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APPLICATION NUMBER: NDA 20036/S-016

STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

sNDA#:	20-927
Applicant:	~~Ciba-Geigy Corporation~~ NOVARTIS
Name of Drug:	Aredia (Pamidronate disodium for injection)
Indication:	Treatment of osteolytic bone metastases in conjunction with standard anti-neoplastic therapy.
Documents Reviewed:	Vols. 1, 56-65, 82-110 dated September 22, 1997 SAS Database dated February 4, 1998
Medical Officer:	Grant Williams, M.D. (HFD-150)

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BACKGROUND

Aredia was approved on October 31, 1991 for treatment of hypercalcemia of malignancy. A supplement NDA (based on protocol 12E) for treatment of osteolytic bone lesions of multiple myeloma was approved on September 1, 1995. A supplement NDA (based on the first 12 months data, i.e., the core phase of protocols 18 and 19) for treatment of osteolytic bone metastases of breast cancer was approved on July 16, 1996.

In September 1997, Novartis submitted a supplement NDA for review. This sNDA contains the extension phase, i.e., the second 12 months, of protocols 18 and 19. They are phase III, randomized, placebo-controlled trials in patients with breast cancer. These studies are in support of an application for palliative treatment for osteolytic bone metastases when given in addition to antineoplastic therapy. The sponsor proposed to "remove the qualifying statement in the indications section of the package insert that states that the effect of Aredia was less pronounced in the hormonally treated patients (Trial 18) than in the chemotherapy treated patients (Trial 19)." This review pertains to the extension phase of Trials 18 and 19. For a summary of the first 12 months evaluation, please see the Statistical Review and Evaluation of sNDA 20-036/s011 dated July 12, 1996.

Sponsor's Tables summarized in this review are labeled Tables #S(#=1, .., 6). This reviewer's evaluations can be found in Tables #R (#=1, .., 4).

PROTOCOL 19

1 BRIEF DESCRIPTION

TRIAL DESIGN - This was a multicenter (89), international, stratified, randomized, parallel, double-blind, placebo-controlled trial.

Three hundred and eighty-two patients with stage IV breast cancer and lytic bone lesions treated with **chemotherapy** were stratified according to their baseline ECOG performance status (0,1 vs 2,3) at trial entry i.e., visit 1 (day -14 to day 0). Those who were eligible were then randomized to receive either Aredia (n=185) or placebo (n=197) at visit 2 (day 0). The enrollment period was a little over 3 years, starting on January 3, 1991 and ending on March 1, 1994. The 90 mg Aredia treatment was administered in 250 ml of 5% dextrose in water where the placebo contained 250 ml of 5% dextrose in water only. Duration of treatment was 2-hour intravenous infusion at intervals of 4-week for 24 months. Phase I (the core phase) including efficacy and safety collected from the first 12 months of treatment was completed on March 13, 1995. Phase II (the extension phase) consisting of the second 12 months was completed on March 21, 1996.

OBJECTIVE - The objective was to determine the safety, especially with respect to survival, of long-term intravenous Aredia administration. The primary safety variable was survival. In order to determine the long-term efficacy of Aredia in the prevention of skeletal-related episodes in patients with stage IV breast cancer receiving chemotherapy, efficacy variables (SMR-HCM: skeletal morbidity rate excluding hypercalcemia, SRE-HCM: proportion of at least one skeletal related events excluding hypercalcemia, and TTSRE: time to first skeletal-related episodes) specified in the core phase were examined.

STATISTICAL PLAN - The planned statistical analyses are: "1) Wilcoxon rank-sum test for between treatment comparisons of SMR (including/excluding HCM), also of each individual type of SMR; 2) Chi-Square test for between treatment comparisons of the proportion of patients having any SRE (including/excluding HCM) and 95% confidence interval for the proportions in each treatment group, also for each individual type of SRE; 3) Kaplan-Meier estimate of the time from randomization to the first occurrence of any SRE within each treatment group, and log-rank test for between-treatment comparisons of the 'survival functions'. Two analysis time points were (1) at the end of the core phase (12 months) and (2) at the end of the extension phase (24 months). No adjustments to the p-values for the two analysis time points are planned...."

2 OVERVIEW OF THE SPONSOR'S RESULTS

Of the 382 patients, the randomization assigned 185 patients to Aredia and 197 patients to placebo. The primary efficacy analysis was based on the set of all randomized patients (ITT) excluding two patients: who were found not to have bone metastases. Premature discontinuation was primarily due to adverse experience, therapy refusal, unsatisfactory therapeutic response and death. The dropout rate was a little higher in the placebo group compared to that in the Aredia group. These dropout rates were 60% vs 52% at the end of the core phase and were 85% vs. 76% at the end of the extension phase. The percentages for these reasons were similar in both treatment groups except those for unsatisfactory therapeutic response (19% in placebo and 10% in Aredia).

The treatment groups (Aredia vs. placebo) at baseline were comparable with respect to number of lytic bone lesions and prior cancer therapy. There was no statistically significant difference between Aredia and placebo at baseline for the quality of life variables overall and

within each stratum. In stratum 2 (worse ECOG baseline values), patients in the Aredia group were older, the median ages were 62 years in Aredia and 55 years in placebo.

Primary safety endpoint - Survival

Survival was monitored for all randomized patients as a safety variable to determine if the survival estimates for the Aredia patients were at least as good as those for the placebo patients. The sponsor stated that no significant difference was found in the survival rates between the Aredia and the placebo treatment groups for all randomized patients. The median survival were 14.0 months (95%CI: 11.7 - 17.2 months) in placebo and 14.8 months (95%CI: 12.6 - 19.9 months) in Aredia. The sponsor stated that none of the deaths were considered to be trial-drug-related (20% in Aredia and 16% in placebo).

Efficacy related endpoints used at the end of the core phase

Skeletal morbidity rate (SMR=#SRE/year)

The median times on trial were 11.9 months for the Aredia group and 10.2 months for the placebo group. Table 1S summarizes the results on the primary efficacy endpoint (the skeletal morbidity rate of any SRE(-HCM) by 12 months) used at the end of the core phase, and on each individual type of SMR by 3 months up to 24 months with an increment of 3 months. For the calculation of the SMR, events occurring at visits 3-15 for Core phase or visits 3-27 for Core+Extension phase were counted and normalized to 28 days then multiplied by 12 to show the event rate per year. Visit 3 was the first post-baseline visit. The mean, median, and p-value based on raw SMR (protocol specified primary analysis) and the p-value based on modified SMR from Wilcoxon rank sum test were presented. The difference between raw and modified SMR is the rank assigned to patients who did not have an SRE during their time on study. The 'raw' method assigned a constant rank but the 'modified' method assigned ranks based on patients' lengths of time on trial.

The raw and modified SMR(-HCM) at 12 months were statistically significantly ($p=.004$ and $p<.001$, Wilcoxon rank sum test) lower in Aredia than in placebo. This is the protocol defined primary efficacy endpoint analysis. There were a total of 374 SRE(-HCM) in Aredia and 591 in placebo at the end of the extension Phase. The raw and the modified SMR(-HCM) were statistically significantly lower in Aredia than in placebo at 15 months, 18 months, 21 months, and 24 months. When these episodes were analyzed by specific types, except for pathological fracture, the Aredia group had lower event rates with p-value $<.05$ by 12 months as well as 24 months in non-vertebral fracture, radiation to bone, radiation to bone for pain relief, surgery to bone, hypercalcemia episode.

Table 1S. Summary of SMR(+/-HCM) and each individual type of SMR (Trial 19)

Ared. Plac. n=185 n=195	3-mon Are Pbo	6-mon Are Pbo	9-mon Are Pbo	12-mon Are Pbo	15-mon Are Pbo	18-mon Are Pbo	21-mon Are Pbo	24-mon Are Pbo
SMR-HCM(/yr)								
Median	0 0	0 0	0 1	**0 1**	0 1.5	0 1.5	0 1.6	0 1.8
Mean	2.8 2.5	2.7 2.9	2.4 3.1	**2.5 3.3**	2.4 3.5	2.5 3.6	2.5 3.6	2.5 3.7
p-value*	p=.517	p=.044	p=.002	**p=.004#**	p<.001	p<.001	p<.001	p<.001
P-value**	p=.306	p=.010	p<.001	p<.001	p<.001	p<.001	p<.001	p<.001
SMR+HCM(/yr)								
Median	0 0	0 1.6	0 1.1	0 1.8	0 1.5	0 1.8	0 1.9	0 2.1
Mean	2.8 2.9	2.7 3.4	2.5 3.7	2.6 3.8	2.5 4.0	2.6 4.2	2.6 4.2	2.6 4.3
p-value*	p=.175	p=.009	p<.001	p<.001	p<.001	p<.001	p<.001	p<.001
Path. Fracture(/yr)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	2.0 1.6	1.8 1.8	1.6 1.9	1.7 2.0	1.5 2.0	1.6 2.1	1.6 2.1	1.6 2.2
P-value*	p=.731	p=.628	p=.336	p=.368	p=.063	p=.044	p=.037	p=.018
Vert. Fracture (/yr)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	0.8 0.5	0.7 0.6	0.7 0.8	0.7 0.8	0.7 0.9	0.7 0.9	0.7 0.9	0.7 0.9
P-value*	p=.067	p=.079	p=.523	p=.416	p=.776	p=.928	p=.905	P=.778
NonV.Fracture								
Median(/yr)	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	1.2 1.1	1.1 1.2	1.0 1.1	0.9 1.2	0.9 1.2	0.9 1.2	0.9 1.2	0.9 1.3
P-value*	p=.620	p=.115	p=.085	p=.037	p=.020	p=.008	p=.007	p=.002
Spinal Cord Com/colla. (/yr)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	0.02 0.02	0.04 0.02	0.04 0.03	0.04 0.03	.04 .04	.04 .04	.04 .05	.04 .05
P-value*	p=.976	p=.295	p=.952	p=.659	p=.589	p=.589	p=.419	p=.419
Radi.t.bone(/yr)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	0.6 0.8	0.7 0.9	0.7 1.1	0.7 1.1	0.7 1.2	0.7 1.2	0.8 1.2	0.8 1.3
P-value*	p=.268	p=.038	p=.002	p=.003	p<.001	p<.001	p<.001	p<.001
Radi.t.bone(/yr) (pain relief)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	0.5 0.6	0.5 0.8	0.5 0.9	0.5 1.0	0.6 1.0	0.6 1.0	0.6 1.0	0.6 1.1
P-value*	p=.455	p=.038	p=.001	p=.003	p<.001	p<.001	p<.001	p<.001
Surg.t.bone(/yr)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	0.12 0.12	0.10 0.14	0.10 0.16	0.10 0.17	.11 .16	.11 .17	.11 .17	.11 .17
P-value*	p=.476	p=.114	p=.028	p=.025	p=.031	p=.026	p=.012	p=.013
Hypercal. (/yr)								
Median	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean	0.03 0.43	0.09 0.50	0.09 0.55	0.09 0.56	.09 .58	.09 .58	.09 .58	.09 .58
P-value*	p=.014	p=.270	p=.031	p=.024	p=.005	p=.002	p=.002	p=.007

the protocol defined primary efficacy analysis
* Wilcoxon-rank-sum test (raw SMR)
** Wilcoxon-rank-sum test (modified SMR)

Proportion of patients with at least one skeletal related event

The proportion of patients having any SRE(-HCM), SRE(+HCM) up to 24 months with an increment of 3 months are summarized in Table 2S.

Table 2S. Proportion of patients having any SRE(+/-HCM) (Trial 19)

Aredia (n=185) Placebo(n=195)	3-mon Are Pbo	6-mon Are Pbo	9-mon Are Pbo	12-mon Are Pbo	15-mon Are Pbo	18-mon Are Pbo	21-mon Are Pbo	24-mon Are Pbo
Any SRE-HCM								
Proportion	27% 30%	35% 47%	37% 52%	43% 56%	43% 62%	45% 64%	45% 64%	46% 65%
95%CI for diff (Pbo-Are)	(-6%, 12%)	(2%, 21%)	(6%, 25%)	(4%, 24%)	(8%, 28%)	(8%, 28%)	(8%, 28%)	(8%, 28%)
Chi-square	p=.487	p=.022	p=.002	p=.008	p<.001	p<.001	p<.001	p<.001
Any SRE+HCM								
Proportion	28% 34%	37% 51%	39% 57%	46% 62%	46% 67%	49% 69%	49% 69%	50% 70%
95%CI for diff (Pbo-Are)	(-3%, 16%)	(4%, 24%)	(8%, 28%)	(6%, 26%)	(10%,30%)	(10%,30%)	(10%,30%)	(10%,30%)
Chi-square	p=.185	p=.006	p<.001	p=.002	p<.001	p<.001	p<.001	p<.001

The proportion of patients having any SRE(-HCM) was statistically significantly lower in Aredia than in placebo during the extension phase. At the end of Phases I and II, the odds ratio of having an event on placebo to that on Aredia was 2.1 with a 95% CI of (1.4, 3.2) indicating that the odds of having an event on placebo are statistically significantly greater than on Aredia. The sponsor stated that "age had a significant effect on the proportion of patients having events however, in that the proportion of patients having SREs was larger among ≤50 years old patients than among > 50 years old patients."

Time to first skeletal related event

Time to first SRE(-HCM) was statistically significantly shorter for placebo than for Aredia (7.0 months vs. 13.9 months; p<.001, log-rank test, see Table 3S) by 24 months. Note that time to first SRE(-HCM) was calculated as time from visit 2 (first drug administration date) to the minimum of time to first fracture, time to first spinal cord compression/collapse, time to first radiation to bone, and time to first surgery to bone. The censoring rates were 35% (placebo) vs. 54% (Aredia). Of those censored patients, 22% (placebo) vs 21% (Aredia) completed the core phase and the extension phase without an SRE.

Table 3S. Time to first SRE analysis for Trial 19

Aredia (N=185) Placebo (N=195)	At the end of 12-months Aredia	Placebo	At the end of 24-months Aredia	Placebo
Time to first SRE(-HCM)				
Median (month)	13.1	7.0	13.9	7.0
(95% CI)	(10.9, -)	(6.1, 9.1)	(11.0, 25.5)	(6.0, 9.1)
Censoring	57%	44%	54%	35%
log-rank test	P=.005		P<.001	

PROTOCOL 18

1 BRIEF DESCRIPTION

TRIAL DESIGN - This was a multicenter, international, stratified, randomized, parallel, double-blind, placebo-controlled trial. Three hundred and seventy-two patients with stage IV breast cancer and lytic bone lesions treated with **hormonal therapy** were stratified according to their baseline ECOG performance status (0,1 vs 2,3) at trial entry. Those who were eligible were then randomized at each study center to receive either Aredia (n=180) or placebo (n=192). The enrollment period was a little over 3 years, starting on Dec. 21, 1990 and ending in March, 1994. The core phase, including efficacy and safety collected from the first 12 months of treatment, was completed on June 23, 1995. The extension phase, consisting of the second 12 months, was completed on July 01, 1996. Additional safety and efficacy data as well as survival follow-up in the extension phase were collected.

The primary trial objective was to determine the effect of monthly 2-hour IV infusion of 90 mg Aredia compared to placebo in stage IV breast cancer patients treated with hormonal therapy and having predominantly lytic metastatic lesions on the prevention of skeletal related episodes. The primary efficacy variable was the SMR(-HCM) during the first 12 months of the trial. Efficacy varibles of secondary interest (SRE related endpoints) and the secondary endpoints (pain, narcotic scores, ECOG, QOL etc.), the statistical plan, the drug dosage and the administration schedule were the same as Protocol 19.

2 OVERVIEW OF THE RESULTS

Of the 372 patients, the randomization assigned 180 patients to Aredia and 192 patients to placebo, but 182 patients received Aredia and 189 patients received placebo, respectively. One patient randomized to placebo group was excluded from the ITT analysis because of no bone metastases. Note that 2 patients randomized to placebo actually received more than 3 infusions of Aredia and were included in the Aredia group for analysis. Several other patients received a wrong treatment infusion during the core phase or the extension phase, or no infusion; those patients were included in their original randomized treatment arm. The dropout rate was a little higher for the placebo group (48%) than for the Aredia group (38%) at the end of the core phase. These rates were similar (67% in placebo and 63% in Aredia) at the end of the extension phase. Reasons of premature discontinuation were primarily adverse experience, unsatisfactory therapeutic response, therapy refusal, and death. The percentages of these reasons were similar in both treatment groups except for those with unsatisfactory response (10% in placebo and 6% in Aredia) and death (11% in placebo and 19% in Aredia).

The demographic and important prognostic characteristics, including origin, age, country, and ECOG performance status at baseline were reasonably well matched in the two treatment groups. There were no statistically significant differences between Aredia and placebo at baseline with respect to the quality of life variables.