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NDA 20-036 Review Completed: 8/15/90

Submitted 12-20-89

Applicant: Ciba-Geigy Corporation
Attention: Irene A. Chow, Ph.D.
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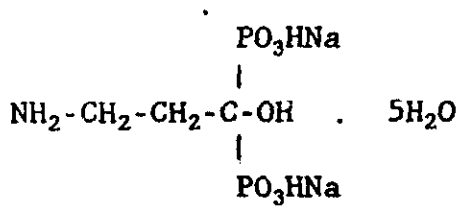
1. General Information:

a. Name of drug:

(1) Generic: Pamidronate disodium (APD)
(2) Trade: Aredia
(3) Chemical: Disodium (3-amino-1-hydroxypropylidene) bisphosphonate pentahydrate
(4) Structural formula:



b. Pharmacologic category: A bone resorption inhibitor

c. Proposed indication: "Aredia, in conjunction with adequate hydration, is indicated for the treatment of hypercalcemia associated with malignancy."

d. Dosage form and route of administration: Available in vials, each containing 15 mg of sterile lyophilized pamidronate disodium and 235 mg of mannitol, USP. The recommended dose of Aredia is diluted in 1000 ml of sterile 0.9% saline or 5% dextrose solution, administered as a single intravenous infusion over 24 hours.

e. Related drugs: Etidronate disodium, EHDP (Didronel I.V. Infusion).

2. Manufacturing Controls: See Chemistry review

3. Pharmacology:

a. A brief summary of pharmacodynamic action:

Several studies in normally growing rats and mice have reported that APD caused selective inhibition of osteoclast-mediated resorption of bone. However, long-term treatment with APD also resulted in gradually increased inhibition of bone apposition. At higher doses, APD caused direct inhibition of bone resorption, as well as bone apposition. In several experimental animal models characterized by

accelerated bone mass loss (e.g., C57 black/Silverberg strain of mice which develop osteoporosis in adulthood, rats with hyperparathyroidism induced by low calcium diet, paraplegic rats, and calcitriol treated rats and mice), APD has been reported to retard bone "wastage" and to promote development of "heavier and stronger" bones.

Experimental evidence of antiresorptive action of APD led to its evaluation in tumor-induced hypercalcemia (induced by injection of Walker carcinosarcoma 256 ascites cell, or injection of ascites cells directly into the iliac artery supplying the leg) in animals. The underlying osteolysis was presumed to be due to osteoclast stimulation by activating factors produced by the bone metastases. These studies reported reduced severity of osteolytic lesions, and decreased recruitment of osteoclasts cells as a result of APD treatment. APD was reported to have no effect on the growth of tumor in these studies. APD at a dose of 9.5 mg/kg (i.v.) for 5 consecutive days was reported to inhibit osteolysis completely. The drug given orally in diet to mice (5T2 MM) with multiple myeloma inhibited bone destruction. In one study, APD was reported to inhibit (in vitro) proliferation of Walker carcinoma culture cells. Another study reported inhibition of mammary carcinoma growth in rats induced by injection of N-methyl-N-nitrosourea. The mechanism of APD-induced inhibition of bone resorption was further tested in several in vitro bone cell culture systems. Furthermore, EM study indicated "prevention of osteoclastic bone excavation by concentration of APD exhibiting no visual evidence of cytotoxicity." The underlying biochemical basis of inhibition of osteoclast mediated bone resorption has not been fully elucidated. The drug has also been reported to inhibit bone resorption by the macrophages.

b. Summary of toxicological studies:

Acute toxicity:

Anim. Species	Route of Administr.	$LD_{50(mg/kg)}$
Mice	I.V.	20
	P.O.	680-1000
Rabbits	I.V.	270
	P.O.	820
Rats	I.V.	80*
	I.V.	57.6**
	P.O.	1560

* Median lethal dose (MLD) in either sex in one study.

** MLD in males of a separate study.

High-dose animals showed lethargy, prostration and variable weight loss.

Multidose Toxicity Studies:

Two-week study in mice at doses of 0.625, 2.5, and 10 mg/kg/day:

Reddening of tails with scabbing and blackening of the tips in all APD treated animals and in some controls. At 10 mg/kg/day dose, 3 of 5 animals (males) died, and the remaining 2 two had elevated SGOT values. In rats, reddening of the tail and severe local irritation developed at the tail injection (i.v.) site, at mid-and high-doses. Subcutaneous injection of APD (0.3, 1, or 3 mg/kg/day) to rats for one month resulted in reduction of food consumption, dose-related increase in spongy bone, and dose-related local irritation at the injection site. Rats given i.v. bolus injection of APD at doses of 5, 10, and 20 mg/kg once every 2 weeks for 3 mo followed by a 1-mo recovery period resulted in broken incisor tooth (in one rat at 10 mg dose), and in 8 of 30 rats at 20 mg dose; reduced body-weight gain and food consumption at 20 mg dose; increased RBC; increased BUN, creatinine, and SGOT values; decreased alk. phosphatase, acute and chronic renal tubular degeneration at all doses, decreased marrow cavity and compensatory increase in marrow cellularity, and thyroid, pituitary and lung changes.

Four-week dog study at doses 50-450 mg/kg/day (administered by gavage):

Gastric and renal toxicities at doses $\geq$ 150 mg/kg dose.

Oral dosing of APD at 12.5 to 50 mg/kg/day through 32 weeks in dogs:

Twelve animals were reported to be in moribund condition between weeks 4 and 25, which prompted discontinuation of treatment at week 32. These animals manifested abnormal biochemical, hematological, and other microscopic and macroscopic evidence of lungs, kidney, bone, and esophageal and gstric mucosal damage.

Beagle dogs treated with p.o. (in 0.1% solution) APD (2.5-25 mg/kg/day) for 6 or 12 months:
Abnormal bone histological changes were reported in almost all doses tested, at 6 or 12 months. Dogs at the 2.5 mg/kg/day were the least affected.

Intravenous bolus injection of APD at doses of 1, 3, and 6 mg/kg once weekly for three months: Animals at 6 mg/kg dose were followed by a recovery period after completion of treatment. The animals manifested reversible renal, pulmonary, and hepatic microscopic lesions associated with abnormal liver enzymes, increased cholesterol, and BUN in blood. These animals also developed "nonre-

versible" bone changes characterized by prominent osteoid seams and extension of metaphyseal primary spongiosa.

Six-month study in rats with APD (p.o.) in doses of 24, 72, and 216 mg/kg/day:

Animals at the mid- and high-dose groups showed "compound-related" decreased food consumption and body-weight gain, decreased erythrocytes, decreased serum alk. phosphatase, plasma sodium and urine calcium values. At necropsy, there were widening of femoral bone metaphyses, decreased bone medullary areas, and femoral bone marrow in majority of the APD-treated animals.

Carcinogenicity Studies:

Four of 55 high-dose (234 to 879 mg/kg/day in the diet for 80 weeks) female mice developed liver-cell tumors. The sponsor states that comparable numbers of this tumor type were also present in control animals (similar strains and age).

Rats were given APD in diet at doses of 62.5, 250, and 1000/mg/kg/day for 104 days. The incidence of the following neoplastic lesions was higher in high-dose animals: benign pheochromocytoma of the adrenal medulla, myeloproliferative disorder in the spleen, mammary gland carcinoma in females, and leiomyoma of the small intestine.

Specific Toxicological Studies:

Eye and skin tests in rabbits: Single topical application of APD (0.1 to 0.5 g) resulted in moderate irritation, and in some instances areas of necrosis.

I.V. and I.M. tolerability of APD: Local inflammatory signs at the site of injections (5 mg/5ml formulation).
Exposure of buccal mucous membrane to effervescent APD (150 mg) tablets for 30 min showed no signs of irritation.

Dermal sensitization test in Guinea-pigs showed no evidence of such effect due to the drug.

Mice were fed with APD in a dose range of 500 to 10,000 ppm. After 6-7 month, high-dose animals showed focal necrosis of bone marrow and liver cells upon histopathologic examination. These animals initially developed edema, anemia, thrombocytopenia, leukocytopenia and died within 2 months after onset of these adverse reactions. Animals fed with APD at 2000 ppm showed no drug-related effects. Rats given APD (s.c.) at doses of 0.6, 2.0, and 6.0 mg/kg/day for 6 weeks, showed increased "spongy bone" formation adjacent to epiphyseal seams, and a widening of tibial and femoral metaphyses.

On Reproduction:

Studies were performed in two species:

Rats: APD at a dose of 150 mg/kg caused adverse maternal F_0 effects. Also decreased the number of live births and pup survival. Fetal and pup development during pregnancy and lactation, respectively was reported to be normal. Fertility of F_1 rats derived from the high-dose parents was normal when they were mated with the members of the same group, normal when they were mated with untreated virgin rats. In either rats or rabbits, no drug-related embryo/fetal toxicity, or teratogenicity in segment II studies were reported. The compound was reported to be nonmutagenic in Ames test, and in Chinese hamster.

Absorption, Distribution, Metabolism, and Excretion of APD:

Experiments were performed with radiolabeled (^{14}C) APD.

Rats: Approx. 2% of an orally administered dose (in aqueous alk. solution) was absorbed in fasted animals. The drug was reported to be selectively taken up by the bone (in rats and dogs). It is released from the bone very slowly (half-life 60-300 days) with i.v. dose of 1 mg/kg. At higher i.v. dosing, dose-related retention in liver, spleen and cartilage occurs. Hepatic biotransformation is negligible, and almost totally eliminated through kidney. After oral administration in rats (20 mg/kg), almost 96% of the dose was reported to be excreted in feces unchanged in 24 hours. I.V. administration in rats resulted in about 18% of the dose excreted in urine within 4 days, and 2% in feces. For additional pharmacological information See Pharmacology review.

Pharmacokinetic profiles in humans:

Two open-label studies were performed:

(A) Twenty malignant patients at risk of developing hypercalcemia were randomly assigned to receive a single dose of APD 60 mg i.v. either over 4 (15 mg/hr) hours or 24 (2.5 mg/hour) hours. The urinary excretion rates were reported to be relatively constant from 4 hours to the end of 24 hours. The overall mean cumulative urinary excretion for all 20 patients was 51% of dose. The calculated half-lives after 4-hour infusion were 1.6 and 27 hours for alpha and beta phases, respectively. Sixty percent of patients in either treatment regimen experienced headache, fever, and phlebitis. The sponsor has concluded that i.v. infusion of APD over 4 or 24 hours showed no significant difference in the percent of a dose recovered from the urine. Thus, the rate of infusion did not influence the extent of retention of APD in the body.

(B) Thirteen Pagetic patients (mean age 71.2 years) were given one or more i.v. infusion of APD. The dose ranged from 30 to 180 mg, with infusion time between 1.6 and 8 hours. The majority of patients received infusion at a rate of 15 mg/hr. At 30 mg dose

level, 4 of 10 patients had complete urine collection over 12 hours, and the cumulative recovery of APD in their urine was reported to be 32% of the dose. A lower cumulative urinary recovery of APD was reported with doses of 120 and 180 mg. At 30 mg dose, a half-life of 2.5 hours was estimated by linear regression of the log urinary excretion versus midpoint time. The plasma APD was reported to reach a steady state during the second hour of infusion at 30 mg dose, and plasma level of APD promptly fell after completion of infusion. The renal and non-renal clearances of APD at this dose were estimated to be 69 (± 61) ml for renal clearance and 225 (± 31) ml non-renal clearance, respectively. Non-renal clearance was attributed to distribution to and binding by bone. The sponsor's conclusions regarding pharmacokinetic profile of APD in humans (cancer and Pagetic patients) are:

a. Rapid urinary excretion of approx. 50% of a dose of APD, and the remainder is retained in the body. For the rapidly eliminated fraction of APD, the mean urinary half-life is reported to be approx. 2.5 hours after infusion. Plasma APD levels are reported to decrease rapidly after cessation of infusion.

b. Urinary excretion of a dose of APD and its retention in the body is not influenced by the infusion rate (within 2.5 to 15 mg/hr).

c. Plasma APD reaches a steady state in most patients within 24 hours.

d. Postinfusion excretion of APD through kidney is biexponential.

4. Clinical Background:

a. Literature references (published reports in vols. 1.54 and 1.55 of this submission):

(1) Van Breukelen et al (1982): Efficacy of aminohydroxypropylidene bisphosphonate in hypercalcemia: Observations on regulation of serum calcium. Calcif. Tis. Intern. 34:321.

In this open-labeled study the effect of oral APD (300-1200 mg/day) on serum total calcium in 27 hypercalcemic (due to malignancy), and 20 normocalcemic patients (with Paget's disease of bone or osteoporosis) was studied over a period of 14 days. Of 27 hypercalcemic patients, 12 patients had osteolytic bone lesions (determined by Tc-EHDP-bone scintigraphy and conventional x-rays), 4 patients were without osteolytic lesions, 3 had myeloma, and 8 patients had primary hyperparathyroidism. Normocalcemic patients received APD therapy for Paget's disease or osteoporosis and were included in the data analysis in retrospect. The hypercalcemic patients received oral fluids or saline infusion until diuresis was 1.5

L/day (days -2 and -1). Saline infusion was discontinued during APD therapy, from Day 0 onward. During the first four days, the dose of APD was 17 mg/kg (average 1200 mg/day in 3 divided doses); from Day 5 the dose was reduced to 300 mg/day for the rest of treatment period. The normocalcemic patients received 600 mg daily in 3 divided doses.

The results in hypercalcemic patients were compared with those observed in pagetic and osteoporotic patients. All hypercalcemic (Day 0 mean serum calcium 3.19 $\pm$ 0.11 mmol/L) patients with osteolytic bone lesions showed normalization of serum calcium by Day 7 of treatment and remained normocalcemic on Day 14 (mean serum calcium 2.14 $\pm$ 0.05 mmol/L). All 4 patients with no osteolytic lesions showed some decrease in their serum calcium as a result of APD treatment, but only one patient had normalization of serum calcium. Two myeloma patients and 5 patients with primary hyperparathyroidism also showed normalization of serum calcium during APD therapy. Serum calcium started to decrease in most patients from Day 2. The mean serum calcium levels in pagetic and osteoporotic patients also showed some decrease as a result of APD therapy and were close to the lower normal limit (2.23 mmol/L). The serum protein levels in hypercalcemic patients were neither increased nor changed during the "observation period." Patients with tumors showed no change in their serum phosphate levels. Urinary excretion of calcium was reported to decrease in all patients during therapy. In tumor patients, urinary hydroxyproline excretion showed variable results (initial decrease in some patients, remained elevated in some patients, or increased in some patients). In some patients symptoms attributable to hypercalcemia were "relieved." Some patients experienced epigastric discomfort or nausea at the beginning of treatment; about one-third of patients had rise in body temperature (max. 2^0C) mostly on the second day of therapy, and lasted for about 48 hours.

The authors have discussed the mechanism of the inhibitory action of bisphosphonates on bone resorption. These agents may inhibit dissolution of hydroxyapatite crystals by a physicochemical process, alter the functions of osteoclasts, and/or affect the mononuclear phagocytes and the functional interactions between these cells and osteoclasts.
Comments: In this study, changes in the serum total calcium was evaluated without doing necessary correction for altered serum albumin. However, the overall results seem to provide some evidence of efficacy of oral APD in the treatment of hyperca-lcemia of malignancy, particularly in patients with established osteolytic lesions. The results in patients with no osteolytic lesions, myeloma patients, and in patients with primary hyperpara-thyroidism are equivocal.

(2) Mundy et al (1983): Comparative study of available medical therapy for hypercalcemia of malignancy Am. J.Med. 74: 421.

A randomized study to compare the relative efficacy of oral phosphate, mithramycin, glucocorticoids, indomethacin, EHDP, and APD in the treatment of hypercalcemia of malignancy. The study has a nonrandomized arm which involved 14 hypercalcemic patients. Five of these patients received glucocorticoids and 9 APD orally. Two additional patients with hypercalcemia due to primary hyperparathyroidism also received APD. Hypercalcemia was defined as a serum calcium (corrected for altered serum albumin) greater than 2.8 mmol/L (11.2 mg/dl). Patients with clinical evidence of dehydration or increased BUN were initially rehydrated with i.v. normal saline infusion until there was no clinical evidence of dehydration or normalization of BUN. Patients were admitted to the study, if at that point their corrected serum calcium levels were greater than 12 mg/dl, or had symptoms of hypercalcemia.

APD was administered orally at a dose of 16.8 mg/kg/day (in 3 divided doses) for 5 days followed by 4.2 mg/kg/day for additional five days. A total of eight patients (6 pt. with malignancy and 2 with hyperparathyroidism) completed full 10 days of APD therapy. Five of 6 patients with hypercalcemia due to malignancy (2 lung CA, 1 breast Ca, 1 pancreatic CA, 1 lymphocytic leukemia, in 1 pt. the site of CA unknown) had normalization of serum calcium as a result of APD therapy. Serum calcium levels started to decrease within 72 hours of treatment. One of these patients was reported to remain normocalcemic for about 4 weeks until death. The duration of normocalcemia was not stated for other 5 patients. Three of 6 patients were reported to have improvement of hypercalcemic symptoms (polyuria, polydipsia, mental confusion, or lethargy). One patient had recurrence of hypercalcemia after APD therapy, but responded well to oral phosphate therapy. One patient with unknown primary site of CA failed to respond to APD therapy (she had unsuccessful EHDP therapy for 14 days prior to APD treatment). Two patients with primary hyperparathyroidism also had normalization of serum calcium during the course of the treatment with APD. In patients with malignant disease, the urine hydroxyproline/creatinine ratio was reported to decrease following APD treatment; suggesting inhibition of bone resorption in these patients. One patient with malignant disease developed mouth ulcer during the course of treatment, which resolved when the drug was withdrawn. Another patient developed fever, which the author says could have been drug-related.

The results of the randomized study in which five other drugs were tested for their efficacy and safety in hypercalcemia, oral phosphate and mithramycin were reported to be most effective in lowering serum calcium levels, but "with serious

disadvantages with the use of each." Six of 11 patients who received oral phosphate therapy, 3 showed loss of effect despite continuation of therapy and in 3 patients treatment needed to be discontinued because of diarrhea. With mithramycin there was lack of predictability regarding the duration of its effect, and the effect was followed by a rapid rebound phenomenon of serum calcium. In fact one patient died due to acute hypercalcemic crisis after an earlier successful response to mithramycin.

Comments: Though a small study, the results seem to provide some evidence of efficacy of a ten-day oral APD treatment in the management of hypercalcemia of malignancy as well as due to primary hyperparathyroidism. All responsive patients became normocalcemic during the course of APD therapy. There was one malignant patient with primary CA site unknown failed to respond to APD; EHDP was also unsuccessful in this patient two weeks prior to APD therapy. Some patients also showed symptomatic improvements along with lowering of serum calcium levels.

(3) Sleeboom et al (1983): Comparison of intravenous (3-amino-hydroxypropylidene)-1,1-bisphosphonate and volume repletion in tumor-induced hypercalcemia. Lancet 2(8344): 239.

The effects of intravenous APD and volume repletion were studied in a group of patients with hyperca-lcemia due to malignancy. The authors claimed that all patients had histologically proven malignancy. However, two patients were subsequently reported to have unknown carcinoma. The majority of patients had breast carcinoma; five patients had hematologic malignancies (4 myeloma and one lymphoma); the remaining patients had malignancies of various organs or soft tissue.

In 19 patients APD was administered at a dose of 15 mg/day, i.v. in saline over 2 hours from the start of volume repletion for up to 10 days. The remaining 11 patients received APD 48 hours or more after beginning of the fluid repletion, and were given at least 3L of saline per day. The dose varied from 1.75-30 mg/day; therapy lasted from 3 to 10 days. Patients in this group received low-hydroxyproline diet, and the daily intake of calcium was less than 15 mmol. The results indicated that all patients but one became normocalcemic after APD therapy. The group of patients who had first volume repletion, showed decrease in urinary excretion of calcium. One patient in this group failed to respond to i.v. APD. Four of 10 patients had serum calcium below lower level of normal rang, but none manifested any symptoms of hypocalcemia. There was decrease in urinary excretion of hydroxyproline, but remained above normal levels in most patients. The follow up of treated patients showed recurrences of hypercalcemia in five patients, 1 to 16 months after the initial hypercalcemia. In some

patients recurrence of hypercalcemia was reported to respond to repeat course of APD.

Comments: This report provides some evidence of efficacy and safety of i.v. APD in the management of hypercalcemia of malignancy including few cases of hematological malignancy. The authors should have evaluated the change in corrected serum calcium levels as a result of APD therapy. However, all but one patient responded with normalization of elevated serum total calcium. The study does not provide information regarding the dose-effect relation. Data on the effect of volume repletion and APD on serum and urinary levels of phosphorus, serum creatinine, glomerular filtration rate, urinary hydroxyproline, and max. tubular phosphate reabsorption seem to suggest that hypocalcemic effect of APD was due to "reduced production of calcium from bone and not through an action on the kidney."

(4) Parsons et al (1983): Tumor-induced hypercalcemia treated with APD. Met. Bone Dis. Rel. Res. 4:363 (Abstract).

In an open-label study 7 patients with persistent hypercalcemia of malignancy after fluid, phosphate and corticosteroid therapy received APD 10 mg/kg orally for 5 days. In all but one patient elevated serum total calcium levels were reported to fall promptly after APD therapy. In 3 patients serum calcium levels decreased below the lower limit of normal and in one patient it reached to "tetanic levels." The patient who failed to respond to APD was with advanced myeloma. The authors have suggested that APD can cause prolonged inhibition of bone resorption in hypercalcemia of malignancy.

(5) Harinck et al (1984): Bisphosphonate (APD) treatment of hypercalcemia of malignancy. Calcif. Tissue Int. 36(suppl. 2): S28 (Abstract).

The results of an open multicenter trial of APD (i.v.) in the treatment of hypercalcemia of malignancy in 100 consecutive patients have been presented. Baseline serum total calcium ranged in these patients from 2.76 to 5.32 mmol/L. APD was administered intravenously at a dose of 15 mg/day (infusion period and the duration of treatment not stated). Ninety-four of 100 patients were reported to manifest lowering of serum calcium below 2.55 mmol/l within 10 days. The report claims that APD therapy improved renal function (normalized urinary excretion of calcium, renal tubular reabsorption of calcium and GFR).

(6) Body et al(1984): Treatment of cancer hypercalcemia with intravenous diphosphonate (APD). Cancer Immunol. Immunother. 18: S7 (Abstract).

An open study involving 20 consecutive hypercalcemic patients who received APD at a dose of 15 mg/day i.v. (over 2 hours) after initial hydration therapy for 24-48 hours. The mean serum calcium was 13.5±0.5 mg/dl after rehydration and prior to initiation of APD therapy. All 20 patients were reported to become normocalcemic within 1-4 days of treatment. Concurrent to lowering of elevated serum calcium, there was decrease in urinary calcium/creatinine, and hydroxyproline/creatinine ratios. Twelve patients who did not receive any anticancer chemotherapy, remained normocalcemic for 1 to 8 weeks (median 3 weeks). The serum phosphate level was reported to decrease (2.0±0.1 mg/dl) after the end of the treatment.

(7) Ralston et al (1986): Comparison of aminohydroxy-propylidene diphosphonate, mithramycin, and corticosteroid/calcitonin in treatment of cancer-associated hypercalcemia. Lancet October 26, p.907.

An open study in which 39 consecutive patients with cancer-related hypercalcemia (serum calcium above 2.8 mmol/L (adjusted for albumin) were enrolled. Some of these patients had symptoms attributable to hypercalcemia. Prior to APD therapy, all patients were rehydrated with intravenous normal saline (500 ml q 4 hours for a minimum of 48 hours), and then 500 ml q 6 hours for 12 hours. Patients were randomly assigned to three treatment groups. During APD therapy saline i.v. was continued (2 L/day) until serum adjusted calcium had decreased below 2.8 mmol/L, and/or patients clinically judged adequately hydrated and liberal fluid intake (2 L/day) was established. APD (15 mg in 250 ml of saline) was administered as i.v. infusion daily until serum calcium was normalized (2.6 mmol/L), or a nadir was reached. Mithramycin (25 mcg/kg in 500 ml of dextrose) was administered by the same route and repeated after 2 days if serum calcium remained above 2.9 mmol/L. Corticosteroid (prednisone) was administered orally at a dose of 40 mg/day in divided doses and salmon calcitonin 400 IU (s.c.) q 8 hours throughout 9 days of the study period. Serum calcium, creatinine, and other electrolytes, urinary calcium excretion "expressed as a molar ratio" relative to creatinine excretion and as Ca_E, derived from the molar ratio multiplied by the serum creatinine concentration (μmol/L glomerular filtrate), urinary hydroxyproline were determined periodically during the course of the treatment. Patients were periodically interviewed for side effects of treatment.

The lung and breast cancers formed the largest (65%) group of patients in the whole study. The remainder patients had various other solid tumors, and one patient had myeloma. Six patients in the APD group and 4 each in other two treatment groups had no evidence of bony metastases based on bone scan and x-rays. One patient in each group received radiation for bone metastasis, one patient in the APD group received stilboestrol,

and one each in the other two groups received tamoxifen. Two patients in the APD group had surgical resection of the primary tumor on Day 7. Biochemical data of these patients were excluded from the efficacy analysis at Day 9. Two patients in the APD group and one each in other two groups "died of complications of tumour" on Days 1 through 7. Two patients of the prednisone/ calcitonin group were withdrawn from the study because of deterioration of their clinical condition and they were successfully treated with mithramycin. One patient in the mithramycin group died due to hypercalcemia despite repeated mithramycin and saline therapy.

The results showed fall in serum calcium during hydration in most patients, but in some patients hypercalcemia "grew worse." A median 0.35 mmol/L fall in serum calcium was reported to occur in 24 hours in the corticosteroid/ calcitonin group, 48 hours in the mithramycin group, and 72 hours in the APD group. Both in the mithramycin and APD groups, the "significant" fall in serum calcium was reported to be sustained (up to Day 9). In the APD group there was progressive fall in urinary calcium and hydroxyproline excretion from Day 1-2. Corticosteroid group showed no significant fall in urinary calcium excretion, but showed a transient fall in hydroxyproline on Day 1. Serum creatinine levels were reported to decrease during rehydration and further decrease during cort./calcitonin therapy. In the remaining two treatment groups, initial fall in serum calcium due to rehydration was attributed to a decrease in renal tubular reabsorption. Subsequent fall in the APD group was reported to be due to decrease in bone resorption. Higher percentages of "specific" symptoms of hypercalcemia were reported to improve in the APD group compared to other two treatment groups. Side effects of APD included transient pyrexia in 4 and thrombophlebitis in two patients. Two patients in the mithramycin group developed nausea, vomiting and malaise; thrombocytopenia in one, and increase in SGOT, SGPT, and gamma glutamyl transpeptidase in 11 patients. The median survival time in the whole study group was reported to be 39 days (range 3-420 days), and it did not differ due to the type of treatment regimen. A total of six patients were reported to survive more than six months; 3 in the APD, 2 in the mithramycin and 1 in the steroid groups. The common factor in these patients which was probably responsible for longer survival was additional anticancer therapy resulting in remission of primary malignancy.

The authors have suggested that all three treatment regimens tested in this study produced significant fall in elevated serum calcium levels in patients with malignancy compared to the fall achieved by hydration alone. Although steroid/ calcitonin combination caused rapid decrease, they seldom caused normalization of serum calcium. The onset of action with APD was slow, but it caused a "progressive and consistent

control of hypercalcemia later." About 50% of patients, who received APD therapy remained mildly hypercalcemic throughout the study, despite almost total inhibition of bone resorption (reflected by normal calcium/creatinine ratios) in all patients by Day 9. This seems to indicate that in hypercalcemia due to malignancy, increased renal tubular resorption of calcium (not affected by APD therapy) probably plays a moderate role in the pathogenesis of hypercalcemia. Soft tissue catabolism rather than bone resorption probably contributed to persistent increase in the urinary excretion of hydroxyproline during APD treatment. Some of the lowest posttreatment serum calcium levels were caused by the mithramycin treatment, but about 50% of the patients treated with this agent experienced recurrence of hypercalcemia by Day 9. The very low survival rate reflects the poor prognosis of patients with cancer-related hypercalcemia.

Comments: This study is well designed and carried out reasonably well. The study population was appropriate. Serum calcium was adjusted for albumin. The dose and duration of APD treatment were different from that used in the Ciba-Geigy-sponsored studies. The study endpoints were appropriate for the evaluation of efficacy as well as for studying the probable mechanism of action of APD. The results provided good supportive evidence of efficacy and safety of the drug in the treatment hypercalcemia of malignancy (particularly associated with lung or breast cancers). The study involved only one case of hypercalcemia associated with hematologic malignancy.

(8) Cantwell and Harris (198[illegible]): Single high dose aminohydroxypropylidene diphosphonate infusions to treat cancer-related hypercalcemia (Letter). Lancet (Jan 18); 1: 165.

An open study involving 10 patients with hypercalcemia due to malignancy (3 females with breast cancer, and 7 males; 3 patients had no bony metastasis, and 7 with bone metastases). All patients received APD 30 mg in 500 ml of saline, i.v. over 2 hours. Five of 10 patients received hydration (3-4 L/day) and three of these also received corticosteroids. Eight of 10 patients were reported to become normocalcemic. Normocalcemia was achieved within 3 days from the initiation of therapy. In the remaining two patients, there was reduction in elevated serum calcium. One patient had recurrence of hypercalcemia at Day 13, and responded to a second infusion of APD. In three patient initial normocalcemic response to APD lasted for more than 5 weeks. Few patients had elevated blood urea and creatinine levels prior to APD therapy. Of these patients, only two showed persistent elevation of blood urea and creatinine. Some patients with hypercalcemia-related symptoms showed symptomatic improvements. Three patients developed transient fever within 1 day of treatment.

(9) Thiebaud et al (1986): Oral versus intravenous AHP_2BP (APD) in the treatment of hypercalcemia of malignancy. Bone 7:247.

An open study involving 20 patients with hypercalcemia (ranging from 2.8 to 5 mmol/L) associated with histologically confirmed malignancy (8 pt. with breast cancer, 6 with lung or upper airway cancer, and 1 each of the following cancer: hypernephroma, multiple myeloma, lymphoma, adenocarcinoma of lung, parotid gland, and colon). Nineteen of twenty patients had bone metastases (4-9 sites at scan), and the patient with lymphoma had bone marrow involvement. All patients received hydration (3 L/day of 0.3% NaCL plus 3.3% glucose for 2 days prior to APD therapy. Then, patients were randomly assigned (with 3 exceptions) to receive either APD i.v. (30 mg in 500 ml saline over 6 hours), or orally (1200 mg/day in three divided doses) for 6 days. From Day 7, all patients received oral APD, 200 mg/day. Three patients were alloted to receive i.v. APD because of their diminished level of consciousness. Except for the patient with multiple myeloma, none received any concomitant medication for two weeks before and after hydration. The patient with multiple myeloma received chemotherapy on Day 5 (after normalization of serum calcium by APD). Corrected plasma calcium was used for all calcium measurements.

Corrected Ca= $\frac{\text{Calcium measured}}{0.60+[\text{protein (g/l)} \times 0.005531]}$

Renal threshold for phosphate (TmP/GFR) was derived theoretically, and serum iPTH was measured.

The results showed normalization of corrected plasma calcium in both treatment groups (n=19). In the i.v. group, the mean plasma calcium decreased from 3.42 $\pm$ 0.13 to 2.40 $\pm$ 0.10, and the oral group from 3.28 $\pm$ 0.12 to 2.30 $\pm$ 0.08 mmol/L on Day 6 (except for two patients) of the treatment. One patient who had baseline corrected serum calcium > 5 mmol/L was evaluated separately, the result showed similar pattern of response as in the majority of patients. A total of 5 patients from both groups experienced mild hypocalcemia (asymptomatic) between Day 6 and Day 12. Plasma phosphate was reported to decrease significantly in both groups by Day 6, and then returned to normal by Day 14. Plasma PTH levels increased in both treatment groups as a result of APD treatment. Twenty-four-hour and 2-hour fasting urinary excretion of calcium decreased rapidly in both treatment groups by Day 9. Twenty-four-hour urinary excretion of phosphate also decreased in both groups. The baseline TmP/GFR was slightly below normal in both groups because of low values in about 50% of patients in each group. It further decreased significantly in both groups at Day 6. A negative correlation between plasma PTH and TmP/GFR was

reported. Symptoms of hypercalcemia, e.g., nausea, constipation, muscle weakness, and drowsiness were reported to be improved as a result of APD therapy. The side effects of APD reported in this study included transient elevation of body temperature (to a max. of 38°C) on the second day of treatment in 3 patients. The rise in body temperature lasted for about 48 hours, and then returned to normal despite continuation of APD therapy. Three patients on oral APD were reported to experience nausea and epigastric discomfort. There was one patient in this study who received oral APD, and became normocalcemic by Day 7. Four months latter she developed vertebral fracture secondary to metastases. She stopped taking APD for 2 1/2 months preceding this episode. Oral administration of APD (1200 mg/day in 3 divided doses for 6 days) for the second time resulted in normalization of serum calcium. About 3 months after she again developed hypercalcemia, and APD was administered orally (at the previous dosage) for the third time. Her plasma calcium became normalized again. The authors have concluded that APD both orally and intravenously is effective and safe for the treatment of hypercalcemia of malignancy.

Comments: The study does provide supportive evidence of efficacy and safety of the product either given orally or intravenously in the treatment of hypercalcemia of malignancy. The study was reasonably well designed to achieve the stated objectives. There are differences in the dosage and the duration of therapy between this study and the Ciba-Geigy sponsored clinical studies. Oral APD appears to be as effective intravenous route in controlling hypercalcemia. Therapeutic benefits seem to outweigh the minor side effects of oral administration of the drug.

(10) Ralston et al (1986): Treatment of cancer associated hypercalcemia with combined aminohydroxypropylidene diphosphonate and calcitonin. Br. Med. J. 292: 1549.

Eight patients with hypercalcemia due to various types of malignant tumors were treated with combined APD (15 mg/day i.v.) and calcimar (100 IU q 8 hours s.c.) for 6 consecutive days. All patients were rehydrated with i.v. saline for at least 48 hours prior to administration of APD and calcitonin. During the course of the treatment they also received 2 L of saline i.v. infusion. Changes in serum calcium (adjusted for albumin levels), fasting urinary calcium to creatinine and urinary hydroxyproline to creatinine ratios to combined treatment regimen were evaluated.

Both serum calcium and fasting urinary calcium to creatinine ratio were reported to decrease significantly between Days 1 and 12; the mean serum calcium (adjusted) normalized by Day 3 of the treatment and remained within the normal range until

Day 12 of follow up. The changes in other parameters to therapy are:

	Baseline	Day 1	Day 12
UOHP/Ca (mmol/L)	63±9.1	38±9.1	42±8.3
Serum Creat. (mg/dl)	1.7±0.3	1.2±0.2	1.1+0.2

The decrease in filtered calcium load was reported due mainly to decrease bone resorption, and partly to improved GFR. All eight patients were reported to experience symptomatic improvement during therapy, and there were no side effects to treatment regimen. Authors have suggested that combined therapy was more rapidly acting compared to APD as reported in other studies.

(11) Thiebaud et al (1986): A single-day treatment of tumor-induced hypercalcemia by intravenous amino-hydroxypropylidene bisphosphonate. J. Bone Min. Res. 1: 555.

An open study in which 20 patients with hypercalcemia due to malignancy, and skeletal metastases received initially a 2-day period of rehydration with glucose/saline (3L/day). Thereafter, patients were sequentially assigned to one of the two treatment groups :(a) a single dose of APD, 60 mg infused i.v. over 24 hours in 1000 ml of saline (n=10), or (b) same number of patients to receive 30 mg of APD by the same infusion method as in group (a). A total of 3 patient had hematologic malignancy (myeloma). Blood samples (for calcium, phosphorus, creatinine, iPTH, magnesium, protein, and alk. phosphatase) were collected daily from 0 to 6 days, on Days 9, and 14, and thereafter, on a weekly basis. The 2-hour urine samples were collected on Days 0, 4,6,9, and 14 for calcium, phosphorus, creatinine, and hydroxyproline. The total calcium was adjusted for serum protein according to the following formula:

$$\text{Ca corrected} = \frac{\text{Calcium measured}}{0.60 + [\text{protein (g/liter)} \times 0.00553]}$$

The results showed decrease in mean plasma calcium in both groups; normalization occurred on Day 4 in group (a), and on Day 5 in group (b) with a nadir on Day 6 in both groups. The nadirs of 2.24 ±0.06 in group (a) and 2.49 ± 0.10 mmol/L in group (b), respectively. The plasma calcium was significantly lower in group (a) compared to group (b) on Days 5,6,9, and 14. In the former group, patients remained normocalcemic through Day 14. Three patients developed asymptomatic hypocalcemia in this group. In 3 patients of Gr (b) plasma calcium never reached the normal level, and in all

patients after the maximum lowering effect, plasma calcium started to rise again. After 2 weeks, 50% of patients were reported to be hypercalcemic again. The mean daily decrease in plasma calcium was -0.24 mmol/L in group (a) and -0.15 mmol/L in group (b). There was a positive correlation between the initial plasma calcium level and the number of days required to achieve the nadir of plasma calcium. Plasma phosphorus also showed decrease in both groups from days 4 to 9. Plasma creatinine decreased in both groups. Plasma PTH increased in both groups. Urinary calcium excretion decreased in both group as a result of APD therapy. It started to increase again in group (b) from days 9 through 14, but remained low in group (a). Urinary OHP also showed decrease in both groups; from days 0 to 9 in group (a) and from days 0 to 6 in group (b). TmP/GFR decrease in both groups at Day 4, and remained low through Day 9. Except for mild rise in body temperature, no other side effects of APD were reported in this study. Symptoms attributable to hypercalcemia, such as nausea, constipation, muscle weakness, or drowsiness were reported to be relived by the APD treatment. One patient was followed for a longer period of time (6 months) because of neurological problems following vertebral fracture. She had recurrence of hypercalcemia 2 1/2 months after the first dose of APD, and received a second infusion of APD (60 mg) to which she responded with normalization of plasma calcium. After about 50 days she again showed progressive hypercalcemia. This time she was reported to respond to APD orally (the dose and duration not mentioned). None of the patients in group (a) was reported to relapse within two months after initial APD treatment.

Comments: APD, 60 mg given as a single infusion over 24 hours appears to be as effective in normalizing the elevated plasma calcium (within 5 days after treatment) as 30 mg/day for 6 days, as reported in a previous study. The compound's high affinity for the bone, its rapid accumulation in the skeletal system, and slow elimination from the body contributed to its efficacy as a single infusion. Single-day infusion seems to reduce the risk of developing thrombophlebitis and/or infection, and duration of hospitalization. The study seems to provide some preliminary data on the repeat administration of APD for the treatment of relapse of hypercalcemia.

(12) Body et al (1986): Treatment malignancy-associated hypercalcemia with aminohydroxypropylidene diphosphonate. J. Clin. Oncology 4(8): 1177.

This open study recruited 26 consecutive patients with hypercalcemia due to histologically proven malignant tumor: head and neck (8 pt.), breast (7 pt.), lung (3 pt.), and miscellaneous (6 pt.). One patient had myeloma. Twenty of 26 patients had bone metastases (confirmed by scintigraphy and

skeletal radiography). In six patients, the evidence for bone metastases was inconclusive. Two patients were excluded from the evaluation for major protocol violations: one patient declined treatment after two days of APD, and the other patient died of aspiration pneumonia early during treatment. Prior to APD therapy, the mean total serum calcium was 13.3± 0.4 mg/dl. Twenty of 24 patients were rehydrated for 24-48 hours prior to i.v. APD therapy. Sixteen patients received 1.5 to 3 L of saline over 24 hours. In four patients APD and rehydration were started simultaneously because of severe condition of patients. APD was administered at a dose of 15 mg in 500 ml of saline i.v. infusion over 2 hours daily. Therapy continued until normalization of serum calcium was achieved. Twenty-four patients were reported to receive at least 4 doses; 20 patients 5 doses and 15 patients received 6 to 9 doses. Patients were not given any anticancer drug until normalization of serum calcium. Blood chemistries including total and ionic serum calcium, iPTH, osteocalcin, urinary (morning 2-hour fasting) calcium and hydroxyproline were determined at designated intervals. Calciuria was expressed as mg/100 ml of glomerular filtrate; hydroxyprolinuria was expressed as mg x 100/mg of urinary creatinine, and urinary phosphate as the renal threshold of phosphate concentration, TmP/GFR.

The reports indicated that rehydration caused variable and generally little effect on elevated serum calcium. Serum calcium was normalized (from baseline 13.3± 0.4 mg/dl to 8.0± 0.1 mg/dl after treatment) after a median of 3 days (range 1 to 6 days). Serum ionic calcium showed parallel decrease. In some patients treatment was continued for 48 hours after normalization of serum calcium. The pattern of decrease in serum calcium in patients with bone metastases was similar to that seen in patients with doubtful bone metastasis. Serum calcium remained within normal limit for a median of 3+ weeks (range 1 to 8+ weeks). Urinary calcium and hydroxyproline excretions were reported to decrease also with fall in serum calcium. Though urinary calcium excretion remained within the normal limit during posttreatment follow up period, hydroxyproline excretion after initial fall started to rise again after about 4 days and always remained above the upper limit of normal range. Except for a decrease in serum phosphate, no other side effects of APD were reported in this study. Renal threshold for phosphorus TmP/GFR, and serum alk. phosphatase showed no significant changes to APD therapy. Serum osteocalcin measure in about half of the patients showed a significant decrease from baseline after APD treatment. Serum iPTH increased with the fall of serum calcium levels, but remained within the normal range.

Comments: The results of this study seems to confirm the findings of similar studies reported in the literature.

(13) Cantwell and Harris (1987): Effect of single high dose of aminohydroxypropylidene diphosphonate on hypercalcemia caused by cancer. Br. Med. J. 294: 469.

Sixteen patients (5 women with breast cancer and 11 males with various other types of cancer) were in included in this study. All but three patients had scintigraphic and radiologic evidence of bone metastases. Two of 16 patients received hydration, furosemide, and corticosteroid or calcitonin prior to APD therapy, but remained hypercalcemic despite treatment. All 16 patients received APD, 30 mg in 500 ml of saline i.v. over 2 hours. Nine of these patients in addition, received i.v. saline 3+ liters/day; four of these patients also received corticosteroid in addition. One patient was treated with APD plus corticosteroid. Serum calcium levels were corrected for serum albumin concentration.

The overall results indicated normalization of elevated serum calcium in 13 of 16 patients. Of these 13 patients, 3 patients received concomitant rehydration and corticosteroid; 4 patients received only APD; 5 received APD plus rehydration, but no steroid; and one patient received corticosteroid plus APD, but no rehydration. Three patients who failed to achieve normocalcemia, the minimum serum calcium after APD therapy was just above the upper limit of normal (2.75 mmol/L). Normocalcemia was reported to occur between Day 1 and 9 after APD therapy. Two patients (13%) were reported to achieve normocalcemia or minimum serum calcium by Day 1. Four patients achieved the same within 3 days after treatment, and about 50% of treated patients showed normocalcemia or minimum calcium by Day 4. Recurrent hypercalcemia was reported to occur in 5 patients at 10, 11, 13, and 69 days. These 5 patients were retreated with 30 mg of APD which led to decrease (0.29-1.03 mmol/L) in serum calcium, but only one patient achieved normocalcemia. Patients with symptoms of hypercalcemia also showed symptomatic improvements. Several patients were reported to have elevated serum urea levels (some with concomitant increase in serum creatinine levels. These parameters were reported to normalize or remained marginally above normal after APD treatment. Two patients showed asymptomatic hypocalcemia, and 3 patients developed transient fever.

The authors have claimed that a single APD (30 mg) i.v. infusion over 2 hours is effective in the management of hypercalcemia of malignancy (irrespective of the tissue involved); with or without concomitant rehydration and/or corticosteroid. It has been suggested that i.v. APD alone may be suitable for ambulatory patients with mild to moderate degree of asymptomatic hypercalcemia. Comments: There was no big difference in the baseline serum calcium levels among patients who responded to APD therapy. Patients with mild to

moderate hypercalcemia should be treated with hydration first rather than APD.

(14) Stevens (1987): Efficacy of aminohydroxypropylidene diphosphonate in malignancy-associated hypercalcemia. Med. J. Austrl. 146: 261.

This is a case report involving two patients with hypercalcemia (adjusted serum calcium 3.31 and 3.16 mmol/L) due to malignancy (one had sq. cell lung cancer and the other had adenocarcinoma of breast). Both patients had scintigraphic evidence of bone metastases and 1-to 2-week symptoms of mild confusion, nausea, anorexia and polyuria. Prior to APD therapy, both received rehydration with i.v. saline 1L q 12 hours until patients' oral fluid intake was considered adequate. APD was administered at a dose of 15 mg in 225 ml of saline intravenously over 2 hours; repeated every day for 4-5 days. Changes in adjusted (for serum albumin) serum calcium, improvements in clinical status, and changes urinary excretion of calcium and hydroxyproline were evaluated for efficacy and elucidation of mechanism of action of APD. Both patients achieved normocalcemia by Day 5 of the treatment. Urinary excretion of calcium and hydroxyproline was reported to decrease also during the same period and nadir of calcium reached on Day 9. Normocalcemia was reported to persist for about 3 weeks after treatment (patients died between days 21 and 24 after treatment). Both patients showed marked depression of differential and absolute lymphocyte counts after therapy (pretreatment values were also depressed). One patient also developed transient fever (on Day 2), and thrombophlebitis at the infusion site. Both patients were reported to experience improvements in clinical symptoms of hypercalcemia. Relief of bone pain occurred in one patient concomitant with the lowering of serum calcium level. The results are similar to findings reported in other studies in the literature.

(15) Body et al (1987): Dose/response study of aminohydroxypropylidene bisphosphonate in tumor-associated hypercalcemia. Am. J. Med. 82: 957.

A dose ranging study was carried out in patients with hypercalcemia of malignancy not responding to hydration for at least 48 hours (50 ml/kg/day; two-thirds given as i.v. infusion). Three different patients were treated consecutively at each of the following doses of APD: 0.01, 0.05, 0.25, 0.75, 1.5,and 3.0 mg/kg/day for three days. If on Day 3, the serum calcium level was higher than at the start of treatment, then the immediate higher dose of APD was given to the patient. Patients were retreated with APD, if the serum calcium was not normalized, or achieved a less than 10% decrease. During the 3-day APD treatment period, the fluid intake of the patient was maintained at 25 ml/kg/day.

A second set of 7 hypercalcemic patients (without previous rehydration) were treated with APD to generate additional data on the safety of i.v. APD. Biochemical and clinical parameters were evaluated for efficacy.

Of twenty-eight patients of the dose-ranging study, 5 patients were reported to be normocalcemic after rehydration. Three additional patients were evaluated separately; 2 with persistent renal insufficiency, and in another patient the dose was decreased after the first dose for side effect. Two patients were excluded from the evaluation, one patient died early due to cancer related cause, and one patient had major protocol violation. At 0.1mg/kg dose, only one of three patients became normocalcemic after therapy; two other patients required higher doses (0.05 and 0.25 mg/kg). Two of three patients initially treated with APD at a dose of 0.05 mg/kg became normocalcemic, but one had recurrence on Day 5, and required a second dose. All three patient treated with 0.25 mg/kg dose, became normocalcemic. However, two of three patients required repeat treatment (one on Day 6, and the other 4 weeks later). At doses 0.75 and 1.5 mg/kg, all patients at each dose level responded well, one patient in each group was reported to have recurrence between 10 days and 4 weeks after the treatment. Similar patter of response to APD at 3.0 mg/kg dose was noted in a group of three patients; one patient required retreatment on Day 5 because of recurrence. A trend of inverse relationship between the day on which normocalcemia was achieved and the duration of normocalcemia was reported, but it was not statistically significant. The urinary excretion of calcium also decreased consistently at the four higher doses of APD. The changes in urinary excretion of hydroxyproline were reported to be variable and "poorly" related to APD doses. Serum phosphate also decreased after treatment, but was not dose-related. Patients with symptoms of hypercalcemia were reported to experience improvement after correction of elevated serum calcium with APD therapy. Two patients at the dose of 0.25 mg/kg, developed transient fever; one patient at 3.0 mg/kg dose developed hypotension and transient dysgeusia about 6 hours after the first dose. One patient was reported to develop thrombocytopenia after treatment at the dose of 0.75 mg/kg, this patient had DIC related to cancer progression. Worsening of preexisting thrombocy-topenia was also reported in one patient at 1.5 mg/kg dose level. Five patients were reported to develop 25% or more decrease in lymphocyte counts, which lasted for at least two days. There were two patients with persistent renal insufficiency after adequate rehydration, but showed no "toxic effects" of APD (at 0.05 and 0.75 mg/kg doses).

Seven dehydrated patients who were treated with APD at a dose of 1 mg/kg/day for three days, also achieved normocalcemia and normocalciuria. The pattern of response was similar to those

of comparable doses of APD in rehydrated patients. Two patients in this group were reported to develop transient fever, and one patient had transient lymphocytopenia.

The authors have concluded that APD at a daily dose of 0.05 mg/kg or less has insufficient efficacy, and dosages more than 0.25 to 1.5 mg/kg are not needed to obtain adequate therapeutic response. It has been suggested that measurement of fasting urinary calcium is a valuable biochemical measure of therapeutic efficacy of antiresorptive agent such as APD. The patient who experienced high fever and hypotension, received a relatively very high dose of APD (total dose of 285 mg over two hours).

Comments: The results of this dose-ranging study indicate that APD is probably effective and safe in a dose range of 0.5 to 1.5 mg/kg/day (30 to 90 mg/day for a 60 kg adult person). This is in agreement with other reports. Though the report indicated that APD was effective in lowering elevated serum calcium in dehydrated patients without rehydration, rehydration is almost mandatory (in absence of a specific contraindication) prior to initiation of treatment of hypercalcemia with any drug, e.g., etidronate disodium, calcitonin, or gallium nitrate). APD appears to elicit adequate therapeutic response in the treatment of recurrence of hypercalcemia. Data are inadequate regarding its efficacy in patients with impaired renal function.

(16) Harnick et al (1987): Role of bone and kidney in tumor-induced hypercalcemia and its treatment with bisphosphonate and sodium chloride. Am. J. Med 82: 1133.

A total of 132 patients with hypercalcemia of malignancy were involved in this multicenter study. Patients were admitted to this study with a mean uncorrected serum calcium of 3.51 ± 0.04 mmol/L (range 3.33 to 3.68 mmol/L). Ninety-six of 132 patients had bone metastases determined radiographically and/or scintigraphy. Ten patients had multiple myeloma, 50 patients had breast cancer, 25 patients had lung cancer, ten patients with head and neck cancer, ten patients with kidney cancer, and 27 patients had other types of cancer.

APD was administered at a dose of 15 mg in 500 ml of normal saline, i.v. infusion over 2 hours daily until one day after normalization of serum calcium, but no more than 10 days. Additional i.v. saline administration was left to the judgement of the treating physician. Data on the effect of saline infusion on urinary excretion of calcium and sodium were available in a total of 77 patients. Of these 77 patients, 25 patients received at least 1 liter of saline per day for more than 48 hours, 18 patient received no additional saline infusion during the course of the study, and 34 patients

received at least 1 liter/day of saline concomitantly with the start of APD therapy. The following measurements were evaluated for the efficacy and safety of APD therapy: serum calcium corrected for serum albumin, serum and urine sodium, phosphate, creatinine. Urinary excretion of calcium was expressed as the molar ratio to creatinine or as the ratio to GFR.

The APD therapy resulted in normalization of serum calcium in most tumor patients (posttreatment mean serum calcium was 2.39 $\pm$ 0.02 mmol/L). The median time to normalization was reported to be between 4 and 5 days. About 10% of patients despite achieving normalization of urinary excretion of calcium, remained slightly hypercalcemic. Serum phosphate level also decreased after APD therapy, and it was attributed to improvement in GFR as well as less resorption from skeletal system. Normalization of serum calcium was associated with decrease in urine calcium and improvement in GFR. The report has discussed the renal handling of calcium and sodium in hypercalcemia of malignancy and the effects of hydration. This issue does not appear to be relevant to efficacy and safety per se of APD therapy.

Comments: The results seem to agree with the findings of other reports regarding the probable efficacy of APD in the management of hypercalcemia of malignancy. This report contains 10 myeloma cases, and in all ten cases elevated serum calcium became normalized after treatment with APD. The dosage schedule of APD was similar to those of other reports.

(17) Yates et al (1987): A comparison of single and multiple intravenous infusions of 3-amino-1-hydroxypropylidene -1,1-bisphosphonate (APD) in the treatment of hypercalcemia of malignancy. Aust. NZ J. Med. 17(4): 387.

In this open-label study 27 patients with hypercalcemia of malignancy received multiple daily doses of APD (n=11) or single infusion of APD (n=16). All patients received i.v. saline (> 3L/day) for at least 24 hours prior to APD therapy. A little over 50% of patients in either treatment group had bone metastases. APD was administered as slow i.v. infusion in normal saline over 30 to 180 minutes. Under multiple-dose schedule the dose of APD was 15 to 25 mg/day, and under single-dose infusion, the dose of APD was 15 to 30 mg. Twenty-seven patients received 32 "courses" of APD. Serum calcium values were adjusted to albumin concentrations by adding 0.02 mmol/L for each g/L of serum albumin below 42g/L. Patients in the multiple-dose schedule received 2 to 6 infusions and were followed up for 10 days following the start of treatment. Serum calcium was reported to show no major change with 24-hr i.v. infusion of saline. Serum calcium was reported to decrease progressively over 5 to 7 days in two studies. The mean corrected serum calcium fell within the reference range (2.56

mmol/L for the multiple dose study and 2.62 mmol/L for the single infusion study). Seven of 12 multiple-dose (63.6%), and 14 of 20 single-dose (87.5%) treatments were reported have normalization of elevated serum calcium. A total of five patients (one in the multiple-dose group and 4 in the single-dose group) were retreated for the second time after recurrence of hypercalcemia. Following retreatment serum calcium decreased, but remain above the upper limit of the reference range. The study showed no significant dose-response relationship, and there was no difference in response between patients with bone metastases and those without them. The duration of hypocalcemic response was not clearly determined because of incomplete follow up of patients after Day 10. However, on day 14, the mean serum calcium in the single-dose group was slightly lower than the multiple-dose group. Two patients (one in each treatment group) were reported to experience "grand mal convulsions" at days 3 and 4 respectively, from the start of the treatment. One of two patients was later on found to have cerebral metastases on brain scan, and in the other the cause and effect relationship could not be determined. Another patient developed paresthesia and symptoms of mild tetany at day 10 (serum calcium 2.05 mmol/L), and treated with i.v. calcium. Seven treatment courses were reported to be associated with the development of mild fever.

Comments: In general, this report confirms the ability of APD to lower the elevated levels of serum calcium in patients with various types of malignancies as reported by others. However, this study differs from other studies in several aspects, the data showed no dose response (in terms of fall in serum calcium, or the minimum serum calcium level achieved after treatment), and the hypocalcemic response in repeat treatments was not the same as the initial response (normalization of calcium in most cases). The side effects of APD reported in this study are similar to those observed in other studies.

(17) Coleman and Ruben (1987): 3(amino-1,1-hydroxypropylidene) bisphosphonate (APD) for hypercalcemia of breast cancer. Br. J. cancer 56: 465.

In this open study, 25 hypercalcemic patients (serum calcium adjusted for albumin > 2.7 mmol/L) with advanced breast cancer were studied. Twenty-one of 25 patients had extensive lytic bone metastases and 4 had minimal or no bone involvement (< 5 lesions on scintigraphy and plain radiography). All patients received rehydration with at least 3L of normal saline i.v. for 48 hours prior to APD therapy. Twenty-two patients were treated with APD at a dose of 15 mg in 500 ml of saline i.v. infusion over 2 hours. One patient received APD at a dose of 5 mg, and i v. fluid every alternate days until for a cumulative dose of 120 mg. Two patients

responded to rehydration alone. Serum calcium, urea and electrolytes, creatinine, albumin, phosphate, alk. phosphatase, urinary calcium excretion, Ca_E, TmP/GFR, and hydroxyproline excretion were determined at designated intervals.

The results are summarized in the table below:

	No. of Pt.
Total	25
Responded to rehydration	2
Pt. achieved normocalcemia	18 (81.8%)
Patients resistant to APD	4

Normocalcemic dose of APD:

5 mg	1
15 mg	14
2 X 15 mg	3

Normocalcemia was reported to occur over 48-96 hours. Patients resistant to APD therapy received the cumulative dose of the drug, 30-120 mg. Three of four patients were also resistant to mithramycin. Urinary calcium excretion expressed as molar ratio to creatinine and Ca_E (molar ratio times serum creatinine) were reported to increase during rehydration and then decreased toward normal as bone resorption was depressed by APD in responders. Hydroxyproline excretion was reported to remain high in responders during APD therapy. Serum phosphorus, and magnesium were reported to decrease in responding patients. All patients with symptoms attributable to hypercalcemia were reported to improve symptoms score up to Day 14 of follow up. The side effects of APD reported in this study included transient fever in two patients. In eight patients the duration of normocalcemia was determined; median duration was 11 days (range 7-17 days).

Comments: This study seems to confirm the findings of other studies reviewed so far regarding the efficacy and safety of APD in the management of hypercalcemia of malignancy. At the dose of 15 mg (single i.v. infusion over a period of 2 hours) caused rapid normocalcemia in about 80% of patients. The drug was well tolerated except for transient fever in only two patients. In some studies, APD was reported to be responsive in patients resistant to mithramycin. In this study, probably the dose of APD was not adequate in nonresponders.

(18) Jordell, Iveson. and Smith (1987) : Symptomatic hypocalcemia after treatment with high-dose aminohydroxypropylidene diphosphonate. Lancet 1: 622 (Abstract).

A case report in which a 47-year-old female patient with hypercalcemia (corrected serum calcium > 4.0 mmol/L) of malignancy (metastatic breast cancer) was given 30 mg of APD (single i.v. infusion over 6 hours) in 500 ml of physiological

saline. Prior to APD, this patient received rehydration, calcitonin, and mithramycin, but none of these treatment regimens were effective. She achieved normocalcemia 6 days after APD treatment, and about 13 days after she developed hypocalcemic symptom (fingertip paresthesia) with serum corrected calcium 1.97 mmol/L. Her symptoms resolved after calcium gluconate therapy and oral calcium supplement.

Comments: A report of development of hypocalcemia after treatment with APD (30 mg) in a patient with marked hypercalcemia of malignancy. Generally, one would not expect development of hypocalcemia at this dose of APD. However, the author has cited one study in which about 10% of patients treated with similar dose of APD developed transient hypocalcemia.

(19) Thiebaud et al (1988) : Dose-response in the treatment of hypercalcemia of malignancy by a single infusion of bisphosphonate AHPrBP. J. Clin. Oncology 6: 762.

An open dose-response/efficacy study of a single-dose APD involving 52 patients with hypercalcemia of malignancy. All patients had histologically proven malignancy; patients with breast and lung cancers comprised 31 of total 52 patients, and 4 patients with hematologic cancer (3 myeloma and 1 with lymphoma). Forty-four of 52 patients had scintigraphic or radiologic evidence of skeletal (5 to 6 bones) metastases. Patients were sequentially assigned to four treatment groups (12 to 14 pt./group). The initial plasma corrected calcium ranged between 2.8 to 4.8 mmol/L (normal 2.15 to 2.55 mmol/L). All patients received hydration therapy for at least 24 hours (2 liters of 0.3% sod. chloride plus 3.3% glucose i.v.) prior to APD infusion. APD was administered (i.v.) at doses of 30 (Gr. A), 45 (Gr. B), 60 (Gr C), and 90 (Gr D) mg in 1 liter of normal saline over 24 hours. The following parameters were measured at designated intervals: plasma calcium, phosphate, protein, creatinine, PTH, and urinary (from 2-hr fasting

morning samples), calcium, creatinine, phosphate, and hydroxyproline. Total calcium was corrected for the level of protein by using the following formula:

Ca corrected= Ca measured/0.60 + (protein g/L x 0.00533).

Summary of changes in plasma calcium (corrected) are presented in the table below:

	Mean Plasma Calcium (Mmol/L)	
	Baseline	Nadir (Between Days 4 and 6)
Gr. A	3.22±0.15	2.49±0.10
Gr. B	3.36±0.1	2.45±0.07
Gr. C	3.24±0.14	2.24±0.06
Gr. D	3.94±0.23	2.31±0.08

The data analyzed (based on initial range of plasma calcium) in 52 patients showed that in the low-dose groups, plasma calcium did not normalize in 8 patients (these patients had the highest initial plasma calcium >3.5 mmol/L). In the high-dose groups (60 and 90 mg), plasma calcium (corrected) was normalized in all but one patient. Six patients in the high-dose groups and two patients in the low-dose groups were reported to experience transient and asymptomatic hypocalcemia. Approx. 10 patients in each group were followed up over 9 months with regard to mortality, and recurrence of hypercalcemia. Almost identical number of patients died in all four groups. The percentage of patients with relapse after 1 months in each group is shown in table below:

	No. of Patients (%)
Gr. A	5 (50%)
Gr. B	3 (30%)
Gr. C	0
Gr. D	1 (10%)

Plasma phosphate and creatinine both were reported to decrease in all groups, but returned to normal in all patients except in group D. Plasma PTH was reported to increase slightly in all groups over Days 0 to 9, and in some patients values were above normal. Urinary excretion of calcium and hydroxyproline was reported to decrease in all four groups. Patients (number

not specified) with symptoms of hypercalcemia (e.g.,nausea, constipation, muscle weakness, and drowsiness) were reported to experience symptomatic improvements following treatment with APD. Side effects of APD reported in this study included transient elevation of body temperature (to a max. of 38°C in six patient lasting for 48 hours or less).

Comments: This study seems to confirms the findings of other studies regarding calcium lowering effect of a single dose of APD (60 to 90 mg i.v. infusion over 24 hours) in the management of hypercalcemia of malignancy. The results tend to indicate a dose-response relationship; the lower doses of APD (30 and 45 mg) are less effective and likely to cause earlier recurrence of hypercalcemia. The majority of patients in high-dose groups (10 in each dose group remained normocalcemic for at least 1 month after treatment).

(20) Ralston et al (1988): Clinical experience with aminohydroxypropylidene bisphosphonate(APD) in the management of cancer-associated hypercalcemia. Qt. J. Med. 69: 625.

An open study of the effects of single doses of APD (15, 25, and 45 mg over 4 hours or 45 mg administered over 3,6, or 24 hours) in the management of hypercalcemia of malignancy. The study enrolled fifty-five patients, but 485 patients were considered evaluable. The initial corrected serum calcium in all patients was above 3.0 mmol/L, and failed to respond adequately to rehydration. The varying doses of APD were tried in 20 consecutive patients, another 22 patients received similar doses of APD with varying infusion times.

Of 48 evaluable patients, 32 (66%) were reported to be normocalcemic after 5 mg APD therapy. Failure to obtain normocalcemia in non-responders was attributed to increased renal tubular resorption of calcium and inadequate suppression of bone resorption by APD. With respect to hypocalcemic response and the duration of effect (median 20 days), no significant difference was observed between three doses of APD, nor there was a difference due to varied durations of infusion. However, with 5 mg dose, decrease in serum calcium level and the duration of action were less marked compared to that at higher doses. Seven patients were reported to receive repeat treatment with APD for two or more occasions, and the results indicated less hypocalcemic effect with the second dose of APD even with higher doses. Patients with symptoms of hypercalcemia were reported to improve after APD therapy. The median survival time for the APD treated patients was reported to be 30 days (range 0-350 days). Tumor progression was reported to be the common cause for death in these patients, but in some patients recurrent hypercalcemia probably was a contributory factor. One patient was reported to die due to hypercalcemia about 12 hours after receiving APD.

Comments: The findings of this study are essentially similar to those reported in other studies with respect to hypocalcemic action of APD in patients with hypercalcemia of malignancy. There was no difference in response between single and multiple infusions schedules, as well as in the effect of APD at doses between 5 and 45 mg on calcium levels. Response to repeat treatment with APD for recurrence of hypercalcemia was reported to be less than the initial response, which is contrary to other studies.

(21) Morton et al (1988): Single dose versus daily intravenous aminohydroxypropylidene bisphosphonate (APD) for the hypercalcemia of malignancy. *Br. Med. J.* 296: 811.

In this open study, 30 patients with clinically established malignancy (12 pt. with CA of bronchus, 6 with multiple myeloma, 5 with CA of breast, and the rest with other types of malignancies) and hypercalcemia (corrected serum calcium > 2.8 mmol/L were enrolled. Excluding patients with multiple myeloma, bone scan was performed in 20 of the remaining patients. Of 20 patients, 10 patients had evidence of skeletal metastases. Patients were randomly assigned to receive one of three treatment regimens: A) 60 mg of APD in 500 ml of normal saline infused i.v. over 8 hours, B) 30 mg APD in 250 ml of normal saline infused i.v. over 4 hours for two consecutive days, and C) 15 mg APD in 125 ml of normal saline infused i.v. over 2 hours for 4 consecutive days. Patients who failed to response adequately to rehydration were considered eligible for entry into this study. Specific chemotherapy was not altered or started until normocalcemia was achieved. Serum and fasting urinary chemistries relevant to this type of study were measured at designated intervals.

The results showed normalization of corrected serum calcium in all but two patients (93%) by day 7 after APD treatment. No significance difference in the hypocalcemic effects (in the rate of fall or in the nadir) was reported between three doses of APD. Serum calcium was shown to remain within the normal range during the follow up period for 28 days. Serum magnesium was reported to be normalized after APD therapy (majority of patients had hypomagnesemia at baseline). Urinary calcium excretion was reported to decrease to normal range after therapy in all patients. Urinary hydroxyproline:creatinine ratio showed no significant change during the course of the study. Patients with symptoms of hypercalcemia were reported to improve significantly with normalization of serum calcium. The drug was reported to have little effect on neurological symptoms or bone pain. With respect to APD response by the tumor type, the patients with multiple myeloma were reported to "most responsive."

The side effects of APD reported in this study included: xanthopsia (lasting for about 2 hours) in one pt., transient asymptomatic fever in 5 pt., and asymptomatic hypocalcemia (corrected serum calcium <2.1 mmol/L) was reported in 4 patients.

Eleven patients were reported to survive longer than one month, and 7 of these patients had recurrences of hypercalcemia. These patients were maintained normocalcemic by repeated administration of APD at a dose of 30 mg (one patient required 60 mg) given every 2 to 3 weeks.

Comments: The study shows normalization of elevated serum calcium (corrected) in 93% of patients with hypercalcemia of malignancy as a result of APD therapy at a total dose of 60 mg given as a single dose, or at consecutive daily dose of 30 mg and 15 mg given for 2 and 4 days, respectively. Normocalcemia was maintained for 21 days. A relatively large group of patients with multiple myeloma were included in this study and they all responded well. This study also provide some information regarding the efficacy of retreatment (dose and frequency of retreatment) with APD. Sixty milligrams of APD appears to be the effective dose in the management of hypercalcemia of malignancy.

(23) Ralston et al (1988): Treatment of severe hypercalcemia with mithramycin and aminohydro-xypropylidene bisphosphonate. Lancet 2 (8605): 277 (Letter).

A small group (n-5) of patients with "severe" malignancy-associated hypercalcemia (not adequately controlled by other treatment regimens) were treated with i.v. mithramycin (25 μg/kg) and a single APD infusion at a dose of 30 mg in saline over 4 hours. Patients continued to receive normal saline i.v. until normalization was achieved or the hydration was judged adequate clinically. Serum calcium corrected for albumin decreased by 0.44 mmol/L within 24 hours, and remained suppressed for over 9 days of follow- up period. Urinary calcium/creat-inine ratios also decreased within 24 hours. Except for a mild and transient increase in aminotransferases (1-4 days posttreatment), the combination therapy was reported to be tolerated well by the patients.

Comments: This small series indicated that a combination of APD (30 mg) and mithramycin (25 μg/kg) i.v. infusion over 4 hours might cause rapid (within 24 hours) decrease in elevated serum calcium.

(24) Heaf and Hansen (1988): Treatment of refractory cancer-associated hypercalcemia with aminohydroxypropylidene diphosphonate. Acta Med. Scand. 224: 287 (Abstract).

A case report showing normalization of elevated serum calcium in a cancer-associated hypercalcemic patient, following a single i.v. infusion of APD (60 mg). This patient was previously unsuccessfully treated with fluids, loop diuretics, prednisone, calcitonin, and repeated doses of mithramycin. No side effect of APD was reported.

(25) Gurney et al (1989): Renal phosphate threshold and response to Pamidronate in humoral hypercalcemia of malignancy. Lancet July 29, p.211.

Fifteen patients with histologically proven malignancy and symptomatic hypercalcemia (corrected serum calcium between 2.65 and 4.0 mmol/L) were enrolled into this study. All patients received i.v. normal saline (1 L q 6 hours) for 24 hours before treatment and for 48 hours after Pamidronate administration. Blood and urinary parameters relevant to this type of study were determined at designated intervals. Pamidronate (APD), diluted in 500 ml saline was administered at the following doses based on corrected serum calcium levels: 30 mg for corrected serum calcium between 2.65-2.99 mmol/L, 45 mg for 3.0-3.99 mmol/L, 60 mg for 3.5-4.0 mg mmol/L, and 90 for > 4.5 mmol/L. APD was infused at a rate of 15 mg/hour.

The results showed normalization of corrected serum calcium in 7 patients within a median of 3 days (range 1-12 days), and 8 patients failed to achieve normalization of calcium. Low renal phosphate threshold has been attributed to poor response to Pamidronate. In addition, negative isotopic bone scan was also common in those patients.

(26) Mannix et al (1989): Single high-dose (45 mg) infusions of aminohydroxypropylidene diphosphonate for severe malignant hypercalcemia. Cancer 64: 1358

In this open study 25 patients with hypercalcemia of malignancy were treated with a single i.v. infusion of APD 45 mg) over 3 hours. Fifteen of these patients had either breast or lung cancer, and the rest had a variety of other cancers. Ten of 25 patients had bone metastases determined by x-rays or scintigraphy. Majority of patients had i.v. hydration with normal saline (two or more liters) prior to APD therapy.

The results showed that 24 patients responded to a single infusion of APD. Eighteen of 24 patients (76%) were reported to achieve normalization of corrected serum calcium (range for the center 2.25 to 2.75 mmol/L). The median pre-APD corrected plasma calcium was 3.57 mmol/L (range 3.07 to 4.56 mmol/L). The median number of days to obtain nadir plasma calcium ranged between 5 and 7 days. Five of 18 normocalcemic patients were reported to have recurrence of hypercalcemia after a median of 19 days (range 11 to 39 days). Another 4 normocalcemic

patients were reported to remain normocalcemic when tested on days 4, 5, 24 and 62. One patient was reported to have an increase in serum calcium after APD infusion (Comments: no explanation provided for this phenomenon). Five patients were reported to manifest a fall in plasma calcium, but remained hypercalcemic. These five patients were non-responsive to other putative calcium lowering agents (rehydration, corticosteroids, furosemide, and calcitonin). Fourteen patients were reported to die from progressive malignancy within 30 days after APD therapy. The median survival time ranged from 29 to 55 days. The side effects APD reported in this study included: hypocalcemia (in 5 pt.) and dyspnea in one patient. For of 5 patients who became hypocalcemic, had their pretreatment plasma calcium values of less than 3.5 mmol/L. The patient who developed dyspnea after APD therapy, received 6 more APD infusions at weekly intervals for recurrence of hypercalcemia and on each occasion experienced identical respiratory episode (considered to be an idiosyncratic reaction). (Comments: The data from this study seem to confirm the findings of other reports concerning the efficacy of APD in decreasing the elevated plasma levels of calcium in patients with hypercalcemia of malignancy. The study provides some relevant information regarding the optimum dose of APD, duration of its i.v. infusion (over 3 hours), and the response of patients irrespective of the type of malignancy. With respect to side effects of APD, there was one case of idiosyncratic reaction (respiratory dyspnea) to APD.

The sponsor has provided additional reports on the efficacy and safety of APD in various disease conditions other than hypercalcemia of malignancy. These reports are relevant with respect to safety of APD. There are more than 23 reports on the effects of APD therapy (oral and i.v.) in the management of patients with Paget's disease of bone. APD was used in these studies for both short-term and long-term periods, and the side effects of the drug were nausea, rise in body temperature (+ 0.5 to 2^{0}C lasting for up to 72 hours), irritation of gastric mucosa, duodenitis, gastric ulceration (confirmed by endoscopy), hiccough, leucopenia, lymphopenia, granulocytopenia, transient exacerbation of bone pain, "deterioration of lytic bone lesions," and transient hypophosphatemia. There are several studies in which APD was used in patients with malignancy and bone metastases, osteoporosis, and metabolic bone disease with osteopenia (juvenile osteoporosis, Goucher's disease, osteogenesis imperfecta). Side effects of APD reported in these studies included gastrointestinal complaints, transient rise in body temperature, grand-mal type seizures, and rash. In some patients G-I complaints required stoppage of APD therapy. With a dose of 150 mg/day, the side effects of APD were infrequent.

5. Clinical Studies:

A. Controlled Studies: Two randomized, double-blind,

clinical trials of APD werw carried out:

(1) Protocol # 01: Dosing study of the treatment of hypercalcemia of malignancy (HCM).

The study objectives were to evaluate the effects of 30, 60, and 90 mg single doses of APD in lowering the elevated levels of serum calcium (corrected for albumin) in patients with HCM. It was a multi-center (study completed at 4 centers, one additional center did not enrol patients), randomized, parallel, double-blind trial using a single i.v. infusion of either 30, 60, or 90 mg APD.

Study Sites and Investigators:

Henry Ford Hospital, Detroit, Michigan	Robert Chapman, M.D.
Baylor College of Med. Houston, Texas	Lawrence Mallette,M.D.
Mass. Gen. Hosp.., Boston, Mass	Sammuel Nussbaum, M.D.
Brigham and Young Hosp., Boston, Mass	Craig Henderson, M.D.
VA and Univ. Colorado Health Sci. Center,* Denver, CO	Scot Sedlacek, M.D.

* Dr. Sedlacek did not enrol any patient

Comments: All the investigators were qualified.

Overall design and plan of the study:

The outline of the this controlled study is presented below:

Visit 1	Visit 2	Visit 3-9	Visit 10-13
		In-Patient	Out-Patient
Hydration	Treatment	Follow-up	Follow-up
IV Fluids*	APD 30,60,or90	Daily Evaluation	Wkly/Monthly Evaluation
Days -2,-1	Day 0	Days 1-7	Days 14,21, 28,60

Three protocol amendments were made in January 1988:

a. To better define the allowed time frame for use of other hypocalcemic agent (e.g., calcitonin, corticosteroids, and plicamycin).

b. Addition of an exclusion criterion for potassium ≤ 3.5 mEq/L, and a statement regarding the close monitoring of serum electrolytes.

c. Additional ECG recording at visits 2 and 5.

Patients who had recurrence of hypercalcemia during or within one year after 2-month core protocol, or who did not respond to initial course of the treatment were included in the Humanitarian Extension phase of the study (submitted as a separate report). The study was designed primarily to evaluate within the group efficacy and safety for each of the three doses.

Study population:

Patients of either sex (aged 18-80 years) with hypercalcemia (corrected serum calcium ≥ 12.0 mg/dl and a histologic diagnosis of malignancy (other than skin cancer). All patients had an estimated life expectancy of at least 3 months. Patients were hydrated adequately for 48 hours and received APD if the serum calcium levels were above ≥ 12 mg/dl. Patients with serum creatinine values above 2.5 mg/dl or potassium values < 3.5 mEq/L were excluded from the study. Other exclusion criteria were satisfactory.

After adequate hydration (i.v./oral fluids in such quantity to result in urine output of at least 2 L/day) patients were randomly assigned (with the help of a computer-generated scheme) to receive one of three doses of APD.

APD was supplied as 5 mg/5 ml ampuls. The assigned dose of APD was added to 0.9% normal saline to make a total volume of 1 L. The prepared solution was administered i.v. over 24 hours. The study was carried out in a double-blind fashion. The patients were monitored closely during i.v. infusion and for up to 7 days after infusion for effects of APD on corrected serum calcium and any adverse reactions. Information on concomitant medications were all recorded in the case report form. During the follow up phase (Days 14, 21, 28, and 60) patients were followed up for the recurrence of hypercalcemia. The details of the experimental procedure are presented in the next table (see page 033 vol 1.34).

Primary efficacy variables: Serum calcium corrected for albumin was the primary efficacy variable. The following formula was used to determine the corrected serum calcium:

Corrected serum calcium (mg/dl)= measures serum calcium (mg/dl) + [(4.0-measured serum albumin g/dl) x 0.8].

A complete response was defined as normalization of serum calcium; a partial response was defined as 15% reduction of serum calcium (corrected) from baseline. The normal range of serum calcium at 5 investigational sites varied from 8.5 to 10.7 mg/dl. The secondary efficacy variables included: onset of effect, duration of normalized serum calcium, and time to relapse, urine hydroxyproline/creatinine ratio, urine calcium/creatinine ratio, and changes in serum PTH levels after APD therapy. The effects of APD on the symptoms of hypercalcemia were also evaluated in the following manner: anorexia, nausea, vomiting, and abdominal pain: no or yes; mental status: alert, confused, obtunded, stuporous, and comatose; bone pain: no or yes.

For safety evaluation, at each visit all medical problems during the study were recorded. The investigator assessed the cause and effect relationship, as well as the severity of the symptoms. The following safety parameters were monitored: cardiovascular, local reactions at the injection site, changes in body temp., clinical lab. investigations (CBC, hematology, blood chemistries, electrolytes, urine chemistries, and serum PTH).

Protocol violations for failing to meet the entry criteria, failure to maintain blinding during therapy, and use of unacceptable concomitant medications were all recorded. Patients were allowed to continue the study and included in the final analysis of the results, unless the investigator felt that their inclusion would have significant impact on the overall efficacy of APD.

Statistical and analytical plan: The sample size for the evaluation of efficacy alone was calculated to be 7 per treatment group (assuming the true response rate is 80%, with $\alpha = .05$ (two-tailed), and the power= .80. However, in each group 15 patients were enrolled in order to gather more information on the safety of APD. Statistical plans used for the final analysis of data are the subject matter of the statistical review.

RESULTS:

Of the 62 patients enrolled into the study, 10 patients discontinued the study prior to entering the double-blind phase. These patients failed to qualify for receiving the study drug, because after hydration their corrected serum calcium levels were no longer $\geq$ 12 mg/dl. Fifty patients were included in the efficacy evaluation and 52 in the safety assessment. One investigator (Dr Nussbaum of Mass. Gen. Hosp.) was aware of the treatment regimen in two patients (at 60 mg APD dose), and these two patients were excluded from the

efficacy analysis. The distribution of patients in three different doses of APD are shown below:

30 mg APD	60 mg APD	90 mg APD
15 pt.	18 pt.	17 pt.

Seven patients each on 30 and 60 mg of APD, and 1 patient on 90 mg, were discontinued from the study during the in-patient phase of the study, mostly because of death or unsatisfactory therapeutic response. A total of 7 patients on APD 30 and 60 mg doses died during the in-patient phase of the study. Four patients were dropped from the study because of unsatisfactory therapeutic response. Four additional patients discontinued the study for various other reasons such as unacceptable concomitant medication, intercurrent medical problem, and relapse of hypercalcemia. Four patients on APD 60 mg and one pt. on 90 mg doses completed the follow-up phase (visits 10-13; See Table 1., p.088, vol. 1.34).

As indicated above, 10 patients were excluded from the study as they failed to meet the criteria for admission into the study. "Numerous" other protocol violations occurred, but these violations were considered by the investigators to have "little impact" on the efficacy results. Four patients were considered to have major protocol violations (2 patients were not randomized, one pt. was receiving high-dose corticosteroid prior to the study and other patient was receiving an experimental drug "hydrazine" before and during the study). Other minor protocol violations were related to fluid intake and output, low-dose or continuous corticosteroid use, and oral phosphate administration (for phosphate replacement). Excluding two patients who were not randomized, an intent-to-treat efficacy analysis was performed.

Demography and baseline data/comparability of treatment groups:

Of the total 50 patients evaluated for efficacy, 64% of patients were male and 36% female. Sixty-eight percent of patients had bone metastases, and 74% of patients had other distant metastatic lesions.

Except for percentage of patients with lung cancer, all three treatment groups had other major cancer types in similar numbers. In the APD 30 mg treatment group, a fewer number of patients had lung cancer. The latter group had 83% of patients with bone metastases, compared to 44% and 41% of patients in the APD, 60 and 90 mg groups, respectively. This implies that latter two groups had more patients with "humoral" hypercalcemia. The mean body weight of patients was slightly higher in APD, 30 mg group, but in many patients accurate body was not recorded because of "poor functional status," or due to protocol violation. There was no statistically significant difference among three treatment groups with respect to the amount of fluids received during Day -2 to Day 6. Also, there was no significant difference in the amount of normal saline received during

the 48 hours preceding Visit 2. The treatment groups were not different based on the changes in corrected serum calcium and serum calcium to hydration. The BUN/creatinine ratio was < 20 for all patients.

Modifications in the statistical analyses of data as recommended by the Agency:

(1) The sponsor was requested to analyze separately the proportions of complete responders (serum calcium decreased to the normal range).

(2) Duration of complete response was analyzed according to the original definition, and according to a modified definitions as recommended by us. The modified definition is the time (in days) between the occurrence of a complete response in the inpatient phase and the last calcium measurement less than 11.5 mg/dl (in the original definition the last calcium measurement was "less than or equal to the upper limit of normal for the center").

(3) Time to relapse for responders and non-responders was also modified to define it as the time (in days) between the occurrence of a complete response or partial response (a 15% reduction from the baseline) in the inpatient phase and the last serum calcium measurement < 11.5 mg.dl or ≥ 15% below the baseline value.

Data were also analyzed by furosemide use during the inpatient phase.

The complete response rates based on corrected serum calcium:

On Day 7 (Visit 9), the complete response rates were 40%, 61%, and 100% for the APD, 30, 60 and 90 mg treatment groups, respectively. At Visits 5-9 (Days 3-7) for APD 60 and 90 mg groups, the complete response rates were greater than the anticipated placebo response rate (20%) (see Tables 8a and 8b on pp. 104, 105, vol. 1.34). In the follow-up phase, at Visit 10 (Day 14), 50%, 44%, and 42% of patients were reported to have complete response at 30, 60, and 90 mg APD doses, respectively. Three patients, one at 30 mg and two on 60 mg APD were reported to have partial response during the inpatient phase of the study, but achieved complete response (normalization) in the follow-up phase.

The proportion of responders (complete and/or partial) in the each treatment group showed no major difference with respect to baseline corrected serum calcium levels greater than or equal to 13.5 mg/dl, or less than 13.5 mg/dl.

Complete response based on uncorrected serum calcium:

The patients in APD 90 mg group had more complete responders (100%) compared to APD 30 mg group (67%) at Visits 7-9 (Days 5-7). There was no statistically significant difference in the percentages of complete responders between 60 and 90 mg groups at Visit 9 (78% vs. 100%). Percent responders in the 60 mg group were not significantly higher than those in the APD 30 mg group, at all (except Visit 5) Visits during the inpatient phase.

In the follow-up phase, 75% (3/4), 56% (5/9), 77% (10/13) of patients were reported to maintain completed response at Visit 10 (Day 14) in APD 30, 60, and 90 mg groups, respectively. On Day 60 (Visit 13), 3 patients in APD 60 mg group, and 1 patient in 90 mg group were reported to have complete response (See Table 9A, p. 110).

The Combined Complete and Partial Response based on Corrected and Uncorrected Serum calcium:

Combined Response Rates at Visit 9 (Day 7) Based on Correc.Ca

APD (mg)	30	60	90
	47%	78%	100%

The response rates were reported to be statistically greater than the anticipated placebo response rate in APD 30 mg at Visits 6-9, and at Visits 5-9 Days (3-7) for 60 and 90 mg groups. There was no statistically significant difference in response rates between APD 60 and 90 mg groups. The complete and partial response rates of the 90 mg group at Visit 5 (Day 3) and Visits (7-9, Days 5-7) were significantly higher than those of the 30 mg group.

In the follow-up phase, the percent of patients who had either complete or partial response at Visit 10 (Day 14) and Visit 13 (Day 60) are shown below:

Comb. Response Rates at Visits 10 and 13 (Days14 and 60)

APD (mg)	30	60	90
Visit 10 (Day 14)	50% (2/4)	67%(6/9)	75%(9/12)
Visit 13 (Day 60)	None	3 pt.	1 pt.

The combined response rates based on uncorrected serum calcium were similar to response rates based on corrected serum calcium. For all three treatment groups, the response rates were reported to be statistically greater than anticipated placebo response rate at Visits 5-9 (Days 3-7). The APD 90 mg group was reported to have statistically significant more responders compared to 30 mg group. The differences between the 90 and 60 mg, and between 60 and 30 mg groups were not statistically significant.

Corrected and Uncorrected Serum Calcium Levels:

At all Visits during the inpatient phase, the mean corrected serum calcium and the mean serum calcium were reported to be decreased from the baseline (Visit 2) values. The mean reduction in corrected serum calcium at the Endpoint from the baseline for all three treatment groups is shown below:

APD (mg)	30	60	90
Mean↓	2.2mg/dl	3.3 mg/dl	3.9 mg/dl

The mean baseline corrected serum calcium values ranged from 13.2 to 13.9 mg/dl. The results showed a significant treatment by Baseline interaction at Endpoint for both corrected and uncorrected serum calcium values. There were small reductions in corrected serum calcium levels in the APD 30 mg group patients with "high" baseline values, compared to reductions achieved at 60 and 90 mg doses. Though patterns of reductions in corrected serum calcium were similar for the 60 and 90 mg groups, the reductions were greater at 90 mg dose than that at 60 mg, for all baseline values. / greater reductions were reported at both 60 and 90 mg doses, when the baseline values were $\geq$ 13.5 mg/dl. At the 30 mg dose, the reductions were similar irrespective of baseline serum calcium values, below or above (or equal to) 13.5 mg/dl.

Time to Response:

Time to response (complete and partial) in the inpatient phase for corrected serum calcium is mentioned below (See also Table 12, p.131):

APD (mg)	30	60	90
By Day	5	6/7	6/7

Duration of Response:

Two definitions (previously mentioned) were used in analyzing the data.

Definition using Normal range:

The median durations of complete response (95% confidence intervals) for corrected serum calcium are presented below:

APD (mg)	30	60	90
Med. Duration in Days (95% C.I.)	4 (1-30)	5 (3-19)	6 (5-11)

For uncorrected serum calcium, the median durations of complete response were 1.5-6 days longer at three doses employed.

Definition using 11.5 mg/dl:

The median durations of completed response based on corrected serum calcium are shown below:

APD (mg)	30	60	90

Med. Duration in Days (95% C.I.)	13.5 (4-30)	6 (3-61)	10 (6-15)

Time To Relapse:

The data presented for both corrected and uncorrected serum calcium levels, for complete or partial response, and for all patients. The time to relapse was considered zero days for patients who failed to elicit a response during the inpatient phase of the study.

Time to relapse (including non-responders): The median times to relapse (corrected serum calcium) are shown below:

APD (mg)	30	60	90
Med.Times in Days (95% C.I.)	0 (0-13)	6 (1-28)	11 (6-15)

Comparison of results between treatment groups showed no differences with respect to corrected serum calcium. The APD 90 mg treatment group showed statistically significant longer time to relapse compared to 30 mg group with respect to uncorrected serum calcium (See also Table 14, p.134).

The results are shown below:

The times to relapse (excluding non-responders): The results for corrected serum calcium are presented below:

APD (mg)	30	60	90
Med. Times in Days (95% C.I.)	13 (5-30)	9.5 (5-54)	11 (6-15)

Between treatment groups, the time to relapse was compared, the results showed no statistically significant differences between groups for either complete or the partial responders.

Subgroup Analyses:

Subgroup based on bone metastases:

Treatment Groups

APD (mg)	30		60		90	
Bone Met.	Bone met.				Bone met.	
	NO	Yes	No	Yes	No	Yes
No. of Pt. 1	14	8	10	7	10	
Response (at Visit 9)						
Complete	100%	36%	50%	70%	100%	100%
Partial	0%	7%	25%	10%	0%	0%
None	0%	57%	25%	20%	0%	0%

The results showed no clear differe.. due to the presence or absence of bone metastases in either complete or partial response rates at three doses. The mean reductions of corrected serum calcium at the endpoint also showed no major difference due to the presence or absence of bone metastases at the test doses.

Subgroup analysis of data based on the use of furosemide showed no difference in either response rates or the mean reductions in corrected serum calcium at three different doses (See Table on page 057).

Serum phosphate was reported to decrease during the study period. Both within-treatment and between-treatment comparisons were performed during the inpatient phase. The mean reductions of serum phosphate from baseline levels at endpoint were in the range of 0.3-0.7 mg/dl at three doses of APD. The maximum reduction occurred between Day 4 and 5. At the higher doses (60 and 90 mg) the reductions in serum phosphate levels were statistically significant from baseline between Days 3-7 and at endpoint. However, the data showed no dose-dependent effect (decrease) of APD on serum phosphate.

Urinary calcium excretion was reported to decrease markedly, median values decreased between 57%-86% from baseline at Visits 6, 9 and Endpoint in all three doses of APD, and showed a dose-response relationship. Urine calcium/creatinine ratios also decreased during the inpatient phase of the study. Urine

phosphate levels were decreased also during this phase of the study.

Changes in serum PTH levels: PTH (intact and midregion) assays were performed at two different centers. The median increases in PTH from Visit 1 to Endpoint are shown in the table below:

Median Increase in PTH From Visit 1 to Endpoint

APD (mg)	30	60	90
Midregion*	(n=2)	(n=4)	(n=4)
Med. Baseline	158.5	67.5	97.0
Med. Increase	122.5	20	39.5
Intact**	(n=8)	(n=9)	(n=10)
Med. Baseline	2.0	5.0	4.7
Med. Increase	3.7	6.9	22.8

* Results expressed as μLeq/mL (normal 50-150 μLeq/mL);
** Expressed as pg/ml (normal 10-65 pg/ml).

The changes in PTH levels should be interpreted with caution as the number of patients/group were relatively small for either assay group.

The serum BUN/creatinine ratios for the inpatient and follow-up phases were evaluated, and the results showed small median reductions (range 1.1-2.0) at endpoint from baseline medians at three doses of APD.

Serum albumin levels (g/dl) were reported to decrease slightly (max. mean decrease 0.3 g/dl) between Days 3 and 5). Corrected serum calcium is the primary efficacy variable, and this eliminates the variability due to changes in serum albumin during therapy.

Bone pain: A slight dose-related decrease (from baseline) in bone pain was reported as a result of APD treatment at endpoint.

Symptoms of hypercalcemia: Nausea and/or anorexia were present at baseline in some treatment groups. There were 30% to 40% reductions in the number of patients with these symptoms at the endpoint.

Mental status: An overall improvement in the mental status was reported at the endpoint at all three treatment groups.

Sponsor's discussion and interpretation: The highlights of the sponsor's discussions are the following:

A single 24-hr infusion of APD (30-90 mg) is effective in the treatment of HCM; 30 mg being the minimum effective dose and the maximum efficacy was noted at 90 mg dose.

Corrected serum calcium

	CR N (%)	PR N (%)	CR + PR N (%)
APD (mg)			
30	6 (40)	1 (7)	7 (47)
60	11 (61)	3 (17)	14 (78)
90	17 (100)	0 (0)	17 (100)

CR= Complete Response; PR= Partial Response

In general, the results of this study are in agreement with the findings of other studies reported in the literature. However, several studies have reported higher serum calcium normalization rates for a single 30 or 60 mg APD dose. A lower response rate in this study at 30 and 60 mg doses could be due to a patient population with more severe baseline hypercalcemia; random assignment to the treatment groups without giving consideration to the levels of hypercalcemia.

The mean corrected serum calcium values at each visit during the inpatient phase of the study were lower than the baseline mean values for all three treatment groups. The values for the 90 mg treatment group were lower than those of the 60 mg group, with overlapping at some visits. The mean corrected calcium values were reported to fluctuate considerably during the follow-up phase and values seemed to rebound.

Normalization of corrected serum calcium first occurred on Day 3 for the 60 and 90 mg groups, and on Day 4 for the 30 mg group. The onset of decrease in serum calcium in most cases occurred during the 24-hour infusion period. The median duration of complete response was 1-2 weeks for the corrected serum calcium and 1-3 weeks for uncorrected serum calcium. However, there was a great patient-to-patient variations and thus, in clinical practice the duration of individual response cannot be reliably predicted.

The data seem to support the use of a dose of APD in 60-90 mg range for the patients with severe hypercalcemia (corrected serum calcium value of≥ 13 mg/dl).

The data on changes in urinary excretion of calcium and hydroxyproline, as well as changes in serum PTH levels from baseline during the study are in agreement with the known pharmacodynamic actions of APD in humans.

The results do not show any clear relationship between the response rate and the primary site of cancer. Patients with hematologic cancer had a maximum 100% (4 of 4) complete response and the minimum response rate was 38% (3 of 8 pt.) in patients with miscellaneous types of cancer. No clinically significant difference was observed with respect to complete response to APD (60 and 90 mg doses) for patients with or without bone metastases.
Within a treatment group, administration of furosemide during the inpatient phase of the study made no difference in the response (complete) rate. A total of 26 patients of all three treatment groups received oral phosphate some time during the study. Eighteen of twenty-six (69%) patients manifested complete or partial response to APD before administration of oral phosphate. Similarly, administration of corticosteroid also had little or no effect on the APD response.

Plotting of max. decrease in corrected serum calcium against calculated creatinine clearance for individual patients of all three treatment groups revealed no relationship between these two variables. Few patients with the lowest clearance rate had the maximum decrease in corrected serum calcium. Decrease in creatinine clearance did not appear to affect the antiresorptive action of APD.

Review of the bone pain questionnaire respnses revealed no significant effect of APD therapy on this symptom. A few patients showed improvement in the frequency of baseline anorexia and nausea as a result of APD therapy. There was some improvement in the mental status score following APD treatment, and this could be possibly attributed to improvement of hypercalcemia.

SAFETY:

A total of 52 patients were included in the safety analysis; one patient was excluded because the patient never received APD. With respect to demography and medical history three treatment groups appear to be comparable.

Safety measurements:

a. Electrocardiogram: About 69% of patients had baseline ECGs performed, and of these, 65%-79% of patients were reported to have baseline ECG abnormalities. Approx. 38% to 81% of patients were reported to manifest ECG abnormalities in the inpatient and follow-up phases of the study. Only three patients at 90 mg dose with normal baseline ECG pattern were reported to have abnormal ECGs after treatment. In only one of these three patients one can reasonably ascertain a time relationship between a normal ECG prior to therapy and posttreatment ECG abnormalities. The clinical significance of this association is unclear. Some patients had a short QT intervals (consistent with hypercalcemia) before treatment, which lengthened during the follow-up period with the normalization of serum calcium.

b. Body Temperature: Fourteen, 39 and 36 percentages of patients in 30, 60, and 90 mg treatment groups, respectively were reported to have at least one time recorded temperature (during the Visits 2 through 5) greater than or equal to $1^{0}C$ above the max. pretreatment temperature. In most cases irrespective of APD dose, increased body temperature occurred on Visit 3 (end of 24-hour APD infusion). At Visits 4 and 5, highest percentage of patients were reported to have increased body temperature at 90 mg dose group. The fever was considered by the investigator as drug-related in about 13% to 20% of patients in all three doses of APD.

Blood Pressure, Pulse Rate, and Infusion Site Reactions:

No "clinically significant changes" in mean blood pressure and pulse rate were reported during the entire course of the study. A total of 8 patients (13%); 7 in the 90 mg and one in 60 mg doses were reported to experience either pain, redness, or swelling/induration during observation period (Visits 3 through 9).

All Medical problems: All medical problems, related or unrelated to the test drug are listed in the Table on page 47 (071), vol. 1.34). Fever, pain, hypertension, anorexia, constipation, nausea, arthralgia (including bone pain), and UTI were the most frequently reported medical problems (occurring in $\geq$ 30% of patients in at least one treatment group). The majority of these experiences were considered by the investigator as unrelated to the test drug. Four patients, 1 in 30 mg, 2 in 60 mg, and one in 90 mg doses were reported to experience seizures during the course of the study. Two of these patients had previous history of seizures. The possible cause of seizures in the remaining two patients was not clear, but according to the investigator it was not related to APD. There were two cases of abnormal renal function during the study, but in both cases it

was a pre-existing clinical condition which showed no change in severity, during or after the treatment. Atrial fibrillation and atrial flutter occurred in one patient each during the study, but both patients had previous histories of cardiac arrhythmias.

Adverse Experiences (medical problems considered remotely to definitely related to the study drug): The list of adverse experiences with their frequency rates are shown in the table below:

Adv. Exp.	Pre-treat. N=52	Treatment Gr. 30 N=15	60 N=20	90 mg N=17
	N (%)	N (%)	N (%)	N (%)
Fever	1 (1.9)	2 (13.3)	4 (20)	3 (17.6)
Inf. React.	0	0	1 (5)	3 (17.6)
Nausea	0	1 (6.7)	0	3 (17.6)
Hypophosp.	0	3 (20)	5 (25)	3 (17.6)
Hypomag.	2 (3.8)	4 (26.7)	2 (10)	2 (11.8)

Fever occurred as adverse reaction in approx. 13% to 20% of patients and lasted from one to three consecutive days in all three doses. All but one of the fever severity were in mild in nature and required no therapeutic measures.

Ten to 25% of patients in the treatment groups were reported to experience hypophosphatemia, hypokalemia, or hypomagnesemia. Hypophosphatemia was attributed to the mechanism of action of APD (i.e., inhibition of bone resorption), and increased renal excretion of phosphate as a result of increase in the serum PTH levels caused by the lowering of serum calcium levels. The cause of hypokalemia or hypomagnesemia was not clear. Three patients (2 at 90 mg and 1 at 30 mg doses) were reported to experience "severe" adverse reactions: at 90 mg, one patient experienced severe anemia ("remotely related to APD), and the other patient experienced "severe" hypophosphatemia (probably related to APD), atrial fibrillation (remotely related to APD), and hypocalcemia (probably related to APD). One patient at 30 mg dose group experienced "severe" somnolence (lethargy), remotely related to APD. Eight adverse experiences in 4 patients were considered "probably" related to APD, and these were anemia, hypophosphatemia, hypocalcemia, hypokalemia, and hypomagnesemia.

Concomitant Medication Records:

Seventeen patients were reported to receive concomitant aminoglycoside antibiotic. There was no elevation of serum creatinine values in these patients; the majority of these patients showed either no change or a decrease in serum creatinine levels.

Nine patients were reported to receive magnesium replacement therapy for hypomagnesemia. In two of these patient the investigators felt that it was APD related. One patient with hypomagnesemia also experienced seizures.

About 60% to 70% of patients were reported to receive potassium, these figures were not consistent with the percentage of patients who developed hypokalemia as a medical problem. A number of patients were on potassium maintenance prior to initiation of treatment.

A total of thirty-three patients received furosemide during the study, and its relation to serum potassium levels was analyzed. A
slightly higher percentage of patients who received furosemide were reported to have lower serum potassium values compared to 21% of patients with lower serum potassium values, and who did not receive furosemide.

About 50% of patients were reported to receive phosphate during the study. However, a higher percentage of patients in the 60 and 90 mg doses received phosphate compared to number of patients in 30 mg dose. About 35% of patients with APD related hypophosphatemia were reported to receive phosphate replacement therapy.

The amount of saline received by patients as a concomitant 'medication was not recorded by the investigators.

Deaths/Dropouts and Serious or Potentially Serious medical Problems:

Sixteen patients died during the course of the study. The causes of death are listed in Table 45 (p.224, vol. 1.34). Of these 16 patients, 3 patients died on Day 2 and one on Day 3. The remaining 12 patients died between Day 11 and 55 of the study, and all of them were reported to die from progression of their malignancy. Of the 4 patients who died on Day 2 or 3 of the study, one patient was reported to die from massive pulmonary embolism, 2 from metastatic lung cancer, and 1 might be due to cardiac arrhythmia (cardiac arrest) resulting from severe hypokalemia (serum potassium). The last patient had previous history of premature ventricular contractions. No death was attributed to the study drug.

The serious adverse reactions during the study are listed in the table below:

No. of Pt.	Adv. Reactions	Relationship to APD
1	Hemolytic anemia	Remote
1	Supraventr. tachy-cardia	Probable
1	↓ Hct & Hb	None*

* Serum haptoglobin during the episode and prior to transfusion was > 100 mg/dl, which precluded consideration of hemolytic reaction.

Two patients were discontinued from the study 2-3 days after receiving APD (30 or 60 mg) for intercurrent medical problems (high-dose dexamethasone administration in one patient and parathyroid surgery in other).

Eight patients were reported to have medical problems during the study which required hospitalization or prolonged hospitalization. These problems are listed in a table on page 079 of vol. 1.34, none appears to be related to the study drug.

Clinical Laboratory Parameters/ Predefined Percent Changes From Baseline (at least one lab. value at any Visit either above or below the baseline lab. values):

Hematology: Thirty to 47% of patients in all three treatment groups were reported to show a 10% or more decrease in hemoglobin. None of these patients had any evidence of hemolysis or bleeding, which prompted the investigator to conclude that these changes probably resulted from hemodilution during rehydration. About equal number of patients were reported to show either increases or decreases in neutrophils, monocytes, and platelets.

Blood Chemistries: Twenty-seven percentage of patients were reported to show a decrease in serum phosphate of ≥ 30% at 30 mg treatment group, and 50% of patients at 60 or 90 mg treatment groups. However, 14% to 19% of patients had either increase (30% or more), or had both increased and decreased values during the course of the study.

No increase (≥25%) in serum creatinine or BUN was reported. A dose dependent decrease (≥10%) in serum creatinine levels was reported in 40% to 77% of patients in all three doses of APD. There was no consistent pattern of changes in BUN levels.

Increased serum alk. phosphatase (25%), SGOT/AST (30%), and total bilirubin (25%) were reported in about 30% to 40% of patients treated with all three doses of APD.

Though hypomagnesemia was reported in approx. 10% to 27% of patients, a total of 20 patients showed increases ≥25% in serum magnesium and 8 patients manifested decreases of equal magnitude.

Changes From baseline to Terminal Lab. Determination: The terminal lab. was defined as the last postbaseline laboratory determination in the inpatient phase (through Visit 9). At study termination, no consistent change from the baseline was reported in hematocrit, hemoglobin, or WBC differential counts. The incidence of decreased serum phosphate was reported to be low, 20%-40% at the terminal lab. determinations in 30-90 mg doses. At the terminal lab., no evidence of increased SGOT/AST, total bilirubin, and serum alk. phosphatase was reported.

Urinalysis: About 25% to 33% of patients from all the treatment groups were reported to have urinary tract infections some times during the course of the study, and this led to increased presence of protein, epithelial cells, bacteria, and casts in urine.

Pooled Summary Statistics:

The means and medians for lab. parameters are presented for baseline, first post-dose (Visit 3), and terminal laboratory. No increases in
BUN and serum creatinine were reported at Visit 3 and terminal laboratory in all three doses of APD. At Visit 3 and terminal laboratory, these parameters were reported to be slightly decreased from baseline values.

For SGOT/AST, total serum bilirubin, and serum alk. phosphatase, data for the Visit 3 are missing except for one patient. There were large increases in mean SGOT/AST in the 30 mg group at the terminal laboratory with a small increases at 60 and 90 mg groups. Similar increases in serum alk. phosphatase were reported at three treatment groups.

The incidence of hypocalcemia (corrected serum calcium below the lower limit of normal range):

	APD Dose (mg)		
	30	60	90
% hypocalcemic Pt.	20	20	6

Overall, fifteen percent of patients became hypocalcemic. Because of higher percentages of hypocalcemic patients in the lower doses, the relationship between the drug dose and hypocalcemia was unclear.

Calculated Creatinine Clearance:

At Visit 6, 10% to 12% increase in creatinine clearance was reported in all treatment groups. There were further increases (= 20%) in creatinine clearance at Visit 9 in 60 and 90 mg doses.

Sponsor's Conclusion:

Protocol violation and exclusion of patients from the efficacy evaluation:

The overall compliance was reported to be good because of a single-dose treatment regimen with APD. Two patients (approx. 4%) were excluded from the efficacy due to protocol violations.

With regard to the efficacy of APD therapy, a single i.v. infusion of APD (30, 60, or 90 mg) over 24-hours was effective in the treatment of moderate to severe

malignancy associated hypercalcemia. Thirty milligram being the minimally effective dose to 90 mg being the most effective dose. Normalization of corrected serum calcium occurred in 40%, 61%, and 100% of patients at 30, 60, and 90 mg doses, respectively. With the inclusion of partial responders, 47% and 78% of patients responded in 30 and 60 mg, respectively. The response rates (at Visit 9/Day 7 post-infusion) at all three doses were statistically greater than the response rate that one would expect with placebo (saline) infusion alone. However, the differences in response rates between the 60 and 90 mg doses were not statistically significant.

Normalization of corrected serum calcium occurred anywhere from 2 to 8 days after APD infusion. Most complete response (normalization) occurred on Day 4 for the 30 mg treatment group, and on Day 3 for 60 and 90 mg groups. The median duration of complete response (the time from the occurrence of normalization of corrected serum calcium until the last calcium value of 11.5 mg/dl, was 13.5, 6, and 10 days for the 30, 60, and 90 mg treatment groups, respectively. The median time to relapse (time from the occurrence of normalization or 15% reduction from the baseline to last corrected serum calcium <11.5 mg/dl or 15% below baseline) were 0, 6, and 11 days for the three treatment groups.

Patients with symptoms of hypercalcemia (i.e., impaired mental status, anorexia, nausea) showed improvement at the Endpoint. There was no clinically meaningful decrease in the number of patients with bone pain.

On Days 4 and 7 after APD infusion, a decrease in urinary excretion of hydroxyproline and calcium and an increase in serum PTH levels from the baseline indicated APD-induced decreased bone resorption.

With regard to safety of APD therapy, approx. 50% of patients in each treatment group experienced adverse reactions. Fever was reported in about 13.3% to 20% of APD treated patients. Infusion site reactions occurred in about 41% of patients treated with 90 mg APD. No patient had infusion site reactions at 30 mg dose, and only one patent (5% of pt.) in 60 mg dose level. Hypophosphatemia occurred in 20% to 46% of patients and it was reported as an adverse event in about 10% to 27% of patients treated with APD.

Sixteen patients were reported to die during the study. All but four patients died due to the progression of the malignancy.

The risks of APD therapy in the treatment of hypercalcemia of malignancy are "mild and transient" compared to major benefits of therapy, which include normalization or 15% decrease in corrected serum calcium and improvements in GI symptoms, mental status, and renal function.

Reviewer's Comments:

Hypercalcemia associated with malignancy is a potentially life-threatening clinical condition with a grave prognostic significance. Currently, salmon calcitonin and Didronel (etidronate disodium) i.v.are approved for the treatment hypercalcemia of malignancy. The medical review of a recent New Drug Application (# 19-961) for gallium nitrate (i.v. infusion) for the treatment of HCM has been completed, and it is awaiting for the final action by this Agency. The clinicians involved in the treatment of HCM generally recognize that there is a need for a better therapeutic regimen for this clinical entity than those currently available.

Pamidronate disodium (Aredia) by virtue of its antiresorptive action on bone appears to be a relevant drug for the treatment of HCM. Although the exact mechanism of its antiresorptive action is not fully understood, the results of both in vitro and in vivo preclinical studies (earlier discussed) provide adequate rationale for its use in the treatment of HCM. The results of several clinical studies also provide some preliminary evidence in support of its efficacy and safety in the treatment of HCM.

This clinical trial carried out under Protocol 01 in the U.S., is a well designed dose-finding/efficacy and safety study. The study population was appropriate and the primary (normalization or a decrease of at least 15% of corrected serum calcium from baseline) and secondary measures (symptomatic improvements) for the assessmenent of efficacy are adequate. The statistical methods employed in the final analyses of results of this study are appropriate (see also Statistical Review and Evaluation for additional comments).

The results of this study showed a clear trend in dose response; the total (complete plus partial) response rates were 47%, 78%, and 100% for 30, 60, and 90 mg treatment groups, respectively. At 90 mg dose, all patients (n=17) had normalization of corrected serum calcium. Both complete and total response rates for 90 mg dose were statistically greater ($p < 0.05$) than the response rates for 30 mg dose. The total response rates at all three doses were greater than 20% ($p < 0.05$); the estimated response rate for saline alone. There was no statistically significant difference in response rates either between 60 and 30 mg doses, nor between 90 and 60 mg doses. From the efficacy standpoint, 30 mg appears to be the minimal effective dose of APD, and 90 mg being

the maximum effective dose in the treatment of HCM. Statistically significant decreases in corrected serum calcium were achieved at 2-7 days and Endpoint in all three treatment groups. The onset of hypocalcemic effect was evident 24-48 hours after initiation of APD therapy, and by Day 4, 46%, 72% and 83 % of patients showed complete or partial response at 30, 60, 90 mg doses, respectively. The median durations of complete response were 4, 5, and 6 days (95% C.I. 1-30, 3-19, and 5-11) at 30, 60, and 90 mg doses, respectively. The median time to relapse was 11 days for the 90 mg dose with 95% C.I. 6-15 days. The results of this study seem to be in agreement with the findings of another dose-response study reviewed under Literature Reports (Thibaud et al, JBMR 1(6):555,1986). The results also showed a dose-response relationship relative to the severity of the baseline hypercalcemia; in patients with baseline serum calcium $\geq$ 13.5 mg/dl, the mean posttreatment calcium was lowest for the 90 mg, intermediate for 60 mg, and highest for the 30 mg group.

Response to APD did not show any clinically significant difference when patients were analyzed according to age, sex, body weight, concomitant use of furosemide, presence or absence of bone metastases, and type of malignancy.

Fever(13% to 20%) and infusion site reactions (41%) were APD-related medical problems reported in this study. The infusion site reactions appear to have a dose-relationship to APD. In approx. 10% to 27% of APD-treated patients developed hypophosphatemia. The safety issues of APD therapy will be discussed in more details after review of the protocol # 03, when the safety data from these two controlled studies will be pooled and compared to Didronel treated patients.

(2) Protocol # 03: A randomized, double-blind, double-dummy controlled clinical study in which the effect of a single infusion of 60 mg of APD was compared to etidronate disodium (Didronel, EHDP), 7.5 mg/kg/day for 3 days. Chemically and pharmacologically, EHDP belongs to the same class of compound as APD.

Study Sites and Investigators:

Salt lake city	Stanley Altman, M.D.
Tulsa	Alan Keller, M.D.
Houston	Lawrence Mallette, M.D.
Albuquerque	James Neidhart, M.D.
Milwaukee	Paul Ritch, M D.
Decatur,Ga	P. Ravi Sarma M.D.
Washington, D.C.	Robert Siegel, M.D.
Memphis	Kurt Tauer, M.D.
Bronx	Peter Wiernik, M.D.

All the investigators were qualified

The study outlines:

Design: A randomized, parallel, double-blind study to compare the effect of a single infusion of 60 mg of APD to daily 2-hour infusion of 7.5 mg/kg EHDP administered for 3 days. Follow-up included an inpatient phase (Days 0-7), and a long-term phase (Days 10, 14, 21, and 30).

Drugs/Dosing: APD-60 mg (in 1000 ml of 0.9% saline) infused i.v. over 24 hours.

EHDP- 7.5 mg//kg (in a total 250 ml of 0.9% saline) i.v. infusion over 2 hours daily for 3 days.

Pre-study	Visit I	Visits 2&3	Visits 4-11
Hydration & Screening	Treat.	Treat.	In-pt./Out pt. Follow -up
	APD 60 mg or EHDP 7.5 mg/kg	Placebo or EHDP 7.5 mg/kg	Wkly/Monthly Evaluation
Day 0	Days 1&2	Days 3-7,	4, 21, 30

The response rate of 78% (complete and partial responses combined) in Protocol # 01 supported the selection of 60 mg dose of APD in this study.

Study Population: Patients (of either sex) aged 18-80 years with hypercalcemia (corrected serum calcium > 12.0 mg/dl) of malignancy (histologically determined).

The patient inclusion criteria were:

a. Hypercalcemia (corrected serum calcium ≥12 mg/dl) on the morning of Visit 1 (Day 0).

b. Estimated life expectancy of at least one month posttreatment.

c. Adequately hydrated with i.v. 3 L of saline and oral fluids when possible so that the urine output exceeded 2L/day, 24 hours prior to Visit 1. The exclusion criteria were similar to those of the study under Protocol # 01. Patients who were on a stable dose of corticosteroid for about 2 weeks, continued to receive corticosteroid, provided there was no change in the dose. Furosemide was permitted for patients with fluid overload.

A computer generated randomization scheme was used for assignment of patients into two treatment groups. Sham infusions were given to maintain blinding of the treatment regimens.

A protocol amendment was made so that the entry and the response criteria would be identical to those of the Protocol 01, the dose finding study.

Primary efficacy variable:

Complete response- Normalization of corrected serum calcium.

Partial response- A decrease of at least 15% in corrected serum calcium values from baseline levels.

Formula for calculating corrected serum calcium:

$Ca_c(mg/dl) = Ca_t + 0.8\ (A_m - A)$

Ca_t= serum calcium concentration
A_m = midrange albumin concentration for the hospital in g/dl
A= albumin concentration for that patient in g/dl

The upper limit of normal ranges of corrected serum calcium for various investigators varied from 10.4 to 11.0 mg/dl. The normal ranges for corrected serum calcium and midrange albumin values for

different centers are presented on page 036A, vol. 1.41.

Secondary Efficacy Variables: Changes in ionized and uncorrected serum calcium, onset and duration of hypocalcemic response, time to recurrence of hypercalcemia, and symptomatic improvements.

Safety parameters: All medical problems during the study were obtained by questioning and/or by examining the patients. The investigators decided whether a particular problem was drug-related or not based on several predefined criteria. In addition, the following parameters were evaluated for safety: cardiovascular, infusion site reactions, body temperature, hematology, blood chemistry/electrolytes, U/A, and serum iPTH.

Removal of patients from the study or analysis: Failure to meet the entrance criteria, failure to maintain blinding of treatment group assignment, and use of unacceptable concomitant medication were considered protocol violation.

Statistical and Analytical Plan: The sample size was calculated using $\alpha = .05$ and power=.80 for detecting a difference between two groups having a 70% response rate and a 30% response rate.

In addition to "acceptable patients' analysis," an "Intent-To-Treat" analysis was also performed involving all randomized patients.

The objective of the primary efficacy analysis was to compare the effectiveness of the two drugs in reducing the corrected serum calcium levels (see Statistical review for comments on the various tests performed in analyzing the data). The secondary objective of the efficacy was to compare between treatment groups during the long-term follow-up phase for a. duration of complete response, b. time to relapse, and c. proportion of patients classified as "successes" at the follow-up Visits (8.5 to 11).

RESULTS

Patients: All 30 patients in the APD group and 35 patients of the EHDP group were evaluated for the efficacy and safety. Six patients the APD and 10 patients of EHDP groups were discontinued from the

study during the inpatient phase (Visits 2-8). The reasons were: death (2 pt. in APD and 4 pt. in the EHDP group), relapse (2 pt. in each group), and unsatisfactory therapeutic response in 3 patients of EHDP group. A total of 8 patients in the APD group, and 7 patients in the EHDP group completed all visits.

Protocol violations: Only two patients were felt by the monitor to have major protocol violation. One patient (#302) had been receiving 400 IU calcitonin prior to Visit 1, and the other patient had corrected serum calcium < 12 mg/dl at baseline (entered into the study prior to protocol amendment). There were other protocol violations which included quantity of fluid intake and output, use of oral phosphate (low dose), low dose or continuous corticosteroid, or chemotherapy throughout the study. In the opinion of the investigator and the monitor, fluid intake and output was not properly "collected or recorded." Hence, did not accurately reflect the actual values. Oral phosphate was administered as a replacement therapy and not for the treatment of hypercalcemia.

All randomized patients were included in the safety analysis and Intent-To-Treat efficacy analysis.

There were some administrative problems reported regarding the Visits during the follow-up phase of the study, and these are presented in the table below:

Visit	Sched. Day	Extended To
8.5	Day 10	Days 9-11
9	Day 14	Days 12-16
10	Day 21	Days 18-24
11	Day 30	Days 27-33

Efficacy:

Sponsor states that the calculated values of corrected serum calcium matched the investigators'values in most cases or differed by no more than 0.2 mg/dl. In one patient (3 315), serum albumin values were not available until Visit 5, as such this patient was excluded from all

analysis of corrected serum calcium. Two patients were reported to have their corrected serum calcium and albumin missing at Endpoint (the last posttreatment measurement in the inpatient phase).

Comparability of treatment groups: All 65 patients (56% male and 43% female; av. age 55 years) had a primary diagnosis of malignancy. Sixty percent of patients had bony metastases. At some point of the inpatient phase of the study, 40% of patients received furosemide (at least 40 mg i.v. or orally); 53% in the APD and 29% in the EHDP treatment groups. The efficacy results were analyzed separately for patients with or without significant furosemide use. There was no statistically significant differences between the two treatment groups.

The primary sites of cancer were :

Breast cancer	25%
Head and neck	20%
Kidney	15%
Lung	14%
Hematologic	11%
Misc.	8%

Breast and hematologic cancer was more common in APD group, and kidney and lung cancer was more common in EHDP group.

There was no statistically significant differences between the baseline values of the two treatment groups.

The fluid intake by the patients of two treatment groups was assessed during (1) 24 hours prior to Visit 1, (2) inpatient phase, and (3) both 24 hours prior to Visit 1 and inpatient phase. Analysis of the results showed no difference in fluid intake by the two treatment groups. Also, there was no significant difference in 0.9% saline (during 24 hours before Visit 1) intake by the two groups (Comments; The sponsor states that caution should be exercised in interpreting fluid intake since its recording in the hospital charts was inaccurate and incomplete). There was some minor difference in the baseline mean values of the corrected serum calcium of the two groups (APD= 13.8 mg/dl, EHDP= 14.6 mg/dl). (Comments: this difference was attributed to very high corrected serum calcium value for one patient with a value of 21.3 mg/dl).

The median baseline corrected serum calcium value for the two groups was 13.8 mg/dl.

Once patient was classified as a complete responder in the inpatient phase, he or she was then classified as a responder at all subsequent visits of the same phase of the study even the patient did not meet the definition of the response at these visits. Patients who had a complete or partial response for one day were classified as responders. Both duration of response and the time to relapse were analyzed according to the original plan of the protocol, and later on modified as recommended by this Agency. The time to relapse could not be analyzed in some partial responders, because their corrected serum calcium never decreased below 11.5 m/dl, or decreased below 11.5 mg/dl several visits after the first partial response was achieved. The sponsor has provided a list of patients who after initial response had serum calcium fluctuated above the definition limits. A subgroup analysis of efficacy was also performed to see if furosemide use during the inpatient phase affected the response.
Within-treatment and between treatment groups serum phosphate measurements were analyzed.

Complete response rate based on corrected serum calcium (Table 5A,p. 102; table 20, p. 151):

At Visit 8, the complete response rates for the two groups were reported to be 70% and 41% for APD and EHDP (p=0.05), respectively. During this phase, the response rates were statistically greater than the anticipated response in (approx 20%) saline alone therapy. However, at Visits 2 and 3 for the APD and at Visit 2 for the EHDP group, the response rates were statistically less than the anticipated response rate in saline alone treated patients historically. At the follow-up phase, the percentages of patients with complete response are shown below:

	APD	EHDP
Visit 8.5(Day10)	58% (11/19)	27% (3/11)
Visit 11 (Day30)	4 pt.	3 pt.

One patient in the EHDP group, who had no response during the inpatient phase achieved normalization

of corrected serum calcium during the follow-up phase (Visit not mentioned).

The number of responders at Visit 8 for the each treatment group by primary site of cancer has also been presented (Table 5D, p. 105, vol 1.41). Breast cancer was the max. number of patients in each treatment group. In the APD group, of total 10 patients, 8 had complete and 2 had partial response. In the EHDP group, of total 5 patients, 4 had complete and 1 had partial response. There were 5 patients with hematologic cancer in the APD group, 4 had complete response and 1 had partial response. Two of two patients with hematologic cancer in the EHDP group achieved complete response. Of total 30 patients in the APD group, only one patient with "other" type of cancer failed to achieve any response, and only 2 of 34 patients with "other" type of cancer in the EHDP group showed no response.

Ninety percent and 66% of patients were reported to achieve complete response based on uncorrected serum calcium le[illegible]s at Visit 8 in the APD and EHDP groups, respect[illegible]y. The response rates at Visits 3-8 for APD [illegible] Visits 4-8 for EHDP were statistically greater than the anticipated response rate of 20%. The response rates during the follow-up phase are shown below:

	APD	EHDP
Visit 8.5 Day 10)	74% (14/19)	47% (7/15)
Visit 11 (Day 30)	5 pt.	4 pt.

Complete and partial response based on corrected serum calcium levels:

The response rates at Visit 8 (Day 7) were 97% and 65% for APD and EHDP groups, respectively. The response rates were statistically greater than the anticipated response rate of 20% at Visits 4-8 (Days 3-7), but less than the anticipated response rate at Visit 2. The results of the follow-up phase at Visits 8.5 and 11 are almost similar to response rates based on the uncorrected serum calcium.

Complete and partial response rates of the two groups based on the uncorrected serum calcium were greater (97% and 75%) than the response rates based on the corrected serum calcium levels. The response

rates in the follow-up phase showed the same pattern of response as observed with corrected serum calcium.

A total of four patients, all in the EHDP group were reported to be treatment failures (serum calcium levels did not change, or increased from the baseline during the inpatient phase).

Based on corrected serum calcium response there were 9 patients who had either complete or partial response for only one day. These patients were considered nonresponder at our recommendation, and the data were reevaluated. Excluding these nine patients, the complete response rates based on the corrected serum calcium were 50% and 41% for the two groups, respecti-vely. The difference between the two groups was not statistically significant. The complete and partial response rates for the same subsets of population were 87% and 62% at Visit 8 for the two treatment groups, respectively, and the difference was statistically significant. When the response was based on uncorrected serum calcium levels, only two patients (one on each treatment group) had complete response which lasted for only one day, and these patients were partial responders at other visits of the trial.

Serum corrected and uncorrected serum calcium levels during the inpatient and follow-up phases:

The mean corrected baseline serum calcium levels were 14.6 and 13.9 mg/dl for the two treatment groups. The mean reduction in corrected serum calcium at endpoint from baseline (Visit 1) was 4.1 and 2.3 mg/dl for the two groups, respectively (Table 7, pp.110-111, vol. 1.41). The APD group had significantly greater reductions in corrected serum calcium levels than the EHDP group at Visits 5-8 (Days 4-7) during the inpatient phase of the study (See Table 20, p.151. vol. 1.41).

Time to response:

The results are shown below:

	APD	EHDP
Corrected sCa		
Complte & Partial	By Day 7	By Day 6
Uncorrect.sCa		
Complt. & Partial	By Day 5	By Day 5

Duration of Complete Response:

The results are shown below for complete response, based on corrected/uncorrected serum calcium:

Def. using the normal range:

	APD(95% C.I.)	EHDP(95% C.I.)
Correct.sCa		
Median Duration /Days	7 (1-14)	5 (2-29)
Uncorrected Serum Ca		
Med. Dur./Days	9 (5-16)	9 (5-15)

Def. using 11.5 mg/dl:

	APD(95% C.I.)	EHDP (95% C.I.)
Correct. sCa		
Med. Dur./Days	8 (2-18)	8.5 (2-29)
Uncorrect. sCa		
Med. Dur./Days	10 (6-17)	9 (5-15)

Time to Relapse:

Based on corrected serum calcium (of all patients), the median times to relapse were 9.5 days with 95% C.I. of 4-14 days, 4 days with C.I. of 0-6 days. The difference between the two groups was statistically significant (p=0.051).

Time to relapse (excluding non-responders): The median times to relapse based on corrected serum calcium were 11 days (C.I. 4-15 days) and 5.5 days (C.I.4-11 days) for the APD and EHDP groups, respectively. There was no statistically significant difference between the two treatment groups.

Subgroup Analyses: Based on the presence or absence of bone metastases, and furosemide (received at least 40 mg i.v. or orally) usage:

The results (modified from tables on p.059, vol.1.41) are shown below:

	Treatment Gr.			
	APD		EHDP	
	Bone Metast.		Bone Metast.	
	No (n=9)	Yes (n=21)	No (n=17)	Yes (n=17)
Response*				
Complete	78%	67%	29%	53%
Partial	11%	33%	24%	24%
None	11%	0%	47%	24%
Mean Reduction** (mg/dl)	3.7	4.3	1.7(n=15)	2.7

* At Visit 8 based on the corrected serum calcium
** At Endpoint from baseline mean

	APD		EHDP	
	Furosemide		Furosemide	
	No (n=14)	Yes (n=16)	No (n=24)	Yes (n=10)
Response*				

Complete	71%	69%	33%	60%
Partial	29%	25%	25%	20%
None	0%	6%	42%	20%
Mean Reduction** (mg/dl)	4.0	4.2	2.1	2.6

* At Visit 8 based on corrected serum calcium
** At Endpoint from baseline mean

Changes in serum phosphorus levels:

In the APD group, the mean changes in serum phosphorus at Endpoint was -0.5 mg/dl, and for the EHDP group, 0.8 mg/dl. The max. mean decrease in the APD group was 1.0 mg/dl and occurred at Visit 5. In the EHDP the mean max. increase (0.8 mg/dl) occufred at Visits 7, 8, and Endpoint. (Comments: The two drugs have opposite effects on the serum phosphorus. EHDP has been suggested to increase serum phosphorus due to increased renal tubular resorption. Comparison of their effect on serum phosphorus seems clinically irrelevant).

Changes in ionized serum calcium: The sponsor states that data were sparse for several investigators. Therefore, only summary results have been presented. Approx. 50% of patients in the APD group and 41% in the EHDP were reported to show complete response at Visit 8. Combining with partial response, the response rates were 88% in the APD and 61% in EHDP group, respectively (Table 21a, p.152, vol. 1.41).

Subgroup analyses (based on ionized calcium) of response rates at VIsit 8 based on the presence or absence of bone metastases and usage of furosemide: In the APD group 67% (n=6) of patients without metastases and 94% (n=18) of patients (n=6) with metastases showed complete or partial response. In the EHDP group, 36% of patients (n=11) without metastases and 80% of patients (n=15) with metastases had complete or partial response. In the APD group, there was no difference in complete response rates for patients with or without bone metastases. Whereas, in the EHDP group, almost twice as much patients with bone metastases had complete response compared to patients without bone involvement. In the APD group, the use of furosemide did not seem to cause any major change

in the response rates compared to patients who did not use the diuretic. However, in the EHDp group, the response rate of patients who received furosemide was greater than those who did not use furosemide.

Changes in serum PTH levels: Serum PTH levels were obtained at Visits 1, 8, and 11 from 12 patients in each treatment group. PTH (for intact mol.) was assayed in one center. Because of the small number of patients, both the mean and median values for increases at Visits 8 and 11 from baseline have been presented (Table 22, p.162, vol. 1.41). The results showed an increase in means as well as in median values from the baseline mean after APD and EHDP therapy, which seem to reflect an expected response attributable to lowering of serum calcium levels.

Changes in baseline hypercalcemia-induced symptoms: The changes are shown below:

	% of Patients With Complaints	
	At Baseline APD/EHDP	At Endpoint APD/EHDP
Bone Pain	63/43	53/38
G-I Symp.		
Nausea	29/29	0/18
Vomiting	20/20	Very few
Abd. Pain	10/30	10/15
Anorexia	50-60	30-40

Mental status of patients was also evaluated, but there was "little difference" in the changes between two treatment groups.

Sponsor's Discussion and Interpretation of Efficacy Data:

Summary:

1. The APD group had higher complete responders than the EHDP group ($p < 0.05$) at Visits 4-8 (Days 3-7), based on corrected serum calcium. There were greater reductions in corrected and uncorrected serum calcium levels at Visits 5-8 (Days 4-7) and at Endpoint Visit in the

APD group than EHDP group. Mean corrected serum calcium levels in the EHDP group were never within the normal range during inpatient phase of the study. There were no "treatment failures" in the APD group as opposed to 4 "failures" in the EHDP group (Comments: One patient in the APD group was "non-responders" see Table D, p. 137, vol.1.1).

2. In the APD group, serum albumin levels remained constant throughout the study. Therefore, serum uncorrected calcium value could be a valid parameter for assessing the effects of APD. Changes in corrected and uncorrected serum calcium values showed a close correlation with changes in ionized calcium values.

3. Analysis of complete response which includes only patients whose serum calcium was normalized for at least 2 days resulted in misleading results, because several patients with significant reduction of serum calcium were considered "non-responders." Yet, combined complete and partial response rate in the APD was statistically greater than that of the EHDP group.

4. The onset of effect was within 24 hours after initiation of therapy in both treatment groups. The rate of decrease in corrected serum calcium in the APD group was greater than that of the EHDP group during the first few days (Figure 1A, p.112, vol. 1.41). In both groups all responses (complete and partial) occurred within one week after initiation of therapy.

5. At Visit 8.5 (days 10), 37% of patients in the APD and 9% of patients in the EHDP group had normal corrected serum calcium values. The duration of complte response was similar for both treatment groups (range 5-10 days)

6. The time to relapse was 9.5 days for the APD group vs. 4 days for the EHDP group. However, there was great individual variations in the length of response.

7. Eighty-nine percent of patients without bone metastases and 100% of patients with

metastases in the APD group achieved complete or partial response. Therefore, APD appears to be equally effective in patients with or without bone metastases. Humoral factors play a major role in the etiology of hypercalcemia of malignancy without skeletal involvement. The mechanism of hypocalcemic effect of APD (due mainly to inhibition of osteoclast activity) in such patient is not clear. In the EHDP group, the number of complete responders was less (29%) in patients without bone metastases compared to 59% of patients with bone metastases.

8. Concomitant administration of furosemide during the inpatient phase of the study did not seem to influence the overall response of APD. In the EHDP group a higher percentage (60%) of furosemide treated patients had complete response compared to 33% of patients who did not receive furosemide.

9. Response by cancer type could not be determined clearly, because of small number of patients in each category. In the EHDP group, 5 patients with renal carcinoma were non-responders.

10. Decrease in serum phosphate in the APD group and increase in serum phosphate in the EHDP group could be explained on the basis of differential effects of these two drugs on kidney, bone and PTH secretion.

11. There were some clinical improvements in the G-I symptoms (nausea, vomiting, and anorexia) of hypercalcemia in both treatment groups; a greater degree in the APD group. Bone pain slightly decreased in both treatment groups. Mental status "showed little change from baseline" in either treatment group during the inpatient phase of the study. Most patients were alert during this phase of the study.

Safety Results:

Comparability of the Treatment Groups:

All 65 randomized patients were included in the safety analysis. There were no major differences

between the two treatment groups with respect to demography and medical history.

Increase in body temperature: Seventy-three percent of patients treated with APD and 44% of EHDP treated patients were reported to experience rise in temperature (greater than or equal to $1^{0}C$ above pretreatment temperature) at least once between Visits 2-8. About 50% of these patients also had bacterial infection at one of these visits, which could have contributed to rise in body temperature. Peak increase in body temperature occurred on Visit 3 for both treatment groups. Fever was reported to be remotely or possibly drug related in approx. 17% of APD treated patients and 9% EHDP treated patients.

Blood pressure and pulse rate changes: No significant changes in these parameters were reported during the course of the study in either treatment group.

Infusion site reactions: Two patients in the APD group and 1 EHDP-treated patient were reported to experience pain on palpation, redness, and swelling/ induration at the infusion site at Visits 2-3.

The sponsor has provided a list of medical problems; at least one of which was experienced by the patient during course of the study. With exception of anemia and hypomagnesemia, these events were reported to occur with same frequency in both treatment groups. Anemia and hypomagnesemia both occurred with twice the frequency in the APD group compared to EHDP group. Couple of events of nausea in EHDP treated patients were considered drug-related by the investigator.

Drug-related adverse experiences:

Two patients were discontinued from the study because of remotely- or probably-drug-related medical problems such as hypophosphatemia or hypocalcemia, and one patient died as a result of severe seizure disorder on Visit 3.

Other drug-related adverse reactions which occurred with almost equal frequency in two treatment groups included: Fever occurred in 5 patients in the APD group, and in 3 patient who received EHDP. It was reported generally on Visit 2 or 3. The fever

episodes were moderate to mild in nature. Mild to moderate hypophosphatemia was reported in 2 APD treated patients and in one EHDP treated patient. Mild hypomagnesemia was reported to occur in 2 APD treated patients, and moderate hypomagnesemia in one EHDP treated patient. One patient developed severe convulsions and respiratory distress, which resulted in his death. One patient in the APD group developed asymptomatic hypocalcemia which was resolved after appropriate treatment. Two patients (one in each treatment group) were reported to develop drug-related hypomagnesemia.

Concomitant Medications:

Eight patients in the APD group and 6 in the EHDP received aminoglycoside antibiotic during the study. The sponsor states that in none of the patients who received antibiotics showed any increase in the serum creatinine values which would indicate impairment of renal function. Increase or decrease in serum creatinine values occurred with almost equal frequency in these patients.

Ten patients in the APD group and 12 patients in the EHDP group were reported to receive magnesium during the study. Eight of ten patients in the APD and 5 of 12 patient in the other group were reported to have hypomagnesemia as a medical problem. Only two of these events (one in each group) were reported by the investigator as study drug-related. One patient in the EHDP group who received magnesium (but without hypomagnesemia) experienced sever seizure disorder on Visit 3, and subsequently died on the same day.

Concomitant administration of potassium was reviewed to identify patient who had hypokalemia. Twenty-seven (90%) patients in the APD and 26 (74%) patients were reported to receive potassium during the study. Forty-two to 44% of these patients had identifiable hypokalemia as medical problem. None of the hypokalemia event was considered by the sponsor as test drug related. However, patients who received potassium in the APD group, had more patients with cardiac medical problems (e.g., failure, fluid overload, atrial arrhythmias, hypertension, hypotension, etc.). Except for fluid overload in one EHDP-treated patient, none of the cardiac symptoms in either group were considered study drug-related.

Twenty-four (80%) patients in the APD group and 17 (49%) of patient in the EHDP group received furosemide during the study. More patients in either treatment group were reported to have elevated (25%0 increase) potassium than patients who did not receive furosemide.

Five patients in each treatment group were reported to receive phosphate during the study. Except two patients in the EHDP group, all of these patients had hypophosphatemia as medical problem. In three of these patients (two in the APD and one in EHDP) hypophosphatemia was reported as an adverse reaction.

Except one patient in the APD group and 2 patients in the EHDP group, all patients received saline during the study. These patients were reviewed for a 25% decrease in hematocrit and a 30% decrease in serum albumin. More patients in the APD group (28% and 14%) were reported to have decreased HCT and albumin, respectively compared to 18% and 6% in the EHDP group.

Deaths:

A total of 13 patient were reported to die during the study. According to the sponsor, all but three patients died due to the progression of the malignancy diagnosed at the entry.

Three deaths:

Pt.# 307 (Dr. Ritch): A 69-year-old male patient with small-cell carcinoma of the lung developed seizures two days after initiation of EHDP infusion. Seizure activity was unilateral in nature. Post seizure blood gas analysis revealed pCO_2 = mmHg, pO_2= mmHg, and pH= . Corrected serum calcium decreased from mg/dl to mg/dl. Brain scan performed five months before the study revealed no "apparent lesions," and he had no previous history seizure or any other neurological problems. The investigator attributed seizure event as "possibly" related to EHDP. The sponsor did not rule out a structural brain lesion or a metabolic disorder. Also, suggested a focal brain lesion rather than a metabolic effect or a drug related event.

Pt. # 306 (Dr. Wiernik): A 38-year-old male patient with head and neck sq. cell tumor died 11 days after initiation of EHDP therapy due to progressive pulmonary distress. Patient had tracheostomy, and he was on TPN, and morphine for pain. At Visit 8 his morphine dose was increased (not stated) for increase in the severity of pain. On the next day (VIsit 9), the patient died. The investigator felt that death was not drug-related.

Pt. # 307 (Dr. Wiernik): A 34-year-old female patient with breast cancer was reported to die 6 days after receiving APD. The cause of death was attributed to cardio-pulmonary arrest. The previous treatments for breast cancer included surgery, radiation and chemotherapy. She was also reported to have pneumonia at entry, received Ensure supplement for nutrition, and oxygen for shortness of breath.

Potential serious medical problems which led to discontinuation from the study:

Pt. # 305 (Dr. Richman): Developed syncopal episode and hypoglycemia on Visit 11 after EHDP therapy. The patient had a previous history of alcohol abuse. The episode was probably metabolic and not drug-related. .

Pt. # 302 (Dr. Wiernik): Developed lower extremity weakness on Visit 4. Subsequent myelogram revealed spinal cord compression and metastases at multiple sites.

Pt. # 302 (DR. Wiernik): The patient was reported to develop "probably" APD-related hypocalcemia on Visit 8.5. The patient recovered (without any sequelae) after administration of 50 mEq of calcium gluconate i.v..

Pt. # 306 (Dr. Wiernik): An APD treated patient developed moderate hypophosphatemia on Visits 5, 6, and 7. The patient received i.v. pot. phosphate, and Neutra-phos orally. The patient received unacceptable concomitant medication for hypophosphatemia. The patient died on the day after Visit 7 due to cardiac arrest. No attempt was made to resuscitate the patient because of the order of "do not resuscitate."

Medical problems associated with concomitant illness:

There were 11 patients in the APD and 10 patients in the APD and 10 patients in the EHDP groups had medical problems which resulted in longer hospitalization. The common problems were :

	APD	EHDP
Anorexia	2 pt.	3 pt.
Abd. pain	2 pt	2 pt.
Nausea & vomt.	0 pt.	4 pt.

With the exception of three events in 2 patients, all other events were considered to be related to concomitant illness, and not drug-related.

Clinical lab. parameters (predefined % change from baseline):

Hemoglobin: Twenty-six of 30 patients in the APD group and 21 of 35 patients in the EHDP group were reported to experience a decrease in hemoglobin 10% or more.

Twenty-five percent increase or decrease in WBC count occurred in either treatment group with similar frequency. Almost equal number of patients in either treatment group also showed increase or decrease in lymphocytes. There was no big differences between the two treatment groups regarding changes (from baseline) in other hematologic parameters.

Twelve of 30 (40%) patients in the APD group compared to 4 of 35 (11%) patients in the EHDP group developed hypophosphatamia (serum phosphorus decreased $\geq$ 30% from baseline). Majority of EHDP patients experienced increase in serum phosphate (possible mechanism discussed earlier).

Almost equal number of patients, 19 of 30 and 20 of 35 patients in the APD and EHDP group, respectively showed an increase by 25% in serum creatinine from the baseline at some point during the study. BUN was reported to decrease (10%) in both treatment groups (APD 37% Vs EHDP 66%). Twenty percent of the APD and 6% of the EHDP groups showed an increase of 25% or more.

SGOT/AST were reported to increase in 60% of APD treated patients compared to about 49% of EHDP treated patients. There was an increase (25% or

more) in alk. phosphatase in both treatment groups, 63% of patients in the APD compared to 37% of EHDP treated patients. The origin (skeletal or extraskeletal) of the alk. phosphatase was not determined.

Almost twice the percentage (47%) of patients in the APD group manifested an increase (25% or more) in serum potassium compared to a fewer percentage (26%) of EHDP treated patients. More patients in the APD group had increase in serum potassium, because 90% of patients in this group received potassium supplement.

Thirty-seven percent of patients in the APD group and 20% of patients in the EHDP group were reported to have increased (25% or more) serum magnesium levels. Fewer patients (7% and 14%) showed a decrease in serum magnesium. However, in two patients (one in each group) hypomagne-semia was considered study drug-related.

Changes in the lab. parameters from baseline to terminal determination:

Hematologic parameters showed no significant changes at the terminal determinations from the baseline values.

Thirty-eight percent of patients had decreased serum phosphate levels at study termination compared to none in the EHDP treated patients. At the termination, both treatment groups showed increase in serum potassium. No other blood laboratory parameters showed significant differences between baseline and at study termination.

U/A: Terminal lab. measurements at Visit 6 showed no significant differences in the U/A parameters between two treatment groups. Calculated creatinine clearance was reported to increase by 22% and 16% APD and EHDP treated groups, respectively at Visit 6. By Visit 8, 37% and 20% increases were reported, and at the Endpoint the mean increases were 29% and 8%, respectively.

Sponsor's Conclusion:

In this randomized controlled study, all 65 patients were included in the efficacy evaluation, and the study had no compliance problem.

The results of this study showed that APD 60 mg is more effective than EHDP 7.5 mg/kg/day for 3 days in the treatment of patients with moderate to severe HCM (corrected serum calcium $\geq$12 mg/dl). Normalization of corrected serum calcium (complete response rate) at Visit 8 (Day 7) after starting the treatment was in 70% of patients in the APD group compared to 41% of EHDP treated patients ($p < 0.05$). Complete plus partial response rate together constituted 97% for the APD and 60% for the EHDP group, at the same Visit 8 (Day 7). At Visit 8.5 (Day 10) after the initiation of treatment, 74% of patients of the APD treated patients had a complete or partial response compared to 45% of patients of EHDP group. APD therapy caused statistically significant greater reduction in corrected or uncorrected serum calcium levels than the EHDP group at Visits 5-8 and Endpoint. There was not much difference between the two treatment regimens with respect tc onset and the duration of response. The median time to relapse for the APD group was 9.5 days (with a 95% C.I. of 4-14 days). The presence or absence of bone metastases caused no difference in the response rates; neither administration of furosemide affected the response rate of APD in this study population. There was some improvement in the symptoms of hypercalcemia (bone pain, anorexia, nausea and vomiting).

With regard to the safety of APD or EHDP therapy, all 65 patients experienced at least one medical problem (related or unrelated to the study drug). The most frequent medical problems which occurred in about 30% of patients in one of the treatment group included: fever, anorexia, constipation, nausea, arthralgia, and dyspnea. Anemia, hypokalemia, hypophosphatemia, hypomagnesemia were reported as medical problems in this group. The incidence of $1^{0}C$ rise in the body temperature during the study period was lower (44%) in the EHDP group compared to APD group (73%). There was one case in the APD with atrial flutter, and one case with atrial fibrillation in the EHDP group. There were three cases of CHF (2 in APD and 1 in EHDP). There was no case of renal failure during the course of the study.

Three patients were discontinued from the study for the following reasons: one patient with moderate hypophosphatemia (remotely related to

APD), one patient with severe asymptomatic hypocalcemia (recovered after i.v. calcium), and one patient with severe seizure and subsequent respiratory distress. The last patient died on the same day of seizure, and it was not sure whether he had metastatic brain lesions as the autopsy was not performed.

Medical problems related to the study drugs occurred with similar frequency in two treatment groups. Thirty-three percent of patient in the APD group and 27% of patients in the EHDP group experienced adverse reactions. Fever is the only adverse reaction which occurred in more than two patients in either treatment group; 17% patients in the APD and 9% patients in the EHDP groups. Three adverse reactions (seizure and respiratory distress, and hypocalcemia were considered serious in nature, and remotely or possibly related to study drug. Other adverse reactions which were considered probably drug related included hypomagnesemia (one in APD and one in EHDP group), and one hypocalcemia in APD group.

Thirteen patients died during the course of the study. Six were in the APD group and 7 patients in the EHDP group. Except three patients, all died due to the progression of malignancy diagnosed at entry of the study. The causes of deaths in other three patients were seizure (1 pt.), progressive respiratory distress (1 pt.), and cardio-pulmonary arrest (1 pt.).

In both treatment groups, majority of patients showed a 10% or more decrease in hemoglobin levels. Almost equal percentage of patients in either treatment group showed decrease in WBC counts. More patients in the EHDP group showed at least 25% increase in white cell counts. Decreases (at least 25%) in lymphocyte and platelets were similar (30%-40%) in either treatment group.

Hypophosphatemia ($\geq$ 30% decrease) occurred in 40% and 11% of patients in the APD and EHDP groups, respectively. Majority of patients (57% of patients) of the EHDP group had increase (at least 30%) in serum phosphate levels. SGOT/AST and total bilirubin levels increased in 50%-60% of patients in either treatment group. However, the terminal laboratory values in the inpatient phase showed no significant differences from the baseline values. In both treatment groups, there was aa

trend in decrease in BUN and creatinine. Seventeen percent of patients in the APD group and 6% of patients in the EHDP group showed hypocalcemia (corrected serum calcium below lower limit of normal) during the study. The lowest corrected serum calcium values ranged between 8.0 and 8.4 mg/dl in the APD group, and between 7.9 and 8/1 mg/dl in the EHDP group. All patients with hypophosphatemia or hypocalcemia were asymptomatic.

Risk/benefit assessment: The risks of APD therapy such as asymptomatic hypophospha-temia, fever, and infusion site reactions were clinically insignificant, considering the major benefit of the therapy, which is the achievement of normocalcemia in hypercalcemic patients. In addition, APD treatment resulted in some improvements in the symptoms of hypercalcemia. Therefore, the benefit/risk ratio for APD therapy in the treatment of hypercalcemia of malignancy is favorable.

Reviewer's Comments:

This multicenter, randomized, controlled clinical trial to compare the hypocalcemic effects of APD with that of i.v. EHDP in the treatment of HCM was adequately designed and carried out, considering the complexities of the primary clinical condition of the study population.

The principal criteria for admission to the study was persistent hypercalcemia (corrected serum calcium $\geq$ 12.0 mg/dl) and a histologic diagnosis of malignancy. In the APD group, 43% of patients had baseline corrected serum calcium values between 12.5 and 13.4 mg/dl, and 57% of patients had their baseline corrected serum calcium levels above 13.5 mg/dl. The mean $\pm$ Std baseline corrected serum calcium values for the two groups were 14.6 $\pm$ 2.2 and 13.8 $\pm$ 1.3 mg/dl for the APD and EHDP groups, respectively. The median values for corrected serum calcium showed no difference between the two treatment groups (for APD= 13.8 mg/dl, and for the EHDP= 13.9 mg/dl).

All patients were required to have received 3L of saline (0.9%) i.v., and fluid orally, and to have had urine output of at least 2L in 24 hours (investigators did not report this accurately) preceding administration of the study drug. (Comments: The sponsor should be requested to

address this issue regarding fluid and 0.9% saline intake both during 24-48 hours before Visit 1 (Day 0), and during the inpatient phase of the study at the forthcoming EMEDP Advisory Committee Meeting).

Because of the small sample size, the study distribution of patients by primary site of malignancy in two treatment groups was not close. Patients with lung, breast, kidney, or head and neck cancer were in relatively large numbers in each treatment group. A total of 7 patients in two treatment groups had hematologic cancers (multiple myeloma, chr. lymphocytic leukemia). Seventy percent of patients in the APD group and 60% of patients in the EHDP group had 1-6 or more bone metastases. At baseline, there were no major clinically significant differences between the two treatment groups with respect to type of cancer and bone metastases.

The exclusion criteria were pertinent. Patients who had received radiation therapy within 7 days before or after Visit 1, and patients with serum creatinine levels above 5 mg/dl were to be excluded from the study.

The study drugs were administered according to the protocol and this issue was discussed earlier. The randomization and blinding procedures were satisfactory. The compliance was not a problem in this study because patients were treated with APD or EHDP in a controlled inpatient setting.

The protocol did provide clearly the indications for concomitant medications (e.g., hormonal therapy and corticosteroid treatment), and exclusions of medications (thiazide diuretics, calcitonin, and other bisphosphonates). Phosphate was use in several patients, but as a replacement therapy for hypophosphatemia.

The efficacy variables were appropriate, and essentially similar to those of the approved NDAs for Didronel i.v.(# 19-945) and Calcimar (# 17-497), and also of the submitted NDA (# 19-961 for Gallium nitrate i.v.) for the same Indications and Usage (hypercalcemia of malignancy). The diffusible fraction of serum calcium is comprised of ionized or free serum calcium (about 50% of the total) and calcium complexed to anions (about 10%). The ionized fraction is physiologically active. In

hypoalbuminemic state a low total serum calcium may not be associated with low levels of ionized calcium. For this reason serum calcium values are adjusted to reflect accurately the ionized calcium levels from the serum total calcium. The formula used to calculate the corrected serum calcium in this study was basically the same one used in the study under protocol 01. The corrected serum calcium in absence of a direct measurement of ionized serum calcium is acceptable.

With regard to the safety of the test drugs, the sponsor's presentation of Medical Problems related or unrelated to therapy, based on predefined relationships (not related, remote, possibly related, probably related, and definitely related) was reasonably well and appropriate. Additional safety parameters such as cardiovascular changes, infusion site reactions, changes in body temperature and clinical laboratory (blood and urine) parameters were appropriate for the study.

The sample size calculation to determine the efficacy of the treatment group, as well as to detect a significant difference between two groups was appropriate. Statistical consult review may have additional comments on this issue.

All 65 patients were evaluated for efficacy and safety of the test drugs. Six patients in the APD group and 10 patients in the EHDP group were discontinued from the study during the inpatient phase. The major reasons were death (2 in the APD and 4 in the EHDP), relapse (2 patients in each group), and unsatisfactory therapeutic response (3 in EHDP).

There were protocol violations with respect to fluid intake and output, use of oral phosphate, and low dose continuous steroid or cancer chemotherapy throughout the study. The investigator and the monitor both felt that violations had "little impact on the efficacy results." The sponsor probably would address these issues in their presentation before the EMEDP Advisory Committee meeting in October 1990. With respect to radiation therapy, the Data Listing 8A on p.133 of vol 1.43 is some what misleading. This reviewer called the sponsor and requested a clarification on the number of patient who had received radiation within 7 days from Visit 1. Dr. [redacted]en of Ciba-Geigy called back on 7/31/90 and said that only

three patients (# 301 and 307 of Dr. Weirnik and # 304 of Dr. Richmasn) received radiation on Visit 1 (Day 0) of the study. There were two major protocol violations; one was concomitant calcitonin therapy (400 IU daily) throughout the study, and the other one was admission of a patient with baseline corrected serum calcium level of < 12 mg/dl. The sponsor states that the latter patient was enrolled into the study before the protocol was amended to enter patients with corrected serum calcium ≥ 12 mg/dl. In the Intent-to-Treat efficacy analysis all 65 patients who received the drugs were included. During the follow up phase of the study there were some deviations from the patients' visit schedule. These deviations appear to be minor and reassigned visits were able to achieve the protocol objectives. The serum PTH assay was initially scheduled on Visit 1, but during the course of the study it was decided to have repeat assays from the blood samples collected on Visits 8 and 11.

Efficacy:

All 65 patients (30 in APD 60 mg and 35 in EHDP 7.5 mg/kg/day groups) were initially included in the efficacy evaluation. The sponsor's calculated values for the corrected serum calcium matched the investigators' values in most cases, but in some differed by 0.2 mg/dl. In the efficacy analysis based on corrected serum calcium, patient (# 315 of DR. Weirnik on EHDP) was excluded because of nonavailability of baseline serum albumin value.

There were no statistically significant differences between the two treatment groups with respect to demographic parameters and baseline data. Fifty-three percent of patients in the APD group and 29% of patients in the EHDP group received at least 40 mg i.v. or orally furosemide at some visit during the inpatient phase of the study. This prompted the sponsor to analyze the efficacy data with and without significant use of furosemide. The comparison of treatment groups with respect to total daily fluid intake, 0.9% saline intake, and BUN/creatinine ratio was appropriate for efficacy and safety evaluations.

The complete (normalization) response rate (based on corrected serum calcium) at Visit 8 (Day 7) for the APD (60 mg) was significantly greater ($p < 0.05$) than the response rate of 41%, achieved with

EHDP (7.5 mg/kg). The response rate in either treatment group was stated to be greater than anticipated response rate of 20% with saline hydration as stated by the sponsor. However, the response rates for the APD and EHDP treatment groups at Visits 2-3, and Visit 2, respectively were statistically less than the anticipated rate for the saline. When partial responders were added to complete responders, the response rates for the two treatment groups were 97% and 65%, respectively at Days 3-7 after initiation of therapy. The difference was statistically significant ($p < 0.01$). One patient (3%) in the APD was non-responder (decrease inadequate to meet the requirement for complete or partial response) compared to 12 patients (35%) in the EHDP group were non-responders/ failures (no decrease). Mean decreases from baseline in corrected serum calcium values at Days 4-7 and at Endpoint were greater ($p < 0.05$) than those in the EHDP treated patients. The mean values of corrected serum calcium in the APD group during the same period ranged between 10.4-10.7 mg/dl, compared to nadir of 11.0 mg/dl at Day 6 in the EHDP group. The onset of hypocalcemic action of both agents was during the first 24 hours after treatment initiation, and 87% of patients in the APD and 58% of patients in the EHDP group achieved complete or partial response by Day 4. The duration of hypocalcemic action of both drugs was analyzed by three different ways: a) number of responders at Day 10 and 14 during the follow-up phase - 47% at Day 10 and 43% at Day 14 in APD group; 15% at Day 10 and 18% at Day 14 in the EHDP group, b) duration of complete response-median duration 7 days (95% C.I. 1-14) for the APD; median duration of 5 days (95% C.I. 2-29) for EHDP, and c) time to relapse-median time (days) to relapse was 9.5 (95% C.I. 4-14) for the APD and 4 (95% C.I. 0-6) for the EHDP ($p < 0.05$ favoring APD).

Subgroup analysis of data based on the severity of hypercalcemia showed that APD 60 mg was able to normalize corrected serum calcium in patients with baseline values <13 mg/dl, but not in patients with baseline values $\geq$ 13 mg/dl. In the EHDP group, corrected serum calcium was not normalized if the baseline mean values were above 12.5 mg/dl. Based on these findings the sponsor has proposed to use APD 60 mg for patients with baseline corrected serum calcium < 13 mg/dl, and 90 mg for patients with baseline values above 13 mg/dl. The

sponsor's assumption appears to be pertinent and also supported by a literature report which suggests higher dose of APD for patients with "severe" hypercalcemia.

Complete response rate analyzed by body weight showed no evidence in support of dose adjustment for patients with low, moderate or high body weights.

Complete plus partial response rates based on corrected serum calcium, and mean corrected serum calcium levels at Endpoint for patients who had received significant amount of furosemide during the inpatient phase showed no difference from those of patients who did not receive any furosemide. The sponsor has concluded that treatment with furosemide is not necessary when HCM is treated with APD. This reviewer feels that some patients may need furosemide to avoid development of hypernatremia and pulmonary edema from aggressive i.v. saline infusion.

The response rates (based on corrected serum calcium) and mean corrected serum calcium levels at Endpoint were very similar in either treatment group with respect to the type of cancer and presence or absence of bone metastases. However, the number of patients per cancer type is not adequate and the results need to be interpreted cautiously.

The APD 60 mg treatment group also showed statistically higher complete and partial response rates than EHDP treatment group.

Following our recommendation (made at the pre-NDA meeting), the sponsor has reanalyzed the data excluding patients who had a complete or partial response of only one day duration. Such patients were considered non-responders. The reanalysis of complete response based on corrected serum calcium showed complete response rates at Visit 8 of 50% and 41% for the APD and EHDP groups, respectively. The complete plus partial response rates for the two treatment groups were 87% and 62%

The complete or partial response rates (based on ionized calcium) also showed a higher percentage of patients responded (88%) to APD than EHDP (60%).

Either treatment with APD or EHDP led to an increase in mean and median serum PTH levels (assayed for the intact molecule for 12 patients in each treatment group) from the suppressed baseline levels. This only suggests an anticipated feedback response of parathyroid glands to lowering of serum ionized serum calcium levels.

The calculated BUN/creatinine ratios during the inpatient and follow-up phases were analyzed. At Endpoint, there was almost an equal median reduction (2-2.5) in both treatment groups. During the inpatient phase (Days 2-6), there was a small reduction in the mean serum albumin level; the maximum mean reduction was 0.3 g/dl.

The data regarding improvement of symptoms of HCM as a result of treatment with APD or EHDP should be interpreted cautiously, because of small number patients with some symptoms of HCM at Visit 1 and the complex nature of the study population.

Safety:

Although 73% of patients in APD and 44% of patients in EHDP groups had at least once rise in body temperature by 1^0C above the pre-treatment temperature during Visits 2-8, the investigators felt that 17% of patients of the former and 7% of patients of the latter treatment groups were related to study drugs. In majority of patients fever (mild to moderate) was reported on only one visit.

Three to seven percent of patients of two treatment groups experienced one of the following symptoms (pain, redness or swelling/induration) at the injection site on Visits 2 or 3. A number of medical problems (such as abdominal pain, arthralgia, hypokalemia) were reported to occur with almost equal frequency in both treatment groups. Anemia and hypomagnesemia occurred in almost twice the number of patients in the APD group compared to EHDP group.

One patient in the APD group developed moderate hypophosphatemia on Visit 5 which appeared drug-related. This patient required i.v. potassium phosphate and Neutra-phos orally. This patient was discontinued from the study. Another patient in the same treatment group developed drug-related

"severe hypocalcemia." Higher incidence (in 17% of patients) of hypocalcemia which ranged between 8.0-8.4 mg/dl occurred in APD group compared 6% of patient in EHDP group with lowest corrected serum calcium ranging between 7.9 and 8.1 mg/dl. One patient in the EHDP group developed "severe seizure" on Visit 3, and died on the same day. The investigator felt that seizure was "possibly related to EHDP administration." An unilateral seizure is likely to be due to a focal lesion rather than a drug-related event. The patient was acidemic (pH and had significantly elevated $paCO_2$, mmHg.

Of total thirteen deaths in two treatment groups during the study, all but three patients were reported to die due to progression of the cancer. Of the three remaining patients, one died due to severe seizure episode in the EHDP group (possible cause discussed earlier), one patient with squamous cell head and neck cancer in the EHDP group died due to progressive pulmonary distress, and one patient in the APD group with metastatic breast cancer died due to cardio-pulmonary arrest. None of the deaths appear to have any relation to test drug, except for the patient with seizure episode due to questionable relation to EHDP therapy.

On page 081 of vol. 1.41, it is mentioned that two patients were either hospitalized or had their hospitalization prolonged due to three "medical problems," and cited Table 40. Table 40 showed only two medical problems, seizure and respiratory distress in one patient which required hospitalization or prolongation of hospital stay. The sponsor needs to clarify this minor discrepancy.

In conclusion, the results of this positive-controlled clinical trial seems provide adequate evidence of efficacy and safety of APD 60 mg and EHDP 7.5 mg/kg in the treatment of patients with persistent cancer related hypercalcemia after hydration. EHDP (Didronel i.v.) is an approved drug for the same indication. In comparison, APD appears to be more effective than EHDP for the following reasons:

1. For APD a single 24-hour i.v. infusion is needed compared to daily 24-hour infusion of EHDP for three consecutive days.

2. Seventy percent of patients treated with APD achieved normalization of corrected serum calcium as opposed to 41% of EHDP treated patients ($p < 0.05$).

3. Ninety-seven percent of patients in the APD group had complete (normalization) plus partial response (at least 15% decrease from the baseline) in the APD group compared to 65% of patients in the EHDP group ($p < 0.001$).

4. Mean decreases in corrected serum calcium levels at Days 4-7 and Endpoint in the APD group were significantly greater ($p < 0.05$) than those of the EHDP group.

5. There were more than twice the number of patients (though not statistically significant) in the APD group with complete or partial response at Days 10 and 14 of the follow-up phase of the study.

6. APD appears to be more effective by severity of baseline hypercalcemia.

7. Subgroup analysis of data seems to indicate that concomitant furosemide use would not affect hypocalcemic effect of APD. Whereas, in the EHDP group, there is some suggestive evidence that concomitant furosemide use would potentiate its effect.

8. APD was equally effective in patients with or without bony metastases; 78% of patients without metastases had normalization of serum calcium in the APD group compared to 29% of patients in the EHDP group. Thus, it appears that APD is equally effective in hypercalcemia caused by humoral factors.

Reviewer's Overall Comments:

The controlled study carried out under protocol 01 was a dose finding and efficacy trial of APD at three doses (30, 60, and 90 mg). The results indicated a dose-response relationship with respect to percentage of patients with normaliz-ation of posthydration elevated ($\geq$ 12.0 mg/dl) corrected serum calcium values (by Day 7) in patients with HCM. Both at 60 and 90 mg doses, APD was shown

to have greater response rate ($p < 0.05$) than "anticipated response rate" with saline alone. APD at 90 mg dose level was shown to elicit complete response rate in 100% of treated patients ($p< 0.05$) when compared to response rates at 30 and 60 mg). The results of this study seems to provide evidence of efficacy of APD in a dose range of 60-90 mg in the treatment of moderate to severe HCM.

The second controlled (involving an active control) study carried out under protocol 03, was to compare the efficacy and safety of a single infusion of 60 mg APD with etidronate disodium (EHDP), 7.5 mg/kg/day for 3 consecutive days. The primary determinant of efficacy in this study were the same as in protocol 01. The results of this study demonstrated a greater efficacy of APD with respect to number of responders (complete and complete plus partial) by Day 7 ($p< 0.05$) in patients with moderate to sever HCM.

Both APD and EHDP had onset of effect within 24 hours after initiation of treatment. APD at doses 60 and 90 mg and EHDP produced complete or partial response in majority of patients (58%-87%) by Day 4 of the study. The duration of response analyzed by three different ways indicated slightly longer duration with respect to "Median time to relapse" and "Median duration of complete response."

Subgroup analyses of data based on concomitant furosemide use ($\geq$ 40 mg orally or i.v. at some day during the inpatient phase), presence or absence of bone metastases, and type of cancer revealed no significant differences in response rates at 60 and 90 mg APD doses. However, the results of subgroup analyses should be viewed cautiously because of small number of patients in some subgroups. APD appears to be effective in HCM irrespective of pathophysiologic etiology of hypercalcemia (i.e., localized osteolysis, humoral factor mediated, and myeloma and related hematologic malignancy). With regard to concomitant use of radiation therapy, there were three patients who received radiation therapy on Day 1 (The sponsor conveyed this information when asked about the timing of the radiation therapy in protocol 03 study).

The data on APD-induced changes in urinary excretion of hydroxyproline and calcium tend to

reflect the principal mechanism of action of APD, i.e., inhibition of bone resorption.

The side effects identified as study drug (APD)-related in these two studies were fever (18%), infusion site reactions (7%), anorexia (5%), nausea (5%), hypophospha-temia (16%), hypomagnesemia (12%). These medical problems occurred in at least 5% of all patients pooled together. A host of other minor study drug-related medical problems (e.g., edema, abdominal pain, tachycardia, constipation, anemia, somnolence, blurred vision) in less than 5% of patients. The frequency of fever, hypophosphatemia and hypomagnesemia was slightly higher in the APD treated patients compared to EHDP group.

Six (7%) of APD-treated patients were reported to experience 8 events of severe (considered by the investigators) medical problems. These events included somnolence (severe lethargy), hypocalcemia, atr. fibrillation, anemia, hypophosphatemia, hypokalemia, and thrombocytopenia/anemia. Three additional patients were reported to experience serious or potentially serious medical problems possibly related to the APD, and these were marked decrease in hematocrit level 2 days after receiving 90 mg of APD (improved after transfusion) in one patient, episode of supraventricular tachycardia four days after receiving 90 mg of APD in one patient, and marked decrease in hematocrit and hemoglobin levels during 48 hours after 30 mg of APD. There was no clear evidence of association of APD and changes in some of these hematologic parameters. It is difficult to ascertain a definite cause and effect relationship between APD and many of these medical problems. In conclusion, single-dose (60 or 90 mg) administration of APD in the treatment of moderate to severe hypercalcemia of malignancy seems to be well tolerated, and the clinical benefits seem to outweigh the risks involved.

A total of 26 published reports on the use of APD in the treatment of HCM have been reviewed. The majority of these reports are open studies and deal with the efficacy and safety of the drug for this indication. Few of them, in addition, have also dealt with the mechanism of action of APD (Harnick et al 1987, # 16). The results of two dose-response studies (Body et al 1987, #15; Thiebaud et al 1988, # 19) seem to support the conclusion

of the study # 01 with respect to effective and safe dosage range of APD for the treatment of HCM. Several studies have compared the efficacy of APD at different doses with that of the other available treatment regimens (e.g, oral phosphate, mithramycin, glucocorticoid, hydration, calcitonin; Mundy et al 1983, #2; Ralston et al 1986, #7). Ralston et al reported that mithramycin, APD, and corticosteroid in combination with calcitonin were all effective in decreasing elevated serum calcium levels in HCM. Corticosteroid and calcitonin caused rapid decrease in serum calcium, but they seldom caused normalization of calcium. Some patients in the mithramycin group developed thrombocytopenia and hepatotoxicity. In one study combined APD (15 mg/day i.v.) and calcitonin (100 IU q 8 hours s.c) resulted in prompt (by Day 3) normalization of corrected serum calcium in 8 patients with HCM. There were no side effects to combination therapy.

The findings of other open-label efficacy studies with APD in HCM provide adequate supportive evidence of efficacy and safety of APD (60 or 90 mg single 24 i.v.infusion in the treatment of HCM, and generally in agreement with the results of two controlled studies of the NDA.

Review of Safety Update Data (submitted on April 26,1990, covering the period from December 1989 to April 1990):

The sponsor states that safety update data have been collected from a total 930 patients, and these patients were involved in 4 U.S. studies (protocols 02, 04, 06, and 07), 14 European studies (11 in HCM and 3 in breast cancer patients with skeletal metastases), 12 studies reported in the literature, and the International Data Base on APD which includes 32 case reports. The protocols 02 and 04 are blinded trials which are still ongoing.

Review of the safety update data reveals no additional clinically significant information on safety of a single 60 or 90 mg of APD infusion over 24 hours in the treatment HCM. In HCM studies, fever, hypocalcemia, and hypomagnesemia were the most commonly mentioned medical problems.

6. Labeling: The proposed draft labeling needs extensive revisions including INDICATIONS and USAGE section. Labeling revisions will be undertaken after presentation of the NDA before the EMEDP Advisory Committee on October 15, 1990.

7. Conclusion and Recommendation: This New Drug Application (#20-036), which provides substantial evidence of safety and efficacy of a single i.v. infusion (over 24 hours) of APD (60 or 90 mg) for the treatment of moderate to severe cancer-related hypercalcemia is approvable. The proposed package insert requires extensive revisions (including the Indications and Usage section), which will be undertaken after presentation of the NDA before the EMEDP Advisory Committee on October 15, 1990.

S.N. Dutta, M.D.

cc: Orig. NDA 20-036
HFD-340
HFD-510
HFD-510/SND/Pierce

excellent.
See team leader's comments.
L. Pierce, MD

DIV

APR 10 1991

NDA 20-036 Rev. Completed: 4/8/91
Pamidronate Disodium Inj.
(Aredia)

Review and Evaluation of Clinical data

1. Name of drug: Trade: Aredia
   Generic: Pamidronate disodium injection

2. Dosage form and route of administration: Available in vials. Each vial contains 30 mg sterile, lyophilized, pamidronate disodium and 470 mg of mannitol, USP. The contents of each vial is reconstituted in 10 ml of S' ile Water for Injection, USP. The recommended dose is diluted in 1 L of sterile 0.45% or 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP prior to i.v. infusion over 24 hours.

3. Category or use of drug: In conjunction with adequate hydration, it is indicated for the treatment of hypercalcemia associated with malignancy, with or without metastases.

4. Reason for submission: Revised Draft Package Insert.

5. Date of submission: February 22, 1991.

6. Summary evaluation:

   The draft package insert has been revised to incorporate recommendations indicated in our Telefax of February 7, 1991 (Copy attached).

   The sponsor has incorporated almost all of our recommendations in this revised draft labeling. However, in the first two lines of this document, the statement " For Intravenous Infusion" has been left out of the heading. According to the sponsor, this has been done to make the presentation "consistent with the recently approved insert for Ganite." This reviewer feels that package inserts for both products should include the statement "For Intravenous Infusion" in the heading.

7. Conclusion and recommendation:

   The sponsor has incorporated almost all of our recommendations in revising the initial draft labeling submitted to the NDA. The revised draft labeling of February 22, 1991 is acceptable.

S.N.Dutta, M.D.

cc: Orig. NDA 20-036
HFD-340
HFD-510/SND Pierce

Agree that for the IV infusion heading should be added.

Draft clinical review, [illegible] 4/10/91

DIV

APR 25 1991

NDA 20-036
Pamidronate Disodium (Aredia)

Review Completed: 4/4/91

Review and Evaluation of Clinical data

1. Name of drug: Generic: Pamidronate disodium injection
   Trade: Aredia

2. Dosage form and route of administration: Available in vials, each contains 30 mg of sterile, lyophilized, pamidronate disodium and 470 mg of mannitol, USP. It should be reconstituted by adding 10 ml of Sterile Water for Injection, USP, to each vial. The recommended dose should be diluted in 1000 ml of sterile 0.45% or 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP. Administered as a single-dose, intravenous infusion over 24 hours.

3. Category or use of drug: For use in the treatment of hypercalcemia of malignancy.

4. Date of submission: 11/21/90

5. Reason for submission: Safety update report to original NDA.

6. Summary Evaluation: This Safety Update report covers the period from December 1989 to November 1990, and includes data from a) ongoing U.S. clinical trials, b) data from from European clinical trials, and c) data from published International literature.

A. Safety data from ongoing U.S. studies:

I. Two controlled studies are ongoing (# 02 and # 04).

The common medical problems reported in these two studies (still blinded) are presented below:

Medical Problems (% of patients)

Protocol 02	Protocol 04
Constipation (59%)	Headache (47%)
Anorexia (39%)	Bone pain (41%)
Nausea (35%)	Gen. pain (38%)
Vomiting (23%)	Hypertension (25%)

Diarrhea 22%) Osteoarthritis (23%)

II. Two open-label studies (# 06 and # 07). Medical problems occurring in patients are presented in table below:

Protocol 06	Protocol 07
Fever (13%-21%)	Pain (7%-19%)
Nausea (6%-29%)	Nausea (6%-22%)
Arthralgia (12%-21%)	
Dyspnea (7%-20%)	

B. Safety data from open European studies:

No. of Trials	Indications
11	HCM
3	

Medical problems with an incidence $\geq$ 15% in above-mentioned studies:

Fever, and hypocalcemia (asymptomatic and transient).

Changes in laboratory values:

hypophosphatemia/hyperphosphatemia, and decreased lymphocyte counts.

C. Medical problems reported in published literature:

The sponsor states that 18 reports have been reviewed. However, data from these reports could not be accurately assessed, because some patients have been included in more than one publications. Seven of 18 reports have no mention of adverse medical problems associated with APD therapy. Again, in these reports the common medical problems associated with pamidronate include fever, rigors, and asymptomatic hypocalcemia.

D. Medical problems from international data base consisted of 53 case reports covering the period from 1987 to 1990:

The most common medical problems were fever (16 reports), rigors (9 reports), and hypocalcemia (5 reports).

Medical problems related to study drug:

The following medical problems have been reported to be study drug-related in one or more of the U.S. studies: fever (8%-13%), pain (22%), bone pain (17%), headache (11%), hypomagnesemia (9%), and dizziness (8%), nausea (6%), and arthralgia (6%). Other study drug-related problems occurred in 1% to 4% of patients of these studies included asthenia, chest pain, local edema, phlebitis, anorexia, constipation, dyspepsia, hematemesis, jaundice, anxiety, leg cramps, hypertonia, hyporeflexia, hematuria, and urinary incontinence.

Assessment of deaths, serious drug-related medical problems, and premature discontinuation of patients from U.S. studies:

Protocol #	No. of Deaths
02	8
04	2
06 and 07	18

In no case was the death considered study drug-related by the sponsor. One death under protocol 02 was considered secondary to "fluid overload." by the sponsor. None of the 6 serious medical problems identified in protocols 02, 04, 06, and 07 was considered to be drug-related. No patient in these studies was discontinued due to a drug-related medical problems. Common reasons for discontinuation were unsatisfactory therapeutic response, concomitant illness, and unacceptable concomitant medication.

Clinical laboratory evaluations;

Studies 02 and 04 are ongoing and still blinded. Findings from the European data base are difficult to analyze mainly because of inconsistency. Six and 3 of 112 patients in protocols 06 and 07 were reported to develop asymptomatic hypocalcemia and hypophosphatemia, respectively. Hematologic changes in these two protocols are difficult to evaluate because of concomitant chemotherapy.

Renal and hepatic functions (in protocols 06 and 07):

Improvement of creatinine clearance from baseline to 3 months posttreatment was reported in "all treatment

groups." Some patients showed increase in serum creatinine ($\geq$ 0.5 mg/dl) from baseline. Liver isoenzymes (SGOT and SGPT) were reported to be within the normal range in these studies.

The sponsor has provided some information from animal studies. In one study, the effects of bisphosphonates on developing enamels during the secretory stage in rat molars have been tested. Under light microscopy, "subameloblastic cyst formation" was noted with APD and EHDP treated rats at relatively high doses. A statement related to this effect may be incorporated in the package insert of the product. Pharmacologists to note this effect.

7. Conclusion and recommendation: The safety update report provides no new clinically significant date. The safety profile of pamidronate disodium reported to this submission is quite similar to that reported to the original NDA.

S.N. Dutta, M.D.

cc: Orig. NDA 20-036
HFD-340
HFD-510
HFD-510/SND/Pierce

4-25-91

DIV

MAY 22 1991

NDA 20-036
Pamidronate Disodium Inj.
(Aredia)

Rev. Completed: 5/21/91

Review and Evaluation of Clinical Data

1. Name of drug: Trade: Aredia
   Generic: Pamidronate disodium injection

2. Dosage form and route of administration: Available in vials. Each vial contains 30 mg of sterile, lyophilized, pamidronate disodium and 470 mg of mannitol, USP. The contents of each vial is reconstituted in 10 ml of Sterile Water for Injection, USP. The recommended dose is diluted in 1 L of sterile 0.045% or 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP prior to i.v. infusion over 24 hours.

3. Category or use of drug: In conjunction with adequate hydration, it is indicated for the treatment of hypercalcemia associated with malignancy, with or without metastases.

4. Reason for submission: Revised draft package insert in which the sponsor has incorporated all of the Division requests (Telefaxed on May 3,1991) for revisions.

5. Date of submission: May 10, 1991.

6. Summary Evaluation: The sponsor has incorporated all of our recommended revisions in this draft package insert. This draft labeling is acceptable. The sponsor should be requested to add baseline mean corrected serum calcium values for each group of patients under subheading Clinical Trials of the labeling.

S.N.Dutta, M.D.

cc: Orig. NDA 20-036
HFD-340
HFD-510
HFD-510/SND/Pierce/Olmstead/5/21/91

Under Clinical Trials subheading, add "(etidronate disodium)", following the first "Didronel".

5-22-91

510

MAY 23 1991

NDA 20-036 Review Completed: 5/22/91
Pamidronate Disodium Inj.
(Aredia)

Review and Evaluation of Clinical Data

1. Name of drug: Trade: Aredia
Generic: Pamidronate disodium injection

2. Dosage form and route of administration: Available in vials. Each vial contains 30 mg of sterile, lyophilized, pamidronate disodium and 470 mg of mannitol, USP. The contents of each vial is reconstituted in 10 ml of Sterile Water for Injection, USP. The recommended dose of Aredia is diluted in 1 L of sterile 0.45% or 0.9% Sodium Chloride, USP or 5% Dextrose injection, USP prior to i.v. infusion over 24 hours.

3. Category or use of drug: Aredia, in conjunction with adequate hydration, is indicated for the treatment of hypercalcemia associated with malignancy, with or without metastases.

4. Reason for submission: Safety update report which covers the period from November 1990 to May 1991.

5. Date of submission: May 17,1991

6. Summary evaluation:

This report contains data from eight U.S. (n=270) and 14 open-label European studies (n=458), published literature reports and from Ciba-Geigy international data base. Of 8 U.S. studies, 4 are blinded ongoing trials

Complete analysis of data from these 4 blinded studies have not been performed. Unblinded U.S. studies involved patients with a variety of ailments,

Fourteen European trials involved patients with cancer-induced hypercalcemia and breast cancer patients with bone metastases.

From published literature reports, a total of 310 patients have been reviewed for medical problems. From the Ciba-Geigy international data base 54 cases with a total of 153 medical problems have been reviewed.

An overview of medical problems:

The "Most common medical problems" and "Serious medical problems" (deaths, CVAs, convulsions, coma, cardiac ischemia, renal failure) from different sources are listed in Tables 1A-1C on pages 028-037.

The types of "Most common medical problems" reported from U.S. blinded studies are similar to those already reported to the original NDA and previous safety update report. Since the frequency of each medical event was calculated among all patients of each blinded study, it was difficult to ascertain what percentage of Aredia-treated patients experienced individual medical problem compared to placebo treated patients. None of the reported serious medical problems (including deaths) appear to be study drug-related.

The medical problems reported in U.S. open-label studies are similar to those reported in the original NDA.

The medical problems/adverse experiences cited from published literature and Ciba-Geigy international database are also similar to those reported in the original NDA.

The medical problems identified as study drug-related in these studies included the following (with percentages of patients in parenthesis):

Fever (3%-18%), hypomagnesemia (9%), bone pain (33%), dizziness(8%), headache (6%-55%), constipation (3%-17%), nausea (10%-17%), vomiting (17%), arthritis (1%-2%), depression (1%-2%), hyporeflexia (1%-2%), breast pain (1%-2%),rigor (2%-30%), phlebitis (5%-12%), abdominal pain (5%), injection site reactions (33%), keratitis (33%), peptic ulcer (6%), hypertension (10%), fatigue (10).

There were 10 deaths in all U. S. studies. None of these deaths appear to be study drug-related. Most of these deaths were due to progression of malignancy. There were few deaths due to respiratory arrest, MI or stroke. In foreign studies there were 4 deaths; two of them were considered as not drug-related and in remaining 2, the causal relationship between the study drug and death could not be determined "due to insufficient data."

The sponsor has reported 4 "serious or potentially serious drug related medical problems," and these are persistent hypocalcemia associated with convulsions, "acute toxic erythema," rigors, pyrexia and bone pain, and "coffee ground" vomiting. Except acute toxic erythema, all other medical problems are mentioned in the draft package insert of the product. Additionally, these medical problems will be

monitored in "postmarketing" ADR reports.

7. Conclusion and recommendation: This safety update report covering the period from November 1990 to May 1991 provides no new clinically significant safety information. No action is indicated on this submission.

S.N.Dutta,M.D.

cc: Orig. NDA 20-036
HFD-340
~~HFD-510~~
HFD-510-SND/Pierce/5/22/91

Convulsions are listed in the proposed PI, but it is not therein stated that these were in association with Aredia-induced hypocalcemia. If the hypocalcemic convulsions reported in this su were in ptr receiving Aredia IV for hypercalcemia of malignancy, convulsions associated with Aredia-induced hypocalcemia should be added to the P.I.

RKP mic, MD
5/23/91

GROUP LEADER'S MEMO

NDA: 20036
DRUG: AREDIA (PAMIDRONATE DISODIUM) FOR IV INFUSION
SPONSOR: CIBA-GEIGY
DATE OF MEMO: 5-30-91

The sponsor has presented adequate data from 2 well-controlled clinical trials (protocols 01 and 03) that establish the efficacy and safety of Aredia in the treatment of symptomatic hypercalcemia of malignancy. While the results of the parallel dose ranging study (protocol 01), suggested a higher complete response rate (100%) with 90 mg dose compared to 60 mg, the 90 mg dose was associated with a greater incidence of pain and local reaction at the infusion site. The revised draft labeling appropriately indicates that the dosage for moderate hypercalcemia (corrected serum calcium 12-13.5 mg/dl) is 60-90 mg, and is 90 mg (infused over 24 hr) for severe hypercalcemia (> 13.5 mg/dl). The dosage and administration section states that consideration should be given to the severity of as well as the symptoms of hypercalcemia.

A discussion of the results of the comparative trial with etidronate (protocol 03) which demonstrated statistical superiority in the proportion of complete responders in the Aredia group is found in the MOR on pp 87-88. This study supports the efficacy of a 60 mg dose of Aredia.

The safety and efficacy profile of Aredia for the treatment of hypercalcemia of malignancy appears to be at least equivalent to, and possible superior to that of recently approved gallium nitrate, as judged from an historical comparison of different studies.

Aredia (pamidronate disodium) is ready for approval for the treatment of hypercalcemia of malignancy.

Ross Pierce, M.D.

cc
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HFD 510-
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