CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-863

STATISTICAL REVIEW(S)

G Buehler
JUN 29 1998

Statistical Review and Evaluation

Addendum to the Original Review Completed June 23, 1998

DATE:

NDA No.: 20-863.

DATE OF DOCUMENT: Stamped by CDER on 9/8/97.

DRUG NAME: Pletal (Cilostazol Tablets).

SPONSOR: Otsuka America Pharmaceutical, Inc.

INDICATION: Intermittent Claudication.

REVIEWERS OF APPENDIX A: Lu Cui, Ph.D. and Kooros Mahjoob, Ph.D.

The purpose of this addendum is to make correction for a typographical error made in the Appendix A of the main Statistical Review, Completed on June 23, 1998.

Correction:

On Page 3 of the Appendix A, the abbreviation "**OXP**" in two places should be substituted by "**PEN**", standing for Pentoxifylline, the active control in Study 21-96-202. The corrected page is attached.

Lu Cui, Ph. D.
Mathematical Statistician

Kooros Mahjoob, Ph. D.
Mathematical Statistician

Concur: Dr. Chi 6/29/98

CC:

Arch. NDA 20-863

HFD-110
HFD-110/Dr. Rodin
HFD-110/Dr. Karkowsky
HFD-110/Dr. Koerner
HFD-110/Mr. Buehler
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Jin
HFD-710/Dr. Cui
HFD-710/Chron.

K. Mahjoob: 4-5301:06/29/1998: Biometrics I/Team 1:km.

- 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 PEN, 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
PEN	212	243	64	127	31	212	128	74	106	45
PLA	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.

JUN 23 1998

Statistical Review and Evaluation

NDA:	NDA 20-863
Date of Document Received by CDER:	9/8/97
Applicant:	Otsuka America Pharmaceutical, Inc.
Name of Drug:	Pletal (Cilostazol Tablets)
Indication:	Intermittent Claudication
Statistical Reviewer:	Kun Jin, Ph.D., DBI/OEB, HFD-710
Medical Reviewers:	Abraham Karkowsky, M.D. and Steve Rodin, M.D., OEB I/DCRDR, HFD-110

The issues in this review have been discussed with Drs. Karkowsky and Rodin, (HFD-110).

1. Introduction

The clinical development of cilostazol for the indication of intermittent claudication (IC) was initiated in 1986 by Frankfurt Research Office of Otsuka Pharmaceutical Co., Germany, in the first of three controlled phase II trials. On November 20, 1990, Otsuka America Pharmaceutical Inc. (OAPI) submitted the US to conduct phase III trials to study cilostazol in patients having peripheral arterial disease (PAD) and symptomatic IC. OAPI has since conducted six controlled phase III trials in the US, of which three are designated key trials for the indication based on a larger sample size and longer patient exposure. Table 1 summarizes all phase III controlled clinical trials. A total of 1,634 patients were enrolled in the six US phase III controlled clinical trials, among them 1,149 were enrolled in the three key studies, 21-91-202, 21-94-201, and 21-94-203. Dosages studied were 100 mg bid (648 patients), 50 mg bid (303 patients), and 150 mg (73 patients), all compared to placebo (610 patients). Treatment duration in these trials ranged from 12 weeks to 24 weeks.

In the phase III controlled trials, the efficacy of cilostazol was assessed primarily by treadmill walking distance of patients on therapy compared to patients on placebo. Two walking distances were assessed on a treadmill test: the initial claudication distance (ICD), the distance patients walked until first onset of claudication pain, and the absolute claudication distance (ACD), the maximal distance patients walked. In later trials, ACD was selected to be the sole primary endpoint. In the Integrated Summary of Efficacy, the sponsor selected ACD as the primary endpoint for summarizing the efficacy of cilostazol, with ICD as secondary.

The sponsor also submitted the data sets for two placebo and active controlled studies (protocols) 21-94-301 and 21-96-202 in June, 1998. The statistical review of these two studies is performed by Drs. Lu Cui and Kooros Mahjoob and their review will be added as an appendix (Appendix A) to this review.

1.1 Key Studies

Study 21-92-202 was a phase III, multi-center, randomized, double-blind, placebo-controlled multidose study conducted in the US to evaluate the safety and efficacy of chronic cilostazol treatment (50 mg bid, 100 mg bid for 24 weeks) for the relief of moderately severe IC secondary to chronic occlusive arterial disease due to atherosclerosis obliterans. A total of 516 patients were randomized to treatment: 171 in the CLZ 50 mg bid group, 175 in the CLZ 100 mg bid group, and 170 in the placebo group. Part of this cohort was recruited solely for safety evaluation and not analyzed for walking distance. In the analysis of treadmill data, log transformation was employed to reduce the impact of variability in walking distances. Log(distance at last visit/distance at baseline) using last observation carried forward (LOCF) for missing data in the efficacy intent-to-treat (ITT) population served as the primary analysis.

Study 21-94-201 was a phase III, multi-center, randomized, double-blind, placebo-controlled multidose study conducted in the US to evaluate the efficacy and safety of the administration of

CLZ 50 mg bid and CLZ 100 mg bid on the amelioration of symptoms in patients with moderately severe IC secondary to peripheral vascular disease (PVD). A total of 394 patients were randomized to treatment: 132 in the CLZ 50 mg bid group, 133 in the CLZ 100 mg bid group, and 129 in the placebo group. In the analysis of treadmill data, log(distance at last visit/distance at baseline) using LOCF for missing data in the efficacy ITT population served as the primary analysis.

Protocol 21-94-203 was a phase III, multi-center, randomized, double-blind, placebo-controlled parallel study conducted in the US to evaluate the safety and efficacy of chronic oral cilostazol treatment (100 mg bid for 16 weeks) in patients with moderate to severe IC secondary to PVD due to atherosclerosis obliterans. A total of 239 patients were randomized to treatment: 119 in the CLZ 100 mg bid group and 120 in the placebo group. Treadmill tests were done at both the end of the dosing interval ("trough") and 3-4 hours post-dose ("peak"). In the analysis of treadmill data, log(distance at last visit/distance at baseline) using LOCF for missing data in the efficacy ITT population served as the primary analysis.

1.2 Outlines of Review

After discussion with the medical reviewers, this reviewer will mainly focus on the efficacy result of the primary endpoint-ACD. Based on the data sets submitted by the sponsor, this reviewer has generally confirmed the sponsor's main efficacy results. This reviewer supports the use of logarithm transformation to ACD and ICD data. This reviewer has estimated the treatment effects by using the sponsor's methods and carried out significant tests by ANOVA and the Kruskal-Wallis test for all studies. Upon a request from Dr. Karkowsky, this reviewer has checked the robustness of the sponsor's efficacy result and the efficacy result on the secondary endpoint, quality-of-life. Dr. Rodin suggested to investigate a possible treatment by baseline interaction. This reviewer did not analyze the effect of treatment in ABI.

Table 2.8.3-1: Listing of All Controlled Clinical Trials for the Indication of Intermittent Claudication by Clinical Phase

Protocol #/ # Study Sites or Principal Investigator/ Phase/ Publication(s) Reference No.	Study Design*	Study Location and Drug Product Code**	Treatment Dose	Pts in Each Treatment Group	Treatment Duration	Mean Age (Range) (years)	Gender (M%/F%) Race (%)	Study Status (Start Date)***
Controlled Phase III Trials								
Key Trials:								
21-92-202 37 Sites III	MC, R, DB, PC, parallel	US B,C	CLZ 100 mg bid, po CLZ 50 mg bid, po Plc bid, po	175 171 170	24 wk	65 (41-88)	76% M/ 24%F 89% white/ 9% black/ 2% other	Complete (4/8/93)
21-94-201 35 Sites III	MC, R, DB, PC, parallel	US B,C	CLZ 100 mg, bid po CLZ 50 mg, bid po Plc bid, po	133 132 129	24 wk	64 (40-86)	76% M/ 24% F 86% white/ 11% black/ 3% other	Complete (7/5/95)
21-94-203 17 Sites III	MC, R, DB, PC, parallel	US B,C	CLZ 100 mg bid, po Plc bid, po	119 120	16 wk	65 (41-91)	75% M/ 25%F 87% white / 9% black / 4% other	Complete (2/10/95)
Supportive Trials:								
21-90-201 3 Sites III	MC, R, DB, PC, parallel	US B,C	CLZ 100 mg bid, po Plc bid, po	54 27	12 wk	66 (44-85)	77%M/ 23%F 99% white/ 1% black	Complete (6/4/91)
21-93-201 16 Sites III	MC, R, DB, PC, parallel	US A,C	CLZ 100 mg bid, po Plc bid, po	95 94	12 wk	66 (42-85)	84% M/ 16%F 85% white / 13% black/ 2% other	Complete (2/1/94)
21-95-201 20 Sites III	MC, R, DB, PC, parallel	US A,B,C	CLZ 150 mg, bid po CLZ 100 mg, bid po Plc bid, po	73 72 70	12 wk	66 (43-84)	79% M/ 21% F 87% white/ 11% black/ 2% other	Complete (12/14/95)

* CO=crossover; DB=double blind; MC=multi-center; OL=open label; PC=placebo-controlled; R=randomized; SC=single center; UC=uncontrolled; CLZ=cilostazol; Plc=placebo; ASA=aspirin.

** Drug Product code Designations: B=50mg CLZ tablet; A=100mg CLZ tablet; C=matching placebo.

*** Study start date reflects the date the first patient ingested study medication.

2. Patient Demographics

Table 2 presents patients' demographics information for Studies 21-92-202, 21-94-201 and 21-94-203. The information was extracted from the sponsor's report. Demographic characteristics for all randomized patients were generally comparable among the treatment and placebo groups. In Study 21-94-203, the placebo group had more patients older than 65 years (50%) than the treatment group (41%).

Table 2 Patients Demographics for Studies 21-92-202, 21-94-201, and 21-94-203

Demographics **Population: All Randomized Patients**								
		CLZ 100 mg bid		**CLZ 50 mg bid**		**Placebo**	
Study 21-92-202	# of Patients	175		171		170	
Age (years)	Mean±SE	64.3±8.5		64.5±9.9		65.1±9.3	
	Range	42 - 85		41 - 88		41 - 86	
Age Category (N, %)	< 65 years	82	46.9	77	45.0	75	44.1
	≥ 65 years	93	53.1	94	55.0	95	55.9
Sex (N, %)	Male	130	74.3	131	76.6	131	77.1
	Female	45	25.7	40	23.4	39	22.9
Race (N, %)	Caucasian	154	88.0	152	88.9	151	88.8
	Black	15	8.6	17	9.9	15	8.8
	Hispanic	3	1.7	2	1.2	4	2.4
	Asian	2	1.1	0	0	0	0
	Other	1	0.6	0	0	0	0
Study 21-94-201	# of Patients	133		132		129	
Age (years)	Mean±SE	63.1±10.2		63.9±8.7		64.4±10.2	
	Range	40 - 85		42 - 86		40 - 84	
Age Category (N, %)	< 65 years	68	51.1	68	51.5	61	47.3
	≥ 65 years	65	48.9	64	48.5	68	52.7
Sex (N, %)	Male	102	76.7	98	74.2	100	77.5
	Female	31	23.3	34	25.8	29	22.5

Race (N, %)	Caucasian	120	90.2	105	79.5	11.5	89.1
	Black	12	9.0	21	15.9	11	8.5
	Hispanic	0	0	4	3.0	2	1.6
	Asian	0	0	1	0.8	1	0.8
	Other	1	0.8	1	0.8	0	0

Table 2 (cont.)

		CLZ 100 mg bid		Placebo	
Study 21-94-203	# of Patients	119		120	
Age (years)	Mean±SE	64.8±9.4		64.5±8.8	
	Range	45 - 91		41 - 88	
Age Category (N, %)	< 65 years	49	41.2	60	50.0
	≥ 65 years	70	58.8	60	50.0
Sex (N, %)	Male	90	75.6	90	75.0
	Female	29	24.4	30	25.0
Race (N, %)	Caucasian	106	89.1	102	85.0
	Black	10	8.4	11	9.2
	Hispanic	2	1.7	7	5.8
	Asian	1	0.8	0	0.0

In study 21-92-202, eight centers were designated to participate for safety evaluation only. The patients in these centers were excluded from efficacy evaluation. The total number of the excluded patients was actually 97, which included some patients randomized for efficacy evaluation but had no post-treatment observations. The sponsor's demographic characteristics table was calculated from all randomized patients. This reviewer calculated the demographic characteristics for the ITT patients in Study 21-92-202, see Table 3. The demographic characteristics were generally comparable among the treatment and placebo groups.

Table 3. ITT Patients Demographics for Studies 21-92-202.

Demographics Population: All ITT Patients							
		CLZ 100 mg bid		CLZ 50 mg bid		Placebo	
Study 21-92-202	# of Patients	140		139		140	
Age (years)	Mean±SE	64.5±8.8		64.2±9.9		65.3±9.1	
	Range	42 - 85		41 - 88		44 - 86	
Age Category (N, %)	< 65 years	64	45.7	63	45.3	60	42.9
	≥ 65 years	76	54.3	76	54.7	80	57.1
Sex (N, %)	Male	103	73.6	104	74.8	109	77.9
	Female	37	26.4	35	25.2	31	22.1
Race (N, %)	Caucasian	123	87.9	123	88.5	122	87.1
	Black	12	8.6	14	10.1	14	10.0
	Hispanic	3	2.1	2	1.4	4	2.9
	Asian	2	1.4	0	0	0	0

3. Primary Endpoint Analysis

In most of the original protocols, the initial claudication distance (ICD) and absolute claudication distance (ACD) were the primary efficacy variables. Table 4 summarizes the pre-specified primary efficacy variables and proposed statistical methods in the original protocols.

In the NDA report, the sponsor chose ACD as the primary efficacy variable to summarize the effectiveness of cilostazol. In the meeting with Otsuka on February 9, 1995, Dr. Lipicky stated that we would not have a problem if the sponsor analyzes the trial data using ACD. The efficacy results using ICD are generally consistent with that using ACD.

3.1 The Sponsor's Protocols

Table 4 summarizes the primary efficacy variables and statistical methods proposed in the original protocols.

Table 4. Summary of the Primary Efficacy Variables and Related Statistical Methods in the Original Protocols.

Protocol	Primary Efficacy Variables	Transformation	Statistical Methods
21-92-202	ICD ACD	Log(distance/baseline)	Mantel-Haenszel; Kruskal-Wallis; ANOVA
21-94-201	ICD ACD	Log(distance/baseline)	ANOVA; Dunn-Sidak adjustment
21-94-203	ICD ACD	Log(distance/baseline)	ANOVA
21-90-201	ICD ACD QOL	Log(distance/baseline)	Mantel-Haenszel and Fisher Tests on logrank scores
21-93-201	ICD ACD TC, LDL, etc.		Wei-Lachin mul. rank; Parametric model on log(distance/baseline)
21-95-201	ACD	Log(distance/baseline)	ANOVA and Dunn-Sidak adjustment

3.2 Logarithm Transformation

The sponsor proposed that the data for ICD and ACD will be analyzed primarily in terms of logarithms of (distance/baseline) ratios in most of the protocols. The sponsor stated that the reason for using logarithm transformation was to reduce the impact of extreme values. This reviewer plotted the raw ACD and log(ACD) over a week of visits of each patient for Studies 21-92-202,21-94-201 and 21-94-203, see Figures 1-3. The logarithm transformation clearly greatly reduced variations in the raw data. This reviewer thinks the logarithm transformation seems appropriate for this type of data. Note that a linear-mixed model might be a good fit to the transformed longitudinal data.

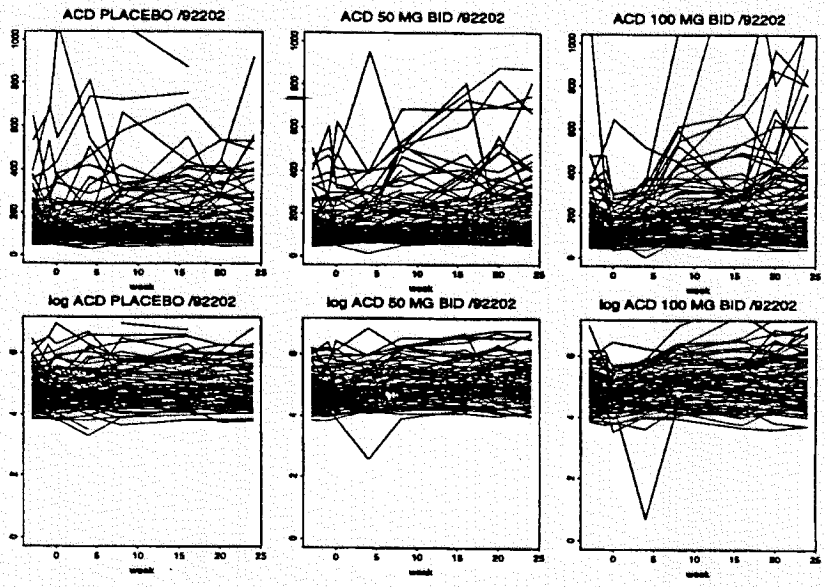

Figure 1. (Study 21-92-202) The top portion is the plots of the patients raw ACD over week of visits. From the left to the right are the placebo, 50 mg bid and 100 mg bid groups. The bottom portion is the corresponding plots for the log(ACD).

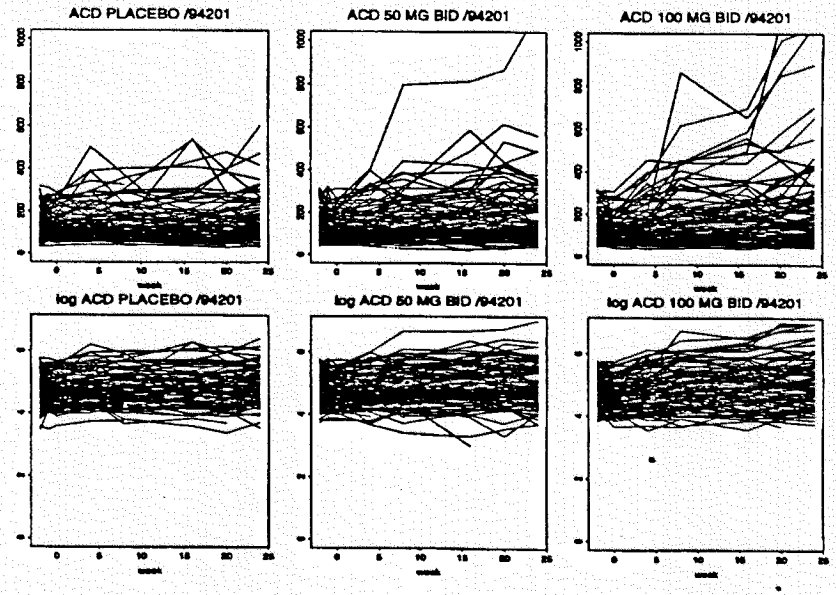

Figure 2. (Study 21-94-201) The top portion is the plots of the patient's raw ACD over week of visits. From the left to the right are the placebo, 50 mg bid and 100 mg bid groups. The bottom portion is the corresponding plots for the log(ACD).

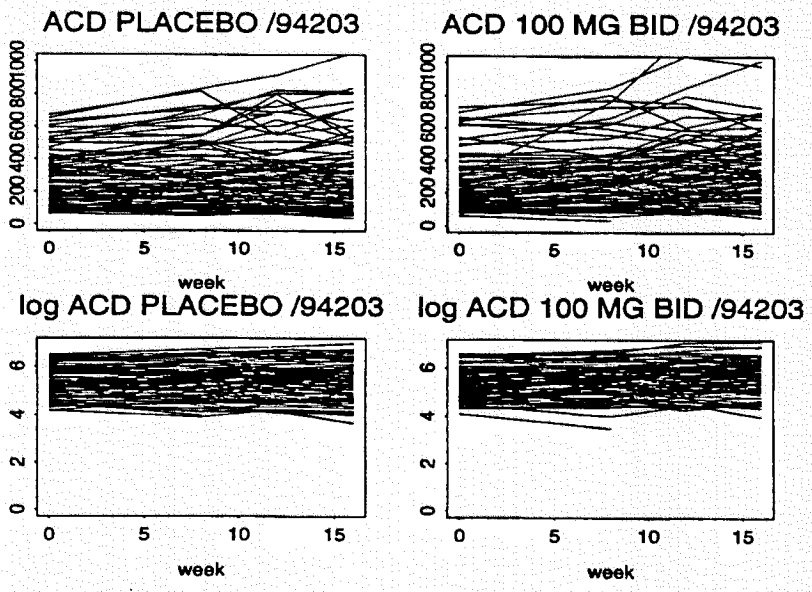

Figure 3. (Study 21-94-203) The top portion is the plots of patient's raw ACD over week of visits. From the left to the right are the placebo, 50 mg bid and 100 mg bid groups. The bottom portion is the corresponding plots for the log(ACD).

3.4 The Sponsor's Methods to Estimate Treatment Effect

Since the logarithm transformation was employed in the primary analysis, the sponsor used geometric mean as a way to transfer the analysis result back to the original scale. It is due to the following fact

$$\exp\{\ \text{mean}[\ \log(\text{distance}/\text{baseline})]\ \} = \prod^{n}_{i=1} (\text{distance})_i^{(1/n)} / \prod^{n}_{i=1} (\text{baseline})_i^{(1/n)}$$

The right side of the equation is a ratio of geometric mean of an endpoint over geometric mean of baseline. According to this reviewer's understanding, the sponsor presented their efficacy results in the following ways:

Percent changes from baseline:

$$(\prod^{n}_{i=1} (\text{distance})_i^{(1/n)} / \prod^{n}_{i=1} (\text{baseline})_i^{(1/n)} - 1) * 100\%;$$

Ratios of a treatment group over placebo:

$$[(\prod^{n}_{i=1} (\text{distance})_i^{(1/n)} / \prod^{n}_{i=1} (\text{baseline})_i^{(1/n)}]_{\text{treatment}} \ / \ [(\prod^{n}_{i=1} (\text{distance})_i^{(1/n)} / \prod^{n}_{i=1} (\text{baseline})_i^{(1/n)}]_{\text{placebo}}$$

In the following sections, the two methods will be called as the "percent" or "ratio" methods, respectively.

3.5 Sponsor's Results:

The sponsor's primary analysis was presented by using either the "percent" or "ratio" method, see previous section for the interpretation of these methods. The following is a summary of the sponsor's primary results. Notice that in Study 21-95-201, the treatment doses were 100 mg bid and 150 mg bid.

Table 5. Estimated Treatment Effect on ACD, Population-ITT

Studies		Sponsor'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	51%	39%	15%		
	Completer	65%	42%	16%		
21-94-201	LOCF				1.21	1.07
	Completer				1.30	1.14
21-94-203	LOCF				29% (1.29)	NA
	Completer				30% (1.30)	NA
21-90-201	LOCF	30.5%	NA	-9.3%		
	Completer	32%	NA	-13%		
21-93-201	LOCF				1.13	NA
	Completer				1.11	NA
21-95-201						**150 mg bid**
	LOCF				1.02	1.18
	Completer				NA	19% (1.19)

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

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

The p-values of comparison of treatment and placebo groups are summarized in the following table.

Table 6. P-values of comparison of treatment and placebo groups reported by the sponsor. Population-ITT, ACD

Studies		**Sponsor's p-values**			
		100 mg bid vs PLC	50 mg bid vs PLC	100 mg bid vs 50 mg bid	Overall
21-92-202	LOCF[b]	0.0001	0.0003	0.3878	
21-94-201	LOCF[a]	0.0003	0.1826	0.0188	
21-94-203	LOCF[a]	0.0001			0.0001
21-90-201	LOCF[a]	<0.001			< 0.001
21-93-201	LOCF[a]	0.0353			0.0353
21-95-201			**150 mg bid vs PLC**	**100 mg bid vs 150 mg bid**	
	LOCF[a]	0.7925	0.0309	0.0602	

a: Based on ANOVA on log(distance/baseline).
b: Based on Wilcox rank sum test on log(distance/baseline).

3.6 Reviewer's Analysis

3.6.1 Comparison of Baseline:

This reviewer compared baseline ACDs for the ITT patients for all six studies. The results are in Table 7. It can be seen that the baseline ACDs are generally comparable among different groups. The placebo groups, however, have numerically higher baseline ACDs than the 100 mg bid groups. In Section 3.6.6, a possible impact of this baseline imbalance on the efficacy result will be discussed.

Table 7. Comparison of baseline ACD for all ITT patients.

Studies	Baseline ACD			
	100 mg bid	50 mg bid	Placebo	p-value[a]
21-92-202	129.66	131.50	147.82	0.83
21-94-201	117.32	123.17	120.87	0.61
21-94-203	236.26		249.68	0.53
21-90-201	141.92		168.56	0.38
21-93-201	279.13		305.42	0.31
21-95-201		**150 mg bid**		
	122.68	120.32	124.59	0.85

a: Based on ANOVA.

3.6.2 Treatment Effect

This reviewer calculated the treatment effects by the "percent" and "ratio" method separately for all six studies, see Table 8. These results are generally consistent with the sponsor's results. For Study 21-90-201, there was no variable identifying "completer." The observed cases at week 12 were analyzed.

Table 8. The reviewer's estimated treatment effect, Population-ITT, ACD

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	51%	38%	15%	1.32	1.20
	Completer	65%	42%	16%	1.42	1.22
21-94-201	LOCF	37%	21%	12%	1.22	1.08
	Completer	48%	29%	13%	1.31	1.14
21-94-203	LOCF	38%	NA	5%	1.31	NA
	Completer	41%	NA	6%	1.33	NA
21-90-201	LOCF	40%	NA	-3%	1.45	NA
	Observed[c]	45%	NA	-4.5%	1.52	NA
21-93-201	LOCF	28%	NA	10%	1.16	NA
	Completer	27%	NA	10%	1.16	NA
21-95-201			**150 mg bid**			**150 mg bid**
	LOCF	23%	42%	22%	1.01	1.17
	Completer	22%	43%	23%	0.99	1.17

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.

Overall p-values and pairwise p-values (when applicable) were calculated by ANOVA, which was specified in most of the sponsor's protocols. The Kruskal-Wallis rank sum test was also applied to calculate the overall p-values. The results are consistent with the sponsor's. Although the sponsor proposed different statistical methods in their original protocols, this reviewer thinks that consistent use of ANOVA and the Kruskal-Wallis test over all studies should provide an adequate efficacy assessment. The efficacy results do not seem dependent on particular methods.