CHEM REVIEW

MAY 16 1990

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA # 20-036 — Division: DMEDP HFD-510

CHEMISTRY REVIEW # 1

Reviewer: Martin K. Bennett PD

APPLICANT: CIBA-GEIGY

ADDRESS Summit, N.J.

Date Completed: 5/15/90

Route/Admin intravenous

PRODUCT NAME(s):

Proprietary: AREDIA

Non-proprietary: pamidronate disodium

Code name: APD
CGP 23339A

Dosage Form: SVP to be diluted

Strength(s) 15mg lyophilized in 5ml vial

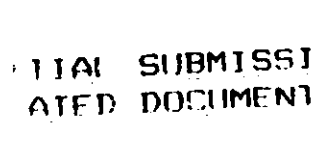
PHARMACOLOGICAL CATEGORY and/or PRINCIPAL INDICATION:

Treatment for hypercalcemia associated with malignancy.

STRUCTURAL FORMULA and CHEMICAL NAME:

Disodium (3-amino-1-hydroxypropylidene) biphosphonate pentahydrate.

Empirical formula:
$C_3H_9NO_7P_2Na_2 \cdot 5H_2O$



CAS # 57248-88-1 for anhydrous

Molecular weight: 369.1 ($5H_2O$)

" " 279.0 (anhydrous)

INITIAL SUBMISSION: 12/20/89 rcd MKB 1/17/90 AMENDMENTS:

RELATED DOCUMENTS: IND

REMARKS:

Facilities involved in manufacture of drug substance and manufacture and packaging of the drug product are being evaluated for CGMP compliance. Method validation by FDA laboratories to be requested. Environmental Impact Report is being evaluated.

CONCLUSIONS AND RECOMMENDATIONS

When the items in the above remarks section are satisfactorily resolved, the application will be approvable from the aspects of chemistry and manufacturing and quality control.

Martin K Bennett 5/15/90

Martin K. Bennett P.D.
Review Chemist

cc: IND/NDA Orig.
HFD-510
HFD-102/Kumkumian (Review # 1 Only)
HFD-510/MKBennett
initialed by G. Chin 5/16/90

FILE 20036NDA

DIV

APR 10 1991

REVIEW OF CHEMISTRY, MANUFACTURING & CONTROLS

NDA # 20-036

Division:DMEDP HFD-510

CHEMISTRY REVIEW # 2

APPLICANT: CIBA-GEIGY

Reviewer: Martin K. Bennett PD

ADDRESS Summit, N.J.

Date Completed: 4/9/91

PRODUCT NAME(s):

Route/Admin intravenous

Proprietary: AREDIA

Non-proprietary: pamidronate disodium for injection

Code name: APD
CGP 23339A

Dosage Form:SVP to be diluted

Strength(s) 15mg lyophilized in 5ml vial;
30mg lyophilized in 10ml vial.

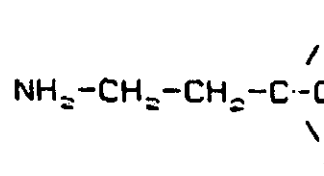
PHARMACOLOGICAL CATEGORY and/or PRINCIPAL INDICATION:

Treatment for hypercalcemia associated with malignancy.

STRUCTURAL FORMULA and CHEMICAL NAME:

Disodium (3-amino-1-hydroxypropylidene) biphosphonate pentahydrate.

Empirical formula:
$C_3H_9NO_7P_2Na_2 . 5H_2O$



CAS # 57248-88-1 for anhydrous
Molecular weight: 369.1 ($5H_2O$)
" " 279.0 (anhydrous)

INITIAL SUBMISSION: 12/20/89 rcd MKB 1/17/90

AMENDMENTS: 4-8-91 (labels).
8/10/90(provides for 30mg/10ml vial),8/6/90(labeling), 9/28/90(sample validation), 12/3/90(sample validation), 12/4/90(SBA), 2/5/91(patent information), 2/22/91(revised pkg insert), 3/12/91(samples to labs), 3/20/91(withdraw use of contract packagers

RELATED DOCUMENTS: IND

REMARKS:

SEE CHEMIST REVIEW #1.

Facilities involved in manufacture of drug substance and manufacture and packaging of the drug product were evaluated for CGMP compliance. Method validation by FDA laboratories has been requested. Environmental Impact Report was evaluated a copy of which is attached at end of this review.

CONCLUSIONS AND RECOMMENDATIONS

The application may be approved from the aspects of chemistry and manufacturing and quality control. The established name must be changed to "Pamidronate disodium for injection"

Martin K Bennett 4/9/91

Martin K.Bennett P.D.
Review Chemist

cc: IND/NDA Orig.
HFD-510
HFD-102/Kumkumian (Review # 1 Only)
HFD-510/MKBennett
R/D initialed by J. Chin 4/10/91

FILE 20036AA2

Review
Internal Colu

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT 1 1990

FROM: Environmental Assessment Officer HFD-102

SUBJECT: NDA 20-036 Pamidronate Disodium
Bone/Calcium-Phosphorous Metabolism
Hypercalcemia of Malignancy

TO: Dr. Martin K. Bennett HFD-510

The Food and Drug Administration Center for Drug Evaluation and Research has reviewed the environmental assessment for subject drug and has determined that a number of serious deficiencies are present. Since this is a 1989 submission, we are not able at this time to require the firm to correct the environmental assessment. However, for your information, we are including an information sheet outlining the deficiencies noted. Because of the necessity to process the drug application, we do not recommend that the approval process be delayed on environmental grounds alone. You should take this matter to your Division Director for concurrence.

cc: M Bennett
N Clerget
Div File

ADDENDUM

APR 26 1991

REVIEW OF CHEMISTRY, MANUFACTURING & CONTROLS

NDA # 20-036 Division:DMEDP HFD-510

→ ADDENDUM TO REVIEW # 2 ←

CHEMIST REVIEWER:
Martin K. Bennett PD

APPLICANT: CIBA-GEIGY
ADDRESS Summit, N.J.

Date Completed: 4/26/91
Route/Admin intravenous

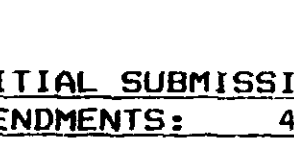
PRODUCT NAME(s):
Proprietary: AREDIA
Non-proprietary: pamidronate disodium
Code name: APD
CGP 23339A

Dosage Form:SVP to be diluted
Strength:
30mg lyophilized in 10ml vial.

PHARMACOLOGICAL CATEGORY and/or PRINCIPAL INDICATION:
Treatment for hypercalcemia associated with malignancy.

STRUCTURAL FORMULA and CHEMICAL NAME:
Disodium (3-amino-1-hydroxypropylidene) biphosphonate pentahydrate.

Empirical formula:
$C_3H_9NO_7P_2Na_2.5H_2O$



CAS # 57248-88-1 for anhydrous
Molecular weight: 369.1 ($5H_2O$)
" " 279.0 (anhydrous)

INITIAL SUBMISSION: 12/20/89 rcd MKB 1/17/90
AMENDMENTS: 4/8/91 (LABELS), 2/22/91 (PACKAGE INSERT)
RELATED DOCUMENTS: IND
REMARKS:
SEE CHEMIST REVIEW #1 & 2

Facilities involved in manufacture of drug substance and manufacture and packaging of the drug product were evaluated for CGMP compliance. Method validation by FDA laboratories has been requested. Environmental Impact Report was evaluated a copy of which is attached at end of REVIEW # 2.

CONCLUSIONS AND RECOMMENDATIONS

The application may be approved from the aspects of chemistry and manufacturing and quality control.
THE ESTABLISHED NAME MUST BE CHANGED TO "PAMIDRONATE DISODIUM FOR INJECTION". "IV" MUST BE CHANGED TO"INTRAVENOUS". ISSUE DATE MUST APPEAR ON PACKAGE INSERT. THE Rx CAUTION SHOULD APPEAR IN THE PACKAGE INSERT.

Martin K Bennett 4/26/91
Martin K.BennettP.D.
Review Chemist

cc: IND/NDA Orig.
HFD-510

HFD-510/MKBennett
R/D initialed by 4/26/91

FILE 20036AA3

JUN 7 1991

REVIEW OF CHEMISTRY, MANUFACTURING & CONTROLS

NDA # 20-036 Division:DMEDP HFD-510

CHEMISTRY REVIEW # 3

APPLICANT: CIBA-GEIGY Reviewer: Martin K. Bennett PD

ADDRESS Summit, N.J.

Date Completed: 6/6/91

PRODUCT NAME(s): Route/Admin intravenous

Proprietary: AREDIA

Non-proprietary: pamidronate disodium

Code name: APD Dosage Form:SVP to be diluted

CGP 23339A Strength(s) 15mg lyophilized in 5ml vial;

30mg lyophilized in 10ml vial.

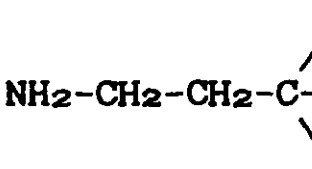
PHARMACOLOGICAL CATEGORY and/or PRINCIPAL INDICATION:

Treatment for hypercalcemia associated with malignancy.

STRUCTURAL FORMULA and CHEMICAL NAME:

Disodium (3-amino-1-hydroxypropylidene) biphosphonate pentahydrate. Empirical formula:

$C_3H_9NO_7P_2Na_2.5H_2O$



$NH_2-CH_2-CH_2-C(PO_3HNa)(PO_3HNa)(OH) \cdot 5H_2O$

CAS # 57248-88-1 for anhydrous

Molecular weight: 369.1 ($5H_2O$)

" " 279.0 (anhydrous)

INITIAL SUBMISSION: 12/20/89 rcd MKB 1/17/90

AMENDMENTS:

5/24/91(revised pkg insert), 6/6/91 fax (hard copy received on 6/7/91) contains the validation of the sterile process.

RELATED DOCUMENTS: IND

REMARKS:

The submitted labeling is satisfactory.

Facilities involved in manufacture of drug substance and manufacture and packaging of the drug product were evaluated for CGMP compliance. (An update was requested 5/31/91)

Validation package of sterilization process has been reviewed and found to be satisfactory.

CONCLUSIONS AND RECOMMENDATIONS

The application may be approved from the aspects of chemistry and manufacturing and quality control.

Martin K. Bennett 6/6/91

Martin K.BennettP.D.
Review Chemist

cc: IND/NDA Orig.
HFD-510
HFD-102/Kumkumian (Review # 1 Only)
HFD-510/MKBennett
R/D initialed by /Chen 6/6/91

FILE 20036AA3

Stat. Rev

1 20036

DIV

NOV 19 1990

Statistical Review and Evaluation

Date: NOV 19

NDA #: 20-036

Applicant: Ciba-Geigy Corporation

Name of Drug: Aredia (Pamidronate Disodium)

Documents Reviewed:

1. NDA submission volume 1.12, Dec. 20, 1989. (Husband, R.F.A., Perry, M.C., and Casey, H.J. (1989) "Disodium APD: 80-week carcinogenicity study in the mouse", Ciba-Geigy (Basle) PS project No. 864004, 10/26/89)
2. NDA submission volume 1.14, Dec. 20, 1989.
3. NDA submission volume 1.19, Dec. 20, 1989. (Perry, M.C., Casey, H.J., and Wood, C.M. (1989) "Disodium APD: 104 week carcinogenicity study in the rat", Toxicol Lab., Ltd., Herefordshire, U.K., for Armour Pharmaceutical Company, Ltd., Sussex, U.K., Report Ref. ARP/26/82, 10/26/89)
4. NDA original amendment, July 24, 1990.
5. Computer diskettes submitted to FDA on April 20, 1990.

I. Background

Two animal carcinogenicity studies (one in rats, and one in mice) were included in this NDA submission. These two studies were intended to evaluate the oral carcinogenic potential of Aredia (Pamidronate Disodium, APD) in rats and mice for 106 and 80 weeks, respectively. Dr. Chhanda Dutta, HFD-510, who is the reviewing pharmacologist of this NDA has requested the Division of Biometrics to perform the statistical review and evaluation of these two studies. The data submitted on computer floppy diskettes were used in the reviewer's independent analyses. The results of this review have been discussed with Dr. Dutta.

II. The Rat Study

II. a. Design

In this study, three groups of 55 male and 55 female Charles River COFS rats of the Wistar Strain received APD via the diet at concentrations initially calculated to achieve dosages of 62.5, 250, or 1000 mg/kg/day. The growth of the animals in the high dose groups showed a definitive trend to stagnation starting around week 10. Hence, high dose was reduced by a fixed but lower dietary concentration for the males and to 600 mg/kg for the females during the study. Table 1 (Table 5 in submission volume 1.19) listed the adjustment of dietary concentrations of APD for high dose group. An additional 105 male and 105 female rats received untreated diet and were designated as controls. Treatment continued for at least 106 weeks. Bodyweights were recorded weekly for the first twenty weeks of

the study and every four weeks thereafter. Food consumption was recorded weekly and achieved dosages calculated. All animals found dead or killed in extremis were necropsied and a full range of tissues were taken where possible. At the end of the treatment period all surviving rats were killed and subjected to a full necropsy. A wide range of tissues were taken into fixative. Histopathologic examination was performed on all tissues from all animals.

II. b. Sponsor's Analyses

The sponsor reported mortality data for each group and sex every 12 weeks in page 29, Volume 1.19 (Table 2). Results of statistical test for the mortality data were not included in this submission.

The methods given in the paper of Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used to test the positive dose-response relationship in the tumor data. One-tailed tests for trend with actual dose or with dose level (similar to trend with log dose) were performed and pairwise comparisons of treated groups with the controls were also made. However, the sponsor did not report time intervals used in the analysis.

In this review, the phrase "dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

The sponsor's results showed a significant positive dose-response relationship in phaeochromocytoma in males rats (actual dose: $p = 0.0003$; dose level: $p = 0.0025$) and female rats (actual dose: $p = 0.024$; dose level: $p = 0.11$). The p-values for pairwise comparisons of low, medium, and high dose groups verses controls for this tumor type were 0.48, 0.20, and 0.0028 for males, respectively, and 0.49, 0.35, and 0.05 for females, respectively. Significant positive dose-response relationships was detected in myeloproliferative disorder of the spleen (actual dose: $p = 0.0031$; dose level: $p = 0.035$) in male rats, in leiomyoma of the small intestine (actual dose: $p = 0.0011$; dose level: $p = 0.0175$), and mammary carcinoma (actual dose: $p = 0.0013$; dose level: $p = 0.019$) in female rats.

II. c. Reviewer's Analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart ("Trend and Homogeneity Analyses of Proportions and Life Table Data", Computers and Biomedical Research, 10, 373-381, 1977) were used to test for heterogeneity in survival distributions. The

p-values of the Cox test were 0.0561 and 0.0001 for females and males, respectively. The p-values of the generalized Wilcoxon test were 0.0602 and 0.0001 for females and males, respectively. Hence, there is no statistically significant difference (at 0.05 level) in the survival distributions in female rats from both tests. However, there is a statistically significant difference in the survival distributions in male rats.

The intercurrent mortality rates for both male and female rats (see Table 3) were tested for the dose-response relationship according to the methods given in the paper of Peto et al. (1980) using time intervals 0-50, 51-80, and 81-105 weeks. The actual dose levels 0, 62.5, 250, and 1000 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. As mentioned in the previous section, the high dose group dose level was reduced during the study due to severe bodyweight decreases. The results of the analyses showed that there are significant positive dose-response relationship in the intercurrent mortality rates in male ($p < 0.00001$) and female rats ($p = 0.0074$).

The reviewer applied the prevalence method described in the paper of Peto et al. (1980) and the exact permutation trend test to test the positive dose-response relationship in the tumor data. The time intervals 0-50, 51-80, 81-105 and terminal sacrifice were used in those methods. The test results show that there are significant positive dose-response relationships in the adrenal phaeochromocytoma ($p < 0.00001$), myeloid tissue myeloproliferative disorder of the spleen ($p = 0.0477$) in male rats, and in mammary gland carcinoma ($p = 0.0308$), adrenal phaeochromocytoma ($p = 0.0249$), and small intestine leiomyoma ($p = 0.0282$) in female rats. The incidence rates of these tumors are given in Tables 4 to 8.

However, the prevalence rate of adrenal phaeochromocytoma in the concurrent control group in female rats is greater than one percent. It is considered as common tumor in this strain of rat. For a common tumor, we consider a positive dose-response relationship not to occur by chance only if the p-value is smaller than 0.01. Therefore we do not regard the positive dose-response relationship in adrenal phaeochromocytoma in female rats as statistically significant.

III. The Mouse Study

III. a. Design

In this study, APD was given by continuous administration of a dietary admixture for 80 weeks to 330 (55 animals/sex/group) Charles River CD-1 strain mice at three dose levels of 62.5, 234, or 879 mg/kg/day. An additional 105 male and 104 female mice received untreated diet and were designated as controls. Animal number 321 initially was allocated to female control group but was found to be a male by week 3 and was

discarded from the study. Food consumption was recorded weekly. Bodyweights were recorded weekly up to week 20 and thereafter at 4 weekly intervals. Animals found dead or killed in extremis were necropsied and a full range of tissues were taken where possible. At the end of the treatment period all surviving rats were killed and subjected to a full necropsy. A wide range of tissues from all animals were taken into fixative processed for, and subsequently subjected to a microscopical examination.

III. b. Sponsor's Analyses

The sponsor reported mortality data for every 12 weeks in page 25, Volume 1.12 (Table 9). The methods described in Peto et al. (1980) were used to test the positive dose-response relationship in the mortality and tumor data. The analyses have been performed with the group numbers used as scores, as well as with scores proportionate to the actual doses (0, 4, 15, and 56). However, the sponsor only reported the results of the analyses with scores proportionate to the actual doses. For small numbers of animals, exact p-values have been computed when the total number of animals showing the lesion under test was ten or less. The sponsor also applied the "closed" procedure which guarantees the observance of the nominal significance level (Marcus, R., Peritz, E., Gabriel, K.R. (1976) "On Closed Testing Procedures with Special Reference to Ordered Analysis of Variance", Biometrika 63, 655-660) to the tumor data. That is, in all cases where an effect could be shown, further investigations were carried out in order to detect the "No Observed Effect Level" (NOEL) by deleting the highest dose group and re-performing the above analysis until a non-significant result was obtained. The results of the above analyses are shown in Tables 10-12.

The sponsor indicates that there are significant dose-response relationship in the intercurrent mortality rates in both sexes (males: $p < 0.0001$; females: $p = 0.0039$).

For all tumors, the "fatal" analysis gives the smaller p-value than the "incidental" analysis. For males, the results of the analyses show that there is a significant dose-response relationship in the liver benign hepatoma from the "fatal" analysis ($p = 0.0329$) but not from the "incidental" analysis ($p = 0.1383$). For females, the results of the analyses show that there are significant dose-response relationships in the combined lung carcinoma and initial carcinoma ("fatal": $p = 0.0397$; "incidental": $p = 0.0811$), liver benign hepatoma ($p = 0.0353$ from both analyses), combined hepatocellular carcinoma and initial hepatocellular carcinoma ($p = 0.0253$ from both analyses), and combined hepatocellular carcinoma, initial hepatocellular carcinoma and benign hepatoma ($p = 0.0017$ from both analyses).

Based on the above analyses, the sponsor stated that "the statistical analysis of lung carcinoma in females and benign hepatomas in the males produced significant p-values. However, the combined occurrence i.e.,

adenomas, initial carcinomas, and clear carcinomas gave no evidence of treatment effect. Thus, no biological relevance was attributed to these results."

III. c. Reviewer's Analyses and Comments

The Cox test and the generalized Wilcoxon test described in the paper of Thomas, Breslow, and Gart (1977) were used to test for heterogeneity in survival distributions. The p-values of the Cox test were 0.5942 and 0.3639 for females and males, respectively. The p-values of the generalized Wilcoxon test were 0.6086 and 0.1619 for females and males, respectively. Hence, there were no statistically significant differences (at 0.05 level) in the survival distributions in either female or male mice.

The intercurrent mortality rates for both male and female mice (see Table 13) were tested for the dose-response relationship according to the methods given in the paper of Peto et al. (1980) using time intervals 0-50, 51-70, and 71-80 weeks. The actual dose levels 0, 62.5, 234, and 879 mg/kg/day were the scores assigned to the control, low, medium, and high dose groups, respectively. The results of the analyses showed that there were significant dose-response relationship in the intercurrent mortality rates in both males ($p < 0.0001$) and females ($p = 0.00149$) mice.

The prevalence method described in the paper of Peto et al. (1980) and the exact permutation trend test were applied to test the positive dose-response relationship in the tumor data. The time intervals 0-50, 51-70, 71-80 and terminal sacrifice were used in those methods. The test results showed that there were statistical significant dose-response relationships in the liver benign hepatoma ($p = 0.0353$) and the combined hepatocellular carcinoma and initial hepatocellular carcinoma ($p = 0.0252$) in female mice. The incidence rates of these two tumors are given in Tables 14 and 15. Note that the reviewer did not analyze the combined tumor data of hepatocellular carcinoma, initial hepatocellular carcinoma, and benign hepatoma as the sponsor did.

IV. Summary

In this review, the phrase "positive dose-response relationship" refers to the increasing linear component of the effect of treatment, and not necessarily to a strictly increasing tumor or mortality rate as dose increases.

IV. a. The Rat Study

The oncogenic potential of APD was evaluated in this rat study when administered continuously to the animals, via the diet, at dosage levels 0, 62.5, 250, or 1000 mg/kg/day for 106 weeks. The Cox and the [illegible] methods were used to test the heterogeneity in [illegible]. The statistical methods given in the paper of

Peto et al. (1980) and an exact permutation trend test were used to test the positive dose-response relationship in intercurrent mortality and incidental tumor rates.

The results of the above analyses show that there is no significant difference in the survival distributions in female rats. However, both tests show that there is a significant difference in the survival distributions in male rats. There are significant positive dose-response relationships in the intercurrent mortality rates in both male ($p < 0.00001$) and female rats ($p = 0.0024$). The test results also show that there are significant positive dose-response relationships in the adrenal phaeochromocytoma ($p < 0.00001$), myeloid tissue myeloproliferative disorder of the spleen ($p = 0.0477$) in male rats, and in mammary gland carcinoma ($p = 0.0308$), and small intestine leiomyoma ($p = 0.0282$) in female rats.

IV. b. The Mouse Study

The oncogenic potential of APD was evaluated in this mouse study when administered continuously to the animals, via the diet, at dosage levels of 0, 62.5, 234, or 879 mg/kg/day for 80 weeks. The Cox and the generalized Wilcoxon methods were used to test the heterogeneity in survival distributions. The statistical methods given in the paper of Peto et al. (1980) and an exact permutation trend test were used to test the positive dose-response relationship in intercurrent mortality and incidental tumor rates.

Our analyses show that no significant difference in the survival distributions in either male or female mice. However, there are significant dose-response relationships in the intercurrent mortality rates in both male ($p < 0.0001$) and female mice ($p = 0.00149$). In addition, the test results show that there are statistical significant dose-response relationship in the liver benign hepatoma ($p = 0.0353$) and the combined hepatocellular carcinoma and initial hepatocellular carcinoma ($p = 0.0252$) in female mice. No statistical significant dose related trends in tumor incidence rates were detected in male mice.

Daphne Lin

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 11/19/90
Karl K. Lin, Ph.D., Group Leader, SARB

NOV 21 1990

cc: Original NDA 20-036
HFD-510/Dr. Sobel
HFD-510/Dr. Jordan
HFD-510/Dr. Dutta
HFD-710/Chron
HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-715/Chron (SARB)
HFD-502/Dr. Weissinger
HFD-715/DRU 2.1.1, Aredia, Ciba-Geigy Corporation

Table 1
High doe Group (Nominal dose 1000mg/kg)
Adjustment of dietary concentrations of APD

	Nominal dose level (mg/kg/day)	Prepared concentration ppm	Achieved dose level (mg/kg/day)
1	1000	7483	1008
2	1000	9147	1012
3	1000	10063	933
4	1000	11030	918
5	1000	11624	875
6	1000	12727	851
7	1000	13236	894
8	1000	13547	766
9	1000	13959	733
10	1000	14000	726
11	1000	17300	819
12	1000	14000	659
15	1000	13000	587
17	1000	12000	545
19	1000	11000	497
33	1000	10500	520
37	1000	10000	416

As of week 37 until the end of the study 10000 ppm was the standard concentration used in every weekly did mix preparation.

Table 2

MORTALITY - NUMBER OF DEATHS BY WEEK

Group	: 1	2	3	4
Treatment	: Control		APD	
Dosage (mg/kg/day)	: 0	62.5	250	1000 (initial dose level)

	Group and Sex															
Period in weeks	1♂		2♂		3♂		4♂		1♀		2♀		3♀		4♀	
	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C
0-13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14-26	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0
27-39	0	1	0	0	0	0	8	9	1	1	1	1	0	0	1	1
40-52	1	2	1	1	1	1	10	19	0	1	0	1	1	1	1	2
53-65	3	5	1	2	1	2	4	23	0	1	2	3	0	1	5	7
66-78	3	8	2	4	1	3	6	29	2	3	0	3	2	3	6	13
79-91	13	21	6	10	5	8	7	36	7	10	5	8	8	11	2	15
92-104	11	32	9	19	8	16	9	45	12	22	6	14	11	22	6	21
105-108	5	37	1	20	6	22	3	48	9	31	3	17	4	26	5	26
Terminal Kill	68		35		33		7		74		38		29		29	
Original Group Size	105		55		55		55		105		55		55		55	
Total Decedents	37		20		22		48		31		17		26		26	
% Decedents	35		36		40		87		30		31		47		47	

A - Actual number of deaths in period
C - Cumulation deaths

Table 3
Intercurrent Mortality Rates
Male Rats

Weeks	Control			Low			Medium			High		
	Start	D	%	Start	D	%	Start	D	%	Start	D	%
0-50	105	2	1.9	55	1	1.81	55	1	1.81	55	18	32.73
51-80	103	8	7.76	54	5	9.26	54	2	3.7	37	13	35.13
81-105	95	27	28.42	49	14	28.57	52	18	34.61	24	17	70.83
Terminal	68			35			34			7		

Female Rats

Weeks	Control			Low			Medium			High		
	Start	D	%	Start	D	%	Start	D	%	Start	D	%
0-50	105	1	0.95	55	1	1.81	55	1	1.81	55	2	3.63
51-80	104	3	2.88	54	4	7.41	54	5	9.26	53	11	20.75
81-105	101	27	26.73	50	12	24.0	49	20	40.81	42	13	30.95
Terminal	74			38			29			29		

Notes: D: Deaths
%: Percent of death during the period

Table 4
Tumor Incidence Rates
Male Rats, Adrenal Phaeochromocytoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	2	0	1	0	1	0	18
51-80	0	8	0	5	0	2	1	13
81-105	2	27	2	14	1	18	7	17
Terminal	6	68	1	35	6	34	4	7
Total	8	105	3	55	7	55	12	55

Table 5
Tumor Incidence Rates
Male Rats, Myeloid Tissue Myeloproliferative Disorder of the Spleen

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	2	0	1	0	1	0	18
51-80	0	8	0	5	0	2	0	13
81-105	0	27	0	14	0	18	2	17
Terminal	0	68	0	35	0	34	0	7
Total	0	105	0	55	0	55	2	55

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 6
Tumor Incidence Rates
Female Rats, Mammary Gland Carcinoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	1	0	2
51-80	0	3	0	4	0	5	0	11
81-105	0	27	0	12	0	20	1	13
Terminal	0	74	0	38	0	29	1	29
Total	0	105	0	55	0	55	2	55

Table 7
Tumor Incidence Rates
Female Rats, Adrenal Phaeochromocytoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	1	0	2
51-80	0	3	0	4	0	5	0	11
81-105	0	27	2	12	0	20	2	13
Terminal	3	74	1	38	0	29	3	29
Total	3	105	3	55	0	55	5	55

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 8
Tumor Incidence Rates
Female Rats, Small Intestine Leiomyoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	1	0	1	0	1	0	2
51-80	0	3	0	4	0	5	0	11
81-105	0	27	0	12	0	20	0	13
Terminal	0	74	0	38	0	29	2	29
Total	0	105	0	55	0	55	2	55

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

Table 9

MORTALITY - NUMBER OF DEATHS BY WEEK

Group	:	1	2	3	4
Treatment	:	Control		APD	
Dosage (mg/kg/day)	:	0	62.5	234	879

Period in weeks	Group and Sex															
	1♂		2♂		3♂		4♂		1♀		2♀		3♀		4♀	
	A	C	A	C	A	C	A	C	A	C	A	C	A	C	A	C
0-13	0	0	1	1	0	0	2	2	1	1	0	0	0	0	0	0
14-26	0	0	0	1	1	1	0	2	1	2	0	0	1	1	0	0
27-39	2	2	0	1	1	2	1	3	2	4	0	0	2	3	2	2
40-52	1	3	1	2	1	3	6	9	3	7	3	3	1	4	3	5
53-65	6	9	4	6	3	6	8	17	3	10	4	7	2	6	4	9
66-78	10	19	7	13	8	14	18	35	8	18	3	10	3	9	9	18
79-82	4	23	2	15	3	17	4	39	3	21	0	10	2	11	4	22
Terminal Kill	82		40		38		16		83		45		44		33	
Original Group Size	105		55		55		55		104		55		55		55	
Total Decedents	23		15		17		39		21		10		11		22	
% Decedents	22		27		31		71		20		18		20		40	

A - Actual number of deaths in period
C - Cumulation deaths

Table 10
HISTOPATHOLOGY REPORT
80 WEEK CARCINOGENICITY STUDY IN THE MOUSE
PS Project No. 864004 Released: 24.10.1989 CGP 23339 A

Table A. Trend test and NOEL computation for males

Organ/type of lesion	table	g	p-value fatal	p-value incid.
Overall mortality (survival analysis; two-sided p-values)	1	4	<0.0001	
		3	0.2420	
Lung:				
Carcinoma	2	4	0.9816	0.9930
Carcinoma, initial	3	4	0.1623	0.4038
Adenoma	4	4	0.8915	0.9849
Carcinoma and initial carcinoma, combined	5	4	0.7442	0.8830
Carcinoma, initial carcinoma and adenoma, combined	6	4	0.9220	0.9941
Liver:				
Hepatocellular carcinoma	7	4	0.4942	0.6933
Hepatocellular carcinoma, initial	8	4	0.8192	0.8792
Benign hepatoma	9	4	0.0329	0.1383
		3	0.0611	0.0648
		2	0.0164	0.0196
Hepatocellular carcinoma and initial hepatocellular carcinoma, combined	10	4	0.6526	0.8515
Hepatocellular carcinoma, initial hepatocellular carcinoma and benign hepatoma, combined	11	4	0.1155	0.4556
		3	0.0118	0.0359
		2	0.0062	0.0091
Lymphoreticular tissue:				
Malignant lymphoma	12	4	0.3811	0.5386
Haematopoietic tissue:				
Myeloid leukaemia	13	4	0.6553	0.9696
Malignant lymphoma and myeloid leukaemia, combined	14	4	0.5579	0.9536
Thymus:				
Benign thymoma	15	4	0.5930	0.5930
Thymic lymphoma			never detected	
Malignant lymphoma, benign thymoma and thymic lymphoma, combined	16	4	0.4760	0.5880
Malignant lymphoma, myeloid leukaemia, benign thymoma and thymic lymphoma, combined	17	4	0.6195	0.9598

(g = highest group in test)

Table B. Trend test and NOEL computation for females

Organ/type of lesion	table	g	p-value fatal	p-value incid.
Overall mortality (survival analysis; two-sided p-values)	18	4	0.0039	
		3	0.8685	
Lung:				
Carcinoma	19	4	0.1220	0.2187
Carcinoma, initial	20	4	0.1610	0.1610
Adenoma	21	4	0.3931	0.4625
Carcinoma and initial carcinoma, combined	22	4	0.0397	0.0811
		3	0.2704	0.2704
Carcinoma, initial carcinoma and adenoma, combined	23	4	0.0620	0.1413
Liver:				
Hepatocellular carcinoma	24	4	0.1610	0.1610
Hepatocellular carcinoma, initial	25	4	0.1610	0.1610
Benign hepatoma	26	4	0.0353	0.0353
		3	0.1990	0.1990
Hepatocellular carcinoma and initial hepatocellular carcinoma, combined	27	4	0.0253	0.0253
		3	1.0000	1.0000
Hepatocellular carcinoma, initial hepatocellular carcinoma and benign hepatoma, combined	28	4	0.0017	0.0017
		3	0.1990	0.1990
Lymphoreticular tissue:				
Malignant lymphoma	29	4	0.6689	0.9051
Haematopoietic tissue:				
Myeloid leukaemia	30	4	0.7881	0.8992
Malignant lymphoma and myeloid leukaemia, combined	31	4	0.7815	0.9673
Thymus:				
Benign thymoma	32	4	1.0000	1.0000
Thymic lymphoma	33	4	0.3469	0.3469
Benign thymoma and thymic lymphoma, combined	34	4	0.5138	0.5138
Malignant lymphoma, benign thymoma and thymic lymphoma, combined	35	4	0.6736	0.8730
Malignant lymphoma, myeloid leukaemia, benign thymoma and thymic lymphoma, combined	36	4	0.7667	0.9455

(g = highest group in test)

Table C. No observed effect level (NOEL)

Organ/type of lesion	NOEL (mg/kg) males fat./inc.		females fat./inc.	
Overall mortality (survival analysis)	234		234	
Lung:				
Carcinoma	879	879	879	879
Carcinoma, initial	879	879	879	879
Adenoma	879	879	879	879
Carcinoma and initial carcinoma, combined	879	879	234	879
Carcinoma, initial carcinoma and adenoma, combined	879	879	879	879
Liver:				
Hepatocellular carcinoma	879	879	879	879
Hepatocellular carcinoma, initial	879	879	879	879
Benign hepatoma	*	*	234	234
Hepatocellular carcinoma and initial hepatocellular carcinoma, combined	879	879	234	234
Hepatocellular carcinoma, initial hepatocellular carcinoma and benign hepatoma, combined	*	*	234	234
Lymphoreticular tissue:				
Malignant lymphoma	879	879	879	879
Haematopoietic tissue:				
Myeloid leukaemia	879	879	879	879
Malignant lymphoma and myeloid leukaemia, combined	879	879	879	879
Thymus:				
Benign thymoma	879	879	879	879
Thymic lymphoma	879	879	879	879
Benign thymoma and thymic lymphoma, combined	879	879	879	879
Malignant lymphoma, benign thymoma and thymic lymphoma, combined	879	879	879	879
Malignant lymphoma, myeloid leukaemia, benign thymoma and thymic lymphoma, combined	879	879	879	879

* not defined (see text below)

Table 13
Intercurrent Mortality Rates
Male Mice

Weeks	Control			Low			Medium			High		
	Start	D	%	Start	D	%	Start	D	%	Start	D	%
0-50	105	3	2.85	55	2	3.63	55	3	5.45	55	8	14.54
51-70	102	11	10.78	53	6	11.32	52	4	7.69	47	25	53.19
71-80	91	9	9.89	47	7	14.89	48	10	20.83	22	6	27.27
Terminal	82			40			38			16		

Female Mice

Weeks	Control			Low			Medium			High		
	Start	D	%	Start	D	%	Start	D	%	Start	D	%
0-50	104	6	5.76	55	3	5.45	55	4	7.27	55	5	9.09
51-70	98	8	8.16	52	5	9.61	51	3	5.88	50	11	22.0
71-80	90	7	7.77	47	2	4.25	48	4	8.33	39	6	15.38
Terminal	83			45			44			33		

Notes: D: Deaths
%: Percent of death during the period

Table 14
Tumor Incidence Rates
Female Mice, Liver Benign Hepatoma

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	6	0	3	0	4	0	5
51-70	0	8	0	5	0	3	0	11
71-80	0	7	0	2	0	4	0	6
Terminal	0	83	1	45	1	44	2	33
Total	0	104	1	55	1	55	2	55

Table 15
Tumor Incidence Rates
Female Mice, Hepatocellular Carcinoma and initial Hepatocellular Carcinoma Combined

Weeks	Control		Low		Medium		High	
	T	N	T	N	T	N	T	N
0-50	0	6	0	3	0	4	0	5
51-70	0	8	0	5	0	3	0	11
71-80	0	7	0	2	0	4	0	6
Terminal	0	83	0	45	0	44	2	33
Total	0	104	0	55	0	55	2	55

Notes: T: Number of necropsies with the above tumor.
N: Number of necropsies.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 14, 1990

FROM: Mathematical Statistician (HFD-713)

Through: Satya D. Dubey, Ph.D. SD
Chief, Statistical Evaluation and Research Branch (HFD-713)

SUBJECT: NDA 20-036, Aredia submission dated September 4, 1990

TO: File (NDA 20-036, Aredia)

The sponsor submitted revised tables regarding their June 5, 1990 and June 27, 1990 submissions.

The revisions do not alter the conclusions stated in the NDA 20-036 Statistical Review and Evaluation dated June 4, 1990 and the NDA 20-036 Memorandum of Consultation dated July 10, 1990.

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius SEN 9-14-90

cc:
Orig. NDA 20-036
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Dutta
HFD-510/Mr. Short
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File DRU: 1.3.2 NDA]
HFD-713/Group 2 file
HFD-713/Mr. Marticello
Chron.

ajd/SERB/writenow/NDA 20-036/9-14-90

This memo consists of 2 pages.

DW file

MEMORANDUM OF CONSULTATION

DATE: July 10, 1990

BETWEEN: Samarendra N. Dutta, M.D. (HFD-510)

AND: Daniel N. Marticello (HFD-713)

SUBJECT: NDA 20-036 Aredia - Sponsor's submissions dated June 5, 1990 and June 27, 1990

In a statistical review of NDA 20-036 dated June 4, 1990, I noted that I had requested that Ciba-Geigy reanalyze their responder proportion data where the responder classification is not automatically carried forward as described in thier Study 01 and Study 03 reports.

As we discussed, the sponsor has complied with my request and the results of their reanalyzes are very similar to their original results.

In addition, as requested during the April 4, 1990 90-day meeting, the sponsor has analyzed their Protocol 01 corrected serum calcium data for two subgroups of patients (baseline corrected serum calcium of at least 13.5mg/dl and of less than 13.5mg/dl). The sponsor's results are consistent with the overall results which were discussed in the above mentioned June 4, 1990 statistical review in that the treatment response increased with increased dose for each of the subgroups.

Consequently, as we discussed, the conclusions stated in the June 4, 1990 statistical review have been further validated by the sponsor's June 5, 1990 and June 27, 1990 submissions.

Daniel N. Marticello
Mathematical Statistician

This memorandum consists of 1 page of text.

cc:
Original: NDA 20-036
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Dutta
HFD-510/Mr. Eastep
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey
HFD-713/Dr. Chi
HFD-713/Mr. Marticello
Chron.
D.N.Marticello:34594:SERB:skj:07/10/90:#2149nWANG

DW file

MEMORANDUM OF CONSULTATION

DATE: July 10, 1990

BETWEEN: Samarendra N. Dutta, M.D. (HFD-510)

AND: Daniel N. Marticello (HFD-713)

SUBJECT: NDA 20-036 Aredia - Sponsor's submissions dated June 5, 1990 and June 27, 1990

In a statistical review of NDA 20-036 dated June 4, 1990, I noted that I had requested that Ciba-Geigy reanalyze their responder proportion data where the responder classification is not automatically carried forward as described in thier Study 01 and Study 03 reports.

As we discussed, the sponsor has complied with my request and the results of their reanalyzes are very similar to their original results.

In addition, as requested during the April 4, 1990 90-day meeting, the sponsor has analyzed their Protocol 01 corrected serum calcium data for two subgroups of patients (baseline corrected serum calcium of at least 13.5mg/dl and of less than 13.5mg/dl). The sponsor's results are consistent with the overall results which were discussed in the above mentioned June 4, 1990 statistical review in that the treatment response increased with increased dose for each of the subgroups.

Consequently, as we discussed, the conclusions stated in the June 4, 1990 statistical review have been further validated by the sponsor's June 5, 1990 and June 27, 1990 submissions.

Daniel N. Marticello
Mathematical Statistician

This memorandum consists of 1 page of text.

cc:
Original: NDA 20-036
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Dutta
HFD-510/Mr. Eastep
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey
HFD-713/Dr. Chi
HFD-713/Mr. Marticello
Chron.
D.N.Marticello:34594:SERB:skj:07/10/90:#2149nWANG

DIV F.6

Statistical Review and Evaluation

NDA #: 20-036/Drug Class: 1B

JUN - 4 1990

Applicant: Ciba-Geigy Corporation

Name of Drug: Aredia (pamidronate disodium)

Indication: Hypercalcemia associated with malignancy

Documents Reviewed: Volumes 1.34-1.47 of NDA 20-036 dated December 20, 1989

Medical Reviewer: This review has been discussed with the clinical reviewer, Samarendra N. Dutta, M.D. (HFD-510).

Relevant Issues Discussed in this Review:

1. The results of Study 03 indicate that APD 60mg patients experience significantly greater reductions in corrected serum calcium levels than EHDP patients.

2. The results of Study 01 may be viewed as supportive of the Study 03 results since corrected serum calcium reductions were generally related to dose and since the APD reductions were consistent between the studies.

3. The sponsor has been requested to reanalyze their responder data.

Study 03

This double-blind, randomized, multi-center (9 centers) study was conducted to compare the effects of Aredia (APD) and intravenous EHDP (etidronate disodium, Didronel I.V. Infusion) in lowering serum calcium levels in patients with cancer who had persistent hypercalcemia (corrected serum calcium of at least 12mg/dl) after adequate hydration. EHDP has been approved for treatment of hypercalcemia of malignancy.

Patients who satisfied protocol criteria were randomized in each center in blocks of size four to receive either a single 60mg 24-hour infusion of APD or a 7.5mg/kg 2-hour infusion of EHDP given daily for 3 days. In order to prevent unblinding of the trial due to differences in the volume or number of infusions, each patient received a placebo saline infusion matching that of the other treatment regimen in addition to their active treatment infusion.

Key Words: dose response, hypercalcemia, serum calcium

Patients were followed closely as inpatients for 7 days (inpatient phase) for effects on corrected serum calcium levels and for any adverse experiences associated with APD or EHDP infusions. In a follow-up phase (days 10-30), patients were followed either as inpatients or outpatients for recurrence of hypercalcemia and for any long-term adverse experiences.

The primary efficacy variable was the reduction in corrected serum calcium levels. Patients whose corrected serum calcium level was reduced to within the patient's center's normal range were considered to have experienced a complete therapeutic response. A partial response was defined to be a decrease of at least fifteen percent in the corrected serum calcium level.

The primary efficacy analysis was based on data obtained during the 7-day inpatient phase.

Reviewer's Comments on Study 03

A total of 65 patients (30 APD, 35 EHDP) were randomized to receive double-blind treatment. Sixteeen (6 APD, 10 EHDP) of these patients failed to complete the 7-day inpatient phase. The most common premature termination reasons were death (2 APD, 4 EHDP), relapse (2 APD, 2 EHDP), and unsatisfactory therapeutic response (3 EHDP).

In examining the adverse reaction data submitted by the sponsor, I noted that each patient reported at least one adverse reaction during the study. However, with the exception of anemia (APD: 15 patients, 50.0%, EHDP: 8 patients, 22.9%, $p = .023$), I failed to detect a significant difference between treatment groups with respect to the proportion of patients reporting any specific adverse reaction. Table 3 displays the most frequently reported adverse reactions.

The sponsor conducted analyses of covariance with the baseline corrected serum calcium value as a covariate in order to compare the treatment groups with respect to reductions in corrected serum calcium levels over the 7-day inpatient phase. The results of these analyses are displayed in Table 1.

In examining Table 1, one notes that APD patients experienced significantly greater mean reductions than did EHDP patients over the last four days of the inpatient phase. Similar results were obtained with respect to reductions in uncorrected serum calcium levels.

The sponsor also compared treatment groups with respect to responder proportions. The results of the responder comparisons which are displayed in Table 2 are consistent with the above mentioned analyses of covariance results. However, once a patient was classified as a responder (complete or partial), that patient was considered a responder at all subsequent inpatient phase visits whether or not that patient still satisfied the responder definition. In order to determine the effect of this procedure, I have requested that the sponsor reanalyze the responder proportion data where the responder classification is not automatically carried forward as described above.

At the request of FDA clinicians, the sponsor considered an alternate responder definition which was identical to the original responder definition except that one-day only responders were considered to be non-responders. Under the alternate responder definition the APD and EHDP complete responder proportions ($p = .478$) were 50.0% and 41.2% respectively. The corresponding "at least partial response proportions" ($p = .024$) were 86.7% and 61.8% respectively.

Study 01

This double-blind, randomized, multi-center (4 centers) study was conducted to assess the effects of 30, 60, and 90mg single doses of APD in lowering serum calcium levels in patients with cancer who have persistent hypercalcemia (corrected serum calcium of at least 12mg/dl) after adequate hydration.

Patients who satisfied protocol criteria were randomized in each center in blocks of size 3 to receive single doses of either 30, 60, or 90mg of APD infused over a 24-hour period. Patients were followed closely as inpatients (inpatient phase) for 4-7 days for effects on corrected serum calcium and for any adverse experiences associated with APD infusions. In a follow-up phase (days 14-60), patients were followed either as inpatients or outpatients for recurrence of hypercalcemia and for any long-term adverse experiences.

The primary efficacy variable was the reduction in corrected serum calcium levels. Complete and partial responses were defined as in Study 03 and the primary efficacy analysis was based on data obtained during the inpatient phase.

Reviewer's Comments on Study 01

A total of 50 patients (15 APD 30mg, 18 APD 60mg, 17 APD 90mg) were randomized to receive double-blind treatment. In addition, two patients received APD 60mg as an open label treatment. The two open patients were included in safety evaluations but were excluded from all efficacy analyses.

Fifteen (7 APD 30mg, 7 APD 60mg, 1 APD 90mg) patients failed to complete the inpatient phase. The most common premature termination reasons were death (3 APD 30mg, 4 APD 60mg) and unsatisfactory response (2 APD 30mg, 2 APD 60mg).

In examining the adverse reaction data submitted by the sponsor, I noted that each patient reported at least one adverse reaction during the study. Table 4 displays the most frequently reported adverse reactions. In examining this table, one notes that nausea was the only frequently reported adverse reaction whose incidence increased with increased dose as significant differences were not detected between treatment groups with respect to the proportion of patients reporting any specific adverse reaction. Also the anemia incidence rate of 21.2% was similar to that experienced by the Study 03 EHDP patients (22.9%) in contrast to the Study 03 APD rate (50.0%).

The objective of the primary efficacy analysis as stated in the protocol was to demonstrate the effectiveness of each APD dose as between-treatment group comparisons were of only secondary interest due to the small sample size. However, in the opinion of this reviewer, the between-treatment group comparison results should be examined closely in order to determine whether or not the results of this study may be viewed as supportive of the Study 03 efficacy results.

As in Study 03, the sponsor conducted analyses of covariance with the baseline corrected serum calcium value as a covariate in order to compare the treatment groups with respect to reductions in corrected serum calcium levels over the inpatient phase. The results of these analyses are displayed in Table 5.

In examining Table 5, one notes that significant between-treatment group differences were detected on days 3 and 7 as well as at endpoint. Also, one notes that the magnitude of the APD reductions are consistent with the magnitude of the Study 03 APD reductions.

The sponsor also compared treatment groups (Table 6) with respect to responder proportions as defined in Study 03. In examining Table 6, one notes that the responder rates generally increased with increased dose and that the responder rates are not inconsistent with the Study 03 APD responder rates.

Reviewer's Concluding Comments (may be conveyed to the sponsor)

The results of Study 03 indicate that APD 60mg patients experienced significantly greater reductions in corrected serum calcium levels than EHDP patients.

However, significantly more APD patients experienced anemia than did their EHDP counterparts.

Also, the sponsor has been requested to reanalyze their responder data where the responder classification is not automatically carried forward.

The results of Study 01 may be viewed as being supportive of the Study 03 results since corrected serum calcium reductions were generally related to dose and since the magnitude of the APD reductions were consistent between the studies.

Daniel N. Marticello
Mathematical Statistician

This review consists of 5 pages of text and 6 pages of tables.

Concur: Dr. Chi 6/1/90

Dr. Dubey 6-6-4-90

cc:
Original: NDA 20-036
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Dutta
HFD-510/Mr. Eastep
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Mr. Marticello
Chron.
D.N.Marticello:x34594:SERB:skj:06/01/90:#2134n

TABLE 1

STUDY 03

Corrected Serum Calcium Means
(mg/dl)

	APD			EHDP			
Day	N	Baseline	Adjusted# Reduction	N	Baseline	Adjusted# Reduction	P-value+
1	29	14.67	.50	31	13.80	.73	.334
2	29	14.64	1.39	30	13.74	1.31	.797
3	29	14.37	2.48	25	13.81	1.99	.137
4	29	14.59	3.28	29	13.74	2.25	.004*
5	26	14.80	3.82	28	13.66	2.70	.005*
6	23	14.78	3.95	26	13.48	2.92	.015*
7	24	14.52	3.85	27	13.66	2.52	.008*
Endpoint[a]	30	14.60	3.89	32	13.88	2.25	< .001*

\# Adjusted for baseline corrected serum calcium

\+ Analysis of covariance with baseline corrected serum calcium as a covariate

* $p < .05$ in favor of APD over EHDP

a last value carried forward

TABLE 2

STUDY 03

Responder Proportions

Day #	Complete			Complete or Partial		
	APD (N = 30)	EHDP (N = 34)	P-value	APD (N = 30)	EHDP (N = 34)	P-value+
1	0 (0.0%)	0 (0.0%)	1.000	0 (0.0%)	1 (2.9%)	1.000
2	1 (3.3%)	2 (5.9%)	1.000	8 (26.7%)	9 (26.5%)	1.000
3	9 (30.0%)	7 (20.6%)	.405	21 (70.0%)	13 (38.2%)	.014*
4	12 (40.0%)	10 (29.4%)	.435	26 (86.7%)	20 (58.8%)	.024*
5	15 (50.0%)	11 (32.4%)	.204	28 (93.3%)	21 (61.8%)	.003*
6	19 (63.3%)	14 (41.2%)	.087	28 (93.3%)	22 (64.7%)	.007*
7	21 (70.0%)	14 (41.2%)	.026*	29 (96.7%)	22 (64.7%)	.002*

\# Cumulative number of patients who respond by the given day

\+ Fisher's Exact Test

TABLE 3

STUDY 03

Adverse Reaction Frequencies+

Reaction	APD	EHDP
Anorexia	21 (7 .0%)	20 (57.1%)
Anemia	15 (50.0%)*	8 (22.9%)
Constipation	14 (46.7%)	19 (54.3%)
Arthralgia	13 (43.3%)	14 (40.0%)
Fever	13 (43.3%)	11 (31.4%)
Hypokalemia	12 (40.0%)	11 (31.4%)
Nausea	11 (36.7%)	17 (48.6%)
Dyspnea	10 (33.3%)	8 (22.9%)
Hypomagnesemia	9 (30.0%)	5 (14.3%)
Abdominal Pain	6 (20.0%)	11 (31.4%)

+ Reported by at least 30% of the patients in at least one of the treatment groups

* $p = .023$

TABLE 4

STUDY 01

Adverse Reaction Frequencies+

Reaction	APD 30mg	APD 60mg	APD 90mg	Total
Constipation	10 (66.7%)	11 (55.0%)	9 (52.9%)	30 (57.7%)
Anorexia	5 (33.3%)	12 (60.0%)	9 (52.9%)	26 (50.0%)
Hypophosphatemia	7 (46.7%)	9 (45.0%)	8 (47.1%)	24 (46.2%)
Hypokalemia	6 (40.0%)	10 (50.0%)	7 (41.2%)	23 (44.2%)
Hypomagnesemia	10 (66.7%)	8 (40.0%)	5 (29.4%)	23 (44.2%)
Pain	6 (40.0%)	6 (30.0%)	7 (41.2%)	19 (36.5%)
Arthralgia	7 (46.7%)	5 (25.0%)	5 (29.4%)	17 (32.7%)
Urinary Tract Infection	5 (33.3%)	5 (25.0%)	5 (29.4%)	15 (28.8%)
Fever	3 (20.0%)	6 (30.0%)	5 (29.4%)	14 (26.9%)
Hypertension	6 (40.0%)	4 (20.0%)	4 (23.5%)	14 (26.9%)
Nausea	3 (20.0%)	5 (25.0%)	6 (35.3%)	14 (26.9%)

+ Reported by at least 30% of the patients in at least one of the treatment groups.

TABLE 5

STUDY 01

Corrected Serum Calcium Means
(mg/dl)

	APD 30mg			APD 60mg			APD 90mg			
Day	N	Baseline	Adjusted# Reduction	N	Baseline	Adjusted# Reduction	N	Baseline	Adjusted# Reduction	P-value+
1	14	13.89	.50	17	13.72	.48	16	13.26	.4[illegible]	.981
2	12	13.52	1.33	16	13.76	1.89	17	13.28	1.47	.247
3	10	13.74	1.54	16	13.82	2.86	17	13.28	2.49	.027*
4	9	13.47	3.22	15	13.89	3.23	16	13 25	3.57	.636
5	9	13.58	3.39	12	13.90	4.20	15	13.25	3.94	.255
6	9	13.69	3.18	13	13.92	3.79	14	13.14	4.40	.109
7	10	13.60	3.00	14	13.99	3.71	16	13.25	4.59	.012*
Endpoint[b]	14	13.89	2.68	18	13.77	3.44	16	13.25	4.72	.001*[a]

\# Adjusted for baseline corrected serum calcium

\+ Analysis of covariance with baseline corrected serum calcium as a covariate

* $p < .05$

Pairwise comparisons were performed using the Tukey multiple comparison procedure to yield a .05 experimentwise error rate. At day 3 the 60mg reduction was significantly greater than the 30mg reduction. At day 7 the 90mg reduction was significantly greater than the 30 day reduction. At endpoint, the 90mg reduction was significantly greater than the 30mg and 60mg reductions.

a Significant ($p = .0006$) treatment by baseline interaction due to the fact that the APD 30mg treatment group had a fairly constant reduction in calcium levels across different baseline levels whereas the ADP 60 and 90mg treatment group reductions increased as the baseline levels increased.

b last value carried forward

TABLE 6

STUDY 01

Responder Proportions

Complete Responders

Day #	APD 30mg (N = 15)	APD 60mg (N = 18)	APD 90mg (N = 17)
1	0	0	0
2	0	2 (11.1%)	2 (11.8%)
3	1 (6.7%)	8 (44.4%)	8 (47.1%)
4	5 (33.3%)	8 (44.4%)	11 (64.7%)
5	6 (40.0%)	9 (50.0%)	15 (88.2%)*
6	6 (40.0%)	11 (61.1%)	17 (100.0%)**
7	6 (40.0%)	11 (61.1%)	17 (100.0%)**

Complete or Partial Responders

1	0	0	1 (5.9%)
2	2 (13.3%)	7 (38.9%)	4 (23.5%)
3	3 (20.0%)	13 (72.2%)+	11 (64.7%)*
4	7 (46.7%)	13 (72.2%)	14 (82.4%)
5	7 (46.7%)	13 (72.2%)	16 (94.1%)*
6	7 (46.7%)	13 (72.2%)	17 (100.0%)*
7	7 (46.7%)	14 (77.8%)	17 (100.0%)*

\# Cumulative number of patients who respond by the given day

* $p < .017$ (Bonferonni multiple comparison significance level) in favor of APD 90mg over APD 30mg

** $p < .017$ in favor of APD 90mg over APD 30mg and APD 60mg

\+ $p < .017$ in favor of APD 60mg over APD 30mg