8.8.8 @Commentary on the evidence (study 21-90-201)

't trough on week 16 the clz group manifested a nominally statistically significant 30.5% ...crease from pre-treatment geometric mean ACD (uncorrected p value = 0.001) 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.

b. In the face of deteriorating walking distances over time in the placebo group, the raw mean placebo-corrected change from pre-treatment at 16 weeks was 31.9 m for ICD and 105.8 m for ACD (the median placebo-corrected ACD change was 26.5 m).

c. the nominal p values are undoubtedly inflated. The primary efficacy endpoints were vaguely prespecified without mention of whether trough or peak measurements would be used, or what exact on-treatment week(s) would be used in the primary analysis. In addition, two walking distances as well as several quality of life measures were included as primary endpoints.

9 SMALL (and PHASE II) PLACEBO-CONTROLLED TRIALS:

Study 21-86-101: !

9.1.1 @Design Summary (study 21-86-101)

This concurrent placebo-controlled, double-blind, parallel-group, single-center study randomized 53 subjects (peripheral atherosclerosis patients with stable, intermittent claudication) to receive placebo, or cilostazol given as a fixed 100 mg bid oral dose for 6 weeks. The primary objectives were to assess safety, and change from pre-treatment ICD after 6 weeks of therapy.

The study was conducted from August 26, 1986 to February 18, 1988.

9.1.2 @Enrollment criteria. (study 21-86-101)

Adult subjects (21-70 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 6 months), not associated with lower extremity ischemic rest pain or ulceration or gangrene. There also had to be objective evidence of peripheral occlusive arterial disease obtained from angiography and illography. Functional capacity needed to be such that ICD was ≤ 100 m on a constant load/constant speed treadmill (10% upward inclination; speed of 3.5 km/hr). To qualify for randomization, enrolled subjects had to meet additional qualifying criteria related to symptom invariability (see below discussion of subject qualification).

Additional bases for exclusion from enrollment were the following:

- female of childbearing potential.
- malignancy.
- rheumatic disease or valve replacement.
- clinically significant (undefined) abnormal laboratory values pre-treatment.
- renal insufficiency (undefined)
- a requirement for the uninterrupted use of platelet-active or vasoactive drugs.
- use of an investigational drug within the past 30 days.
- diabetes mellitus, either insulin-dependent or with duration > 5 years.
- status post vascular surgery, splenectomy, or gastrointestinal surgery.

9.1.3 @**Qualifying criteria.** (study 21-86-101)

After enrollment there was to be at least a 3 week placebo lead-in period during which subjects were to be discontinued from prohibited medications. Subjects qualified for randomization if there was less than 30% variation in ICD at the start and end of the run-in.

9.1.4 @**Treatment regimen.** (study 21-86-101)

Subjects were randomized to receive placebo, or cilostazol given as fixed 100 mg bid oral dose for 6 weeks. The drug was formulated as 100 mg cilostazol tablets (lot 6F79-100).

9.1.5 @**Endpoints.** (study 21-86-101)

9.1.5.1 @**Endpoint Descriptions** (study 21-86-101)

The primary efficacy endpoint was the change from pre-treatment ICD after 6 weeks of therapy. The secondary outcome variables included:
- subjective claudication improvement as per patient
- Doppler-measured limb pressures.

.5.2 @**Measurement methods** (study 21-86-101)

The "immediate-incline" treadmill method was used wherein the incline load started immediately at 10% (and remained constant), with speed also constant at 3.2 km/h (2 mph). Testing was employed at the end of the run-in, and at the end of weeks 3 and 6. 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.

Physical examination, and laboratory tests were performed pre-treatment, and at the end of weeks 3 and 6.

9.1.5.3 @**Statistical analyses.** (study 21-86-101)

Testing was to be be two-sided at an alpha level of 0.05. The sponsor reports that there was no interim look. Analysis were conducted by the intent-to-treat principle. Patient 22 was excluded reportedly because the treatment randomization code is unknown.

9.1.6 @Results other than Efficacy outcomes (study 21-86-101)

.6.1 @Covariates: (study 21-86-101)

Demographic and pre-treatment characteristics of subjects are shown in the table below. The ethnic makeup of the sample was not described. The groups were reasonably well- balanced.

Table: 30

@Demographic and pre-treatment characteristics of subjects in study 21-86-101 (all-randomized dataset):

	CLZ 100 mg bid	Placebo
# randomized	n= 28	n= 25
Male	89%	84%
female	11%	16%
age (mean)	62	58
wt mean (kg)	73	76
concomitant tobacco use	50%	56%
diabetes	11%	4%

[source: pg 35, vol 198]

9.1.6.2 @Disposition of subjects: (study 21-86-101)

Fifty three subjects were randomized to treatment; 7 clz subjects (25%) and 5 placebo subjects (20%) dropped out. The attributed reasons for all dropouts are shown in the following table.

Table: 31

Subject dropouts in study 21-86-101:

	CLZ 100 mg bid	Placebo
# randomized	n =28	n =25
Total dropouts	7 (25%)	5 (20%)
All dropouts, by reason:		
nonfatal adverse event	3	1
noncompliance	1	2
other	3	2

[source: addendum dated 5/15/98]

Forty nine subjects had a nonmissing pre-treatment walking distance datum, and at least 1 nonmissing post-randomization walking distance datum (distributed as 25 in the clz group, and 24 in the placebo group).

9.1.7 @**Efficacy outcomes**: (study 21-86-101)

At baseline in the efficacy dataset, the raw mean walking distances were slightly higher in the cilostazole group, as shown in the following table.

Table: 32

Baseline raw mean walking distances in study 21-86-101:

baseline metric	*CLZ 100 mg bid*	*Placebo*
trough ACD	106.9	102.2
trough ICD	67.4	60.7

The estimated treatment effect on trough ICD at week 6 (the ratio of geometric means clz:placebo) was reportedly 1.32 (95% CI 1.07-1.64; p = 0.01). Unlike this ICD result, the treatment effect on ACD did not reach statistical significance (point estimate 1.17, 95% CI = 0.97-1.42; p= 0.09) at week 6. The raw changes from pre-treatment walking distances are shown below.

Table: 33

Placebo-corrected raw mean change from trough pre-treatment walking distances
(study 21-86-101)

Week	ACD	ICD
3	42.2 m	28.9 m
6	49.7 m	41.9 m

[source: page 39, volume 198]

9.1.8 @**Commentary on the evidence** (study 21-86-101)

a. this study is not conclusive on its own, but it's results are consistent with the more definitive studies.

9.2 Study 21-86-103: !

2 @Design Summary (study 21-86-103)

This concurrent placebo-controlled, double-blind, parallel-group, single-center study randomized 33 subjects (peripheral atherosclerosis patients with stable intermittent claudication) to receive placebo, or cilostazol given as a fixed 150 mg bid oral dose for 21 weeks. The primary objectives were to assess safety, and change from baseline ACD and ICD after 6 weeks of therapy.

The study was conducted from October 15, 1986 to February 9, 1988.

9.2.2 @Enrollment criteria. (study 21-86-103)

Adult subjects (at least 21 years old) of both sexes were eligible for enrollment if they had atherosclerotic occlusive arterial disease-based intermittent claudication which was chronic (at least 6 months), stable (without significant improvement within the past 6 months). There had to be objective evidence of peripheral occlusive arterial disease obtained from angiography and oscillography. Functional capacity needed to be such that ICD was ≤ 100 m on a treadmill set at a speed of 3.5 km/hr with a 10% upward inclination.

Additional bases for exclusion from enrollment were the following:

- female of childbearing potential.
- lower extremity ischemic rest pain, ulceration, or gangrene.
- malignancy.
- cardiac valve disorder or replacement.
- clinically significant (undefined) abnormal laboratory values pre-treatment.
- renal insufficiency (undefined)
- a requirement for the uninterrupted use of platelet-active or vasoactive drugs.
- use of an investigational drug within the past 30 days.
- diabetes mellitus, either insulin-dependent or with duration > 5 years.
- vascular surgery, splenectomy, or gastrointestinal surgery within the past 12 months.

9.2.3 @Qualifying criteria. (study 21-86-103)

After enrollment there was to be at least a 3 week placebo lead-in period during which subjects were to be discontinued from prohibited medications. Subjects then qualified for randomization if there was ≤ 30% variation in ICD at the start and end of the run-in.

9.2.4 @**Treatment regimen.** (study 21-86-103)

bjects were randomized to receive placebo, or cilostazol given as a fixed 150 mg bid oral dose . 21 weeks. Drug was formulated as 50 mg cilostazol tablets (lot 6H88-50).

9.2.5 @**Endpoints.** (study 21-86-103)

9.2.5.1 @**Endpoint Descriptions** (study 21-86-103)

The primary efficacy endpoint was the change from baseline ACD and ICD after 6 weeks of therapy. The secondary outcome variables were:
- subjective claudication improvement as per patient
- palpation of arterial pulses
- Doppler-measured limb pressures.
- sitting arm blood pressure

9.2.5.2 @**Measurement methods** (study 21-86-103)

The "immediate-incline" treadmill method was used wherein the incline load started immediately at 10% (and remained constant), with speed also constant at 3.2 km/h (2 mph). Treadmill lking tests, physical examinations, and laboratory tests were performed pre-treatment and on weeks 6, 9, 13, 17, and 21.

9.2.5.3 @**Statistical analyses.** (study 21-86-103)

Testing was to be be two -sided at an alpha level of 0.05. The sponsor reports that there was no interim look. Analysis were conducted by the intent-to-treat principle. There appears to have been no formal power calculation.

9.2.6 @**Results other than Efficacy outcomes** (study 21-86-103)

9.2.6.1 @**Covariates:** (study 21-86-103)

The pre-treatment covariates were generally well balanced, with the exception of an excess of tobacco users and diabetics in the placebo group, as shown in the table below.

Table: 34

@Demographic and Pre-treatment characteristics of subjects in study 21-86-103:

	CLZ 150 mg bid	Placebo
# randomized	n= 17	n= 16
male	82%	88%
female	18%	12%
age (mean)	56	59
wt mean (kg)	75	76
concomitant tobacco use	35.3%	62.5%
diabetes	5.9%	18.8%

[source: pg 38, vol 200]

6.2 **@Disposition of subjects:** (study 21-86-103)

A total of 33 subjects were randomized (evenly distributing among treatment groups as 17 cilostazole, 16 placebo). Thirty two subjects had a nonmissing pre-treatment ACD datum, and at least 1 nonmissing post-randomization ACD datum (evenly distributed as 16 in the clz group, and 16 in the placebo group).

The rate of dropouts for AE was higher in the clz-treated group (29.4%) than in the placebo group (12.5%). The attributed reasons for all dropouts are shown in the following table.

Table: 35

Subject dropouts in study 21-86-103:

	CLZ 150 mg bid	Placebo
# randomized	n =17	n =16
Total dropouts	5 (29.4%)	2 (12.5%)
All dropouts, by reason:		
nonfatal adverse event	3	1
noncompliance	1	2
other	3	2

[source: addendum dated 5/15/98]

9.2.7 @**Efficacy outcomes**: (study 21-86-103)

At baseline, the raw mean trough walking distances were roughly comparable in the 2 groups, as shown in the following table.

Table: 36

Baseline raw mean walking distances in study 21-86-103:

baseline metric	*CLZ 150 mg bid*	*Placebo*
trough ACD	115.8	119.1
trough ICD	68.8	62.5

The estimated treatment effect on trough ACD (the ratio of geometric means clz:placebo) at week 6 was statistically significantly less in the clz group, relative to the placebo group (point estimate 83, 95% CI = 0.70-0.98; p=0.03). At that timepoint, relative to pre-treatment, the clz group had deteriorated by a mean of 6.9 m, whereas the placebo group had improved by a mean of 30.3 m. At all later observation points (through 21 weeks), with respect to ACD, clz was could not be statistically distinguished from placebo.

Quantitatively similar (although temporally dissimilar) results were obtained for ICD. At week 9 the clz group performed statistically significantly less well than did the placebo group (point estimate 0.69, 95% CI = 0.53-0.91; p=0.01). At that timepoint, relative to pre-treatment, the clz group had deteriorated by a mean of 2.5 m, whereas the placebo group had increased by a mean of 34.4 m. At all other observation points clz was merely not statistically distinguishable from placebo.

9.2.8 @**Commentary on the evidence** (study 21-86-103)

a. While the results of this trial fail to confirm other trials, it's conclusiveness is greatly limited by its small sample size, and it's reliance on single-center observations.

9.3 Study 21-87-101: !

.1 @Design Summary (study 21-87-101)

This concurrent placebo-controlled, double-blind, parallel-group, single-center study randomized 19 subjects (peripheral atherosclerosis patients with stable intermittent claudication) to receive placebo, or cilostazol given as a fixed 100 mg bid oral dose for 12 weeks. The primary objectives were to assess safety, and change from baseline ACD and ICD after 12 weeks of therapy.

The study was conducted from June 29, 1987 to March 2, 1988.

9.3.2 @Enrollment criteria. (study 21-87-101)

Adult subjects (aged 45-70) of both sexes were eligible for enrollment if they had stable (without significant change within the past 3 months), and not associated with lower extremity ischemic rest pain, ischemic ulceration, 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).

ditional bases for exclusion from enrollment were the following:

- female of childbearing potential.
- decompensated CHF, MI within 6 months, cardiac valve disorder or replacement,
- respiratory insufficiency.
- vascular surgery, splenectomy, or gastrointestinal surgery in the past 12 months.
- clinically significant abnormal laboratory test values at screening.
- decreased mobility due to joint disorders, or chronic lumbar vertebral column syndrome.
- malignancy.
- decompensated renal insufficiency.
- neuropathy.
- history of analgesic abuse or use of an investigational drug within the past 30 days.
- diabetes mellitus, either insulin-requiring or of >5 years duration.
- a requirement for the uninterrupted use of pentoxifylline, dipyridamole, certain vasodilators (Dusodril®, Bufedil®, or Asasantin®), acetylsalicylic acid, PDE inhibitors, or prostacyclin.

9.3.3 @Qualifying criteria. (study 21-87-101)

After enrollment there was to be at least a 3 week lead-in period during which subjects were to be continued from prohibited medications. Subjects then qualified for randomization if during standardized treadmill testing conducted prior to to study treatment they attained a ≤100 meter ICD, with no greater than 20% variation between the observations.

9.3.4 @**Treatment regimen.** (study 21-87-101)

ojects were randomized to receive placebo, or cilostazol given as a fixed 100 mg bid oral dose for 12 weeks. The patient were not explicitly instructed to avoid concomitant food intake. Study medication was formulated as 100 mg CLZ tablets from lot 6F79-100. The doses of any permitted concomitant medication were to be kept constant throughout the trial.

9.3.5 @**Endpoints.** (study 21-87-101)

9.3.5.1 @**Descriptions** (study 21-87-101)

The prespecified primary efficacy endpoint was the change from baseline ACD and ICD after 12 weeks of therapy.

9.3.5.2 @**Measurement methods** (study 21-87-101)

The "immediate-incline" treadmill method was used wherein the incline load started immediately at 10% (and remained constant), with speed also constant at 3.2 km/h (2 mph). These tests were performed pre-treatment, and at post-randomization weeks 4, 8, and 12. Prior to treatment, and at post-randomization weeks 4, 8, and 12 the patients were evaluated with assessment of adverse events and concomitant medications, as well as vital signs, serum chemistry, and hematology

9.3.5.3 @**Statistical analyses.** (study 21-87-101)

Testing was to be be two-sided at an alpha level of 0.05. The sponsor reports that the date of the study's unblinding for analysis is not available, but that there was no interim look. There was apparently no formal power calculation for this study.

9.3.6 @**Results other than Efficacy outcomes** (study 21-87-101)

9.3.6.1 @**Covariates:** (study 21-87-101)

There were imbalances in pre-treatment rate of tobacco use, and concomitant history of diabetes, as shown in the table below.

Table: 37

@Demographic and Pre-treatment characteristics of subjects in study 21-87-101:

	CLZ 100 mg bid	Placebo
# randomized	n= 10	n= 9
male	60%	67%
female	40%	33%
age (mean)	62	65
wt mean (kg)	67.8	69.7
concomitant tobacco use	30%	22.2%
diabetes	40%	11.1%

[source: pg 36, vol 202]

5.3.6.2 @Disposition of subjects: (study 21-87-101)

A total of 19 subjects were randomized (evenly distributing among treatment groups as 10 cilostazole, 9 placebo). Each had at least one nonmissing pre-treatment ACD datum, and at least 1 nonmissing post-randomization ACD datum. Dropouts numbered 7 in the clz-treated groupand 4 in the placebo group.

The attributed reasons for all dropouts are shown in the following table.