L_ACD and L_ICD and the results are summarized in the following table.

Table 3.b: Resulting P-Values of Non-Parametric Analysis on LOCF of ACD and ICD.

Non-Parametric Method	ACD P-Value	L_ACD P-Value	ICD P-Value	L_ICD P-Value
Kruskal-Wallis Test	0.39925	0.5950	0.9987	0.9940
Median 1-Way Test	0.6206	0.6594	0.9752	0.8310

As can be seen from Table 3.b, the non-parametric results confirm the ANCOVA findings of Table 2.b.

III. OVERALL CONCLUSION:

Overall, the results show that:

Study 21-96-202: CLZ demonstrated to be statistically significantly superior to PLA in improving ACD. The results also show that CLZ is statistically significantly superior to PEN with respect to ACD and ICD.

Study 21-94-301: The results show that there is no statistically significant difference among the three treatment groups with respect to improving patients ACD and ICD.

Lu Cui, Ph.D.
Mathematical Statistician

Kooros Mahjoob 6/23/98
Kooros Mahjoob
Mathematical Statistician

Buehler

STATISTICAL REVIEW AND EVALUATION

MAY 12 1998

NDA #: 20-863
Applicant: Otsuka America
Drug Name: Pletal (Cilostazol) Tablets
Document Reviewed: Vols 18-24 and SAS datasets

This review was completed after consultation with Drs. Joseph and Resnick.

1. INTRODUCTION

This review pertains to the sponsor's submission that reported the results of a 2-year carcinogenicity study on mice and a 2-year study on rats. In all studies, animals were inspected twice daily for evidence of reaction to treatment or ill-death. All animals were handled and palpated once weekly throughout the treatment period.

For mortality analysis, an overall test for homogeneity of survival curves and pairwise comparison against control were performed using Cox's test. Tarone's extension of Cox's test was used to examine linear trend on dose and to assess deviation for linearity. For analysis of tumor incidence, three methods (life-table analysis, incidental tumor analysis, unadjusted analysis) were used to provide a test for linear trend with dosage and for pairwise comparisons of treated and control groups.

2. MOUSE STUDY

The objective of this study was to assess the oncologic potential of cilostazol during its prolonged administration to mice via diet. The dosages selected were 0, 100, 300 and 1,000 mg/kg body weight/day. Each treatment group comprised 52 male mice and 52 female mice of the B6C3F1 strain obtained from The treatment commenced on August 30, 1983 and continued without interruption until necropsy of the last surviving animal. The terminal sacrifice was initiated on August 28, 1985 after completion of 104 weeks of treatment and completed on September 12, 1985.

<u>The sponsor's results</u>

a) Mortality

Sixty two male and thirty six female mice died or were killed during the scheduled 104-week treatment period. The 300

or 1000 mg/kg/day group had more deaths among males than the respective controls; the differences were dose related (Tarone's trend analysis: $p < 0.01$); however, pairwise comparisons only attributed statistical significance to the difference in survival between 1000 mg/kg/day and control ($p < 0.05$).

The survival pattern among males receiving 100 mg/kg/day and females receiving any dosage was similar to that among the respective controls.

b) Tumor incidence

According to the report, among animals receiving 300 or 1000 mg/kg/day, `hepatic neoplasia' was the most commonly recorded disorder; no single disorder predominated among the controls.

The results are summarized in the following tables. Only liver tumors appeared to reveal a potential significant increased dose related trend. The analysis unadjusted for age differences gave a similar result as that of the incidental tumor analysis.

Life-table analysis (assuming that all tumors of a given type were either directly or indirectly the cause of death) revealed that the incidences of hepatocellular adenoma were significantly higher than the control incidence among males receiving 300 or 1000 mg/kg/day, and the positive trend with dosage was borderline significant. However, the incidental tumor tests (assuming that all tumors of a given type observed in animals that died before the end of the study were merely observed at necropsy in animals dying of an unrelated cause) were only significant with respect to the difference between the 300 mg/kg/day dosage and the control.

Both the life-table and the incidental tumor analyses revealed a significant positive trend with dosage in the incidence of females bearing hepatocellular adenoma. However, these apparent trends are not a reflection of any progressive increase in incidence in relation to the control.

The results of analyses performed on the incidences of animals bearing anaplastic carcinoma or hepatocellular carcinoma or hepatocellular adenoma generally reflected those for hepatocellular adenoma.

The sponsor concluded that with no clear evidence of an effect for males receiving 1000 mg/kg/day or for treated females, the higher incidence of adenoma in males of the 300 mg/kg/day group was considered to be spuriously related to treatment. OPC-21 had no influence on the incidences of any tumor.

Table MM-1. Incidence of hepatocellular adenoma in male mice

	Control	100 mg/kg/d	300 mg/kg/d	1000 mg/kg/d	Trend p-value
Incidence rate	(12%)	(17%)	(52%)	(25%)	
Life table test		p=0.28	p<0.001	p=0.022	p=0.051
Incidental tumor test		p=0.30	p<0.001	p=0.083	p=0.19
Cochran-Armitage test; Fisher Exact test		p=0.29	p<0.001	p=0.063	p=0.17

Table MM-2. Incidence of anaplastic carcinoma or hepatocellular carcinoma in male mice

	Control	100 mg/kg/d	300 mg/kg/d	1000 mg/kg/d	Trend p-value
Incidence rate	(17%)	(27%)	(23%)	(19%)	
Life table test		p=0.16	p=0.18	p=0.28	p=0.41
Incidental tumor test		p=0.16	p=0.26	p=0.39	p=0.44
Cochran-Armitage test; Fisher Exact test		p=0.17	p=0.31	p=0.50	p>0.50

Table MM-3. Incidence of anaplastic carcinoma or hepatocellular carcinoma or hepatocellular adenoma in male mice

	Control	100 mg/kg/d	300 mg/kg/d	1000 mg/kg/d	Trend p-value
Incidence rate	(29%)	(38%)	(65%)	(42%)	
Life table test		p=0.20	p<0.001	p=0.028	p=0.053
Incidental tumor test		p=0.21	p<0.001	p=0.093	p=0.20
Cochran-Armitage test; Fisher Exact test		p=0.20	p<0.001	p=0.11	p=0.24

Table FM-1. Incidence of hepatocellular adenoma in female mice

	Control	100 mg/kg/d	300 mg/kg/d	1000 mg/kg/d	Trend p-value
Incidence rate	(12%)	(4%)	(10%)	(25%)	
Life table test		p>0.50	p>0.50	p=0.051	p=0.002
Incidental tumor test		p>0.50	p>0.50	p=0.064	p=0.002
Cochran-Armitage test; Fisher Exact test		p>0.50	p>0.50	p=0.063	p=0.002

Table FM-2. Incidence of anaplastic carcinoma or hepatocellular carcinoma in female mice

	Control	100 mg/kg/d	300 mg/kg/d	1000 mg/kg/d	Trend p-value
Incidence rate	(6%)	(2%)	(4%)	(8%)	
Life table test		p>0.50	p>0.50	p=0.48	p=0.23
Incidental tumor test		p>0.50	p>0.50	p=0.49	p=0.25
Cochran-Armitage test; Fisher Exact test		p>0.50	p>0.50	p=0.50	p=0.24

Table FM-3. Incidence of anaplastic carcinoma or hepatocellular carcinoma or hepatocellular adenoma in female mice

	Control	100 mg/kg/d	300 mg/kg/d	1000 mg/kg/d	Trend p-value
Incidence rate	(17%)	(6%)	(12%)	(31%)	
Life table test		p>0.50	p>0.50	p=0.063	p=0.002
Incidental tumor test		p>0.50	p>0.50	p=0.083	p=0.003
Cochran-Armitage test; Fisher Exact test		p>0.50	p>0.50	p=0.084	p=0.002

3. RAT STUDY

This was a 104-week carcinogenicity study. Dosages selected were 0, 50, 150 and 500 mg/kg/day. Each treatment group comprised 50 male and 50 female F-344 rats obtained from The treatment commenced on April 3, 1984 and continued without interruption until necropsy of the last surviving animal. The terminal sacrifice was initiated on April 1, 1986 after completion of 104 weeks of treatment, and was completed on April 9, 1986.

The sponsor's results

a) Mortality

One hundred and one male and thirty three female rats died or were killed during the scheduled 104-week treatment period. Mortality were generally similar in all groups until Week 79 in males and Week 89 in females. Thereafter survival deteriorated in treated rats, relative to controls; Cox's and Tarone's tests revealed a trend with dosage in both males and females ($p<0.05$). Pairwise comparisons suggested that only in female rats receiving the highest dosage of OPC-21 did overall survival differ significantly from the control ($p<0.05$).

b) Tumor incidence

There appeared to be a statistically significantly ($p < 0.05$) increased incidence of adrenal medullary adenoma in male rats receiving the highest dosage (500 mg/kg/day) when compared with controls. A higher incidence of this tumor was also noted in males receiving the 150 mg/kg/day dosage, although a level of statistical significance was not attained ($p > 0.05$).
The sponsor explained that the incidences of this tumor noted for treated groups which had received cilostazol and for control groups were generally within those of historical data all of which were obtained from untreated animals. Therefore, the intergroup differences in this study were presumed to have arisen by chance and are thought unlikely to reflect an oncogenic potential of cilostazol.

Other nominally statistically significant results are:

1) a lower incidence of pituitary adenoma of the pars distallis in females of the lowest dosage group when compared to the control
2) an increased incidence of monocytic leukemia in males of the lowest and intermediate dosage groups and in females of the highest dosage group, when compared to the controls.

4. REVIEWER'S ANALYSIS AND EVALUATION

In what follows, all p-values reported were based on the reviewer's survival-adjusted analyses.

1) Mouse study

Incidences were reported for 31 types of tumors in male mice and 27 in female mice. In female mice, there were incidences for solid A type of hepatocellular adenoma. The trend test gives a significant p = 0.002, but the trend is difficult to interpret because both the low and the middle doses had a numerically lower incidence rate than the control (Table R-1). The 1000 mg/kg/day group seemed to have a higher incidence rate of hepatocellular adenoma in female mice, but the difference was not statistically significant (p = 0.064). Combining hepatocellular adenoma with hepatocellular carcinoma showed a similar result (Table FM-3, page 4).

Table R-1. Tumor incidences in mice

Organ	Tumor	Sex	Dosage (mg/kg/day)				Trend p-value*
			0	100	300	1000	
Liver X 2	Hep Adenoma$	F	(12%)	(4%)	(10%)	(25%) p=0.064@	0.002

$ only solid A type adenoma observed
For control incidence rate > 1%,
* Trend is significant if p < 0.005
@ Pairwise comparison is significant if p < 0.01
For control incidence rate <= 1%,
* Trend is significant if p < 0.025
@ Pairwise comparison is significant if p < 0.05

There was no significant trend observed for the incidence of hepatocellular adenoma in male mice, see Table R-2. If all the hepatocellular adenomas were fatal tumors, then the nominal p-value of the exact trend test would be 0.034 (the sponsor's p-value is 0.051, the difference is small); the trend is not significant (p > 0.005). In male mice, only the 300 mg/kg/day group appeared to have a significantly higher incidence of hepatocellular adenoma than the control (p < 0.001, regardless of whether the tumors were fatal or incidental). The 1000 mg/kg/day group seemed to have a higher incidence than the control group, but the difference was not statistically significant (p > 0.08).

Table R-2. Tumor incidences in mice

Organ	Tumor	Sex	Dosage (mg/kg/day)				Trend p-value*
			0	100	300	1000	
Liver X 2	Hep Adenoma Solid A (1)	M	(12%)	(17%)	(46%) p<.001@	(21%) p=0.098@	0.22
Liver X 2	Hep Adenoma Trabecular B (2)	M	(0%)	(0%)	(8%)	(4%)	0.28
Liver X 2	Hep Adenoma (1)+(2)	M	(15%)	(17%)	(52%) p<.001@	(25%) p=0.083@	0.15

For control incidence rate > 1%,
* Trend is significant if p < 0.005
@ Pairwise comparison is significant if p < 0.01
For control incidence rate <= 1%,
* Trend is significant if p < 0.025
@ Pairwise comparison is significant if p < 0.05

Combining hepatocellular adenoma with hepatocellular carcinoma showed a similar result (Table MM-3, page 3).

Survival curves are illustrated in Figures 1 and 2. There was a dose related trend for mortality in male mice ($p < 0.01$); only the difference in survival between 1000 mg/kg/day and the control was statistically significant ($p < 0.05$). No significant trend in mortality was found in female mice.

2) Rat Study

Incidences were reported for 43 types of tumors in male rats and 32 in female rats. Table R-3 lists the tumors with a trend test p-value < 0.05. Based on the method of multiplicity adjustment by the Agency's document on Guidance on Statistical Aspects of Design, Analysis, and Interpretation of Animal Carcinogenicity Studies, only Uterus Leiomyoma in female rats might show a statistically significant trend (see the last row of Table R.3 for explanation) with incidence rates of 0%, 0%, 0%, and 6% for the control, 50 mg/kg/day, 150 mg/kg/day, and 500 mg/kg/day groups, respectively. The difference between 500 mg/kg/day and the control was not statistically significant (p=0.13).

Table R-3. Tumor incidences in rats

Organ	Tumor	Sex	Dosage (mg/kg/day)				Trend p-value*
			0	50	150	500	
Adrenals (L&R)	Medullary Adenoma	M	(8%)	(6%)	(19%) p=0.063@	(21%) p=0.035@	0.011
Preputial Glands	Preputial Gland Adenoma	M	(2%)	(4%)	(2%)	(10%) p=0.18@	0.032
H'Poietic Tissue	Monocytic Leukaemia	F	(4%)	(4%)	(13%) p=0.14@	(17%) p=0.068@	0.020
Uterus	Leiomyoma	F	(0%)	(0%)	(0%)	(6%) p=0.13@	0.016

For control incidence rate > 1%,
* Trend is significant if $p < 0.005$
@ Pairwise comparison is significant if $p < 0.01$
For control incidence rate <= 1%,
* Trend is significant if $p < 0.025$
@ Pairwise comparison is significant if $p < 0.05$

Survival curves are illustrated in Figures 3 and 4. There was a dose-related trend in mortality in both male and female rats ($p < 0.05$). Only the highest dosage differs significantly from the control for survival in female rats.

5. CONCLUSION

An increased dose-related trend in mortality was observed in male mice, male rats and female rats. Only the differences in mortality between the highest dosage (1000 mg/kg/day for mice and 500 mg/kg/day for rats) and the control were statistically significant in male mice and female rats.

The trend test for the incidence of hepatocellular adenoma in female mice was significant, but the trend is difficult to interpret because both the low and the middle doses had a numerically lower incidence rate than the control (Table R-1). The 1000 mg/kg/day group of female mice seemed to have a higher incidence rate of hepatocellular adenoma, but the difference was not statistically significant. No significant trend was observed in male mice; the 300 mg/kg/day group appeared to have a significantly higher incidence of hepatocellular adenoma than the

control (Tables MM-1 and R-2). The 1000 mg/kg/day group seemed to have a higher incidence than the control group, but the difference was not statistically significant. Combining hepatocellular adenoma with hepatocellular carcinoma showed a similar result (Tables MM-3 and FM-3).

In the rat study, only uterus leiomyoma in female rats seemed to have a significant trend (Table R-3), with incidence rates of 0%, 0%, 0%, and 6%, for the control, 50 mg/kg/day, 150 mg/kg/day, and 500 mg/kg/day groups, respectively, but the difference between the 500 mg/kg/day and the control groups was not statistically significant (Table R-3).

H.M. James Hung, PH.D.
Mathematical Statistician

This review consists of 9 pages of text and 4 figures.

Concur: Dr. Mahjoob 05/05/98
Dr. Chi 5/12/98

cc: Archival NDA
HFD-110/Dr. Joseph
HFD-110/Dr. Resnick
HFD-110/Mr. Buehler
HFD-344/Dr. Barton
HFD-700/Dr. Fairweather
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/chron

JHung/594-5436/DB1/pletal.*/04-23-98

Figure 1. Percentage Survival vs. Weeks — Male Mice

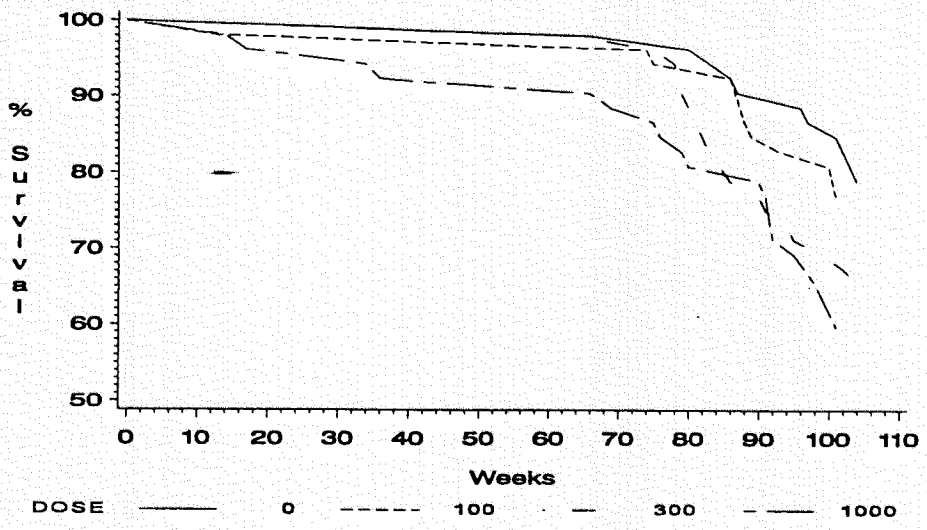


Figure 2. Percentage Survival vs. Weeks — Female Mice

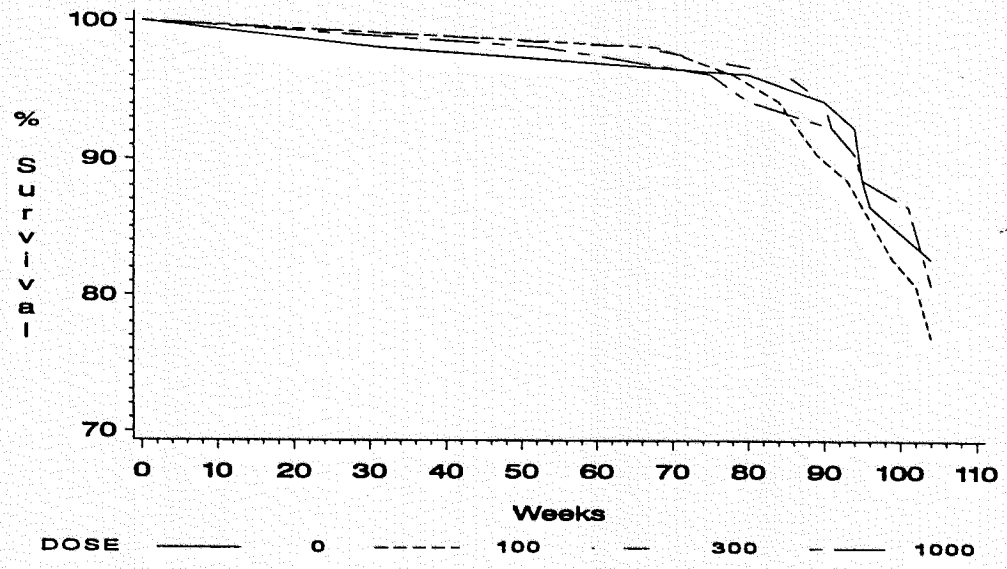


Figure 3. Percentage Survival vs. Weeks — Male Rats

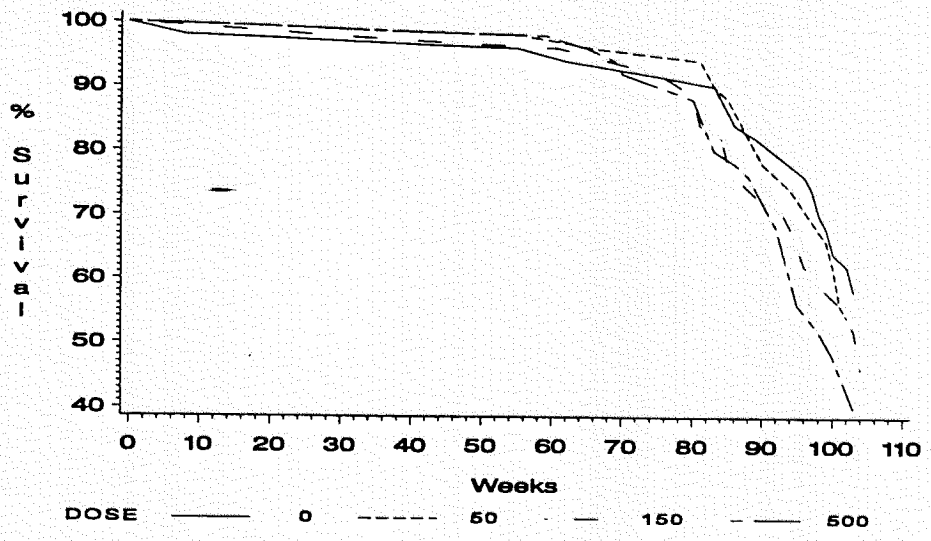
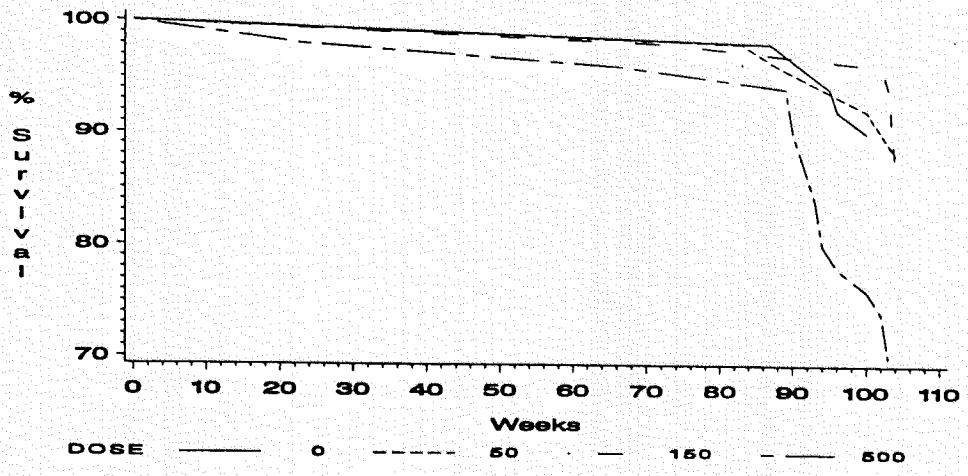


Figure 4. Percentage Survival vs. Weeks — Female Rats



JAN 15 1999

NDA REVIEW SUMMARY

NDA 20-863 Pletal (cilostazol) Tablets, 50 and 100 mg

Sponsor: Otsuka America Pharmaceutical, Inc.
2440 Research Boulevard
Rockville, MD 20850

Contact: Tanveer Ahmad, Ph. D.

Submission Date: September 19, 1997

User Fee Date: September 19, 1998

Classification: 1S

Indication: Intermittent Claudication

CHEMISTRY - Dr. Zielinski

Final Chemistry review finds deficiencies noted in Chemistry Review #1 adequately addressed. Methods Validation is in progress. Labeling comments relating to the DESCRIPTION and HOW SUPPLIED sections have been incorporated into the draft.

EER

The establishment evaluation report issued 7/23/98 was acceptable. The report is included in the review package.

L and N Committee

The L and N Committee could find no reason to find the trade name, Pletal, unacceptable.

BIOPHARMACEUTICS - Dr. Uppoor/Dr. Marroum

Dr. Uppoor has noted comments to the Medical Officer (p 12) , Sponsor (p 13) and for the Labeling (p 14). Comments to the Medical Officer related to populations studied and interactions studies that were or were not done. Comments to the sponsor related to advice for future submissions and to changing the dissolution specification. Labeling comments related to activity of metabolites, special populations, renal and hepatic impairment, drug interactions and food effect. The labeling comments have been incorporated into the labeling draft.

The recommended dissolution method, medium and specifications, after discussing them with the firm on 8/12/98, are:

PHARMACOLOGY - Dr. Joseph/Dr. Koerner

The pharmacology reviewers could not identify any issues that would prohibit approval. Labeling comments were made by Drs. Joseph and Koerner. They are incorporated into the labeling draft.

CAC Recommendation

The Executive CAC recommended accepting the mouse and rat carcinogenicity studies.

STATISTICAL - Dr. Jin
Studies 96-202 and 94-301 - Dr. Cui/Dr. Mahjoob

The overall conclusion drawn by the statistician reviewing the initial primary efficacy studies was that the cilostazol patients showed significant improvement in their ACD scores over the placebo patients in the trials reviewed. The results from the ICD scores supported this conclusion. There was no credible evidence, however, that cilostazol improved patients' quality of life.

Regarding the two comparator studies, the conclusion was that cilostazol was statistically significantly superior to placebo and pentoxifylline in Study 21-906-202, but there was no statistically significant difference between the groups in study 21-94-301.

MEDICAL - Dr. Rodin/Dr. Karkowsky

Dr. Rodin stated that he thought that the firm demonstrated the anti-claudication efficacy of cilostazol at a dose of 200 mg/day, but there still was not convincing evidence that cilostazol is more efficacious than pentoxifylline.

The submitted safety data were adequate to describe the adverse morbidity profile of the drug, but in the absence of an adequately powered, placebo-controlled survival trial there is inadequate precision in the present mortality estimate to be able to exclude a clinically important PDE-3 inhibition-based adverse survival effect in the claudication population studied.

Safety Update - Dr. Lipicky

Dr. Lipicky told the firm that they need not submit a final safety update. It is noted in his transmittal memo.

DSI Audits - Dr. El Hage

All DSI inspections have been completed. Three sites received VAI-no response required and one site received an NAI

Gary Buehler 8/14/98
Gary Buehler
Project Manager

Buehler

STATISTICAL REVIEW AND EVALUATION
(Addendum)

NDA #: 20-863
Applicant: Otsuka America
Drug Name: Pletal (Cilostazol) Tablets
Document Reviewed: SAS datasets

JUN 15 1998

This addendum is to respond to the request of Dr. Joseph for an additional analysis by combining uterus leiomyoma, uterus leiomyosarcoma, uterine cervix leiomyoma, and uterine cervix leiomyosarcoma in female rats.

Table 1. Incidence of the combined tumors in female rats

Organ	Tumor	Dosage (mg/kg/day)				Trend p-value*
		0	50	150	500	
Uterine Cervix	Leiomyoma	0	1	0	1	
	Leiomyosarcoma	1	0	0	0	
Uterus	Leiomyoma	0	0	0	3	
	Leiomyosarcoma	1	0	1	1	
Combined		2 (4%)	1 (2%)	1 (5%)	5 (10%) @p=0.36	0.034

For control incidence rate > 1%,
* Trend is significant if p < 0.005
@ Pairwise comparison is significant if p < 0.01
For control incidence rate <= 1%,
* Trend is significant if p < 0.025
@ Pairwise comparison is significant if p < 0.05

The trend test for the incidence of the combined tumors in female rats was not significant (p=0.034). The difference in the incidence of the combined tumors between the 500 mg/kg/day dosage and the control was not significant (p=0.36).

James Hung

H.M. James Hung, Ph.D.
Mathematical Statistician

This review consists of 2 pages of text.

Concur: Dr. Mahjoob 06/15/98
Dr. Chi 6/15/98

cc: Archival NDA
HFD-110/Dr. Joseph
HFD-110/Dr. Resnick
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HFD-710/Dr. Hung
HFD-710/chron

JHung/594-5436/DB1/pletal1.*/06-12-98