8.6 Study 21-95-201: !

8.6.1 @Design Summary (study 21-95-201)

This concurrent placebo-controlled, double-blind, parallel-group, study randomized (in a 1:1 ratio) 215 subjects (peripheral atherosclerosis patients with moderate-to-severe, stable, intermittent claudication) to receive placebo, or cilostazol given as a fixed 200 or 300 mg/d dose in equally-divided twice-daily (100 or 150 mg bid) oral administrations for 12 weeks. The primary objectives were to assess safety (although not including a mortality or cardiovascular morbidity endpoint), and log transformation of change from baseline ACD, at trough, after 12 weeks of therapy.

The study was conducted from December 14, 1995 to September 5, 1996.

8.6.2 @Enrollment criteria. (study 21-95-201)

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, ischemic ulceration, gangrene, or Buerger's disease. 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:

- female of childbearing potential, unless surgically sterilized, or at least 1 year postmenopausal.
- sympathectomy or lower extremity arterial reparative surgery, including endovascular procedures, within the previous 3 months.
- greater than 60% above ideal body weight.
- supine arterial BP >200 mmHg systolic or >100 mmHg diastolic.
- current metastatic malignancy.
- 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, PTCA or CABG within 6 months, symptomatic cardiac arrhythmias, or angina pectoris.
- risk of, or tendency to, bleeding.
- pericarditis, pericardial effusions.
- platelet count below 130,000/cm3 or hematocrit below 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.

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

8.6.3 @**Qualifying criteria.** (study 21-95-201)

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 observations were obtained during standardized treadmill testing conducted prior to study treatment:

- attainment of ACD no greater than 320 meters, with variance no greater than 20%.
- attainment of ICD between 30 and 200 meters with a treadmill incline of 12.5% incline and speed of 3.2 km/h.
- test terminated for intermittent claudication only.
- exercise-induced 10 mmHg decrease in estimated BP of at least one ankle artery, measured one minute following the end of symptom-limited treadmill testing
- Doppler ABI < 0.90.

8.6.4 @**Treatment regimen.** (study 21-95-201)

Subjects were randomized to receive placebo, or cilostazol given as a fixed 300 or 200 mg/d dose in equally-divided twice-daily (b.i.d.) oral administrations for 12 weeks. Patients were instructed to take their daily doses 30 minutes before breakfast and 30 minutes before the evening meal. Study medication was formulated as 100 mg and 50 mg cilostazol tablets and matching placebo tablets. The 100 mg CLZ tablets were from lot 4K79PA1, the 100 mg placebo tablets were from lot 4L75P100, the 50 mg CLZ tablets were from lot 4K77PB1, and the 50 mg placebo tablets were from lot 4K76PP1.

8.6.5 @**Endpoints.** (study 21-95-201)

8.6.5.1 @**Endpoint Descriptions** (study 21-95-201)

The prespecified primary efficacy endpoint was log (trough ACD at week 12 /trough ACD at pre-treatment baseline), but there was *no* prespecification that just one of the two cilostazole doses would serve as primary endpoint.

The prespecified secondary outcome variables were:

- trough ACD at weeks 4 and 8.
- trough ICD at weeks 4, 8, and 12.
- Subjective claudication improvement as per patient and physician.

- Doppler-measured limb pressures.
- Quality of Life questionnaires.

8.6.5.2 **@Measurement methods** (study 21-95-201)

The "immediate-incline" treadmill method was used wherein the incline load started immediately at 12.5% (and remained constant), with speed also constant at 3.2 km/h (2 mph). Walking tests were conducted at weeks 4, 8, and 12, and 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. Treadmills were to have been calibrated within 6 months of testing, and every attempt was to be made to assure that patients used the same treadmill with the same technician for each test.

Twenty four hour Holter monitoring was performed at baseline, week 2, and week 8. These results were analyzed and reported by Biomedical Systems, Inc.

Quality of Life questionnaires (Medical Outcome Scale Short Form 36, Walking Impairment Questionnaire, and Physical Activity Recall) were administered at baseline, and at weeks 4, 8 and 12. Prior to treatment, and every two weeks for the first eight weeks, then again at week 12 the patients were evaluated for the status of adverse events and concomitant medications. Prior to treatment, and at weeks 2, 4, 6, 8, and 12 the patients underwent vital sign, hematology, and EKG determinations. Prior to treatment, and at weeks 2, 4, 6, and 12 the patients underwent serum chemistry determinations. Urinalysis was performed at weeks 6 and 12. Physical examination was performed at baseline, and week 12. Blood samples were drawn at baseline, and at weeks 2, 6, and 12 for an assessment of plasma concentration of cilostazol and its two main metabolites.

8.6.5.3 **@Statistical analyses.** (study 21-95-201)

Primary analyses were conducted by the intent-to-treat principle, in a dataset including all subjects with nomissing ACD data both at baseline and at 1 or more post-baseline observation. The LOCF method was used to handled missing data, and testing was two-sided at an alpha level of 0.05. There were no adjustments for multiple comparisons. Continuous efficacy measures were analyzed by ANOVA (where normally distributed), or the Wilcoxon rank sum test.

Subjective improvement in claudication condition as assessed by the patient and by the investigator was analyzed using the Cochran-Mantel-Haenszel test. The sample size of this study appears to have been based on the ACD endpoint, and assumed a geometric mean change from baseline of 24% for cilostazol. The sponsor reports that 60 patients per arm were needed to provide greater than 90% power, at a two-sided significance level of 5%.
There was reportedly no interim analysis.

8.6.6 @**Results other than Efficacy outcomes** (study 21-95-201):

8.6.1 @**Code breaks:** (study 21-95-201)

The sponsor reports that no patients codes were unblinded during the course of the study.

8.6.6.2 @**Covariates.** (study 21-95-201)

Pre-treatment covariates were reasonably well balanced, as shown in the table below.

Table: 20

@Demographic and Pre-treatment characteristics of in study 21-95-201:
(all-randomized dataset)

	CLZ 150 mg bid	CLZ 100 mg bid	Placebo
	n= 73	n= 72	n= 70
male	81%	75%	81%
female	19%	25%	19%
age (mean)	65	68	66
age <65 yr	48%	33%	37%
Caucasian	84%	92%	84%
Black	16%	7%	10%
wt mean (kg)	84	79	84
concomitant cigarette use	33%	36%	39%
diabetes	34%	31%	34%
resting ABI mean	0.63	0.64	0.64
SD	0.19	0.19	0.17

[source: table on pg 84, vol 180; & submission 7/6/98]

8.6.3 @**Disposition of subjects.** (study 21-95-201)

A total of 215 subjects were randomized (evenly distributing among treatment groups as 72 in the clz 100 mg bid, 73 in the clz 150 mg bid, and 70 in the placebo group). Their disposition was as 'ows:

- 179 subjects comprised the "efficacy" dataset (distributing as 53 in the clz 100 mg bid group, 60 in the clz 150 mg bid group, and 66 in the placebo group). 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.

- 165 subjects (distributed as 48 in the clz 150 mg bid group, 55 in the clz 150 mg bid group, and 66 in the placebo group) had at least one nonmissing pre-treatment ACD datum, and at least one nonmissing ACD datum at each planned observation point.

The total rate of subject dropouts was higher in both clz groups than in the placebo group. The attributed reasons for dropouts are as shown in the following table.

Table: 21

Subject dropouts in study 21-95-201:
(all-randomized dataset)

	CLZ 150 mg bid	CLZ 100 mg bid	Placebo
# randomized	n = 73	n = 72	n = 70
Total dropouts	25 (34%)	17 (24%)	8 (11%)
Dropouts for any AE	24 (33%)	14 (19%)	6 (9%)
All dropouts, by reason:			
adverse event	24	14	6
lack of efficacy	0	0	1
clinical deterioration	0	1	0
failed screening	0	1	0
noncompliance	1	0	0
other	0	1	1

[source: pg 76, vol 180]

The most frequent protocol deviations involved nonadherance to the window for dosing before assessment visits, and use of prohibited medications, primarily use of aspirin and NSAIDS. No data were excluded as a result of these.

8.6.7 @**Efficacy outcomes:** (study 21-95-201)

.7.1 @**Tests stopped for nonspecific reasons:** (study 21-95-201)

The stopping of final tests for nonspecific reasons (defined as reasons other than claudication) occurred in approximately 29% of clz 150 mg bid randomized subjects, 20% of clz 100 mg bid-randomized subjects and 15% of placebo-randomized subjects.

8.6.7.2 @**Primary analyses:** (study 21-95-201)

The baseline ACD data had a non-normal distribution.[2] At baseline in the efficacy ITT/LOCF dataset, the raw mean trough ACD was roughly comparable across treatment groups, as shown in the following table.

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

Table: 22

Baseline raw mean walking distances, at trough, in study 21-95-201:
(dataset= efficacy ITT/LOCF)

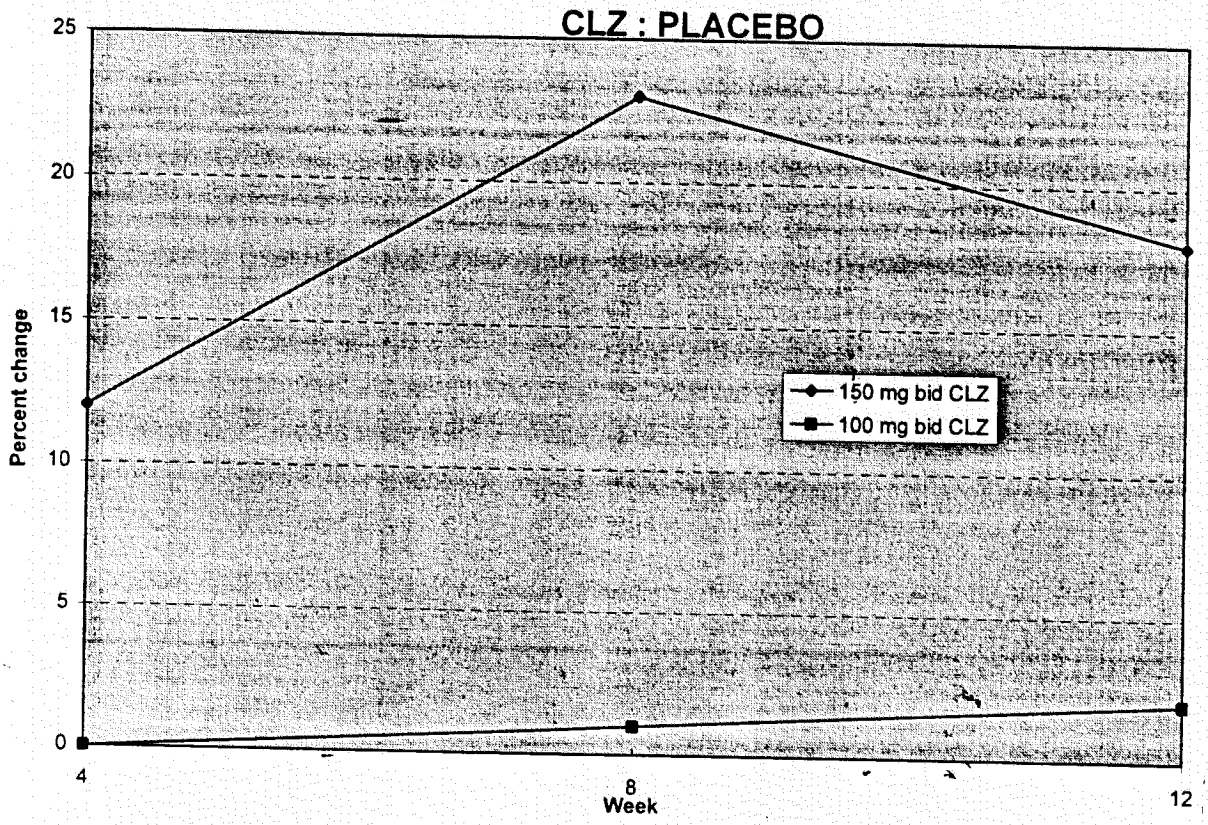
baseline metric	*CLZ 150 mg bid*	*CLZ 100 mg bid*	*Placebo*
ICD	64 m	66 m	68 m
ACD	120 m	123 m	125 m

[source: submission 5/6/98]

As depicted in the figure below, the sponsor's analysis showed a nominally significant 18% change from pre-treatment, in the ratio (clz 150 mg bid : placebo) of geometric mean trough ACD at week 12 (95% CI = 2-37%; uncorrected p= 0.03), and a nonsignificant 2% change 100 mg bid clz (95% CI = -12 to 18%; uncorrected p= 0.79).

Figure: 14

Percent change from pre-treatment, in the ratio (CLZ:plac) of geometric mean trough ACD (study 21-95-201, ITT/efficacy/LCOF)

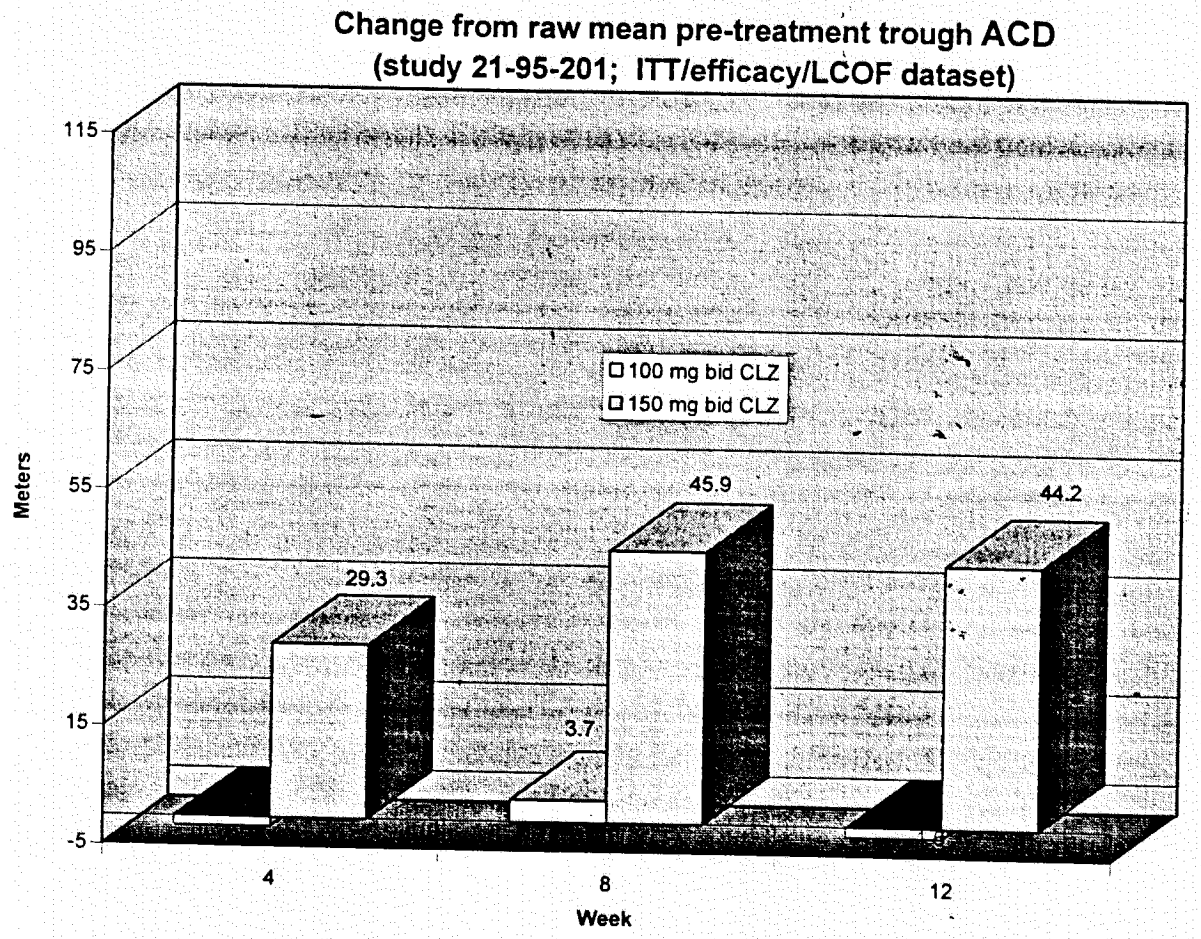


There was reportedly no significant treatment-by-center interaction, and there was no significant treatment-by-baseline interaction for ACD.

..5.7.3 **@Other efficacy analyses:** (study 21-95-201)

The raw data for the CLZ 150 mg bid group showed (as depicted in the figure below) a placebo-corrected mean increase from baseline ACD of approximately 29, 46, and 44 meters at trough at the end of weeks 4, 8, and 12, respectively. The lower clz dose showed essentially no better effect on raw mean trough ACD than did placebo.

Figure: 15



There were only trivial placebo-corrected raw changes from baseline mean ICD at trough: 11 meters for CLZ 150 mg bid, and 3.6 meters for CLZ 100 mg bid.

Although there were occasional differences in point estimates of cilostazole effect among subgroups (e.g. a roughly 2-times larger raw mean change from baseline in the ≥65 yr group, relative to the ≤65 yr group), the small size of subgroup samples (e.g. some having no more than 13 subjects) precludes conclusive interpretation; quite reasonably, no inferential statistical analyses were performed by the sponsor.

While investigators judged 47-48% of patient outcomes to be "better" or "much better" relative to pretreatment in both CLZ groups, nearly as high a rate of perceived improvement (44.3%) was reported for placebo-receiving patients. The patients' own therapeutic assessment was not able to differentiate clz from placebo; approximately half in each treatment group (including placebo) rated their own outcome as "better" or "much better" relative to pretreatment.

There was little in the way of even nominally significant difference between the three treatment groups in quality of life measures.

8.6.8 @Commentary on the evidence (study 21-95-201)

The sponsor's analysis showed a nominally significant 18% change from pre-treatment, in the ratio (clz 150 mg bid : placebo) of geometric mean trough ACD at week 12 (95% CI = 2-37%; uncorrected p= 0.03), whereas the raw placebo-corrected mean increase from baseline ACD was about 44 meters. This nominal p value is subject to inflation because of uncorrected multiplicity. There was no prespecification that just one of the two cilostazole doses would serve as primary endpoint, and even a third comparison (of clz high dose to clz low dose) was available with which to spend alpha.

b. The 100 mg bid clz dose produced, at trough on week 12, only a nonsignificant 2% change from pre-treatment, in the ratio (clz 100 mg bid : placebo) of geometric mean trough ACD at week 12 (95% CI = -12 to 18%; uncorrected p= 0.79), and showed near zero placebo-corrected raw mean and raw median effect in this study.

8.7 Study 21-93-201

.1 @Design Summary (study 21-93-201)

This concurrent placebo-controlled, double-blind, parallel-group, study randomized (in a 1:1 ratio) 189 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 12 weeks. The primary objectives were to assess safety, and change from baseline for trough ACD, trough ICD and serum high density lipid (HDL) levels after 12 weeks of therapy.

The study was conducted from February 1, 1994 to February 16, 1995.

8.7.2 @Enrollment criteria. (study 21-93-201)

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, ischemic ulceration, gangrene, or Buerger's disease. 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:

- female of childbearing potential, unless surgically sterilized, or at least 1 year postmenopausal.
- sympathectomy or lower extremity arterial reparative surgery, including endovascular procedures, within the previous 3 months.
- greater than 60% above ideal body weight.
- treated supine arterial blood pressure (BP) >200 mmHg systolic or >100 mmHg diastolic.
- current metastatic malignancy.
- 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 an MI which occurred > 6 months, PTCA or CABG within 6 months, symptomatic cardiac arrhythmias, and angina pectoris.
- pericarditis, pericardial effusions.
- risk of, or tendency to, bleeding.
- clinically significant hematologic disease
  twice the normal values for AST or ALT
  erum creatinine > 2.5 mg/dL.
- a requirement for the uninterrupted use of pentoxifylline, NSAIDs (with exception of acetaminophen), the following antiplatelet meds (acetylsalicylic acid, sulfinpyrazone,

dipyridamole, ticlopidine), the following anticoagulants (warfarin, heparin, dicumarol), the following vasoactive agents (papaverine, isoxsuprine, nylidrin, cyclandelate), or lipid-altering agents.
- current alcohol or other drug abuse, or use of an investigational drug within the past 30 days.
- poorly controlled diabetes as defined by glycosylated hemoglobin > 6.5%.

8.7.3 **@Qualifying criteria.** (study 21-93-201)

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 observations were obtained during standardized treadmill testing (12.5% incline, speed = 3.2 km/h) conducted prior to to study treatment:

- attainment of ACD no greater than 320 meters, with no greater than 20% variation.
- test terminated for intermittent claudication only.
- exercise-induced 10 mmHg decrease in estimated BP of at least one ankle artery, measured one minute following the end of symptom-limited treadmill testing
- supine Doppler ABI of 0.90 after 10 minutes at rest.

8.7.4 **@Treatment regimen.** (study 21-93-201)

Subjects were randomized to receive placebo, or cilostazol given as a (fixed 200 or 300 mg/d dose in equally-divided twice-daily (100 or 150 mg bid) oral administrations for 12 weeks. Study medication was formulated as 100 mg and 50 mg cilostazol tablets and matching placebo tablets. The 100 mg CLZ tablets were from lot 3G76PA1, the placebo tablets were from lot 3G76-100P.

8.7.5 **@Endpoints.** (study 21-93-201)

8.7.5.1 **@Endpoint Descriptions** (study 21-93-201)

The prespecified primary efficacy endpoints were change from baseline for trough ACD, trough ICD and serum high density lipid (HDL) levels after 12 weeks of therapy. Two analysis methods were prespecified: the Wei-Lachin multivariate rank test using change from baseline, and log(distance/baseline) using parametric methods of analysis and LOCF.

The prespecified secondary outcome variables were:
- subjective claudication improvement as per patient and physician.
- Doppler-measured limb pressures.
- quality of life questionnaires.

In addition to trough measures, walking distances were also assessed at presumed peak (3 hours post-dosing) during the pre-treatment phase, and at post-treatment weeks 8 and 12.

8.7.5.2 @**Measurement methods** (study 21-93-201)

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. Treadmill tests (trough, and presumed peak), and Quality of Life questionnaires were performed pre-treatment, and at weeks 8 and 12.

Prior to treatment, and at weeks 2, 4, 6, 8, and 12 the patients were evaluated with assessment of adverse events and concomitant medications, as well as vital signs, serum chemistry, hematology, EKG, blood samples (for assessment of plasma drug concentrations), and lipid analysis. Urinalysis was performed pre-treatment, and at weeks 2, 6, and 12. Physical examination was performed at baseline, and week 12.

8.7.5.3 @**Statistical analyses.** (study 21-93-201)

Testing was two-sided at an alpha level of 0.05. Analysis were conducted according to the intent-to-treat principle. The sponsor reports that no interim analyses were performed on the data from this study.

The sample size of this study was based on the goal of detecting a 4 mg/dl between-group difference in effect on serum HDL level at 80% power, and a 5% two-sided significance level. The sponsor reports that 75 patients per arm (with 1:1 randomization) were needed to provide this power.

8.7.6 @**Results other than Efficacy outcomes** (study 21-93-201):

8.7.6.1 @**Code breaks**: (study 21-93-201)

The sponsor reports that there were no premature randomization code breaks.

8.7.6.2 @**Covariates.** (study 21-93-201)

Pre-treatment covariates were well balanced, as shown in the table below.

Table: 23