CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20036/S-015

MEDICAL REVIEW(S)

Aredia Efficacy Supplement for Breast Cancer
(Two-year data on efficacy and safety in breast cancer)

1. General Information:

1.1 **NDA#** 20-927
- 1.1.2 **Review:** Type 6 NDA review
- 1.1.3 **Submission date:** September 22, 1997
- 1.1.4 **Date of Review** September 18, 1998
- 1.1.5 **Related applications:** IND
  NDA 20,036

1.2 **Drug Name**
- 1.2.1 **Generic name:** Pamidronate disodium for injection
- 1.2.2 **Trade name:** Aredia

1.3 **Applicant:** Novartis

1.4 **Pharmacologic Category:** Biphosphonate anti-hypercalcemia agent

1.5 **Proposed Indication:** Extension of treatment and follow-up from one year to two years in treatment of patients with osteolytic bone metastases from breast cancer.

1.6 **Dosage Form:**

Available in vials each containing 30, 60, or 90 mg of lyophilized pamidronate disodium and varying amounts of mannitol, USP for i.v. infusion

1.7 **Recommended Dose and schedule:**

90 mg diluted in 250 ml sterile saline or D5W intravenously over 2 hours repeated every 2-3 weeks.

2.0 TABLE OF CONTENTS

3.0 Material Reviewed

The following are the locations of the most important documents utilized in review of the submission:

Proposed Labeling:	Volume 1
Study report, patients receiving chemotherapy (P19)	Volume 30
Study report, patients receiving hormones (P18)	Volume 18
Integrated summaries of Safety and Efficacy	Volume 55

4.0 Introductory comments

Aredia was approved for treatment of patients with osteolytic lesions from breast cancer in 1996 based on 1-year data from 2 studies, Study P19, a study in patients receiving chemotherapy, and P18, a study in patients receiving hormone therapy. This supplement is submitted to update the labeling with data extending followup and treatment to 2 years. The reviewer will briefly review the design of the trials, the efficacy data, the safety data, and the proposed labeling.

5.0 Design of Protocol 19 (Chemotherapy)

COMPARATIVE TRIAL OF AREDIA VERSUS PLACEBO IN THE PREVENTION OF SKELETAL-RELATED COMPLICATIONS IN PATIENTS WITH BREAST CANCER AND LYTIC BONE LESIONS TREATED WITH CHEMOTHERAPY. PROTOCOL 19

STUDY DATES

FIRST PATIENT TREATED:	JANUARY 3, 1991
STUDY CLOSED TO ENROLLMENT:	MARCH 1, 1994
PREVIOUS STUDY REPORT:	10/20/95
PHASE II END	MARCH 1996

Summary of design

The following are excerpts from the original medical officer review of the efficacy supplement for breast cancer.

Objective

- Primary: To determine whether patients treated with Aredia 90 mg IV monthly will have significantly fewer skeletal-related events at 12 months (the end of study 'Phase I') than patients treated with placebo (250 ml 5% dextrose in water). The primary efficacy variable is the mean number of SRE (excluding instances of hypercalcemia) per patient per month.

- Secondary -Assess differences in palliative treatment (pain relief, QOL, performance status) of patients with breast cancer being treated with chemotherapy.

  -Assess safety and tolerableness of repeated doses of Aredia during 'phase II' (second year follow-up of study patients).

Reviewer comment:
Note that the final analysis for efficacy was to occur after phase I. The phase II objective was only to evaluate safety and tolerableness. This design would not support additional efficacy claims being made at 2 years.

Design:

This was a multi-center, randomized, parallel, double-blind, placebo-controlled stratified trial comparing 90 mg Aredia in D5W to D5W alone (placebo). Drug or placebo were given intravenously over 2 hours at intervals of 4 wks in patients with breast cancer who at least one predominantly osteolytic lesion and were being treated with chemotherapy. Phase I of the trial, which was to assess efficacy, was to last 12 months while the safety phase (phase II) was to continue for 24 months.

Strata:

ECOG performance status 0,1 versus 2,3.

The anticipated trial duration was to be 36 months: 12 months accrual, 12 months treatment, and 12 months additional follow-up (for phase II).

Selected Inclusion Criteria

The most pertinent inclusion criteria are listed below:

- Osteolytic lesions:
  - -2 osteolytic lesions, one of which is 1 cm2 and no radiation to lesion in past 3 months.

    or

  - -One osteolytic lesion 1 cm2 which has never been treated with radiotherapy and presence of extra skeletal metastases.
- Must be receiving chemotherapy with marketed drugs.

Selected Exclusion Criteria

- Serum creatinine > 2.5 mg/dl.
- Clinically significant ascites or bilirubin > 2.5 mg/dl.
- Treatment for hypercalcemia or a corrected Calcium ≥ 12.0 mg/dl during the 14 days prior to visit 2 (date of first treatment).
- Pathologic fracture, spinal cord compression or radiation therapy for bone pain within 12 days of visit 2.

Visit schedule

The following table was created from selected elements from the follow-up schema in the protocol:

Tests	Phase I (year 1)	Phase II (year 2)
Bone Scan and Skeletal Radiographs	0,6,9,12 months	18, 24 months
Recording Skeletal-Related Events and interim physical exam	Monthly	Monthly
Routine labs (CBC,calcium,serum chemistries)	Monthly	Monthly
CEA	0,2,4,6,9,12 months	15,19,24 months
QOL Assessments (Pain, Narcotic, QOL index, and ECOG PS)	-14 to 0d; 0,3,4,6,9,10,12 months	15,16,18,21,22,24 months

Starting with visit number 4, scheduled visits were at 28 day intervals. Visit 1 and Visit 3 (occurring 2 weeks before and 2 weeks after the first treatment, respectively) were for recording baseline information whereas visit 2 and all visits after visit 3 were for both treatment and information gathering.

At visits 6,9,15,21, and 27, Bone Lesion Response of bone surveys was to be determined by the central radiologist. At visit 12 a study termination form (for efficacy phase) was to be completed for each patient.

Details of Data Collection for Specific Endpoints

Skeletal Related Event:

At Visit 1 (baseline), the number of SRE's in the previous 3 months were to be noted. At visit 2, any patient with an SRE in the previous 14 days was to be excluded from the trial. SRE's were also to be recorded at each monthly visit. A skeletal related event was defined as any of the following:

1. Hypercalcemia: need for treatment of hypercalcemia (symptoms or a corrected

calcium ≥ 12 mg/dl).

2. Pathologic Fracture

3. Spinal cord compression/collapse

4. Radiation to bone for Pain Relief (expanded in 3/94 to include use of Strontium)

5. Radiation to Prevent spinal cord compression

6. Radiation to prevent pathologic fracture

7 Surgery to prevent spinal cord compression

8 Surgery to prevent pathologic fractures.

Reviewer Comment
Terms such as 'pathologic fracture' are not defined.

Toxicity Criteria:

NCI common toxicity criteria were used. Special criteria were utilized for some laboratory tests not included in those criteria.

Off-study Criteria

Unlike most oncology studies, patients were to remain onstudy regardless of disease progression. The only reasons for going offstudy were to be patient or investigator assessment that it was in the patient's best interest to do so. Any time a patient went off-study, the final visit data form was to be filled out.

Efficacy Considerations

Primary Endpoint:

The primary efficacy analysis was declared to be an intent to treat analysis of the 'Skeletal Morbidity Rate, excluding hypercalcemia [SMR(-HCM)]' during the first 12 months of the trial (phase I). SMR(-HCM) is defined as the number of SRE's, excluding hypercalcemia, divided by the number of months a patient participated in Phase I.

Reviewer comments:

The calculation and comparison of rates seems to suggest that rates are constant over a patient's time on-study. If there is significant dropout, and if event rates differ according

to time on-study, differential dropout between the 2 arms could produce spurious differences in rates.

Prognostic factors prospectively defined for use with the efficacy analyses included:

-Renal function (Cr < 2.0 vs ≥2.0)
-PS (ECOG 0-1 vs >1))
-age (≤50 vs >50)

Secondary Efficacy endpoints

The protocol specified analysis of several endpoints at 3, 6, 9, 12 months, and at last visit ('endpoint visit') as secondary analyses. These endpoints included the SMR (+/-HCM), proportion of patients with any SRE (+/-HCM), time to first occurrence of first SRE, evaluation of each individual type of SRE, pain and narcotic scores, quality of life index, performance status, response measurements from radiologic results on lytic lesions, and serum CEA measurements.

Pain score and Narcotic score were calculated as follows:

Pain score = (pain severity) X (Pain frequency)

For severity:
none = 0
mild = 1
moderate = 2
severe = 3

For frequency:
none = 0
occasional= 1
intermittent (at least once a day) = 2
Constant (most of the time) = 3

Reviewer comments:
Multiplication by the frequency category seems just as likely to obscure as to clarify the meaning of the pain severity.

Narcotic score = (medication type) X (medication frequency)

For medication type:

0 = none
1 = mild analgesic (OTC)
2 = mild narcotic (30 mg codeine, oxycodone, meperidine.)

3 = Strong narcotic (60 mg codeine, morphine, hydromorphone, etc.)

The quality of life index is from Spitzer (Spitzer, W.D. Measuring the quality of life of cancer patient,. A concise QL-index for use by physicians. J Chron Dis 34: 585-597, 1981.) The categories are rated 0-2 and include:

Activity
Daily Living
Health
Support
Outlook

Statistical Issues (protocol, p 39)

The trial was initially designed to have 80% power to detect a 15% difference in proportion of patients with any SRE (including hypercalcemia) during the first 12 months. 268 patients were needed; 300 were to be enrolled assuming a 5% loss to follow-up rate. Analyses were to be intent-to-treat analyses. The sample size calculation was based on this endpoint rather than the SMR endpoint since only data on proportions of patients were available for estimation.

The following tests were to be used for endpoints discussed above under Efficacy:

-The primary analysis method is ratio of occurrences divided by time of exposure in each patient and was to be compared between arms by Wilcoxon Rank Sum test.

-Proportions of patients with any SRE (including and excluding hypercalcemia) were to be compared at 3, 6, and 9 months on-study using the chi-squared statistic. Time to occurrence of SRE was to be compared using Kaplan-Meier plots and the logrank test.

-Between-treatment comparisons for change in the various QOL scores were to use the Wilcoxon Rank Sum Test. Within-treatment differences from baseline were to be analyzed using the Wilcoxon signed-rank statistics. Survival was to be analyzed using the logrank test at the end of Phase I (12 months) and Phase II (24 months).

Summary points from review of Protocol P 19:

In general, this is a well-designed, double-blind, placebo-controlled trial to evaluate the occurrence of morbid events associated with bone destruction caused by metastatic breast cancer.

- The primary endpoint specified by the sponsor was Skeletal Morbidity Rate. Underlying assumptions of using this endpoint should be considered:

-Is event rate constant over time? Do drop-outs occur at similar times on the 2 arms?

-In the proposed modified Wilcoxon rank sum test, patients with no events are ranked the highest, and of these, those with the longest time of followup the highest. If there were an imbalance of dropouts, with numerous dropouts of short-follow-up on one arm, such an analysis might not be appropriate. Such an analysis would place higher value on a dropout followed for a short time than on a patient with a single event followed for the full time. Such a value-judgment would have to be re-examined in light of the actual frequency and timing of events in the data.

-Analysis of time to first event could demonstrate whether these findings are robust.

Design of P18

A COMPARATIVE TRIAL OF AREDIA® VERSUS PLACEBO FOR THE PREVENTION OF SKELETAL-RELATED COMPLICATIONS IN PATIENTS WITH BREAST CANCER AND LYTIC BONE LESIONS TREATED WITH HORMONAL THERAPY

STUDY DATES

FIRST PATIENT TREATED:	DECEMBER 21, 1990
STUDY CLOSED TO ENROLLMENT:	MAY 2, 1994
LAST STUDY REPORT:	10/20/95
PHASE II COMPLETE	JULY 1996

Objective

Same as P19 for this population.

Design:

Same as P19.

Selected Inclusion Criteria

- Must be receiving hormonal therapy with marketed drugs.

Selected Exclusion Criteria

- No chemotherapy was allowed for 3 months prior to first treatment visit. Patients changing to chemotherapy during the trial were to be continued in the study. Originally, these patients were not to be included in the primary analysis. However, the 3/94 amendment specified that all patients were to be included in the primary analysis.

- Study design was essentially identical to that of the chemotherapy trial (P19) except that hormonal therapy was required instead of chemotherapy.

6.0 Updated Efficacy Data

6.1 Patient Disposition

382 patients were treated in Protocol 19 (chemotherapy patients) as outlined in the following table from the submission:

Distribution of patients by treatment group

Number of patients	Aredia	Placebo	Total
Randomized	185	197	382
Received	185	197	382
Excluded from Intent-To-Treat	0	2	2
Included in Intent-To Treat Analysis:	**185**	**195**	**380**
Stratum 1	121 (65%)	128 (66%)	249 (66%)
Stratum 2	64 (35%)	67 (34%)	131 (34%)
Completed Phase I +	99 (54%)	82 (42%)	181 (48%)
Completed Phase II	47 (25%)	35 (18%)	82 (22%)

+ Include patients who discontinued at Visits 15

Similarly, 372 patients were enrolled in protocol 18 (hormone patients):

Distribution of patients by treatment group

Number of patients	Aredia	Placebo	Total
Randomized	180	192	372
Received	182	190	372
Excluded from Intent-To-Treat	0	1	1
Included in Intent-To-Treat Analysis:	**182**	**189**	**371**
Stratum 1	144 (79%)	139 (74%)	283 (76%)
Stratum 2	28 (21%)	50 (26%)	88 (24%)
Completed Phase I	113 (62%)	98 (52%)	211 (57%)
Completed Phase II	68 (37%)	65 (34%)	133 (36%)

Notice that only about a third of the hormone-treated patients and less than a forth of the chemotherapy-treated patients finished 2 years of Aredia or placebo therapy.

Reasons for dropout are listed in the following tables:

Protocol 19 (chemotherapy)

Protocol 19

Summary of Reason for Premature Discontinuation

	Phase I		Phase I and II	
	Aredia	**Placebo**	**Aredia**	**Placebo**
For Adverse experience	28 (15%)	28 (14%)	45 (24%)	45 (23%)
Unsatisfactory Therapeutic Response	14 (8%)	25 (13%)	18 (10%)	36 (19%)
Use of Unacceptable Medication	3 (2%)	3 (2%)	5 (3%)	9 (5%)
Failure to Follow Appointment Schedule	3 (2%)	5 (3%)	4 (2%)	5 (3%)
Therapy Refusal	20 (11%)	23 (12%)	26 (14%)	28 (14%)
Lost to Follow-up	1 (<1%)	3 (2%)	2 (1%)	4 (2%)
Administrative Problem	1 (<1%)	5 (3%)	2 (1%)	6 (3%)
Abnormal Lab Values	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Death	26 (14%)	25 (13%)	38 (20%)	31 (16%)
Total Discontinued	96 (52%)	117 (60%)	140 (76%)	165 (85%)

Protocol 18(hormone therapy)

Summary of Reason for Premature Discontinuation

	Phase I		Phase I and II	
	Aredia	**Placebo**	**Aredia**	**Placebo**
For Adverse experience	19 (10%)	24 (13%)	36 (20%)	31 (16%)
Unsatisfactory Therapeutic Response	8 (4%)	14 (7%)	10 (6%)	19 (10%)
Use of Unacceptable Medication	1(<1%)	4 (2%)	6 (3%)	8 (4%)
Failure to Follow Appointment Schedule	2 (1%)	4 (2%)	3 (2%)	6 (3%)
Therapy Refusal	21 (12%)	24 (13%)	26 (14%)	33 (18%)
Abnormal Laboratory Value	0 (0%)	2 (1%)	0 (0%)	2 (1%)
Lost to Follow-up	0 (0%)	1 (<1%)	0 (0%)	2 (1%)
Administrative Problem	0 (0%)	2 (1%)	0 (0%)	4 (2%)
Death	18 (10%)	16 (9%)	34 (9%)	21(11%)
Total Discontinued	69 (38%)	91 (48%)	115(63%)	126(67%)

There has been no appreciable change in the reasons for going offstudy in either study from the phase I analysis (year 1) to the phase II analysis (year 2).

6.2 Efficacy: SMR

The results for skeletal morbidity rate are outlined in the following table from the submission:

Mean SMR (#SRE/year)

	Protocol 18 Phase I	Protocol 18 Phases I and II	Protocol 19+ Phase I	Protocol 19 Phase I and II
	SRE(-HCM)	SRE (-HCM)	SRE(-HCM)	SRE(-HCM)
Aredia	2.4	2.4	2.1	2.5
Placebo	3.5	3.6	3.3	3.7
P-value	0.051	.021	.004	<0.001

+ Exclude the Patient

The applicant also lists the morbidity rates for each of the components of the scale outlined in the following table from the application:

Mean SMR (#SRE/year)

	N	Pathologic Fractures	Vertebral Fractures	Non-Vertebral Fractures	Radiation To Bone	Surgery To Bone	Spinal Cord Compression	HCM
Protocol 19 (Phase I)								
Aredia	185	1.4	0.7	0.7	0.6	.10	.02	.09
Placebo	195	2.0	0.8	1.2	1.1	.17	.03	.56
P-Value		.368	.416	.037	.003	.025	.659	.024
Protocol 19 (Phase I and II)								
Aredia	185	1.6	0.7	0.9	0.8	.11	.04	.09
Placebo	195	2.2	0.9	1.3	1.3	.17	.05	.58
P-Value		.018	.778	.002	<0.001	.013	.419	.007
Protocol 18 (Phase I)								
Aredia	182	1.7	0.6	1.0	0.6	.10	.04	.05
Placebo	189	2.1	0.8	1.4	1.1	.12	.09	.14
P-Value		.108	.581	.744	.005	.570	.980	.143

Protocol 18 (Phase I and II)								
Aredia	185	1.6	0.7	0.9	0.6	.10	.05	.06
Placebo	189	2.2	0.9	1.4	1.2	.13	.10	.17
P-Value		.040	.429	.359	.013	.241	.734	.037

The next analysis is the proportions of patients with events. The following analysis summarizes the proportions of patients with any SRE (-HCM):

		Phase I		Phase I and II	
	N	SRE(-HCM)		SRE (-HCM)	
Protocol 19					
Aredia	185	79 (43%)		86 (46%)	
Placebo	195	110 (56%)		126 (65%)	
P-Value		.008		<0.001	
Protocol 18					
Aredia	182	85 (47%)		100 (55%)	
Placebo	189	104 (55%)		120 (63%)	
P-Value		.109		.094	

The following table derived from a table in the submission summarizes the proportions analysis of the individual components of the SRE endpoint:

	N	Pathologic Fractures	Vertebral Fractures	Non-Vertebral Fractures	Radiation To Bone	Surgery To Bone	Spinal Cord Compression	HCM
Protocol 19 (Phase I)								
Aredia	185	63 (34%)	42 (23%)	37 (20%)	36 (19%)	7 (4%)	4 (2%)	11 (6%)
Placebo	195	76 (39%)	37 (19%)	59 (30%)	65 (33%)	19 (10%)	3 (2%)	24 (12%)
P-value		.320	.371	.021	.002	.021	.651	.032
Protocol 19 (Phase I and II)								
Aredia	185	67 (36%)	47 (25%)	42 (23%)	51 (28%)	9 (5%)	4 (2%)	13 (7%)
Placebo	195	95 (49%)	51 (26%)	74 (38%)	88 (45%)	24 (12%)	7 (4%)	30 (15%)
P-value		0.014	.868	.001	<0.001	0.010	.407	.010

Protocol 18 (Phase I) Aredia Placebo P-value	 182 189	 66 (36%) 83 (44%) .133	 37 (20%) 42 (22%) .656	 56 (31%) 59 (31%) .926	 39 (21%) 63 (33%) .010	 10 (6%) 13 (7%) .581	 4 (2%) 4 (2%) .957	 5 (3%) 11 (6%) .145
Protocol 18 (Phase I and II) Aredia Placebo P-value	 182 189	 81 (45%) 103 (55%) .054	 50 (28%) 58 (31%) .496	 66 (36%) 75 (40%) .498	 56 (31%) 76 (40%) .058	 13 (7%) 20 (11%) .245	 7 (4%) 6 (3%) .725	 8 (4%) 19 (10%) .036

Time to first SRE is updated in the following table derived from a table in the submission:

Median Time to First SRE (months)

	Phase I		Phase I and II	
	SRE (-HCM)		SRE (-HCM)	
Protocol 19 Aredia Placebo P-Value	 13.1 7.0 .005		 13.9 7.0 <0.001	
Protocol 18 Aredia Placebo P-Value	 10.9 7.4 .163		 10.9 7.4 .118	

Notice that the difference between the arms became more significant from phase I to phase II in the chemotherapy group (Protocol 19) but the difference was still not significant in the hormonal group (Protocol 18).

6.3 Quality of life

Updated analyses of quality of life are summarized in the following 2 tables from the application.

Protocol 19 (Phase I and II)

	Mean Change from Baseline at the Last Measurement				
	N	Aredia	N	Placebo	Between-Treatment P-Value
Pain score	175	+0.93	183	+1.69	.050
Analgesic score	175	+0.74	183	+1.55	.009
ECOG	178	+0.81	186	+1.19	.002
Spitzer QOL	177	- 1.76	185	-2.21	.103

Protocol 18 (Phase I and II)

	Mean Change from Baseline at the Last Measurement				
	N	Aredia	N	Placebo	Between-Treatment P-Value
Pain score	173	+0.50	179	+1.60	.007
Analgesic score	173	+0.90	179	+2.28	<.001
ECOG	175	+0.95	182	+0.90	.733
Spitzer QOL	173	-1.86	181	-2.05	.409

Reviewer comment

The sponsor wishes to reword the section of the labeling by replacing

with

This last statement seems misleading since only % of the patients actually completed phase II.

6.4 Sponsor's efficacy conclusions:

The following are the sponsor's efficacy conclusions copied from page 42 of the ISE: