**Table 9.** P-values of comparison of treatment and placebo groups calculated by this reviewer. Population-ITT, ACD

| Studies | | P-values calculated by this reviewer[a] | | | | |
|---|---|---|---|---|---|---|
| | | 100 mg bid vs PLC | 50 mg bid vs PLC | 100 mg bid vs 50 mg bid | Overall | Kruskal-Wallis overall[b] |
| 21-92-202 | LOCF | 0.00002 | 0.00107 | 0.14721 | 0.00002 | <1e-04 |
| | Completer | 0.00001 | 0.00210 | 0.02773 | 0.00001 | <1e-04 |
| 21-94-201 | LOCF | 0.00037 | 0.14104 | 0.03574 | 0.00155 | 0.0048 |
| | Completer | 0.00007 | 0.02579 | 0.03088 | 0.00018 | 6e-04 |
| 21-94-203 | LOCF | 2.8e-07 | | | 2.8e-07 | <1e-04 |
| | Completer | 1.3e-07 | | | 1.3e-07 | <1e-04 |
| 21-90-201 | LOCF | 0.00079 | | | 0.00079 | 4e-04 |
| | Observed[c] | 0.00053 | | | 0.00053 | 3e-04 |
| 21-93-201 | LOCF | 0.01124 | | | 0.01124 | 0.005 |
| | Completer | 0.01620 | | | 0.01620 | 0.0101 |
| 21-95-201 | | | **150 mg bid vs PLC** | **100 mg bid vs 150 mg bid** | | |
| | LOCF | 0.91087 | 0.04088 | 0.06545 | 0.07448 | 0.0608 |
| | Completer | 0.92058 | 0.05633 | 0.06644 | 0.08925 | 0.0775 |

a: Using ANOVA on log(distance/baseline).
b: The Kruskal-Wallis rank test on log(distance/baseline).
c: Patients with observed ACD at week 12.

From the analyses, we can see that cilostazol 100 mg bid group demonstrated superiority over placebo in improving ACD, except Study 21-95-201. Among the two studies with the 50 mg bid group, one (21-92-202) showed that cilostazol 50 mg bid group was significantly better than placebo in improving ACD, the other (21-94-201) only provided numerical evidence in favor of cilostazol 50 mg bid.

Although the sponsor's "percent" and "ratio" methods in estimating treatment effect were reasonable approaches for handling the log transformed ACD or ICD data, such estimated treatment effects would be difficult to interpret to the public. This reviewer calculated the medians of changes of ACD from baseline. It might be useful for labeling cilostazol.

**Table 10**. Median of change of ACD from baseline, Population-ITT

| **Studies** | | **Median (ACD -baseline)** | | |
|---|---|---|---|---|
| | | 100 mg bid | 50 mg bid | PLC |
| 21-92-202 | LOCF | 34.5 | 27 | 9 |
| | Completer | 55 | 40 | 4 |
| 21-94-201 | LOCF | 27.5 | 17.5 | 10 |
| | Completer | 41 | 19 | 10.5 |
| 21-94-203 | LOCF | 70.5 | NA | 9 |
| | Completer | 74 | NA | 9.5 |
| 21-90-201 | LOCF | 24.5 | NA | -2 |
| | Observed[a] | 30 | NA | -8 |
| 21-93-201 | LOCF | 58.5 | NA | 28 |
| | Completer | 53.5 | NA | 30 |
| 21-95-201 | | | **150 mg bid** | |
| | LOCF | 16.5 | 37 | 23 |
| | Completer | 14.5 | 43 | 23 |

a: Patients with observed ACD at week 12.

### 3.6.3 Center Contributions

To see whether a particular center excessively contributed to the efficacy results of log(ACD/baseline). The treatment effect of each center, defined by

mean(log(ACD/baseline)|drug) - mean(log(ACD/baseline)|placebo)

on all patients in that center, was calculated and plotted in Figure 4 for studies 21-92-202 and 21-94-201. It does not appear that any particular center contributed excessively to the efficacy result.

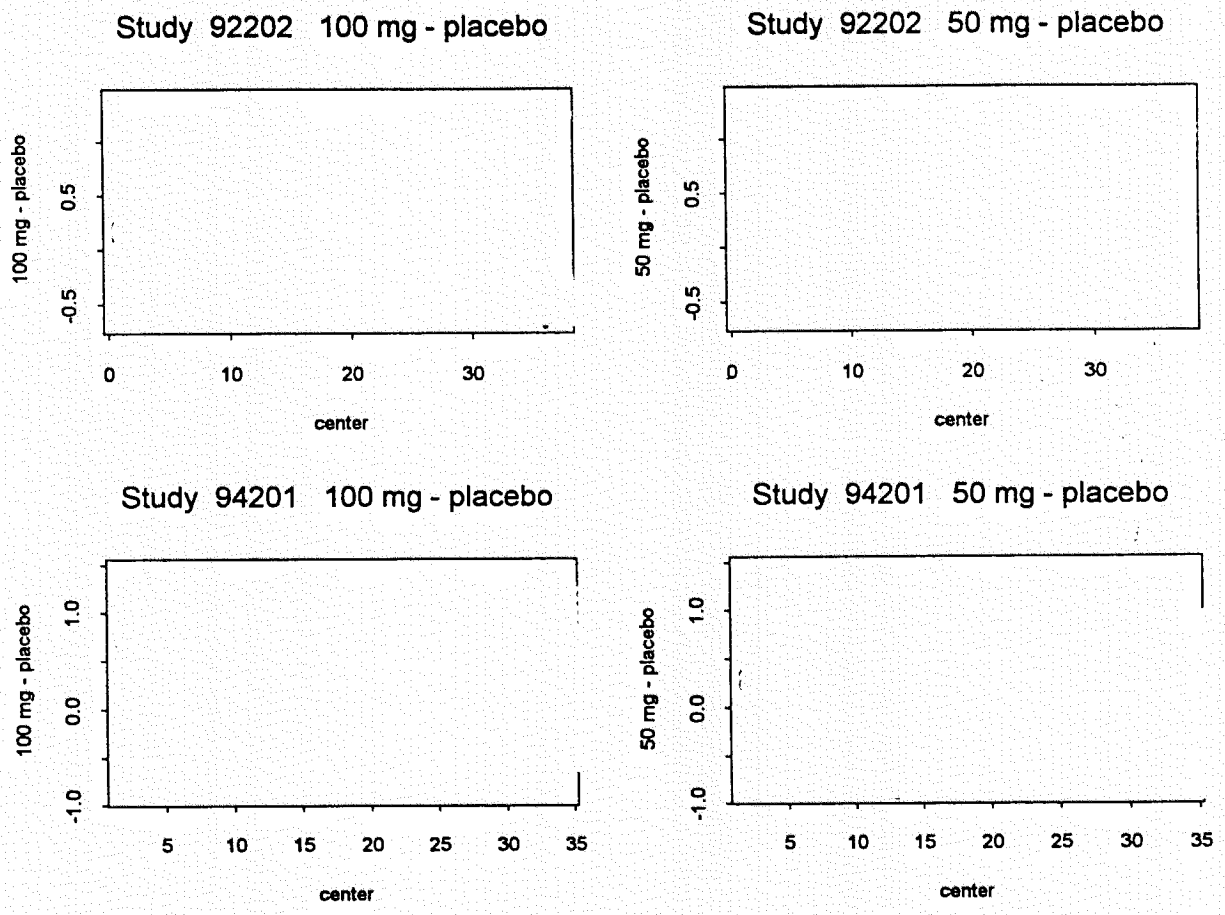



Figure 4. Center contributions are plotted against the natural order of centers on x-axis. The top numbers are center IDs and the numbers of patients are in parentheses.

### 3.6.4 Subgroup Analysis:

Since most of the patients in the studies were Caucasian, the subgroup analysis for race was not carried out. Subgroup analyses for sex and age were tabulated descriptively for three key studies. The results of the subgroup analyses are not contradictory to the main efficacy results.

Table 11 Subgroup analysis of mean of log(ACD/baseline) for sex

| Study | Sex | Mean of log(ACD/baseline) ITT-LOCF (# of patients) | | |
|---|---|---|---|---|
| | | 100 mg bid | 50 mg bid | PLC |
| 21-92-202 | F | 0.323 (37) | 0.408 (35) | 0.139 (31) |
| | M | 0.446 (103) | 0.296 (104) | 0.138 (109) |
| 21-94-201 | F | 0.291 (31) | 0.017 (34) | 0.087 (29) |
| | M | 0.318 (102) | 0.247 (98) | 0.120 (100) |
| 21-94-203 | F | 0.309 (29) | NA | 0.034 (30) |
| | M | 0.322 (90) | NA | 0.057 (90) |

Table 12. Subgroup analysis of mean of log(ACD/baseline) for age

| Study | Age | Mean of log(ACD/baseline) ITT-LOCF (# of patients) | | |
|---|---|---|---|---|
| | | 100 mg bid | 50 mg bid | PLC |
| 21-92-202 | < 65 | 0.472 (64) | 0.317 (63) | 0.215 (60) |
| | ≥ 65 | 0.364 (76) | 0.329 (76) | 0.081 (80) |
| 21-94-201 | < 65 | 0.346 (68) | 0.166 (68) | 0..066 (61) |
| | ≥ 65 | 0.277 (65) | 0.214 (64) | 0.155 (68) |
| 21-94-203 | < 65 | 0.295 (49) | NA | 0.053 (60) |
| | ≥ 65 | 0.337 (70) | NA. | 0.049 (60) |

### 3.6.4 Robustness of Efficacy Results:

Dr. Karkowsky asked whether the efficacy results reported in the previous sections were reliable. He suggested to look into the following two problems

**Excluded Patients**

As mentioned in Section 2, some patients in Study 21-92-202, who were randomized for efficacy evaluation, were excluded from the efficacy analysis due to the lack of post-randomization walking distance measurements. It is unclear why these patients had no post treatment measurements. There were similar problems in studies 21-94-201 and 21-94-203. The numbers of such patients in each group are as follows:

| Randomized patients for efficacy evaluation without post-randomization measurements | | | |
|---|---|---|---|
| Study | Placebo | 50 mg bid | 100 mg bid |
| 21-92-202 | 4 | 7 | 8 |
| 21-94-201 | 4 | 4 | 9 |
| 21-94-203 | 9 | N/A | 11 |

Dr. Karkowsky suggested to assign the worst LOCF score 1 to the patients in drug groups, and their own baseline ACD's to the patients in placebo group. With the modified data sets, the Kruskal-Wallis nonparametric test on log(ACD/baseline) yielded p-values of 0.0012, 0.0811 and 0.0001 for studies 21-92-202, 21-94-201 and 21-94-203, respectively. Hence, the efficacy results on ACD still hold under the worst case scenario for studies 21-92-202 and 21-94-203, but not for 21-94-201.

**Baseline Problem**:

For these studies with more than two baseline measurements, the sponsor used the last one as patient's baseline. They did not, however, specify this in the protocols. Dr. Karkowsky suggested an alternative way to check the robustness of the efficacy results by taking average of the last two baseline measurements as a new baseline. Among the three key studies, only the two largest studies, 21-92-202 and 21-94-201 had three baseline measurements. The results with the new baseline are as follows:

**Table 13.** The efficacy results of ITT ACD data sets with averaging the last two baselines.

| Study | Data Set | Mean of log(ACD/new baseline) | | | Overall p-values | |
|---|---|---|---|---|---|---|
| | | 100 mg bid | 50 mg bid | Placebo | ANOVA | Kruskal-Wallis |
| 21-92-202 | LOCF | 0.3764 | 0.3167 | 0.1579 | 0.00092 | 0.0014 |
| | Completer | 0.4606 | 0.3396 | 0.1645 | 0.00015 | 0.0001 |
| 21-94-201 | LOCF | 0.2999 | 0.1799 | 0.1135 | 0.00374 | 0.0111 |
| | Completer | 0.3875 | 0.2411 | 0.1207 | 0.00028 | 0.0006 |

We can see that the efficacy results still hold with the new baseline.

### 3.6.6 Treatment and Baseline Interaction:

Dr. Rodin suggested that a possible treatment by baseline interaction concerning ACD endpoint should be investigated. To study this problem, a linear regression of ln(ACD) on ln(baseline) was conducted to test whether the slopes are parallel among different treatment groups for the ITT-LOCF data sets. It appeared that the slopes of treatment and placebo groups are parallel for study 21-94-203. For studies 21-92-202 and 21-94-201, the slopes for different treatment groups are significantly different. The results are plotted in Figure 5.

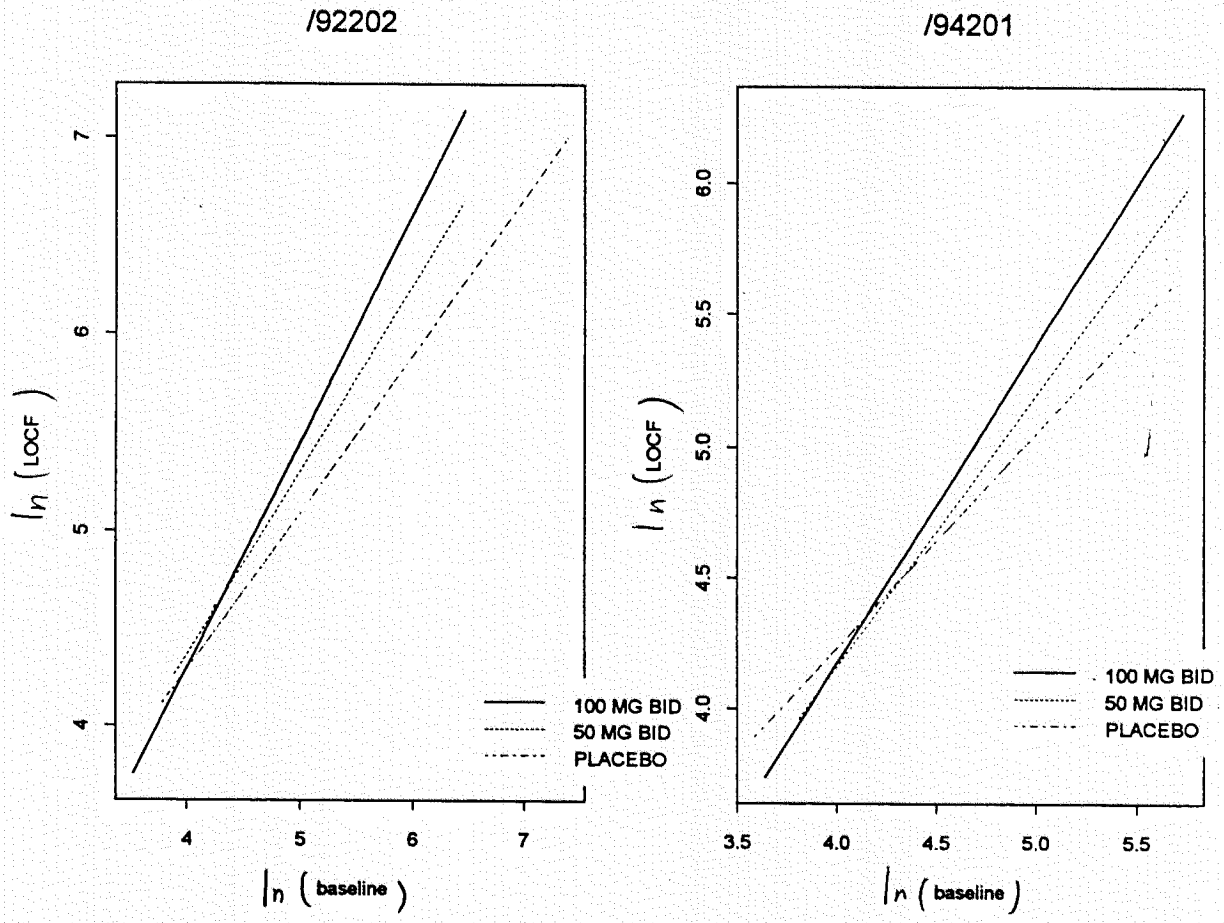



Figure 5. Regression of ln(ACD) on ln(baseline) for the ITT-LOCF data sets.

The results seem to show that cilostazol is more effective in patients with higher baseline measures. In Section 3.6.1, it was noticed that the placebo group patients had, although not statistically significant, higher baseline measurements than the CLZ group patients, particularly higher than the 100 mg bid patients. Based on this observation, this reviewer thinks that it is

unlikely that the possible interaction, or baseline imbalance, will lead to a bias in favor of placebo.

## 4. Secondary Endpoint-ICD:

This reviewer has calculated the treatment effects based on ICD. The results are in Table 12 and they are consistent with the sponsor's results.

**Table 12**. Reviewer estimated treatment effect on ITT-ICD data sets.

| Studies | | Reviewer's Estimated Treatment Effect | | | | |
|---|---|---|---|---|---|---|
| | | Percent[a] | | | Ratio[b] | |
| | | 100 mg bid | 50 mg bid | PLC | 100 mg vs PLC | 50 mg vs PLC |
| 21-92-202 | LOCF | 59% | 48% | 20% | 1.32 | 1.23 |
| | Completer | 72% | 54% | 19% | 1.45 | 1.30 |
| 21-94-201 | LOCF | 49% | 33% | 20% | 1.24 | 1.10 |
| | Completer | 60% | 38% | 20% | 1.33 | 1.15 |
| 21-94-203 | LOCF | 50% | NA | 23% | 1.22 | NA |
| | Completer | 55% | NA | 26% | 1.23 | NA |
| 21-90-201 | LOCF | 40% | NA | 3% | 1.35 | NA |
| | Observed[c] | 41% | NA | 2% | 1.37 | NA |
| 21-93-201 | LOCF | 40% | NA | 26% | 1.11 | NA |
| | Completer | 40% | NA | 25% | 1.12 | NA |
| 21-95-201 | | | **150 mg bid** | | | **150 mg bid** |
| | LOCF | 43% | 54% | 39% | 1.03 | 1.11 |
| | Completer | 48% | 58% | 38% | 1.08 | 1.15 |

a: $(\prod(\text{distance/baseline})^{(1/n)} - 1) * 100\%$

b: $[\prod(\text{distance/baseline})^{(1/n)}]_D / [\prod(\text{distance/baseline})^{(1/m)}]_P$

c: Patients with observed ACD at week 12.

## 5. Secondary Endpoint-Quality of Life:

Upon a request from Dr. Karkowsky, this reviewer has checked the efficacy results of a secondary endpoint, quality of life (QOL), in the sponsor's report. The two largest studies, 21-92-202 and 21-94-201, have **5** and **6** secondary endpoints pre-specified in the protocols, respectively. Applying the Bonferroni criteria, the nominal test level for the quality of life will be 0.01 for Study 21-92-202 and 0.008333 for 21-94-201.

There are many items in quality of life assessment, and there was no mention of any plan in the protocols as to how to assess the significance of QOL. In the sponsor's report, QOL assessment was summarized in the following three areas: 1) physical health concepts; 2) mental health concepts; and 3) combined physical-mental health concepts. Therefore, the nominal level for assessing each of these areas will be 0.003333 for 21-92-202 and 0.002777 for 21-94-201.

For each area, the sponsor reported the efficacy results by different dose groups, time points, or subscales. This would warrant a further reduction in the nominal level. Even at the current level, 0.00333 for 21-92-202 and 0.002777 for 21-90-201, **this reviewer has not seen a single p-value** in the sponsor's report (Vol. 119, pages 110-113; Vol. 137, pages 105-108) **as being statistically significant.**

## 6. Dropouts and Possible Impact:

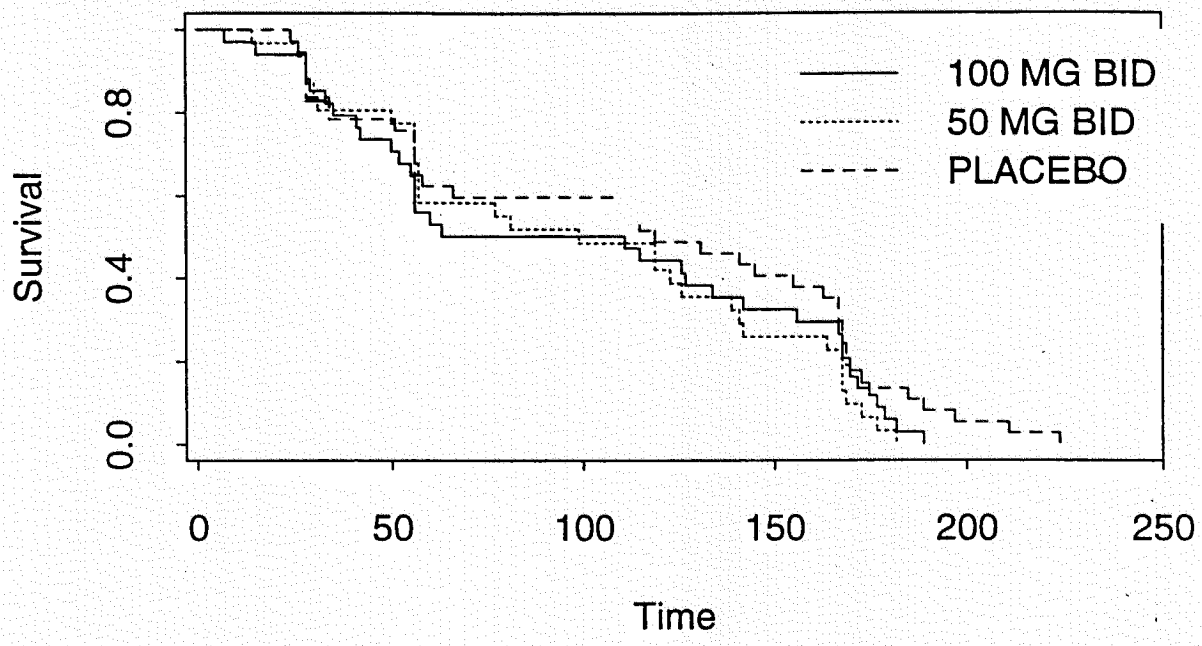
This reviewer has studied the patterns of dropout patients in studies 21-92-202 and 21-94-201, the two largest studies. For all patients who did not complete trials, their days in trial were calculated by taking the difference of the last walking distance date from the date of randomization. Two patients, ID 0339 in Study 21-92-202 and ID 0420 in Study 21-94-201, generated wrong records, and were removed from the analysis. The Kaplan-Meier survival curves of the dropout patient's days in trial are plotted in Figures 6. It can be seen for both studies, cilostazol patients dropped out earlier than placebo patients.

The average days in trial of the dropout patients are given in the following table:

| Study | | 100 mg bid | 50 mg bid | Placebo |
|---|---|---|---|---|
| 21-92-202 | Average days in trial | 98.97 | 99.39 | 120.37 |
| | # of patients | 34 | 31 | 38 |
| 21-94-201 | Average days in trial | 65.05 | 79.90 | 107.97 |
| | # of patients | 44 | 29 | 35 |

To test whether there are statistical significant differences among three groups, the log-rank test yielded p-values 0.3132 for Study 21-92-202 and 0.21 for Study 21-94-201. This reviewer is not attempting to assess the impact of dropouts on the efficacy results in the previous sections.

## The Kaplan-Meier Curves of Dropouts in Study 92202




## The Kaplan-Meier Curves of Dropouts in Study 94201

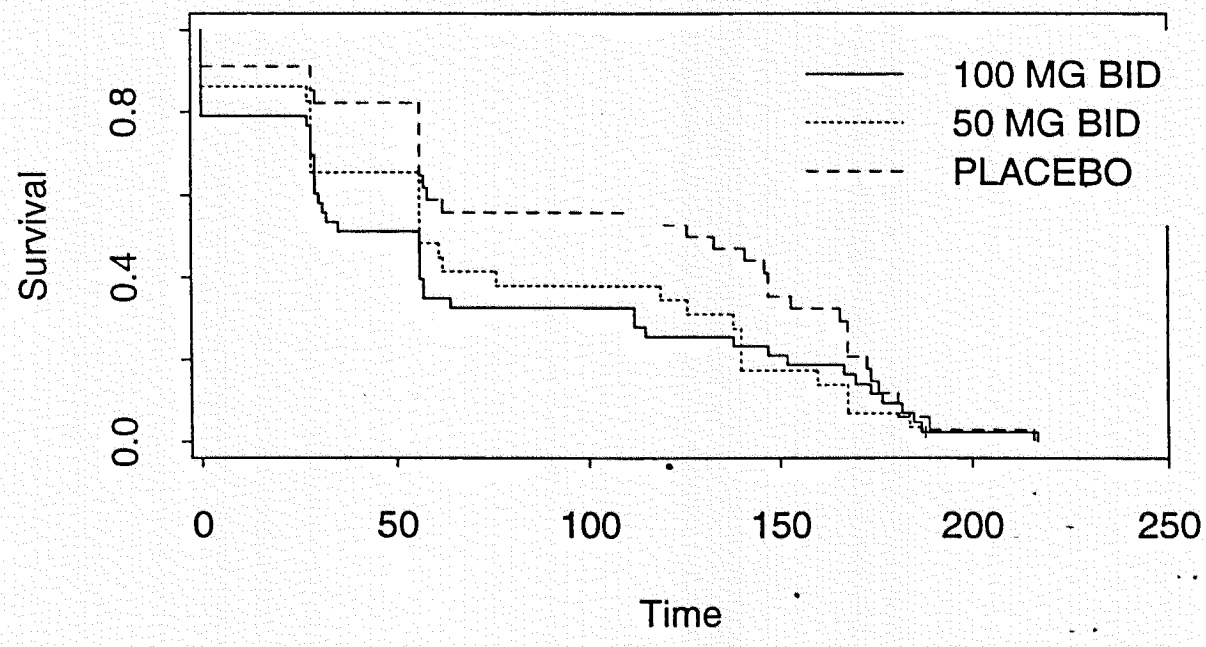



Figure 6.

**7. Conclusion:**

Base on the data sets submitted by the sponsor, this reviewer thinks that cilostazol patients, particularly the 100 mg bid group, showed a statistical significant improvement in their ACD scores over placebo patients. The results from ICD scores also support this conclusion. The efficacy results seem reliable.

This reviewer, however, sees no credible evidence to support that cilostazol improved patients' quality of life.

6/23/98

Kun Jin, Ph.D.
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Concur: 6/23/98
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Arch. NDA 20-863

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# APPENDIX A

# NDA 20-863 (CILOSTAZOL)

## Review of Studies (Protocols) 21-96-202 and 21-94-301

## I. INTRODUCTION

This appendix pertains to present the reviews of two placebo and active control studies 21-96-202 and 21-94-301. Review of these two studies were requested by Drs. Steve Rodin and Abraham Karkowsky, the medical reviewers from the Division of Cardio-Renal Drug Products (HFD-110). This review will serve as an appendix to the main statistical review of Dr. Kun Jin, from the Division of Biometrics I (HFD-710).

Basically, the two studies had similar design, the same primary and secondary objectives, but were conducted on patient populations satisfying different inclusion criteria. For instance, the patients in Study 202 could have larger baseline ACD (≤ 537.6 meters) and ICD (at least 54 meters) as compared to those of patients in Study 301 (≤ 450 meters for ACD and at least 30 meters for ICD).

**Design:** The studies are: Randomized Double-Blind Study of the Effects of Cilostazol Versus an Active-Control or Placebo in Patients with Intermittent Claudication (moderate to severe) Secondary to Peripheral Vascular Disease. These are patients with moderate to severe intermittent claudication.

It is specified that, active-control is Pentoxifylline (**PEN**) in Study 21-96-202 and Oxpentifylline (**OXP**) in Study 21-94-301.
The doses used are:

- placebo, cilostazol (**CZL**) 100 mg b.i.d. and PEN 400 mg t.i.d. in Study 21-96-202
- placebo, cilostazol (**CZL**) 100 mg b.i.d. and OXP t.i.d. in Study 21-94-301

**Primary Objective:** As specified in the protocol, the objectives are:

a. To compare cilostazol (**CZL**) to PEN/OXP and to placebo (**PLA**), with respect to the primary and secondary efficacy parameters, in patients with moderate to severe intermittent claudication.

b. To compare the safety profile of CZL to that of PEN/ OXP and PLA in the same patient population.

**Primary Efficacy:** The primary efficacy variable is Absolute Claudication Distance (**ACD**) on standardized treadmill testing.

**Secondary Efficacy variables:** Secondary efficacy variables are:

- Initial Claudication Distance (**I CD**) on standardized treadmill testing.
- Quality of Life (**QOL**).
- Walking impairment Questionnaire (**WIQ**).

## II. REVIEWERS' ANALYSIS

For both studies, the main analysis will be the Intent-to-Treat (**ITT**) Analysis, namely, by using the last-observation-carried-forward (**LOCF**) imputation for earlier withdrawals. The LOCF is for the patients who had at least one **post randomization** observation. Thus, the patients with only the baseline values are eliminated from the analyses. It needs to be mentioned that the analysis presented here are the prospective analyses.

The analyses primarily consist of:

- Descriptive statistics on ACD and ICD for the LOCF.
- Analysis of Covariance (ANCOVA) on log transformation of ACD and ICD, using the transformed variables[1]

  L_ACD = log(LOCF_ACD/Baseline_ACD)

  L_ICD = log(LOCF_ICD/Baseline_ICD).

  We denote: L_Base = log(baseline).

  To examine the significance of interactions, a preliminary analysis of covariance (ANCOVA), in which model included L_Base, center, treatment, L_base-by-Treatment and Center-by-Treatment interactions was performed. It was found that L_base-by-Treatment and Center-by-Treatment interaction were statistically non-significant. Therefore, simpler ANCOVA models which excluded the non-significant interactions, were conducted.

- For Study, 21-94-301, a Non-Parametric test using the LOCF, to compare the three treatment groups with respect to ACD, ICD, L_ACD and L_ICD.

---

[1]- Because of the drastic skewness of the distribution of ACD and ICD observations, as well as large variability among the observations, the log transformation was considered, by the sponsor, to reduce the skewness and the variability. These reviewers are agreeing with the sponsor's log transformation.

- For Study 21-96-202, the homogeneity of treatment effect was tested, using a chi-square test on categorized values of Ankle Brachial Index (**ABI**), for both affected and non-affected limbs. In addition, an ANCOVA model, similar to those for L_ACD and L_ICD, was performed on ABI. For Study 21-94-301, ABI data was not available.

The results are presented below.

## II.a. Study 21-96-202

### *Descriptive Statistics on ACD and ICD:*

A total of 643 randomized subjects (205 in CLZ, 212 in OXP, and 226 in PLA groups) with post-baseline measurements were included in the analyses. The major baseline and demographic characteristics were comparable among the treatment groups.

The following table presents a summary of descriptive statistics on the ACD and ICD.

**Table 1.a:** Descriptive Statistics Using **LOCF** for Change from Baseline in ACD and ICD.

| Treatment | ACD (in meter) | | | | | ICD (in meter) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | | SD | Median | n | Mean | | SD | Median |
| | | Baseline* | Change | | | | Baseline* | Change | | |
| CLZ | 205 | 243 | 107 | 158 | 63 | 205 | 124 | 94 | 127 | 58 |
| OXP | 212 | 243 | 64 | 127 | 31 | 212 | 128 | 74 | 106 | 45 |
| Place | 226 | 235 | 65 | 135 | 39 | 226 | 123 | 57 | 93 | 35 |

* Baseline ACD and ICA are included for the reference. The entries of n, SD and Median are calculated form the change from baseline values.

### *ANCOVA on L_ACD and L_ICD :*

The analyses were performed on the log transformation of the ACD and ICD observations.

**Table 2.a:** Resulting P-Values* of ANCOVA on LOCF for the Variables L_ACD and L_ICD.

| Source | ACD | | | ICD | | |
|---|---|---|---|---|---|---|
| | Full Model | Reduced Model | Reduced Model | Full Model | Reduced Model | Reduced Model |
| L-Base | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 |
| Center | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 |
| Treatment | 0.0606 | 0.2318 | **0.0002** | 0.0768 | 0.1298 | **0.0002** |
| L-Base-by-Trt interaction | 0.0874 | 0.3758 | --- | 0.1624 | 0.2871 | --- |
| Ctr-by-Trt interaction. | 0.6147 | --- | --- | 0.9744 | --- | --- |
| Pairwise Comparisons | CLZ vs. PLA: 0.0006<br>CLZ vs. PEN: 0.0003 | | | CLZ vs. PLA: 0.0001**<br>CLZ vs. PEN: 0.0203 | | |

* p-values are given for the terms included in the model
** with significant treatment-by-baseline interaction

**Discussion:** Following presents a description of the ANCOVA results on L_ACD and L_ICD.

***L_ACD:*** (1) A statistically significant baseline effect was found (p=0.0001); (2) A statistically significant difference in the mean L_ACD was found among the treatment groups (p=0.0002); (3) Pairwise comparisons showed that there was a statistically significant superiority of CLZ over PLA (p=0.0006). Also, there was a statistically significant superiority of CLZ over PEN (p=0.0003). For the pair-wise comparisons, no adjustment for the multiplicity was necessary because of only three hypotheses about the group means were tested (Closure Method); (4) A mild treatment-by-baseline interaction was found for CLZ vs. PEN (p=0.1101). However, the uncrossed regression lines of the change in L_ACD on the baseline were slightly unparalell in the range of observed L_Base, indicating an ignorable impact of such an interaction.

***L_ICD:*** (1) A statistically significant difference in L_ICD among the treatment groups was found (p=0.0002); (2) Pairwise comparisons showed a statistically significant superiority of CTZ over PEN (p=0.0203). (3) There was a statistically significant superiority of CLZ over PLA (P=0.0001). However, an interaction between the treatment and L_base was found (p=0.12) in this case. From the regression lines of the L_ICD on the L_base, it appears that L_ICD was lower in CLZ group than that in PLA at the upper end of the range of the L_base. Caution may be needed to interpret the pair-wise comparison result.

***Analyses on ABI:***

Upon the request of Dr. Karkowsky, the ABI values were arbitrarily categorized as:

ABI $\leq$ 0.5: Severe
0.5 < ABI $\leq$0.7: Moderate
0.7 < ABI $\leq$0.9: Mild

**Statistical Reviewers:** Lu Cui & Kooros Majoob

0.9 < ABI : Normal

***Homogeneity Test:*** Homogeneity of the severity of ABI among the treatment groups, for both affected and non-affected limbs, at baseline and for LOCF was tested via a chi-square test, using the following 3-by-4 tables.

**Table 3.a:** Degree of Risk of ABI at Baseline and for LOCF, by Treatment, for Affected Limb

| Treatment | Baseline or LOCF | ABI Categories | | | | Total |
|---|---|---|---|---|---|---|
| | | ABI ≤ 0.5 Severe | 0.5 < ABI ≤ 0.7 Moderate | 0.7< ABI ≤0.9 Mild | ABI > 0.9 Normal | |
| CLZ | Baseline | 36 (17.9%) | 89 (44.3%) | 58 (28.9%) | 18 (9.0%) | 201 (100%) |
| | LOCF | 24 (11.9%) | 85 (42.3) | 59 (29.4) | 33 (16.4%) | |
| PEN | Baseline | 45 (21.6%) | 84 (40.4%) | 51 (24.5%) | 28 (13.5%) | 208 (100%) |
| | LOCF | 41 (19.7%) | 72 (34.6%) | 55 (26.4%) | 40 (19.2%) | |
| PLA | Baseline | 52 (23.2%) | 91 (40.6%) | 66 (29.5%) | 15 (6.7%) | 224 (100%) |
| | LOCF | 44 (19.6%) | 92 (41.1%) | 61 (27.2%) | 27 (11.1%) | |
| Total | Baseline | 133 (21.0%) | 264 (41.7%) | 175 (27.6%) | 61 (9.6%) | 633 |
| | LOCF | 109 (17.2%) | 249 (39.3%) | 175 (27.6%) | 100 (15.8%) | |
| **Chi-Square Test of Homogeneity at Baseline: P-Value = 0.216**<br>**Chi-Square Test of Homogeneity for LOCF: P-Value = 0.106** | | | | | | |

**Table 4.a:** Degree of Risk of ABI at Baseline and for LOCF, by Treatment, for Non-Affected Limb

| Treatment | Baseline or LOCF | ABI Categories | | | | Total |
|---|---|---|---|---|---|---|
| | | ABI ≤ 0.5 Severe | 0.5 < ABI ≤ 0.7 Moderate | 0.7< ABI ≤0.9 Mild | ABI > 0.9 Normal | |
| CLZ | Baseline | 19 (6.0%) | 43 (21.4%) | 80 (39.8%) | 59 (29.4%) | 201 (100%) |
| | LOCF | 12 (9.5%) | 53 (26.4%) | 70 (34.8%) | 66 (32.8%) | |
| PEN | Baseline | 22 (10.6%) | 54 (26.0%) | 62 (29.8%) | 70 (33.7%) | 208 (100%) |
| | LOCF | 17 (8.2%) | 55 (26.4%) | 60 (28.9%) | 76 (36.5%) | |
| PLA | Baseline | 19 (8.5%) | 61 (27.3%) | 74 (33.0%) | 70 (31.3%) | 224 (100%) |
| | LOCF | 16 (7.1%) | 63 (28.1%) | 74 (33.0%) | 71 (31.7%) | |
| Total | Baseline | 60 (9.5%) | 158 (25.0%) | 216 (34.1%) | 199 (31.4%) | 633 |
| | LOCF | 45 (7.1%) | 171 (27.0%) | 204 (32.2%) | 213 (33.6%) | |
| **Chi-Square Test of Homogeneity at Baseline: P-Value = 0.216**<br>**Chi-Square Test of Homogeneity for LOCF: P-Value = 0.106** | | | | | | |

Here the term "homogeneity" refers to the homogeneity among the three treatments with respect to

the patients' distribution in the four ABI categories.

Based on the chi-square test, at baseline and for LOCF, no statistically significant difference in ABI among the treatment groups was found for both patients with affected and those without affected limbs.

ANCOVA was performed on change from baseline in ABI using LOCF values. The resulting P-values are presented in the following table.

**Table 5.a:** ANCOVA Results on ABI Using LOCF Values.

| Source | P-Value | |
|---|---|---|
| | Affected Limb | Non-Affected Limb |
| Baseline | 0.0001 | 0.0001 |
| Center | 0.0006 | 0.0001 |
| Treatment | 0.2314 | 0.4324 |
| Baseline-by-Treatment | 0.1852 | 0.3925 |
| Center-by-Treatment interaction. | 0.7987 | 0.0001 |

For both affected and a non-affected limbs, no statistically significant difference among the treatment groups was found with respect to ABI. For a non-affected limb, the results show significant treatment-by-center interaction (P=0.0001). However, because of no significant treatment effect, further investigation does not seem to be necessary.

## II.b. Study 21-94-301

***Descriptive Statistics on ACD and ICD:***

A total of 370 patients were randomized and out of those, 363 patients (123 in CLZ, 118 in OXP, and 122 in PLA groups) with post-baseline measurements were included in the analyses. The major baseline and demographic characteristics were comparable among the treatment groups.

The following table presents a summary of descriptive statistics on the ACD and ICD.

**Table 1.b:** Descriptive Statistics on **LOCF** for Change from Baseline in ACD and ICD.

| Treatment | ACD (in meter) | | | | | ICD (in meter) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | | SD | Median | n | Mean | | SD | Median |
| | | Baseline* | Change | | | | Baseline* | Change | | |
| CLZ | 123 | 128 | 86 | 166 | 31 | 123 | 78 | 52 | 110 | 25 |
| OXP | 118 | 135 | 87 | 158 | 29 | 117 | 81 | 47 | 83 | 23 |
| Place | 122 | 103 | 53 | 99 | 23 | 122 | 74 | 36 | 59 | 23 |

* Baseline ACD and ICA are included for the reference. The entries of n, SD and Median are calculated form the change from baseline values.

***ANCOVA on L_ACD and L_ICD :***

The analyses were performed on the log transformation of the ACD and ICD observations.

**Table 2.b:** Resulting P-Values* of ANCOVA on LOCF for the Variables L_ACD and L_ICD.

| Source | ACD* | | ICD* | |
|---|---|---|---|---|
| | Full Model | Reduced Model | Full Model | Reduced Model |
| Baseline | 0.3782 | --- | 0.0057 | --- |
| Center | 0.0001 | 0.0001 | 0.0001 | 0.0001 |
| Treatment | **0.5751** | **0.5266** | **0.1464** | **0.9390** |
| Baseline-by-Treatment | 0.5773 | --- | 0.1637 | --- |
| Center-by-Treatment interaction. | 0.5333 | --- | 0.6586 | --- |

* P-Values are given for the terms included in the model.

Table 2.b shows that there is no statistically significant difference among the three treatment groups.

At the request of Dr. Karkowsky, a nonparametric analysis was performed on LOCF of ACD and ICD to see if the results confirm the findings in ANCOVA. The analysis was carried for ACD, ICD,