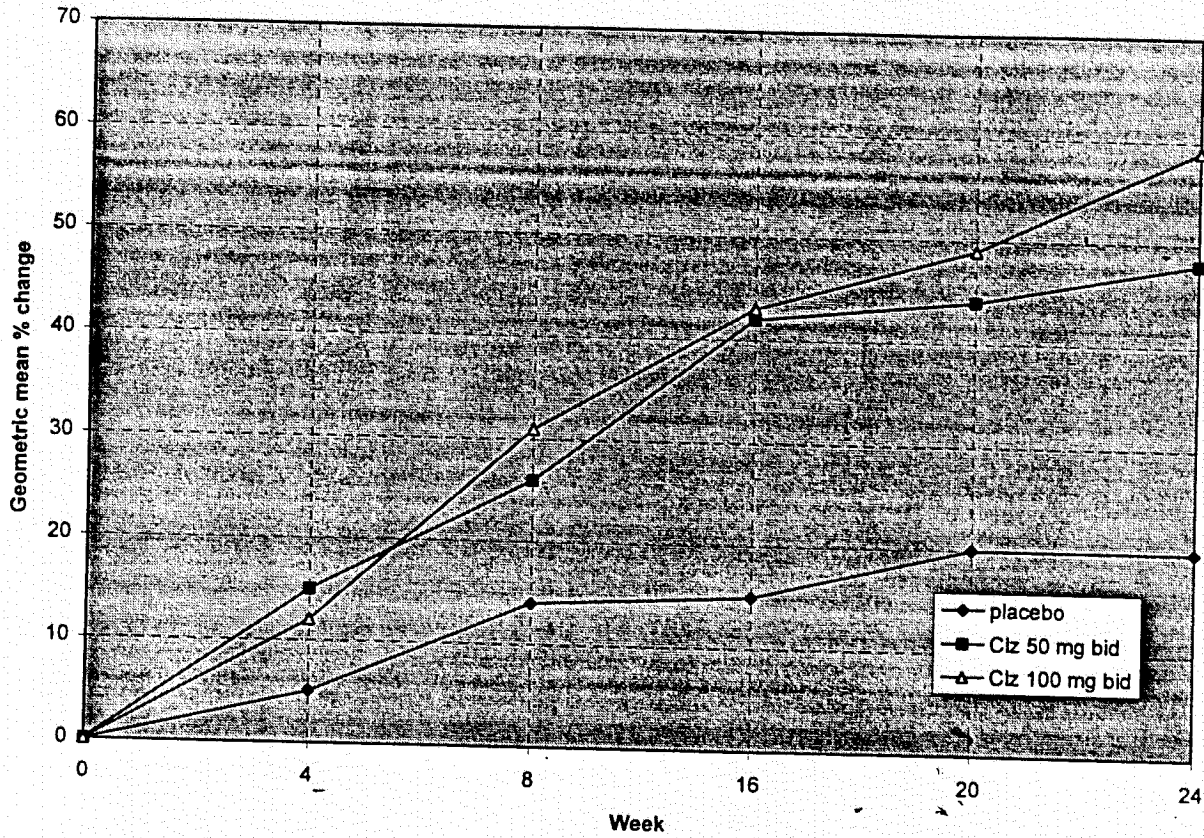(study 21-92-202, ITT/LOCF/log-transform)

Figure: 2

Geometric mean percent change from pre-treatment ICD, at trough
(study 21-92-202, ITT/LOCF/log-transform)

— There was a statistically significant treatment-by baseline interaction for ACD^9 wherein the estimated magnitude of effect on ACD was lesser in those with smaller pre-treatment ACD. A different (and also statistically significant) treatment-by-baseline interaction was found for ICD wherein treatment effect on ICD was greater in those with smaller pre-treatment ICD.

Treatment-by-center interactions for the primary efficacy endpoints reportedly showed no statistical significance.

8.1.8.3 @**Other efficacy analyses**: (study 21-92-202)

The raw trough walking distances, 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, change from raw mean pretreatment ACD was 26.8 m, 67.3 m, and 129.1 m in the placebo, CLZ 50 mg bid, and CLZ 100 mg bid groups, respectively; while with respect to ICD this change from pretreatment was 23.0 m, 48.6 m, and 67.5 m, respectively.

Figure: 3

Placebo-corrected change from raw mean pre-treatment walking distances, at trough (study 92-202, ITT/LOCF)
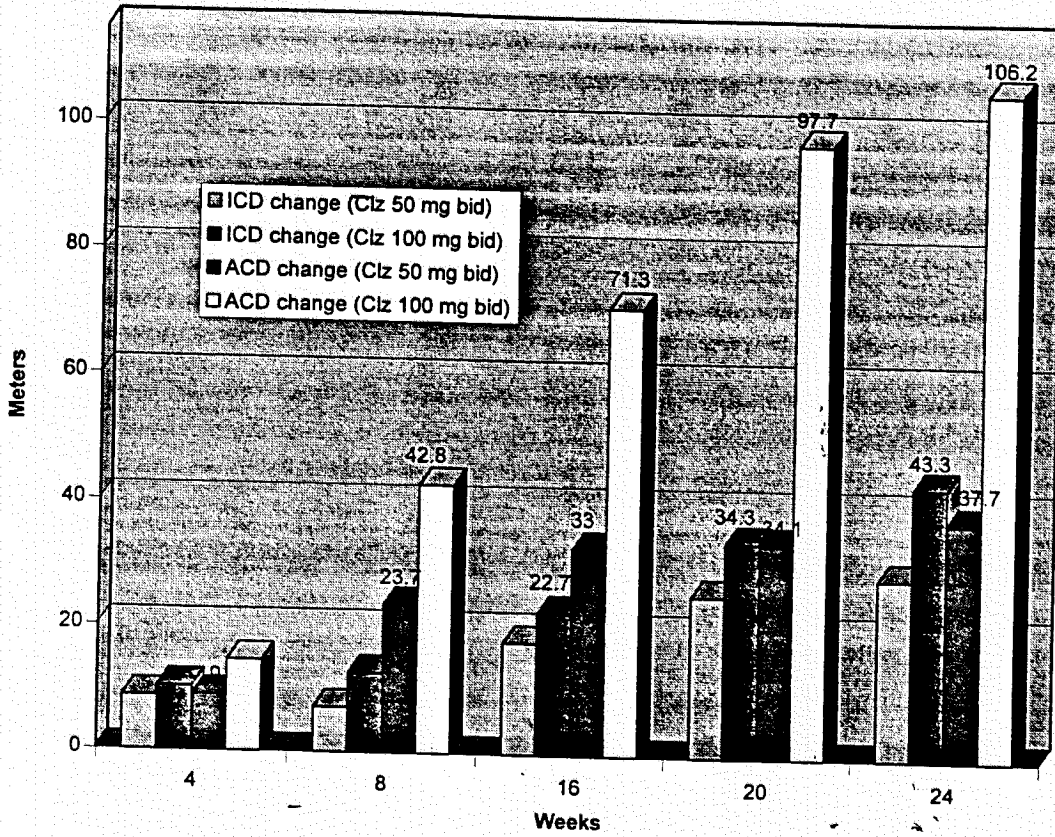
Some post-hoc effort was made by the sponsor to describe the time of onset of appreciable trough effect. For this the primary approach to analysis (log transform, LOCF dataset) was retrospectively extended, by the sponsor, to times prior to week 24. See the above figures to garner a descriptive sense of those data. There I suspect apparent trends towards effect greater than placebo to be suggested (for both doses) at 1, 2, 3, and perhaps even 4 months prior to the week 24. Nonetheless, no rigorous statement can be made about the onset of placebo-distinguishable trough effect, since no protection against Type I error is afforded when retrospectively, and with high multiplicity, undertaking this analysis.

In other posthoc datasets (that employed other than the LOCF method of handling missing), the reported results of the log-transform analysis were consistent with the primary endpoint finding in the prespecified LOCF dataset. At week 24 in the "completers"[10] dataset the geometric mean percent increase in ACD was 16%, 42%, and 65% in the placebo, CLZ low dose, and CLZ high dose groups, respectively. ICD was increased 19%, 54%, and 72% in the placebo, CLZ low dose, and CLZ high dose groups, respectively. At week 24 in the "efficacy"[11] dataset the geometric mean percent increase in ACD was 16%, 41%, and 57% in the placebo, CLZ low dose, and CLZ high dose groups, respectively; ICD was increase 21%, 53%, and 65% in the placebo, CLZ low dose, and CLZ high dose groups, respectively.

a conservative check on the impact of the 6 subjects from center 32 who each had only one post-randomization walking distance datum reported the sponsor re-analyzed ACDs after excluding these subjects. The following week 24 changes from pre-treatment ACD at trough (CLZ : placebo ratio based on a log transformed, LOCF analysis) were then reported: for CLZ 100 mg bid the point estimate was 1.31 (95% CI = 1.17-1.47); for CLZ 50 bid the point estimate was 1.18 (95% CI = 1.05-1.32).

It is noted for solely descriptive purposes that apparent trends towards dose-relatedness (of the effect to increase trough walking distances) are suggested, particularly at the final observation timepoint. Based on analyses which were unprotected against Type I error, the sponsor's attempt at quantifying dose-response reports that no difference between doses at discrete time points, and a nominal linear dose response relationship among the three groups for ICD and ACD. Again, nominal p values are plausibly greatly inflated here.

One can speak only to very general qualitative features of response as a function of demographic subgroup; small sample sizes and lack of prespecified analyses limit any attempt to draw solid inferences. Reported changes from pre-treatment walking distances were generally no different

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[10] this included only those subjects who had at least one non-missing walking distance datum at each of the observation timepoints. This dataset excluded subjects for whom both distances were missing at any observation time.

[11] this included all subjects with at least one on-therapy walking distance datum; excluding (rather than employing a carry-foward method) those timepoints where data were missing.

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among subgroups divided according to age (patients < 65 vs ≥ 65 years of age), sex, race (non-caucasian vs caucasian), study-concurrent tobacco use vs non-use, or presence vs absence of a diagnosis of diabetes.

There were additional endpoints for which the reported analyses have not been protected against Type I error, either because of retrospective defining of endpoints and/or because of multiplicity (e.g., the 2° endpoints, although prespecified, were numerous). These were generally consistent with the prespecified analysis, and generally nominal statistical significance of drug effect was reported. For example, the percent changes from pre-treatment walking distance at week 24 in the CLZ 100 mg bid, CLZ 50 mg bid, and placebo groups, respectively, were reportedly as follows: for ICD, 91.6%, 69.6%, and 40.6%; and for ACD, 86.0%, 55.9%, and 30.6% (nominal p values were reportedly 0.0001 for this analysis). The results of categorical analysis (using the Cochran-Mantel-Haenszel test) of the percent change from pre-treatment ACD and ICD were also reportedly consistent with the results of primary analyses. Patient questionnaires reportedly showed results consistent with the primary analyses.

The quality of life results reported by the sponsor were as follows (here a higher measure represents an improvement in quality of life): The Role-Physical scale, Mental Health scale, Role Emotional, Social Function, and General Health and Vitality scales did not differentiate CLZ from placebo over 24 weeks. The Physical Function scale reportedly showed numerically better function in the CLZ-treated (nominal p = 0.02 for CLZ 100 mg bid versus placebo), as reportedly did the Bodily Pain scale (nominal p = 0.04 - 0.05, depending on dose).

— 8.1.9 @**Commentary on the evidence** (study 21-92-202):

The week 24 increase from pre-treatment ACD, at trough was reportedly 51% in the CLZ 100 g bid group, 38% in the CLZ 50 mg bid group, and 15% in the placebo group.

b. At trough on week 24 the placebo-corrected raw *mean* changes from pretreatment ACD were 37.7 m, and 106.2 m in the CLZ 50 mg bid and CLZ 100 mg bid groups, respectively; while the placebo-corrected raw *median* changes were 18 and 25.5 m respectively.

c. The significance level the sponsor ascribed ascribed to CLZ's treatment effect does not reflect adjustment for multiplicity. One can conservatively count 6 primary efficacy endpoints, nonetheless the uncorrected p value of 0.001 has "room" to spend alpha without becoming nonsignificant.

d. There was reportedly a statistically significant interaction between treatment and baseline ACD. The estimated magnitude of effect on ACD was less in those who were "more sick" at baseline. Insofar as there was also imbalance of this covariate (the cilostazol groups had smaller mean baseline ACD than did the placebo group), the covariate-unadjusted analysis would tend to underestimate the ACD-increasing effect of CLZ, relative to placebo.

The week 24 increase from pre-treatment ICD, at trough (and not placebo-corrected), was 59% ... the CLZ 100 mg bid group, 48% in the CLZ 50 mg bid group, and 20% in the placebo group). The associated placebo-corrected raw mean changes from pretreatment ICD were roughly 50 m and 30 m in the CLZ 100 mg bid and CLZ 50 mg bid groups, respectively.

f. it is not known whether the third a priori primary endpoint (a vaguely described group comparison of median ICD and ACD, no analysis of which was submitted) supports the same conclusions.

g. Here, as in the other studies, the sponsor's analyses of health-related QOL are limited by the exclusion of dropouts. Since an appreciable fraction of dropouts were for AE (i.e. entities which plausibly worsened QOL), this method of handling missing data plausibly results in an overestimation of the quality of life. The QOL endpoints also present an appreciable multiplicity problem (see Dr. Kun Jin's statistical review for discussion of this). It is also noted that these instruments did not measure something fully independent from walking distance itself (subjects' evaluations of their difficulty with walking distance, speed, and physical function all correlated with ACD at end of treatment).

8.2 Study 21-96-202: !

?.1 @Design Summary

This concurrent placebo-controlled, double-blind, parallel-group study randomized (in a 1:1 ratio) 467 subjects to either CLZ or placebo, and additionally randomized 232 other subjects to a parallel, positive-control (pentoxifylline) arm. Subjects were atherosclerotic PAD patients with moderate to severe, stable, intermittent claudication. They received oral administrations of placebo, cilostazol (given as a fixed 100 mg bid dose), or pentoxifylline (PTX) given as a fixed 400 mg tid dose) for 24 weeks. The objectives were to assess safety, and improvement in trough ACD after 24 weeks of therapy.

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

Table: 5

@Chronology of the execution of study 21-96-202

Event Completed	Date
Original Protocol	8/29/96
1st Amendment	10/23/96
2nd Amendment	10/25/96
IND submission of 1st Amendment	11/8/96
1st subject randomized	11/20/96
3rd Amendment	2/24/97
4th Amendment	2/24/97
5th Amendment	7/9/97
Last Subject's Final Follow-up	11/19/97
Final Analysis	5/27/98

[source: submissions dated 5/4/98]

8.2.2 @Enrollment criteria.   (study 21-96-202)

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

Additional bases for exclusion from enrollment were the following:

use of pentoxifylline within 30 days.
- termination of a treadmill test for reasons unrelated to intermittent claudication.
- female of childbearing potential, unless surgically sterilized, at least 1 year postmenopausal, or willing to use two barrier methods of contraception plus spermicide.
- greater than 60% above ideal body weight.
- supine arterial BP >200 mmHg systolic or >100 mmHg diastolic.
- current malignancy, except for basal cell carcinoma, *in situ* cervical cancer, or history of prostatic carcinoma.
- sympathectomy or lower extremity arterial reparative surgery, including endovascular therapeutic procedures, within the previous 3 months.
- deep vein thrombosis within the past 3 months, other than isolated calf vein thrombosis.
- history or current evidence of concomitant exercise-limiting disease other than intermittent claudication. For example, such conditions as CHF, MI within 6 months or incomplete recovery from any MI, PTCA or CABG within 6 months, symptomatic cardiac arrhythmias, or angina pectoris.
- risk of, or tendency to, bleeding.
- platelet count < 130K, hematocrit < 30%, twice the normal values for AST or ALT, serum creatinine > 2.5 mg/dL.
- current alcohol or other drug abuse, or use of an investigational drug within the past 30 days.
- history of pentoxifylline or xanthine hypersensitivity, or previous discontinuation of pentoxifylline because of adverse event.
- a requirement for the uninterrupted use of certain antiplatelet agents (ticlopidine, sulfinpyrazone, dipyridamole),[12] certain anticoagulant agents (warfarin, heparin, dicumarol), agents with NSAID activity (with the exception of ibuprofen at doses up to 1200 mg/d).

8.2.3 @Qualifying criteria   (study 21-96-202)

After enrollment there was to be a 2 week lead-in period during which subjects were to be discontinued from prohibited medications. Subjects then qualified for randomization if the following additional observations were obtained during standardized treadmill testing (0% incline increasing by 3.5% every 3 minutes; speed of 3.2 km/h (2 mph)) conducted prior to study treatment:

- claudication-limited ACD ≤ 537.6 meters in 10 minutes, with no greater than 20% variation on two consecutive pre-treatment tests.
- claudication-limited ICD ≤ 54 meters in 1 minute.

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[12] aspirin (ASA) use was not disallowed.

- 20 mmHg decrease in Doppler limb pressure in the symptomatic leg, measured one minute following the end of symptom-limited treadmill testing, or a 10 mmHg such decrease and supine oppler ABI ≤0.90 after 10 minutes at rest.

8.2.4 @Treatment regimen: (study 21-96-202)

Qualified subjects were to undergo double-blind randomization to placebo, cilostazol (given as a fixed 100 mg bid dose), or pentoxifylline (given as a fixed 400 mg tid dose) for 24 weeks. CLZ, PTX and placebo tablets were encapsulated into identical gelatin capsules, and blinding of the dose interval was to be preserved by administered a third daily dose of placebo to CLZ-randomized subjects.

The sponsor reports that the dissolution profile of the CLZ preparation was "very similar" to the dissolution profile of CLZ tablets, and a comparable assertion was made for the PTX formulation, relative to PTX tablets.

The PTX preparation was 400-mg tablets of lot number 0781796. The sponsor received information from the marketer of Trental® that reports this PTX preparation to be "clinically equivalent" to the U.S.-marketed Trental® preparation.

itients were to be instructed to take their doses 30 minutes before or 2 hours after meals, and any deviations from this approach were to be captured in the case report form by investigators.

Concomitant use of calcium channel blockers, beta blockers and prn nitrates were allowed, but no dose of these agents was to be taken the morning of a treadmill test.

8.2.5 @Endpoints: (study 21-96-202)

8.2.5.1   @Prespecifications:

The primary efficacy endpoint was the CLZ vs PTX comparison of the log (week 24 ACD /pre-treatment ACD), in an all-randomized/intent-to-treat dataset which handles missing data by the last observation carry foward method.

Prespecified secondary efficacy endpoints were:

- change from pre-treatment ACD and ICD at post-randomization weeks 4, 8, 12, 16, 20, and 24. This was to be calculated as log (distance at the observed visit/distance at pre-treatment).
- examination of efficacy in a "per protocol" dataset, defined as protocol compliers with evaluable ita at the observation point included in the analysis.
- physician and patient assessment of subjective improvement.
- resting Doppler limb pressures.