8.4.2 @**Enrollment criteria**: (study 21-94-301)

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), and stable (without significant change within the past 3 months). 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:

- current use of OXP, or previous discontinuation of this agent for inefficacy or AE.
- female of childbearing potential, unless surgically sterilized, or at least 1 year postmenopausal.
- greater than 60% above ideal body weight.
- supine arterial BP >200 mmHg systolic or >100 mmHg diastolic.
- 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.
- termination of a treadmill test for reasons unrelated to intermittent claudication.
- history or current evidence of concomitant exercise-limiting disease other than intermittent claudication. For example, such conditions as CHF, MI within 6 months, PTCA or CABG within months, symptomatic cardiac arrhythmias, or angina pectoris.
- history of bleeding tendency.
- history of cerebrovascular bleed, cerebral or dissecting aortic aneurysm, pericarditis, or pericardial effusion.
- active peptic disease.
- recent or anticipated surgical procedures.
- platelet count < 120 X 10^9/L, twice the normal values for AST or ALT, or serum creatinine > 220 µmol/L.
- current alcohol or other drug abuse, or use of an investigational drug within the past 30 days.
- history of OXP or xanthine hypersensitivity.
- a requirement for the uninterrupted use of vasoactive medications for intermittent claudication, certain antiplatelet agents (acetylsalicylic acid, sulfinpyrazone, dipyridamole), certain anticoagulant agents (warfarin, heparin, pheninidione, nicoumalone), agents with NSAID activity, or the haemorheologic agent known as cinnarizine.

8.4.3 @**Qualifying criteria**: (study 21-94-301)

After enrollment there was to be at least a 4-8 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 constant load/constant speed treadmill testing (10% incline, reaching a speed of 3.2 km/h (2 mph) within 30 seconds) conducted prior to study treatment:

- test terminated for intermittent claudication only.
laudication-limited ACD ≤ 450 meters in ≤ 8 mins 26 secs, and with no more than 20% ariability on two consecutive pre-treatment tests.
- claudication-limited ICD of at least 30 meters in 34 seconds.
- supine Doppler ABI of ≤ 0.80 after 10 minutes at rest.

8.4.4 @**Treatment regimen**. (study 21-94-301)

Qualified subjects were to undergo double-blind randomization to placebo, cilostazol (given as a fixed 100 mg bid dose), or OXP (given as a fixed 400 mg tid dose) for 24 weeks. CLZ, PTX and placebo tablets were encapsulated into identical capsules, and blinding of the dose interval was to be preserved by administered a third daily dose of placebo to CLZ-randomized subjects. Within each capsule was either placebo, CLZ (a 50mg tablet, batch #4A81PB2. or OXP (the European-marketed Trental® 400 mg tablet[23] (batch 01D032)

There were no pre-specified instructions for patients to avoid interaction of CLZ with food. The sponsor asserts that subjects were to be verbally told to take study medication 1/2 hour prior to meals, but there is no documentation of the adequacy of success of these retrospective instructions.

Concomitant use of prn nitrates was allowed, but not during the morning of treadmill test.

8.4.5 @**Endpoints**: (study 21-94-301)

8.4.5.1 @**Prespecifications**: (study 21-94-301)

The pre-specified primary efficacy endpoints were several, numbering 4 in total. These all had in common the calculation of log (week 24 ACD/pre-treatment ACD) during constant load/constant speed treadmill testing (10% incline, speed of 3.2 km/h (2 mph), and the handling of missing data by the last observation carry foward method, but they differed in terms of the comparison being made (CLZ vs placebo, or CLZ vs OXP), and the dataset being evaluated (intent-to-treat (presumably all-randomized as well) vs "efficacy analyzable").

Thus, the pre-specified primary efficacy endpoints were the following ACD analyses:

- CLZ vs placebo comparisons of log (week 24 ACD/pre-treatment ACD) in an intent-to-treat dataset.

[23] the sponsor reports this to be clinically equivalent to the U.S.-marketed Trental® formulation.

- CLZ vs placebo comparisons of log (week 24 ACD/pre-treatment ACD) in an "efficacy analyzable" dataset.
- CLZ vs OXP comparisons of log (week 24 ACD/pre-treatment ACD) in an intent-to-treat dataset.
- CLZ vs OXP comparisons of log (week 24 ACD/pre-treatment ACD) in an "efficacy analyzable" dataset.

In the second protocol amendment, ICD assessments were changed from primary to secondary efficacy endpoints. These were as follows:
- CLZ vs placebo comparisons in an intent-to-treat dataset.
- CLZ vs placebo comparisons in an "efficacy analyzable" dataset.
- CLZ vs OXP comparisons in an intent-to-treat dataset.
- CLZ vs OXP comparisons in an "efficacy analyzable" dataset.

The prespecified secondary efficacy endpoint was a combined morbidity/mortality endpoint (which was not adjudicated). The components of this composite endpoint were:
- all-cause death
- cardiac arrest: defined as cardiac arrhythmia requiring resuscitation.
- MI: it was planned to capture both acute MIs, and non-acute or asymptomatic MIs. Acute MIs were defined as cases in which evidence obtained of at least 2 of the following 3 conditions:
  - central chest discomfort for ≥ 30 minutes.
  - ST elevation ≥0.1 mv in ≥2 contiguous leads.
  - total CPK ≥150% of the upper limit of normal (ULN) accompanied by ≥3% CK-MB).

  Non-acute MIs were defined as the presence of "pathologic Q waves" (presumably new onset) in ≥2 contiguous leads (II, III, aVF or I, aVL, V6 or I, V4-6) and meeting the following detailed criteria; Leads I, II, aVF: .04 seconds in duration, > 0.2 mv amplitude and > 25% of the amplitude of the succeeding R wave; Lead aVL: ≥0.04 seconds in duration, > 0.2 mv amplitude and > 15% of succeeding R wave; Leads V4-V6: ≥0.04 seconds in duration, > 0.2 mv amplitude and > 15% of succeeding R wave; Lead III: similar to Lead I criteria, but only important if leads II and aVF are also abnormal.
- stroke: no diagnostic criteria were pre-specified.
- arterial revascularization: angioplasty or surgical vascular reconstruction.
- amputation.

Blood samples were obtained (prior to treatment, and at post-randomization weeks 2, 12, and 24) but the analysis of these reportedly proved to be obviated by assay artefact. Safety endpoints included: 12-lead EKG (obtained pre-treatment, and at post-randomization weeks 2, 4, 12, and 24), AE and vital signs (assessed pre-treatment, and at post-randomization weeks 2, 4, 8, 12, 16, 20, and 24), serum chemistry and hematology were obtained pre-treatment, and at post-

randomization weeks 2, 4, 12, and 24), and urinalysis (obtained pre-treatment, and at post-randomization weeks 2, 4, 12, and 24).

8.4.5.2 **@Measurement methods** (study 21-94-301)

The "immediate-incline" treadmill method was used wherein the incline load started immediately at 10%[24] (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. Attempts were to have been made to use the same treadmill and same technician in a given patient.

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.

8.4.5.3 **@Statistical analyses.** (study 21-94-301)

Multiplicity correction was to be performed on the primary efficacy analyses by means of the Dunn-Sidak procedure.

The sample size was calculated on the basis of "walking distances" (not distinguishing between ACD and ICD), making the following assumptions:
- two-sided significance level of 5%.
- 35% increase from pre-treatment for CLZ, 25% for pentoxifylline, and 15% for placebo.
- standard deviation of 37.
- power of 90%.

Exploratory analyses of the time-courses of log (post-randomization walking distance/pre-treatment walking distance) were to be undertaken via repeated measures ANOVA.

An interim analysis was planned (in protocol amendment #3), but was designed to not influence the scheduled completion of the study, and thus to reportedly require no spending of alpha. This early look was undertaken (by unblinding group summary statistics rather than individual patient data) in order to ascertain effect sizes and thereby optimize the power calculation for a subsequent trial, study 21-96-202.

Safety comparisons were pre-specified to be assessed using Fisher's exact test, Chi-square or Mantel-Hainszel tests.

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[24] unlike the other deployments of the "immediate-incline" method among the 8 large placebo-controlled trials, the present study used a 10% rather than a 12.5% incline.

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8.4.6 @Results other than Efficacy outcomes (study 21-94-301):

6.1 @Covariates: (study 21-94-301)

Pre-treatment covariates were well balanced, as shown in the table on the next page.

Table: 14

@Demographic and pre-treatment characteristics of subjects in study 21-94-301:
(all-randomized dataset)

	CLZ 100 mg bid	*OXP 400 mg tid*	*Placebo*
# randomized	*n=123*	*n= 123*	*n= 124*
male	70%	72%	73%
female	30%	28%	27%
age (mean)	66	66	66
Caucasian	100%	99%	99%
Black	0%	1%	1%
wt mean (kg)	74	73	72
concomitant tobacco use	39%	33%	36%
diabetes	12%	11%	12%
resting ABI			
mean	0.62	0.61	0.62
SD	0.12	0.13	0.14

[source: table 3, vol 2, addendum 5/6/98; & submissionS 6/9/98 & 7/6/98]

8.4.6.2 **@Disposition of subjects**: (study 21-94-301)

Subject disposition was as follows:

- 370 subjects were randomized (distributing among treatment groups as 123 to CLZ, 123 to OXP, and 124 to placebo).

- 363 subjects comprised the "efficacy" dataset (these were relatively evenly distributed among treatment groups as 123 CLZ, 118 OXP, and 122 placebo). These received at least one dose, had

at least one nonmissing pre-treatment walking test datum, and had 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.

- 280 subjects received ≥one dose, had ≥1 nonmissing pre-treatment walking test datum, and a nonmissing walking distance datum at week 24 (distributing among treatment groups as 89 to CLZ, 86 to OXP, and 105 to placebo).

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

Table: 15

@Dropouts in study 21-94-301
(all randomized dataset)

	CLZ 100 mg bid	*OXP 400 mg tid*	*Placebo*
# randomized	n = 123	n = 123	n = 124
Total dropouts	34 (27.6%)	37 (30.1%)	19 (15.3%)
Dropouts for any AE	31 (25.2%)	33 (26.8%)	15 (12.1%)
All dropouts, by reason:			
nonfatal adverse event -	30	33	14
death	1	0	1
clinical deterioration	1	0	0
noncompliance	1	2	2
other	1	2	2

[source: table 2, vol 2, addendum 5/6/98]

8.4.7 **@Efficacy outcomes**: (study 21-94-301)

8.4.7.1 **@Tests stopped for nonspecific reasons** (study 21-94-301)

The stopping of final tests for nonspecific reasons (defined as reasons other than claudication) occurred in approximately 19% of CLZ-randomized subjects, 12% of placebo-randomized, and 20% of OXP-randomized subjects.

8.4.7.2 **@Primary efficacy analyses:** (study 21-94-301)

e baseline ACD data had a non-normal distribution.[25] At pre-treatment baseline, in the efficacy ..aset, the raw mean trough ACD was comparably (albeit modestly) smaller in the CLZ and placebo groups, relative to the OXP group. These data are provided in the table below.

Table: 16

Baseline raw mean trough walking distances (in meters) in study 21-94-301:

baseline metric	*CLZ 100 mg bid*	*OXP 400 mg tid*	*Placebo*
ACD	128.1	135.4	128.1
ICD	77.7	81.4	74.3

[source: table 4, vol 2, addendum 5/6/98]

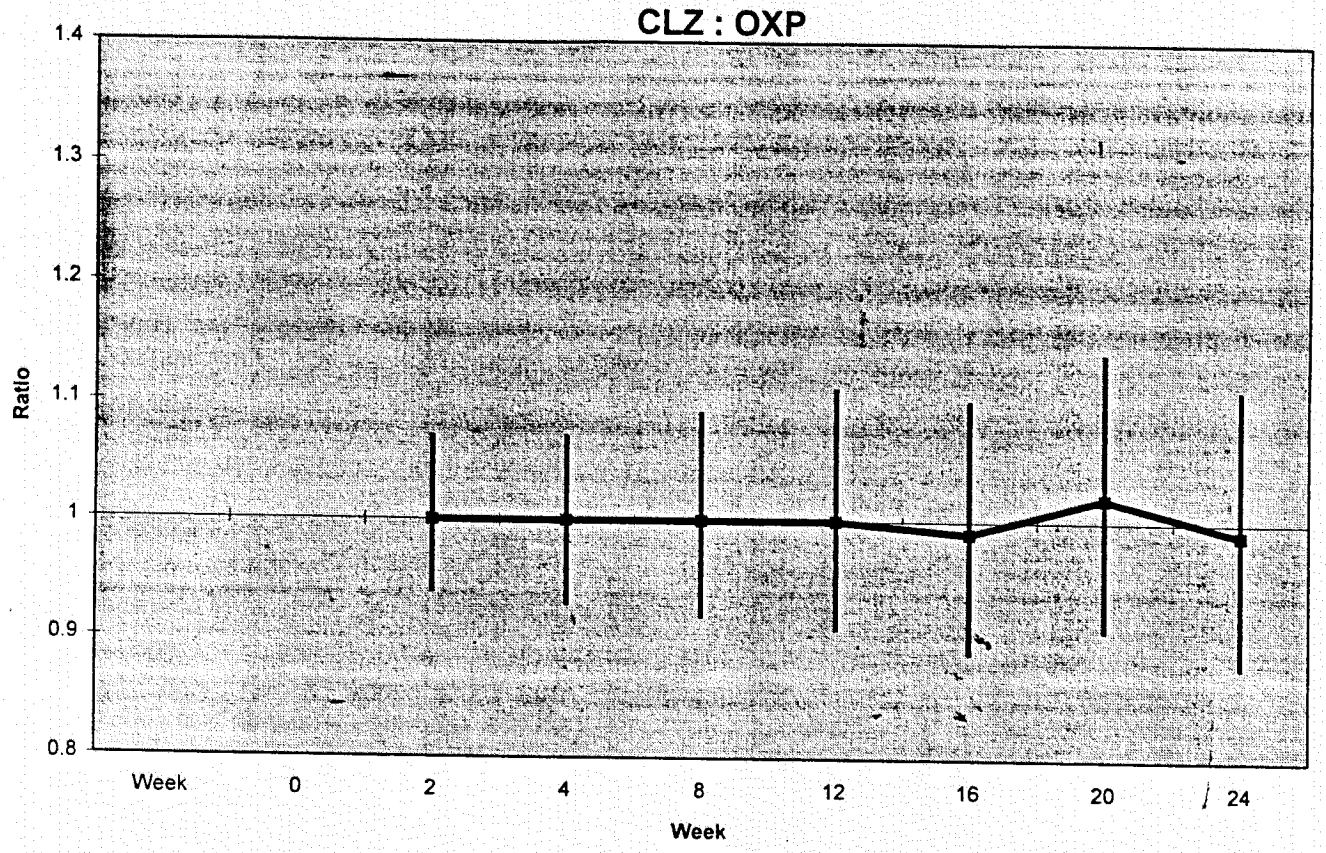
ne of the 4 prespecified primary analyses showed statistically significant differentiation between any of the treatments at week 24, according to the sponsor's results. Irrespective of which pre-specified primary analysis was used (*ITT*/ LOCF or "*efficacy* "/ LOCF), CLZ was not statistically distinguishable from either placebo or OXP. There was no significant treatment-by-center interaction or treatment-by-baseline interaction for ACD.

As shown in the figure below, the point estimated ratio of treatment effect (CLZ: OXP) to change pre-treatment ACD was 0.99 at trough on week 24. This same metric (although not shown in the figure) gave a result of 1.06 for the ratio of CLZ: placebo effect, and 1.07 for the ratio of OXP:placebo.

[25] as per Dr Karkowksy's discussion with Dr. Mahjoob.

Figure: 8

Ratio (point estimate & 95% CI) of log transformed change from pre-treatment trough ACD (study 21-94-301, ITT/LOCF)



Only in posthoc analyses employing retrospective methods of handling missing data (i.e. either not carrying foward, or including only completers) were there reportedly even nominal trends towards larger effect of CLZ than placebo, with respect to change from pre-treatment ACD.

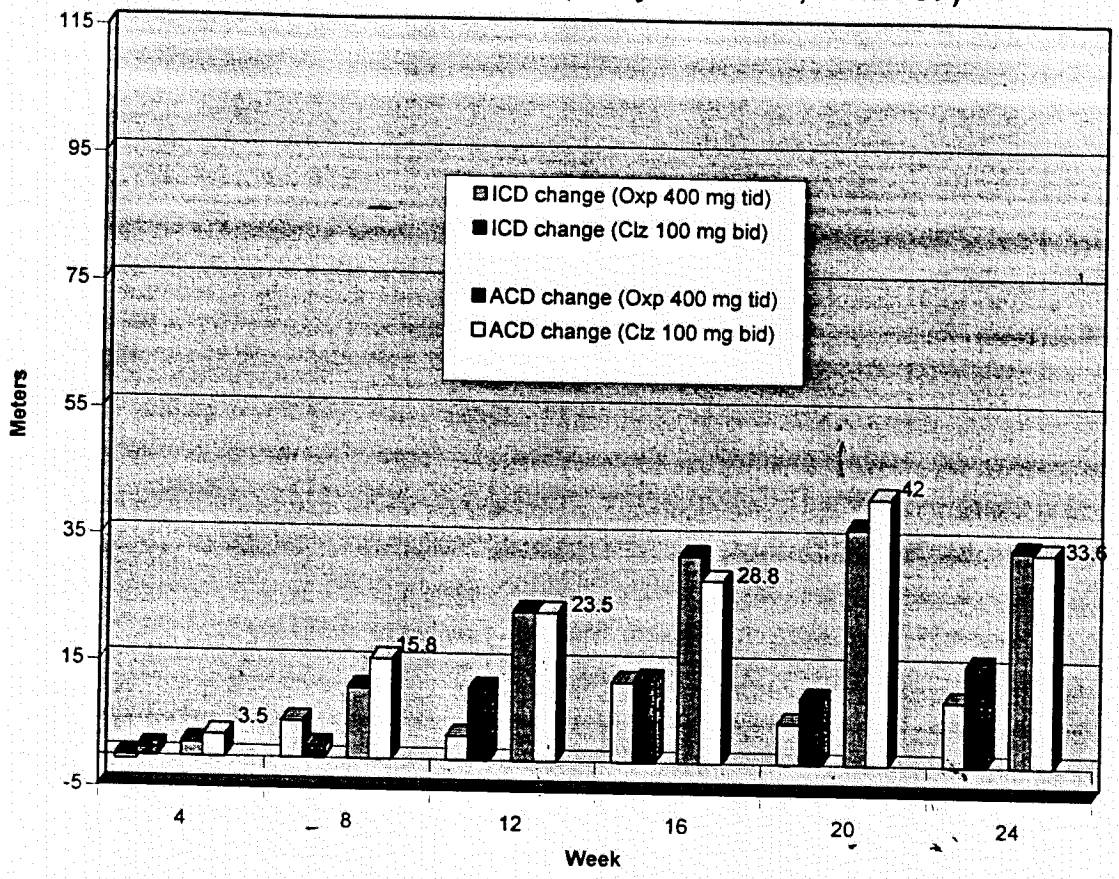
The point estimated treatment effect on pre-treatment ICD at week 24 (based on analysis of log (ICD at last observation/ICD at baseline) for the ITT/LOCF dataset) was 1.02 (OXP:CLZ), and 1.01 (CLZ:placebo).

8.4.7.3 **@Other efficacy analyses:** (study 21-94-301)

The raw (nontransformed) 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, at the end of week 24 the reported placebo-corrected mean changes from pretreatment ACD were 33.6 and 34 meters for the CLZ 100 mg bid and OXP 400 mg tid groups, respectively.

Figure: 9

Placebo-corrected change from raw mean pre-treatment trough walking distance (study 21-94-301, ITT/LCOF)



The post-hoc results of physician and patient subjective assessment of improvement, relative to pre-treatment, were partially reported as follows: according to physicians' opinions 55% of CLZ subjects, 51% of OXP subjects, and 48% of placebo subjects improved. According to patients' opinions: 65% of CLZ subjects, 51% of OXP subjects, and 48% of placebo subjects improved. I have found no discussion of the rates of treatment-emergent worsening.

8.4.8 @**Commentary on the evidence** (study 21-94-301):

a. None of the 4 prespecified primary analyses showed statistical significance.

b. At trough on week 24, CLZ 100 mg bid showed an approximately 30 meter raw *mean* placebo-corrected increase from pre-treatment ACD, whereas the *median* increase was only 8 m.

c. CLZ 100 mg bid had an appreciably smaller effect on ACD in this trial, relative to study 21-92-202. In study 21-92-202 the placebo-corrected raw *mean* change from pretreatment ACD at trough at the end of week 24 was about 100 m; in contrast the present study showed a change at that time of only about 30 m. Similarly, the placebo-corrected raw *median* change was only about 30% of that seen in study 21-92-202. The reason for this discepancy is not clear, despite consideration of potential explanatory factors (as discussed below in the conclusions section of this review).

d. the exclusion of users of pentoxifylline, or those with previous discontinuation of this agent for inefficacy or AE would tend to enrich the study with PTX nonresponders and/or non-tolerators. To the extent that it was non-responders who enriched the sample, this would bias the analysis towards underestimation of the general population responsiveness to PTX.