Table 7-3. Demographic summary by treatment group (Safety evaluable patients)

	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg
Age (years)			
n	563	524	556
mean ± SD	59.7 ± 12.00	58.9 ± 12.33	58.8 ± 12.65
median	60.0	59.0	58.5
Age - n (%)			
≤ 60	301 (53.5)	290 (55.3)	307 (55.2)
> 60	262 (46.5)	234 (44.7)	249 (44.8)
Sex - n (%)			
male	104 (18.5)	96 (18.3)	92 (16.5)
female	459 (81.5)	428 (81.7)	464 (83.5)
Race - n (%)			
Caucasian	495 (87.9)	442 (84.4)	484 (87.1)
black	34 (6.0)	43 (8.2)	44 (7.9)
other	34 (6.0)	39 (7.4)	28 (5.0)
Weight (kg)			
n	538	504	539
mean ± SD	72.7 ± 16.41	72.8 ± 16.16	73.5 ± 16.43
median	70.2	70.7	72.0

Source: Post-text table 7.4-1.

Additional tables in the NDA submission evaluated these factors by stratum. The median age in each stratum was 54 y for breast cancer-chemotherapy, 59 y for breast cancer-hormonal therapy, and 62 y for Myeloma.

Baseline disease characteristics for the myeloma patients are outlined in the following table from the application:

Baseline Disease Characteristics in Myeloma

Disease characteristic	Zol 4 mg N=186	Zol 8/4 mg N=160	Aredia 90 mg N=167
Previous SRE			
Yes	150 (80.6%)	130 (81.3%)	136 (81.4%)
No	36 (19.4%)	30 (18.8%)	31 (18.6%)
Time from Init Diag of Cancer to Visit 2 (months)*			
Mean ± SD	18.3 ± 32.28	13.6 ± 22.30	17.3 ± 28.54
Median	2.9	2.5	2.7
Baseline serum creatinine			
Normal (<1.4 mg/dL)	147 (79.0%)	127 (79.4%)	145 (86.8%)
Abnormal (≥1.4 mg/dL)	36 (19.4%)	32 (20.0%)	22 (13.2%)
Missing	3 (1.6%)	1 (0.6%)	0 (0.0%)

As noted above, most patients were recently diagnosed; the median time from diagnosis to randomization was less than 3 months.

The following table summarizes the Applicant's evaluation of baseline disease characteristics of patients in the two breast cancer strata combined:

The Applicant evaluated together the disease characteristics of patients in the two breast cancer strata as documented in the following table from the submission:

Baseline Disease Characteristics in Breast Cancer

	Zol 4 mg N=377	Zol 8/4 mg N=364	Aredia 90 mg N=389
First-Line Anti-neoplastic Therapy			
Yes	161 (42.7%)	180 (49.5%)	182 (46.8%)
No	216 (57.3%)	184 (50.5%)	207 (53.2%)
Previous SRE			
Yes	232 (61.5%)	207 (56.9%)	244 (62.7%)
No	145 (38.5%)	157 (43.1%)	145 (37.3%)
Site of Mets:			
Bone	377 (100%)	364 (100%)	389 (100%)
Liver	82 (21.8%)	69 (19.0%)	97 (24.9%)
Lung	69 (18.3%)	81 (22.3%)	80 (20.6%)
Brain	6 (1.6%)	5 (1.4%)	9 (2.3%)
Other	82 (21.8%)	76 (20.9%)	97 (24.9%)
Time from Init Diag of Cancer to Visit 2 (months)*			
Mean ± SD	78.6 ± 67.19	79.1± 74.89	71.9 ± 63.69
Median	59.8	60.3	54.1
Time from Init Diag of Cancer to Bone Mets (months)**			
Mean ± SD	61.2 ± 60.63	65.1± 69.75	59.3 ± 59.42
Median	46.0	42.2	44.6
Time from Init Diag of Cancer to 1st Met Disease (months)**			
Mean ± SD	57.0 ± 57.40	60.4± 65.83	54.4 ± 57.73
Median	42.0	39.4	37.9
Time from 1st Bone Mets to Visit 2 (months)*			
Mean ± SD	17.5 ± 33.85	14.1± 22.87	12.6 ± 21.68
Median	4.0	4.4	3.6
Baseline serum creatinine			
Normal (<1.4 mg/dL)	364 (96.6%)	348 (95.6%)	369 (94.9%)
Abnormal (≥1.4 mg/dL)	11 (2.9%)	11 (3.0%)	15(3.9%)
Missing	2 (0.5%)	5 (1.4%)	5 (1.3%)

* 28 days in a month

** Time from initial diagnosis of cancer to bone metastases or 1st metastatic disease is assigned to 0 when metastatic disease occurred before initial cancer diagnosis.

Source: Post-text table 7.4-2A.

In addition to these Applicant analyses of baseline factors according to the combined breast cancer strata, the following are reviewer analyses of important factors by stratum:

Percent patients with a prior SRE:

STRATUM	Zol 4	Pam
Breast-Chemo	85%	81%
Breast-Horm	61%	64%

Percent patients receiving first-line chemotherapy:

STRATUM	Zol 4	Pam
Breast-Chemo	50%	47%
Breast-Horm	37%	47%

Time since initial diagnosis of breast cancer:

STRATUM	Zol 4	Pam
Breast-Chemo	51 mo	51 mo
Breast-Horm	64 mo	62 mo

Finally, symptom findings combined from all three strata (breast-chemotherapy, breast-hormonal, myeloma) at baseline are summarized in the following table from the application:

Baseline quality of life variables by treatment group

	Zol 4 mg N=563	**Zol 8/4 mg N=524**	**Aredia 90 mg N=556**
ECOG status - n (%)			
ECOG 0-1	476 (84.5)	429 (81.9)	437 (78.6)
ECOG □ 2	86 (15.3)	94 (17.9)	116 (20.9)
Missing	1 (0.2)	1 (0.2)	3 (0.5)
Analgesic score – n (%)			
0	133 (23.6)	107 (20.4)	133 (23.9)
1	125 (22.2)	124 (23.7)	120 (21.6)
2	31 (5.5)	29 (5.5)	31 (5.6)
3	161 (28.6)	159 (30.3)	146 (26.3)
4	113 (20.1)	105 (20.0)	125 (22.5)
Missing	0 (0.0)	0 (0.0)	1 (0.2)
BPI composite pain score			
n	506	479	506
Median	3.0	3.0	2.8
FACT-G total score			
n	496	467	499
Median	76.0	75.0	77.2

Source: Post-text table

The reviewer evaluated several factors by disease (stratum):

Percent patients with ECOG >=2:

	Zol 4	Pam
Myeloma Stratum	20%	27%
Breast-Chemo Stratum	14%	19%
Breast-Horm Stratum	11%	17%

Median Analgesia Score:

STRATUM	Zol 4	Pam
Myeloma	25	29
Breast-Chemo	20	21
Breast-Horm	25	22

Median BPI composite pain score:

STRATUM	Zol 4	Pam
Myeloma	3	2.8
Breast-Chemo	2.9	3.1
Breast-Horm	3.0	3.0

Reviewer's comments:
In each stratum, 3% to7% more poor performance status patients in the Pam arm than in the Zol 4 mg arm. Other than this, the sponsor's evaluation of a large number of potential prognostic factors according to arm and stratum did not reveal any major imbalance of apparent relevance to efficacy analysis.

Novartis did not present an analysis of the extent of bone disease at baseline, a potential prognostic factor for the occurrence of an SRE. The following tables present results from reviewer analyses of bone scan and skeletal survey data. Again, the factors appear balanced in the most relevant study arms (Pam and Zol 4) for each stratum.

 # Lesions on bone scan per patient (median, mean)

Stratum	**Zol 4**	**Pam**
Breast-Chemo	5, 5.36	5, 5.24
Breast-Hormone	5, 5.08	5, 5.04

Table 57: #Lesions on plain film per patient (median, mean)

Stratum	Zol 4	Pam
Breast-Chemo	4, 4.31	4, 4.39
Breast-Hormones	4, 4.10	4, 4.26
Myeloma	5, 4.92	4, 4.75

Table 58:% Patients with 1 or less lesions on skeletal survey

Stratum	Zol 4	Pam
Breast cancer with chemotherapy	13% (23/179)	12% (30/183)
Breast cancer with hormonal therapy	11% (22/201)	14% (30/208)
Multiple myeloma	11% (20/184)	7% (12/167)

Table 59: % Patients with 2 or less lesions on skeletal survey

STRATUM	Zol 4	Pam
Breast cancer with chemotherapy	27% (49/179)	27% (49/183)
Breast cancer with hormonal therapy	30% (60/201)	28% (58/208)
Multiple myeloma	20% (36/184)	20% (33/167)

A potentially important factor not evaluated in the Novartis study report was whether patients had lytic bone lesions at baseline. Entry criteria for the historical Aredia breast cancer studies (which established the efficacy of Aredia versus placebo) required at least one lytic bone lesion. The following table presents the results of the reviewer analysis how many patients in each stratum had at least one baseline lytic lesion in Study #010

Table 60:Number of patients with at least one lytic lesion at baseline

Stratum	Patients with lytic lesions (N,%)	
Treatment Arm	Zol 4	Aredia
Breast Cancer (Chemo)	89/179 (50%)	74/183 (40%)
Breast Cancer (Hormone)	101/201 (50%)	90/208 (43%)
Myeloma	174/184 (95%)	149/167 (89%)

*Analysis used dataset BONE2, element TYPCODE where 1= lytic

There does seem to be a slight imbalance with 7 to 10% more patients with at least one baseline lytic bone lesion on Zol 4 than on Aredia. The presence of a baseline lytic lesion also appears to be an adverse prognostic factor in this trial, as the following analysis shows that 52% of patients with a lytic lesion subsequently had an SRE compared to 37% without.

Table 61:Proportion of Patients with SRE according to presence or absence of baseline lytic bone lesion

Baseline Lytic event?	Proportion of Breast Cancer Patients with SRE During Study
NO	226/605 (37%)
YES	275/531 (52%)

Another potential prognostic factor is antineoplastic treatment received. FDA asked Novartis to evaluate the starting therapy on the two arms. The following are the most common baseline antineoplastic agents on each arm at baseline:

STRATUM	ANTINEOPLASTIC AGENT	Zol 4 (%)	Pam (%)
Multiple myeloma	MELPHALAN	34	40
	DEXAMETHASONE	33	23
	DOXORUBICIN	29	26
	PREDNISONE	28	37
	VINCRISTINE	24	23
Breast cancer with chemotherapy	PACLITAXEL	37	35
	DOCETAXEL	31	39
	CYCLOPHOSPHAMIDE	30	31
	DOXORUBICIN	28	27
	FLUOROURACIL	25	25
	TRASTUZUMAB	22	17
Breast cancer with	ANASTROZOLE	37	27

STRATUM	ANTINEOPLASTIC AGENT	Zol 4 (%)	Pam (%)
hormonal therapy			
	TAMOXIFEN	30	36
	LETROZOLE	10	14

Medication Received

The mean duration of treatment was about 10 months for patients in all three strata and was similar in the study arms.

Reviewer's Comments
Multiple comparisons of the study arms for baseline demographic and disease factors demonstrate no critical imbalances. A few more patients with poor performance status and a few more breast cancer patients with lytic lesions were entered on the Zol 4 arm than on pamidronate.

Results of Study #010, Primary Efficacy Analysis: Non-inferiority Comparison of Proportions of Patients with an SRE, Zoledronate 4mg versus Pamidronate

The goal of Study 010 was to demonstrate that Zoledronate is effective by comparing the proportion of zoledronate-treated patients to the proportion of pamidronate-treated patients suffering an SRE during the study. This non-inferiority comparison depends upon historical knowledge of the treatment effect of pamidronate, i.e., the historical value of the event rate of placebo minus pamidronate. One must show that conditions and study populations of the historical trial, which demonstrated pamidronate efficacy, are similar to the current trial, which is comparing efficacy outcomes of zoledronate and pamidronate. Statistical tests are then performed to assure us that the new drug, zoledronate, retains, with confidence, an acceptable amount of the pamidronate treatment effect.

The ideal methodology for performing non-inferiority analyses is a topic of statistical research and is widely discussed in academic and regulatory settings. The Applicant and FDA present different analyses, but they both conclude that the zoledronate 4mg arm is effective in decreasing the proportion of patients suffering an SRE. The Applicant's prospective analysis uses methodology that is no longer accepted by FDA. In that analysis, the historical pamidronate effect size is calculated using "point estimates." Current FDA thinking considers also the probability that the effect size is correctly estimated, and the FDA analysis uses 95% confidence intervals to estimate the original effect size.

The review sections below present the Applicant's results, the FDA results, and a comprehensive comparison of the historical pamidronate-versus-placebo study and the current zoledronate-versus-pamidronate study.

Applicant's Primary Analysis of Efficacy

The following table displays the Applicant's findings for the proportion of patients having at least one SRE, the primary endpoint of the study:

Table 9-1. Proportion of patients having any SRE (-HCM) up to Month 13 by stratum and treatment group (intent-to treat patients)

		95% C.I. and P-value for the difference	
	Proportion	Zol 4 mg	Zol 8/4 mg
Multiple myeloma			
Aredia 90 mg	82/167 (49%)	(-12.6%, 8.4%), p=0.694	(-10.6%, 11.1%), p=0.961
Zol 4 mg	86/183 (47%)	-	(-8.2%, 13.0%), p=0.660
Zol 8/4 mg	79/160 (49%)	-	-
Breast cancer with chemotherapy			
Aredia 90 mg	78/181 (43%)	(-9.0%, 11.6%), p=0.806	(-7.0%, 13.8%), p=0.519
Zol 4 mg	79/178 (44%)	-	(-8.3%, 12.6%), p=0.690
Zol 8/4 mg	80/172 (47%)	-	-
Breast cancer with hormonal therapy			
Aredia 90 mg	97/207 (47%)	(-15.0%, 4.3%), p=0.277	(-13.4%, 6.1%), p=0.467
Zol 4 mg	83/200 (42%)	-	(-8.1%, 11.5%), p=0.729
Zol 8/4 mg	83/192 (43%)	-	-
Total			
Aredia 90 mg	257/555 (46%)	(-7.9%, 3.7%), p=0.461	(-6.1%, 5.8%), p=0.963
Zol 4 mg	248/561 (44%)	-	(-3.9%, 7.9%), p=0.495
Zol 8/4 mg	242/524 (46%)	-	-

Proportion = (no. of patients with the event)/(total no. in the group) up to Month 13;
Confidence interval for the difference (treatment labeled in the column minus row) of percent of patients with events.
P-values are based on stratified Cochran-Mantel-Haenszel test for the proportion.
Source: Post-text tables 9.1-1 and 9.1-2.

The Applicant notes that in the overall analysis comparing Zol 4 to Aredia, 46% of the Aredia patients had an SRE compared to 44% on Zol 4, and that the 95% confidence interval of the difference excluded Zol 4 being 3.7% worse (more patients with events) than Aredia. Because the goal was to exclude being 8% worse, the Applicant claims that non-inferiority of Zol 4 with respect to Aredia has been demonstrated. Further, the Applicant notes that results were similar in the per protocol (PP) analysis (48% on Aredia, 47% on Zol 4, with upper 95% ci = 5%).

The Applicant also performed an analysis stratified by performance status (ECOG = 0-1 vs. >1) which gave upper 95% ci = 5%. By all analyses, the Applicant notes that the non-inferiority goal of 8% was met.

FDA's Primary Analysis of Efficacy

FDA analyses also demonstrate non-inferiority of Zoledronate to Aredia in the proportion of patients with an SRE during Study 010 and are described in more detail in the FDA statistical

review. The following table describes the treatment effect estimated from the historical trials of Aredia versus placebo.

Active Control (Aredia vs. Placebo) Effect by Stratum

	Placebo	**Aredia**	**Difference Δ (95% CI)***	**p-value***
Myeloma	44% (79/179)	28% (56/198)	16% (6.2%, 25.5%)	0.001
Breast (Chemo)	56% (110/195)	43% (79/185)	13.7% (3.8%, 23.7%)	0.007
Breast (Hormonal)	55% (104/189)	47% (85/182)	8% (-1.8%, 18.5 %)	0.108
Total	52.0% (293/563)	38.9% (220/565)	13.1% (7.3%, 18.9%)	<0.0001 OR=1.702

Combining the data from the historical trials, the point estimate of effect is 13.1%, but the 95% confidence intervals allow us to determine with confidence that the effect size is at least **7.3%.**

Recall the results of the proportions analysis of the combined strata of Study 010 comparing zoledronate 4mg and Aredia:

	Zol 4	**Aredia**	**Difference Δ (95% CI)**	**p-value**
Total	44% (248/561)	46% (257/555)	-2% (-7.9%, 3.7%)	0.461

95% confidence intervals of the difference between the zol 4 and Aredia exclude a difference of **3.7%** or greater. The preservation of active treatment effect using the SRE rates can be determined by (7.3%-3.7%)/7.3% = 49.3%. Hence, using conservative methodology (the "two-95% confidence limit method") the current trial demonstrated at least 49.3% retention of Aredia vs. placebo effect .

Results of Study #010, Primary Efficacy Analysis: FDA Evaluation of Design Assumptions for Analysis of the Primary Efficacy Endpoint

When designing a non-inferiority study, we make a critical assumption, *the constancy assumption*, a determination that the active control drug (Aredia) would have shown efficacy in the new study or current setting. While we cannot directly test this assumption, we can compare the historical and current study populations, study design, and study conduct. The Applicant's initial submission did not provide sufficient information or analyses to support the *constancy assumption*. During the course of the NDA review, at the reviewer's request, the Applicant submitted a thorough analysis that compared the designs and populations of the historical Aredia trials and the Zoledronate trials (submission dated November 27, 2001) and provided electronic data sets from the Aredia trials. This section describes results from analyses requested or performed by the reviewer to evaluate the constancy assumption.

Reviewer Approach to Comparing Historical and NDA Trials:

The reviewer's goal was to determine that the NDA Zoledronate clinical trial setting was sufficiently similar to the historical pamidronate clinical trial setting so that, were placebo substituted for Zoledronate, the pamidronate treatment effect versus placebo would be fully apparent. Considerations include:

- Evaluating whether historical and NDA populations were similarly responsive to pamidronate.
- Determing whether trial design and conduct would allow detection of the pamidronate effect. One difference between a "superiority trial" and a "non-inferiority trial" are the potential ramifications of poor study conduct. Sloppiness, which hides differences between treatment arms, generally makes superiority more difficult to detect, but sloppiness assist a claim of non-inferiority. Evaluation of the design and conduct of the study is one approach to addressing this issue. A second is to perform a per protocol (PP) analysis as the Applicant has done. The PP analysis excludes data of questionable utility which could obscure differences between study arms.

Comparison of baseline factors in historical trials of Aredia versus placebo and NDA trials of Zoledronate versus Aredia

The following are three Applicant tables comparing baseline factors in historical Aredia trials with the corresponding strata of the Zoledronate NDA trials (from the submission of 11/27/01). "Protocol 12" was the Aredia myeloma trial, "Protocol 18" was the Aredia breast cancer trial in patients receiving hormonal therapy, and "Protocol 19" was the Aredia breast cancer trial in patients receiving chemotherapy.

Summary of demographic and prognostic variables for multiple myeloma patients from Aredia 12 and Zoledronate 010

	Aredia study 12		Zoledronate study 010		
Demographic/ Prog.variables	**Aredia 90 mg**	**Placebo**	**Aredia 90 mg**	**Zoledronate 4 mg**	**Zoledronate 8/4 mg**
Number of patients	198 (100%)	179 (100%)	167 (100%)	183 (100%)	160 (100%)
Sex					
Male	110 (55.6%)	107 (59.8%)	91 (54.5%)	103 (56.3%)	92 (57.5%)
Female	88 (44.4%)	72 (40.2%)	76 (45.5%)	80 (43.7%)	68 (42.5%)
Age (yrs)					
Mean ± s.d.	64.1 ± 9.4	62.7 ± 10.1	62.6 ± 11.41	63.1 ± 10.52	62.2 ± 11.37
Median	66.0	63.0	62.0	62.0	63.0
ECOG					
0 - 1	141 (71.2%)	126 (70.4%)	120 (71.9%)	146 (79.8%)	117 (73.1%)
≥ 2	57 (28.8%)	53 (29.6%)	46 (27.5%)	37 (20.2%)	43 (26.9%)
Missing	N/C	N/C	1 (0.6%)	0 (0.0%)	0 (0.0%)
Myeloma Subtype					
IgA	28 (14.1%)	43 (24.0%)	31 (18.6%)	25 (13.7%)	41 (25.6%)
IgG	113 (57.1%)	83 (46.4%)	100 (59.9%)	115 (62.8%)	83 (51.9%)
Light Chain	42 (21.2%)	46 (25.7%)	28 (16.7%)	32 (17.5%)	27 (16.9%)
Other	15 (7.6%)	7 (3.9%)	7 (4.2%)	10 (5.5%)	5 (3.1%)
Time from Init Diag of Cancer to Visit 2					
Mean ± s.d.	30.5 ± 32.2	27.7 ± 33.5	17.3 ± 28.62	18.0 ± 32.24	13.5 ± 21.75
Median (mo.)	19.3	14.4	2.7	2.8	2.6
Prior type of therapy					
Chemo	152 (76.8%)	139 (77.7%)	156 (93.4%)	169 (92.3%)	147 (91.9%)
Other	46 (23.2%)	40 (22.4%)	11 (6.6%)	14 (7.7%)	13 (8.1%)
Previous SRE*					
Yes	63 (31.8%)	54 (30.2%)	135 (80.8%)	149 (81.4%)	128 (80.0%)
No	135 (68.2%)	125 (69.8%)	31 (18.6%)	34 (18.6%)	31 (19.4%)
Missing	N/C	N/C	1 (0.6%)	0 (0.0%)	1 (0.6%)

N/C: Not collected

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ON ORIGINAL

Summary of demographic and prognostic variables for breast cancer patients with hormonal therapy from Aredia 18 and Zoledronate 010

	Aredia study 18		Zoledronate study 010		
Demographic/ Prog. variables	Aredia 90 mg	Placebo	Aredia 90 mg	Zoledronate 4 mg	Zoledronate 8/4 mg
Number of patients	182 (100%)	189 (100%)	207 (100%)	200 (100%)	192 (100%)
Sex					
Male	N/C	N/C	0 (0.0%)	0 (0.0%)	0 (0.0%)
Female	N/C	N/C	207 (100%)	200 (100%)	192 (100%)
Age (yrs)					
Mean ± s.d.	60 ± 12.0	62 ± 11.0	58.9 ± 13.11	59.9 ± 12.63	59.0 ± 12.96
Median	62	64	60.0	59.0	59.0
ECOG					
0 – 1	144 (79.1%)	139 (73.5%)	169 (81.6%)	177 (88.5%)	171 (89.1%)
≥ 2	38 (20.9%)	50 (26.5%)	36 (17.4%)	23 (11.5%)	21 (10.9%)
Missing	N/C	N/C	2 (1.0%)	0 (0.0%)	0 (0.0%)
Time from Init Diag of Cancer to Visit 2					
Mean ± s.d.	90.6 ± 73.1	82.1 ± 61.4	75.5 ± 65.14	82.3 ± 64.62	82.6 ± 81.16
Median (mo.)	75.3	71.9	62.6	63.5	62.6
Time from bone mets to Visit 2					
Mean ± s.d.	25.6 ± 34.2	24.2 ± 26.7	11.2 ± 22.3	16.1 ± 26.3	13.7 ± 25.0
Median (mo.)	13.0	14.9	3.2	4.4	4.1
Prior type of therapy					
Chemo	93 (51.1%)	95 (50.3%)	127 (61.4%)	115 (57.5%)	100 (52.1%)
Other	89 (48.9%)	94 (49.7%)	80 (38.6%)	85 (42.5%)	92 (47.9%)
Previous SRE*					
Yes	46 (25.3%)	57 (30.2%)	132 (63.8%)	123 (61.5%)	110 (57.3%)
No	136 (74.7%)	132 (69.8%)	75 (36.2%)	77 (38.5%)	81 (42.2%)
Missing	N/C	N/C	0 (0.0%)	0 (0.0%)	1 (0.5%)

N/C: Not collected

APPEARS THIS WAY
ON ORIGINAL

Summary of demographic and prognostic variables for breast cancer patients with chemotherapy therapy from Aredia 19 and Zoledronate 010

	Aredia study 19		Zoledronate study 010		
Demographic/ Prog. variables	**Aredia 90 mg**	**Placebo**	**Aredia 90 mg**	**Zoledronate 4 mg**	**Zoledronate 8/4 mg**
Number of patients	185 (100%)	195 (100%)	181 (100%)	178 (100%)	172 (100%)
Sex					
Male	N/C	N/C	1 (0.6%)	1 (0.6%)	4 (2.3%)
Female	N/C	N/C	180 (99.4%)	177 (99.4%)	168 (97.7%)
Age (yrs)					
Mean ± s.d.	57 ± 12	56 ± 12	54.9 ± 12.15	56.0 ± 11.68	55.8 ± 11.70
Median	58	56	54.0	54.5	57.0
ECOG					
0 - 1	121 (65.4%)	128 (65.6%)	147 (81.2%)	151 (84.8%)	140 (81.4%)
≥ 2	64 (34.6%)	67 (34.4%)	34 (18.8%)	26 (14.6%)	31 (18.0%)
Missing	N/C	N/C	0 (0.0%)	1 (0.6%)	1 (0.6%)
Time from Init Diag of Cancer to Visit 2					
Mean ± s.d.	80.9 ± 71.6	71.0 ± 66.3	65.9 ± 57.73	73.8 ± 69.72	73.7 ± 67.31
Median (mo.)	60.6	53.0	49.7	51.3	51.0
Time from bone mets to Visit 2					
Mean ± s.d.	24.8 ± 32.6	21.1 ± 22.4	13.8 ± 20.0	18.8 ± 40.7	14.4 ± 20.5
Median (mo.)	12.3	14.6	4.2	3.6	4.5
Prior type of therapy					
Chemo	175 (94.6%)	189 (96.9%)	174 (96.1%)	173 (97.2%)	166 (96.5%)
Hormonal	10 (5.4%)	6 (3.1%)	7 (3.9%)	5 (2.8%)	6 (3.5%)
Previous SRE*					
Yes	61 (32.9%)	80 (41.0%)	112 (61.9%)	109 (61.2%)	96 (55.8%)
No	124 (67.0%)	115 (58.9%)	68 (37.6%)	68 (38.2%)	76 (44.2%)
Missing	N/C	N/C	1 (0.6%)	1 (0.6%)	0 (0.0%)

N/C: Not collected

The reviewer notes three major differences between the populations in the historical Aredia trials and the Zoledronate NDA trials. These are listed below and then discussed in subsequent sections:

- Time since diagnosis of bone metastases (or time since diagnosis of myeloma which usually would include a bone lesion) was shorter for the Zoledronate NDA trial.
- More patients gave a history of a previous SRE in the Zoledronate NDA trial.
- Lytic bone lesions were present in all breast cancer patients in the Aredia trials compared to only about half of the breast cancer patients in Zoledronate trial.

The concern raised by these differences is whether bisphosphonates have demonstrable efficacy in the subpopulations over-represented in the Zoledronate NDA trial. If the Applicant demonstrates that Zoledronate is no different from Aredia in a setting where Aredia does not work, this proves nothing about the efficacy of Zoledronate. To evaluate the appropriateness of including these subpopulations in the Zoledronate trials, the reviewer performed the following exploratory subgroup analyses of efficacy with data from Aredia NDA. The purpose was to evaluate whether the Aredia effect (versus placebo) in these subgroups was at least similar to that in the overall study population where Aredia efficacy was established.

Time Since Diagnosis of Bone Metastases

The striking difference between the Aredia trials and the Zoledronate trial in time since diagnosis of myeloma (and hence time since diagnosis of bone metastasis) was evaluated in the following subgroup analysis of patients diagnosed within 6 months of study entry (similar to the Zoledronate trial population). Although numbers were small, benefit of Aredia is suggested in this subgroup with 23% more placebo patients than Aredia patients having an SRE.

Proportion of Myeloma Patients with SRE versus Time Since Diagnosis		
	Time since diagnosis	
	> 6mo	<6mo
Aredia Proportion with SRE	36/150 (24%)	11/55 (20%)
Placebo Proportion with SRE	50/127 (39%)	26/60 (43%)
Placebo - Aredia	15%	23%

History of Previous SRE

The number of patients with a history of a previous SRE at baseline was also different between the Aredia and Zoledronate NDA studies. However, as the Applicant notes, the findings were counterintuitive...time since diagnosis was longer in the Aredia trials yet history of an SRE was much less common. This apparent difference may stem from differences in the way data was collected. In the Aredia trials as history of SREs was solicited only for the three months prior to entry whereas in the Zoledronate trial a history of SRE was solicited for the prior year. Nevertheless, the Aredia data were evaluated to determine whether patients with a prior history of an SRE appeared to derive benefit from Aredia.

Proportion of Myeloma Patients with SRE versus History of Previous SRE		
	History of SRE in previous 3 months	
	Yes	No
Aredia Proportion with SRE	35% (23/65)	17% (24/240)
Placebo Proportion with SRE	58% (33/57)	33% (43/130)
Placebo - Aredia	23%	16%

This analysis suggests that patients in the Aredia myeloma trial with a history of a recent SRE were more likely to have a subsequent SRE and were also at least as likely to derive benefit from Aredia.

Lytic bone lesions at baseline

In the studies comparing Aredia to placebo, inclusion criteria required at least one lytic bone lesion whereas the Zoledronate 010 trial allowed lytic or blastic lesions. As noted in a prior section of this review, about half of the breast cancer patient in Study 010 had no baseline lytic bone lesions. Is it possible that biphosphonates are effective only in patients with lytic lesions? If so, the breast cancer strata of Study 010 are grossly underpowered for comparing Zoledronate 4 mg and Aredia.

Two lines of evidence suggest that inclusion of breast cancer patients with non-lytic (blastic and "mixed") lesions is appropriate.

First, in subsets of Study 010 patients with baseline lytic bone lesions, the Zom 4 event rate is similar to the Aredia event rate:

- As discussed above, in the myeloma stratum of Study 010, where 95% of patients had lytic lesions, 49% of the Aredia arm had an event compared to 47% in the Zom 4 arm.
- The following reviewer exploratory subset analysis of the breast cancer strata of Study 010 shows no trend toward more SRE events occuring with Zom 4 relative to Aredia in patients with baseline lytic lesions; in fact, a trend in the opposite direction is suggested. (bolded):

Proportion of Patients in Zoledronate study 010 with an event, according to whether lytic bone lesion was present at baseline*

			#(%) of Patients with SRE		
Stratum	**Lytic Lesion at baseline?**	**# pts**	**Aredia**	**Zom 4**	**Zom 8**
Breast cancer with chemotherapy	No	284	37/109 (34%)	35/90 (39%)	34/85 (40%)
	Yes	251	42/74 (57%)	44/89 (49%)	46/88 (52%)
Breast cancer with hormonal therapy	No	321	44/118 (37%)	36/100 (36%)	40/103 (39%)
	Yes	280	53/90 (59%)	47/101 (47%)	43/89 (48%)

*(Analysis used dataset BONE2, element TYPCODE where 1= lytic)

Other data supports the claim that Zoledronate can be effective in blastic cancer metastases. Zoledronate Study 039 in prostate cancer, a different disease setting where essentially all patients have blastic disease, demonstrates that Zoledronate can be effective in decreasing SREs in patients with blastic metastases.

Comparison of type of SREs Between Aredia Trials and the Zoledronate Trial

Because the primary endpoint of the 010 trial is a composite endpoint (SRE), thorough comparison of the Zoledronate NDA Study 010 and the Aredia NDA studies includes comparison of the specific events observed. The reviewer's concern may be expressed by the following worst-case theoretical scenario:

> Imagine that a composite endpoint (EP) consists of elements A and B. An event consists of an occurrence of either A or B. Aredia efficacy is shown by a decrease of EP on Aredia relative to placebo, and this is predominantly due to an advantage in decreasing type A events. Zoledronate is then compared to Aredia, and shows non-inferiority for the EP composite endpoint. However, in the Zoledronate trial, there are mostly B events. With this scenario, although the Zoledronate EP rate is identical to that of Aredia, Zoledronate has not been proven to be effective... without inclusion of "A" events, we cannot assume that the efficacy of Zoledronate with respect to Aredia has been tested.

In the Aredia NDA trials and the Zoledronate Study 010, the most frequent SRE events were *radiotherapy to bone* and *pathological fractures*. The following displays the effect of Aredia on these events and compares the frequency of these events in the corresponding trials/strata.

Type of SRE in Trials of Aredia versus Placebo and Zoledronate versus Aredia*

Cancer Type	Type of Event	Proportion with Event in Aredia Arm of study		Difference in Proportions Compared to Control Arm	
		Aredia NDA Study	Zoledronate Study 010	Aredia NDA Study**	Zoledronate Study 010***
Myeloma	Any SRE	28%	49%	16%	2%
	- Fractures	22%	42%	10%	2%
	- RT to bone	16%	14%	12%	-1%
Breast Cancer (Hormone)	Any SRE	47%	47%	8%	5%
	- Fractures	36%	34%	8%	3%
	- RT to bone	21%	25%	12%	9%
Breast Cancer (Chemo)	Any SRE	43%	43%	13%	-1%
	- Fractures	34%	34%	5%	-3%
	- RT to bone	19%	20%	14%	5%

* Derived primarily from tables in the 11/27/01 submission
** Placebo minus Aredia
*** Aredia minus Zol 4

Examination of this table demonstrates that reviewer worst-case scenario described above does not apply to these trials. The Aredia benefit versus placebo was apparent in both major types of SREs (RT to bone and fractures) and both types of events were well represented in the Zoledronate NDA Study 010.

Results of Study #010, Secondary Efficacy Analyses

Time to occurrence of an SRE

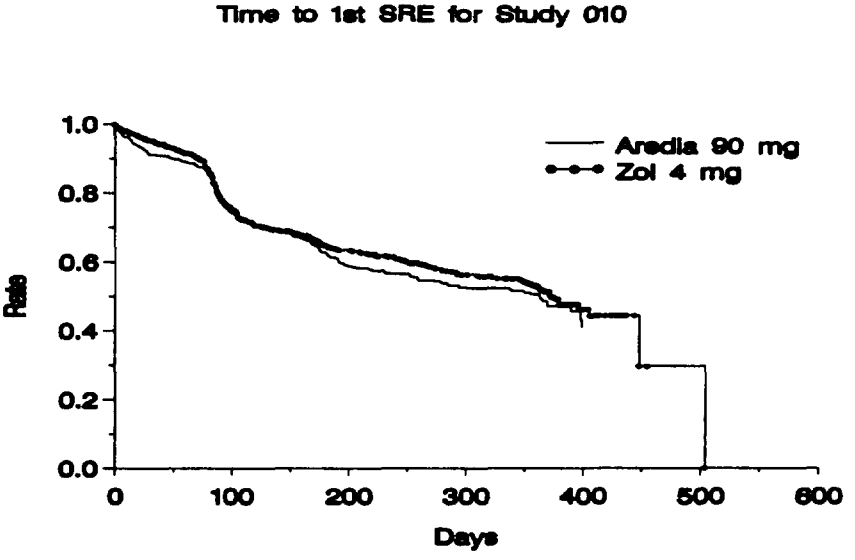
Time to first SRE was similar on Zom 4 and Aredia arms by both the Applicant's analysis and the FDA's analysis. Results from the FDA statistical review are displayed in the following table and Figure.

Time to first SRE by stratum and treatment arm

	N	Median (95%CI)	Hazard Ratio (95% CI)	p-value*
Myeloma				0.82
Aredia	167	301(191, ---)	.97(.71, 1.31)	
Zol 4 mg	183	372(225, 504)		
Breast(CT)				0.81
Aredia	181	366(259, ---)	.96(0.70, 1.32)	
Zol 4 mg	178	364(249, ---)		
Breast(HT)				0.22
Aredia	207	370(258, ---)	.83(.62, 1.12)	
Zol 4 mg	200	>380 (---, --)		
Total				0.31
Aredia	555	363(273, 399)	.92(.77, 1.09)	
Zol 4 mg	561	373(350, 504)		

*Log-rank test

APPEARS THIS WAY
ON ORIGINAL



Other Secondary Efficacy Analyses

In any trial, secondary analyses and exploratory analyses are usually of marginal value for making a firm conclusion about efficacy. In a non-inferiority trial such as Study 010, one also must consider whether a non-inferiority conclusion is even remotely possible for that secondary or exploratory analysis. Since non-inferiority conclusions depend on careful documentation of historical evidence that control (Aredia) produces the effect of interest, these secondary analyses must also have been done with the historical data. It seems unlikely that historical data on the effect of the active control will be sufficient to serve as the basis for a non-inferiority analysis. Secondary analyses will be useful only if:

- They demonstrate superiority.
- Strong evidence of benefit is substantiated by evidence from other trials or strata.
- The findings are sufficiently robust to overcome the doubt (inflation of type one error) associated with performing multiple analyses.

Skeletal Morbidity Rate(SMR)

The SMR is the # events divided by time onstudy. The Applicant found no statistical difference between the study arms.

Proportion of Events by Type of Event

The following Applicant displays the proportion of events according to the event type:

Proportion of patients having a SRE, for each type of SRE, up to Month 13 by treatment group

	Zol 4 mg N=561	Zol 8/4 mg N=524	Aredia 90 mg N=555
Proportion of pathological fracture	200/561 (36%)	179/524 (34%)	203/555 (37%)
Proportion of vertebral fracture	109/561 (19%)	84/524 (16%)	108/555 (19%)
Proportion of non-vertebral fracture	145/561 (26%)	135/524 (26%)	148/555 (27%)
Proportion of spinal cord compression	11/561 (2%)	12/524 (2%)	16/555 (3%)
Proportion of radiation therapy to bone	85/561 (15%)	112/524 (21%)	112/555 (20%)
Proportion of surgery to bone	21/561 (4%)	15/524 (3%)	31/555 (6%)
Proportion of hypercalcemia	7/561 (1%)	5/524 (1%)	12/555 (2%)

P-values are based on stratified Cochran-Mantel-Haenszel test for the proportion.
Source: Post-text tables 9.2-9, 9.2-12, 9.2-15, and 9.2-18.

The proportions are similar beteween Zol 4mg and Aredia for each of the major event subtypes.

Brief Pain Inventory (BPI) composite endpoint

A higher composite score was meant to indicate more pain. According to the Applicant's analyis, the mean change from baseline was similar in each arm (-.5 on Zol 4 and -.4 on Aredia).

Analgesic score

Analgesic scores ranged from 0-4 with higher score indicating stronger analgesics. According to Applicant analyses, mean scores changes from baseline were similar for the Zol 4 and Aredia arms (-0.1 for each 3 month visit for each arm).

Performance status (PS)

In Applicant analyses, mean changes from baseline in ECOG PS were similar on the Zol 4 mg and Aredia arms at each 3-month comparison. Within each arm, mean PS increased from 0.1 at 3 months to 0.3 at 13 months.

Quality of Life (QoL)

QoL was evaluated by FACT-G. As shown in the following table from the Applicant's submission, results were statistically inferior in the Zol 4mg arm than Aredia, but also were worse on Zol 4mg than Zol 8mg. These results cannot be easily explained, and are probably due to chance and the inflation of alpha due the large number of secondary efficacy analyses.

Table 9-13. Mean/Median changes from baseline in quality of life scores at Month 13 by treatment group

	Zol 4 mg N=561	Zol 8/4 mg N=524	Aredia 90 mg N=555
Change in FACT-G total score			
Total no. of patients *	446	418	445
Mean ± SD	0.5 ± 14.9	3.1 ± 14.9	2.1 ± 15.6
Median	0.3	3.0	2.0
P-value: vs Aredia 90 mg	0.031	0.839	-
P-value: vs Zol 4 mg	-	0.020	-
Change in physical subscale			
Total no. of patients *	456	425	452
Mean ± SD	0.8 ± 6.0	1.2 ± 6.1	0.8 ± 6.2
Median	1.0	1.0	0.0
Change in functional subscale			
Total no. of patients *	457	422	453
Mean ± SD	0.0 ± 6.2	0.7 ± 6.4	0.9 ± 6.3
Median	0.0	0.0	1.0
Change in social subscale			
Total no. of patients *	454	424	450
Mean ± SD	- 0.6 ± 5.0	- 0.1 ± 4.5	- 0.1 ± 4.5
Median	0.0	0.0	0.0
Change in emotional subscale			
Total no. of patients *	455	423	454
Mean ± SD	0.3 ± 4.3	1.2 ± 4.3	0.5 ± 4.3
Median	0.0	1.0	0.0

* Number of patients who had a non-missing score at both baseline and Month 13 with last observation carried forward.
P-values are from GLM model for the between treatment comparisons of least square means using Analysis of Covariance with baseline value as a covariate and treatment group as a factor at Month 13.
Source: Post-text tables 9.2-45, 9.2-46, 9.2-47, 9.2-49, 9.2-51, and 9.2-53.

Time to Progression (TTP)

In the Applicant's analysis of overall time to progression (Volume 69, post text table 9.2-56), median TTP was 134 days on Zol 4mg (p = 0.174 versus placebo) 125 days on Zol 8mg, and 111 days on placebo. Examination of the KM curves (post text figures 9.2-25) within each stratum shows the study arms to be nearly identical for myeloma and breast cancer treated with chemotherapy. In the stratum of patients with hormone-treated breast cancer, placebo appeared worse, with a median of 94 days compared to 104 days on Zol 4 mg (p =0.063) and 107 days on Zol 8 mg (p = 0.035). (The low p values reflect differences in the curves beyond the median.) These TTP trends are not supported by Applicant analyses of time to bone event (NDA post text table 9.2-55 and figure 9.2-24).

Reviewer's Comments

Collection of data on tumor progression was not a primary goal of this study. Again, isolated subgroup findings which are of marginal statistical significance are questionable, especially when they represent only one of many secondary analyses performed.

Bone resporption markers

As documented in the Applicant's study report, markers of bone resporption (N-telopeptide, Pyridinoline, and Deoxypyridinoline) were decreased in all study arms relative to baseline and parathyroid hormone was increased 10 to 23%.

Survival

Median survival had not been reached in the study at the time of NDA submission. The following table presents the Applicant's analysis of survival. There were no significant differences or trends between the study arms.

ITT Population N=1119	Median (95%CI) (Days)	Hazard Ratio	95% CI for Hazard Ratio	Log-rank P-value
Aredia (179/556)	802(684-802)			
Zol. 4mg (171/563)	Not reached	0.958	0.776-1.182	0.55

Efficacy Summary and Conclusions from Study #010 (multiple myeloma and breast cancer)

Study 010 was an international, multicenter, stratified, double-blind, study that randomized patients 1:1:1 to Zol 4 mg, Zol 8mg, or Aredia 90 mg i.v. every 3-4 weeks for 12 months. Randomization was stratified by center and 3 disease strata: myeloma, breast cancer treated with hormones, and breast cancer treated with chemotherapy. The primary analysis was to be a non-inferiority analysis of the proportion of patients with at least one SRE, performed after 13 months (12 months of treatment and one month of followup)

The Applicant randomized 1648 patients to the three study arms. Results suggest that zoledronate 4 mg is effective in decreasing the skeletal morbidity of myeloma and breast cancer metastatic to bone. As outline below, conservative non-inferiority methodology using the *two 95% confidence interval method of estimation* demonstrate that zoledronate retains at least 49.3% of the Aredia-versus-placebo effect:

- The first step in this method is to estimate the size of the Aredia effect based on historical data. The combined data from the three Aredia trials show that 52.0% (293/563) on placebo compared to 38.9% (220/565) on Aredia had an SRE. The treatment effect is thus 13.1% (95% ci: 7.3%,18.9%). This method uses the conservative limit of the confidence interval to estimate effect size (7.3%).
- The next step is to estimate how much of that Aredia effect is retained (with 95% confidence) by zoledronate. On the zoledronate arm of this non-inferiority trial 44% (248/561) of patients had at least one SRE compared to 46% (257/555) on the Aredia arm (95% ci: -7.9%, 3.7%). Although the estimate from these data favors zoledronate by 2%, again this method uses the conservative limit of the confidence interval to estimate the zoledronate effect. The

confidence interval excludes zoledronate being 3.7% worse than Aredia. The following are the calculations estimating that at least 49.3% of the Aredia-versus-placebo effect has been retained: (7.3%-3.7%)/7.3% = 49.3%.

A critical aspect of making conclusions from non-inferiority trials is the *constancy assumption.* This aspect of trial design, discussed in more depth in the FDA statistical review, requires a determination that the active control drug (Aredia would have shown efficacy in the new study or current setting, and it also requires an estimation of the size of the effect that Aredia would have shown in the current setting. The FDA reviewers carefully evaluated the historical Aredia studies with this assumption in mind. Important differences were found between the current and historical studies. Compared to the Aredia-versus-placebo studies, more patients on Study 010 had:

- a short time since diagnosis of bone metastases
- history of a previous SRE
- no lytic bone lesion

As discussed in detail in the review, each of these differences was carefully examined, and none of them appeared to violate the constancy assumption.

FDA reviewers agree with the ODAC that these results represent substantial evidence of Zoledronate efficacy in treatment of patients with myeloma and breast cancer metastases.

7 Integrated Review of Safety

This integrated safety review discusses safety findings from all submitted zoledronate studies. Detailed FDA safety reviews of the studies in breast cancer and myeloma (010), prostate cancer (039), and other solid tumors (011) can be found in the appendices to this briefing document

7.1 Brief Statement of Reviewer's Conclusions

Zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks has an acceptable safety profile, and is comparable in toxicity to Aredia 90 mg i.v. over 2 hours every 3-4 weeks as an adjuvant to standard anticancer therapy in patients with bone metastases from breast cancer and lesions of multiple myeloma. Zoledronate 4 mg i.v. over 15 minutes every 3 weeks has an acceptable safety profile, but is more toxic than placebo when used as an adjuvant to standard anticancer therapy in patients with prostate cancer and other solid tumors.

The major safety concern identified in the randomized trials is increased risk of renal function deterioration, which is dose-related and increases with duration of therapy. Most incidences were mild and reversible, with rare incidences of acute renal failure. During the course of the studies, the renal safety of zoledronate was improved by prolonging the infusion time to 15 minutes (instead of 5 minutes) and eliminating the 8 mg dose. The safety of the 4 mg dose was improved by requiring assessment of serum creatinine before each dose and holding zoledronate for renal deterioration, until the return of creatinine to within 10% of the baseline. When compared with Aredia 90 mg i.v. over 2 hours, zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks in patients with metastatic breast cancer to bone and multiple myeloma (study #010), the incidence of renal deterioration was similar (8.8% and 8.2%, respectively). The incidence of renal deterioration for patients with prostate cancer (study #039) and solid tumor malignancies other than prostate and breast (#011) was higher than placebo, but the difference was not statistically significant.

Symptoms possibly associated with bisphosphonates as a class, such as arthralgias, pyrexia, as well as electrolyte disturbances, were noted for zoledronate and Aredia, but were not a major concern.

Anemia was slightly more common with zoledronate 4 mg, compared with placebo. In the Aredia-controlled study, more patients in the zoledronate 4 mg group had a decrease of > 25% from baseline hemoglobin. This is of uncertain significance.

7.2 Description of patient exposure

Zoledronate was approved by FDA in August 2001 for treatment of hypercalcemia of malignancy. This was based on two identical randomized trials in which a total of 86 patients received zoledronate 4 mg i.v. over five minutes, with Aredia 90 mg i.v. infusion over two hours as the control. The approved dose of zoledronate was 4 mg by 15-minute i.v. infusion. The

infusion duration was prolonged because of the increased risk of renal deterioration associated with shorter infusions.

The primary safety population for the current NDA includes 3,337 safety evaluable patients (2,251 treated with zoledronate) in phase 2 and phase 3 randomized trials for cancer patients with metastatic disease to bone. Zoledronate was given i.v. every 3 or 4 weeks, usually to correspond with the schedule of concomitant anti-cancer therapy. The planned treatment duration for these studies was 9 months for protocol 011, 10 months for protocol 007, 12 months for protocol 10 and 15 months for protocol 039. Applicant table 1-1 provides a summary of the studies.

Applicant table 1-1

Table 1-1. Primary safety population: Summary of studies

Study no.	Tumor type	Zol < 4 mg	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Placebo	Total No. of Patients
007	breast, multiple myeloma	145	68	-	75	-	288
010	breast, multiple myeloma	-	563	524	556	-	1643
011	solid tumor other than breast or prostate	-	254	265	-	247	766
039	prostate	-	214	218	-	208	640
Total	all	145	1099	1007	631	455	3,337

For the primary safety population, the applicant provided all data available until the data base lock on 2/28/01 for the time to death and renal function deterioration analyses.

The applicant provided safety data for an additional 493 patients from 8 studies and study extensions as the "supportive safety population." For this supportive population, only 27 patients received Zoledronate 4 mg; 61 received < 4 mg; 197 received zoledronate 8/4 mg; 22 received zoledronate 8 mg, and 186 received Aredia 90 mg i.v.

The cut-off date of February 28, 2001, was used for reporting data on deaths and serious adverse events (SAEs) in trials for other indications. Applicant's table 1-3 summarizes ongoing trials and trials in other indications.

Applicant table 1-3

Table 1-3. Summary of ongoing trials and trials in other indications

Study No.	Purpose & Design	Type of Control	No. of Patients	Population
Completed trials				
001, 002	Efficacy and safety	None, placebo	16, 176	Paget's disease of bone
701 (terminated)	Randomized, double-blind	placebo	6	primary breast cancer
AT01 (closed)	Double-blind	placebo	20	renal transplant
041	Treatment of osteoporosis: Randomized, double-blind, dose-ranging	placebo	351	women with postmenopausal osteoporosis
US03 (closed)	Osteoporosis: open, randomized	active (Fosamax®)	12	patients on corticosteroids
036, 037	HCM, double-blind, randomized	Aredia	149, 138	cancer with HCM
CJ/HC1	open, phase 1, dose escalation	none	33	cancer with HCM
Ongoing trials				
010 Extension	Long-term safety: randomized, double-blind	active (Aredia)	704	breast cancer, multiple myeloma
011 Extension	Long-term safety: randomized, double-blind	placebo	101	solid tumor other than breast or prostate
039 Phase 2	Long-term safety: randomized, double-blind	placebo	204	prostate cancer

Applicant table 2-1 summarizes the duration of exposure of the primary safety population to zoledronate and controls.

Applicant table 2-1

Table 2-1. Summary statistics for duration of exposure – primary safety population

	Zol < 4 mg	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Placebo
No. of patients	145	1099	1007	631	455
Mean (months)	7.53	8.50	8.12	9.64	6.44
SD	2.88	4.77	4.80	3.90	4.92
Median (months)	9.04	9.07	8.61	11.96	5.43
Range (months)	0.04 – 12.29	0.04 – 18.54	0.04 – 18.82	0.04 – 15.82	0.04 – 18.07

Source: Post-text table 4.2-1.

The mean and median duration of exposure were shortest for the placebo group, in part because placebo served as the control for the study (#011) with the shortest duration of treatment, 9 months. The mean and median for zoledronate 4 mg was 8.5 and 9.07 months, respectively, similar to zoledronate 8/4 mg, and slightly shorter than for Aredia.

Applicant table 2-2 summarizes additional information about duration of exposure for the primary safety population.

Applicant table 2-2

Table 2-2. Summary of duration of exposure – primary safety population

Months[a]	Zol < 4 mg	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Placebo
No. of patients	145 (100.0)	1099 (100)	1007 (100)	631 (100)	455 (100)
< 3	16 (11.0)	193 (17.6)	206 (20.5)	66 (10.5)	142 (31.2)
3 to < 6	19 (13.1)	174 (15.8)	152 (15.1)	58 (9.2)	95 (20.9)
6 to < 10	96 (66.2)	235 (21.4)	204 (20.3)	133 (21.1)	122 (26.8)
10 to < 12	13 (9.0)	69 (6.3)	87 (8.6)	63 (10.0)	18 (4.0)
12 to < 15	1 (0.7)	350 (31.8)	303 (30.1)	306 (48.8)	20 (4.4)
15 to < 18	0 (0.0)	77 (7.0)	54 (5.4)	3 (0.5)	57 (12.5)
18 to < 24	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.2)

[a] duration from randomization: (last known date patient took study medication – Visit 2 date + 1)/28

Source: Post-text table 4.2-2.

The duration of exposure was at least 12 months for 38.9% of zoledronate 4 mg patients, 35.6% for zoledronate 8/4 mg, and 49.3% for Aredia patients.

For the three phase 3 trials, patients were to be randomized to zoledronate treatment arms of 4mg and 8 mg. After it was determined that 8 mg was associated with excess renal toxicity, no patient received more than 4 mg per dose and the 8 mg arm was renamed "8/4 mg". This occurred June 2000. The percentage of infusions in the 8/4 mg groups that was actually 4 mg

was 10% for #039 (prostate cancer), 20% for #010 (multiple myeloma and breast cancer, and 22% for #11 (miscellaneous solid tumors).

In June 1999 amendments to studies 039, 010, and 011 increased the infusion time from 5 to 15 minutes, which was shown to decrease the renal toxicity of zoledronate. See individual study safety reviews, which are contained in the Appendix, for details of the separate renal safety analyses done for patients according to whether they were randomized pre or post the 15-minute infusion amendment. Applicant table 2-4 demonstrates the total number of patients and infusions and the total number of 15-minute infusions by study.

Applicant table 2-4

Table 2-4. Total infusions and 15-minute infusions by study

Study	All patients		15-minute infusion		Zol 4 mg 15-minute infusions	
	no. of patients	no. of infusions	no. of patients	no. of infusions	no. of patients	no. of infusions
007	288	2486	0	0	0	0
010	1643	22565	830	10310	281	3610
011	766	5474	571	4026	186	1355
039	640	9048	274	3589	97	1330
Total	3337	39573	1675	17925	564	6295

Source. Post-text table 4.2-4

In studies 010, 011, and 039, 69.4%, 26.3% and 53.6% of patients, respectively, received at least twelve 15-minute infusions (from applicant table 2-5).

Detailed reviews of the individual studies, 010, 011, 039 (see Appendix for details), show a balance among treatment arms of age and baseline renal function. Applicant table 3-1 shows a summary of demographic information for the pooled primary safety population

Applicant table 3-1

Table 3-1. Summary of demographics – primary safety population

	Zol < 4 mg	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg	Placebo
Total no. of patients	145 (100)	1099 (100)	1007 (100)	631 (100)	455 (100)
Sex (n, %)					
male	42 (29.0)	494 (44.9)	500 (49.7)	103 (16.3)	367 (80.7)
female	103 (71.0)	605 (55.1)	507 (50.3)	528 (83.7)	88 (19.3)
Race (n, %)					
white	124 (85.5)	962 (87.5)	863 (85.7)	544 (86.2)	395 (86.8)
black	10 (6.9)	77 (7.0)	76 (7.5)	56 (8.9)	31 (6.8)
other	11 (7.6)	60 (5.5)	68 (6.8)	31 (4.9)	29 (6.4)
Age (years)					
mean ± SD	57.1 ± 13.07	62.7 ± 11.86	62.1 ± 12.05	58.6 ± 12.55	66.6 ± 10.82
median	56.0	63.0	63.0	58.0	69.0
Age (n, %)					
≤ 60	85 (58.6)	462 (42.0)	433 (43.0)	354 (56.1)	113 (24.8)
> 60	60 (41.4)	637 (58.0)	574 (57.0)	277 (43.9)	342 (75.2)
Weight (kg)					
no. of patients	144	1069	983	614	452
mean ± SD	74.5 ± 15.50	75.0 ± 16.10	75.3 ± 16.43	73.6 ± 16.45	77.0 ± 17.09
median	73.1	73.2	74.0	71.9	75.2
Primary cancer site					
breast	84 (57.9)	418 (38.0)	364 (36.1)	435 (68.9)	0 (0.0)
multiple myeloma	61 (42.1)	213 (19.4)	160 (15.9)	196 (31.1)	0 (0.0)
prostate	0 (0.0)	214 (19.5)	218 (21.6)	0 (0.0)	208 (45.7)
lung	0 (0.0)	124 (11.3)	134 (13.3)	0 (0.0)	123 (27.0)
renal cell	0 (0.0)	27 (2.5)	28 (2.8)	0 (0.0)	19 (4.2)
other	0 (0.0)	103 (9.4)	103 (10.2)	0 (0.0)	105 (23.1)
Baseline serum creatinine					
< 1.4 mg/dL	135 (93.1)	961 (89.3)	875 (86.9)	585 (92.7)	390 (85.7)
≥ 1.4 mg/dL	10 (6.9)	110 (10.0)	123 (12.2)	40 (6.3)	58 (12.7)
missing	0 (0.0)	8 (0.7)	9 (0.9)	6 (1.0)	7 (1.5)

Source: Post-text table 2.2-1.

The imbalance in gender for the pooled population of patients treated with placebo and Aredia relates to the design of the studies, with placebo controlling the prostate study and Aredia controlling the breast cancer (and myeloma) study.

Prior to the start of the study drug, 90% or more of patients were taking antineoplastic therapies. After the start of the study drug, the percentage of patients receiving antineoplastic therapy was 42.6% for the placebo group, 74.3% for zoledronate 4 mg, 69.7% for zoledronate 8/4 mg. 94.8% for the Aredia group. The percentage of patients in these groups receiving cisplatin was 9%, 4.4%, 5.1%, and 0.6%, respectively.

7.3 Methods and specific findings of the safety review

Adverse events (AEs), serious adverse events (SAEs), laboratory studies and survival data were the main safety variables. Safety analysis was based on the type and frequency of adverse events and laboratory values outside of pre-determined ranges. Results were tabulated. Data was cut at the end of the study drug period, which was the end of the core study phase or 28 days following the last study medication. However, any available data was included up to the date of the data base lock for time to death or time to renal deterioration analyses.

Clinical study reports for the three phase 3 trials used the IMN dictionary to code adverse events. AEs are reported using MedDRA preferred terms. AEs were mapped from the IMN preferred terms to the corresponding MedDRA terms.

Following the occurrence of 3 renal failure SAEs in patients receiving zoledronate 8 mg, a Renal Advisory Board (RAB) was formed and amendments were made to the protocol. The effect on renal function was analyzed according to the number of patients who experienced renal adverse events using selected terms suggested by the RAB and the number of patients who met pre-defined criteria of renal deterioration. Kaplan-Meier curves were used to describe the time course to first renal function deterioration.

The "all terms criteria" from the RAB used to describe renal AEs and SAEs are as follows:

- Anuria
- Bladder retention
- Creatinine blood increased
- Hematuria
- Hydronephrosis
- Hyperuricemia
- Micturition frequency
- Nephritis
- Nephrolithiasis
- Nephropathy toxic
- Nephrotic syndrome
- Obstructive uropathy, urethral obstruction or urethral disorder
- Oliguria
- Proteinuria
- Pyelonephritis
- Renal calculus
- Renal failure acute
- Renal function abnormal
- Renal insufficiency
- Renal tubular disorder
- Tumor lysis syndrome
- Uremia
- Urinary retention

Baseline serum creatinine was considered normal if <1.4 mg/dL and abnormal if ≥ 1.4mg/dL. Renal function deterioration was defined as any of the following:

- Normal baseline with change from baseline ≥ 0.5 mg/dL
- Abnormal baseline with change from baseline ≥ 1.0 mg/dL
- Post-baseline value ≥ 2 time the baseline value.

Reviewer's comments:

Clinical Review Section

The Applicant has provided an Integrated Summary of Safety with data pooled for the three randomized phase 3 trials (039, 10, 11) plus study 007. Study 007 is a phase 2 study in breast cancer and multiple myeloma patients comparing zoledronate 0.4 mg, 2 mg, and 4 mg i.v. over 5 minutes with Aredia as control. This last study adds little to the safety analysis since only 67 patients received the recommended 4 mg zoledronate dose and all zoledronate infusions were 5 minutes, rather than the recommended 15-minute infusion. Comparison of the major findings of each of the phase 3 studies with each other seems more useful than pooling the data for 4 studies without reference to the specific control in each case and the type of malignant disease. Furthermore, pooling the safety data without reference to duration of infusion significantly obscures the fact that the safety of zoledronate was improved when infused over 15 minutes rather than over 5 minutes.

For detailed safety information pertaining to each of the phase 3 randomized trials analyzed separately, refer to the Appendix. Some of the major points will be reviewed here, as well.

The major safety concern identified in the randomized trials is increased risk of renal function deterioration, which is dose-related and increases with duration of therapy. Most incidences were mild and reversible, with rare incidences of acute renal failure. During the course of the studies, the renal safety of zoledronate was improved by prolonging the infusion time to 15 minutes (instead of 5 minutes) and eliminating the 8 mg dose. The safety of the 4 mg dose was improved further by requiring assessment of serum creatinine before each dose and holding zoledronate for renal deterioration, until the return of creatinine to within 10% of the baseline.

In patients with breast cancer or multiple myeloma, the incidence of renal deterioration was similar for treatment with Aredia 90 mg i.v. over 2 hours compared to zoledronate 4 mg i.v. over 15 minutes every 3-4 (8.8% and 8.2%, respectively) and less than that observed with zoledronate 8/4 mg (18.6%). The incidences of renal deterioration for patients with prostate cancer (study #039) and solid tumor malignancies other than prostate and breast (#011) were higher than placebo, but the difference was not statistically significant. For prostate cancer patients treated with zoledronate 4 mg infused over 15 minutes, the incidence of renal deterioration was 15.2% compared with 11.5% on placebo and 20.7% with zoledronate 8/4 . For patients with solid tumor malignancies other than prostate and breast cancer (#011), the incidence of renal deterioration was 10.9% for zoledronate 4 mg, 6.7% for placebo, and 11.6% for zoledronate 8/4 mg. In all studies, deterioration of renal function was observed in patients with normal baseline creatinine and in patients with abnormal creatinine ($\geq$ 1.4-3.0).

There appeared to be an increased incidence of or renal deterioration in patients with abnormal baseline creatinine, but this phenomenon was primarily limited to the prostate cancer study (#039), and the number of such patients was small. There were *fewer* patients with abnormal baseline creatinine in study #010 (breast/myeloma) who showed deterioration with zoledronate 4mg, compared with those with normal baseline creatinine. For study #011, the deterioration of renal function with zoledronate 4mg was similar for both baseline creatinine groups.

Symptoms possibly associated with bisphosphonates as a class, such as arthralgias, pyrexia, as well as electrolyte disturbances, were noted for zoledronate and Aredia, but were not clinically

problematic. The incidence of ophthalmic AEs and injection site problems were less frequently reported for zoledronate than for Aredia.

Anemia was slightly more common with zoledronate 4 mg compared with placebo. In the prostate study (#039), the incidence of anemia in the zoledronate groups was approximately 27% compared with 17.8% for placebo. In the miscellaneous solid tumor study (#011), anemia was present in 7.9% of the zoledronate 4 mg group and 3.6% of the placebo group. In the Aredia-controlled study (#010, breast/myeloma), more patients in the zoledronate 4 mg group had a decrease of > 25% from baseline hemoglobin than in the Aredia.

7.4 Safety Update: 120-Day Report

For patients in the Primary Safety Population, data is presented for the core of studies — 010, 011, and 039 and — ate — Follow-up creatinine values were updated to October 24 and survival to October 26, 2001. The updated information includes Adverse Events (AEs), Serious Adverse Events (SAEs), creatinine abnormalities and notable laboratory abnormalities. For other patient populations defined in the Integrated Review of safety (ISS), the report presents SAEs only.

The update identifies no new safety problems and demonstrates no change in the pattern of events compared with the ISS, which was released July 30, 2001.

Survival analysis shows no significant differences between zoledronate 4 mg and Aredia in study 010 (multiple myeloma and breast) nor for zoledronate 4 mg and placebo in study 011 (solid tumors).

A summary of patients requiring dialysis in the phase 3 bone metastasis trials is provided in applicant's table 5-6.

Applicant table 5-6. Incidence of patients requiring dialysis

Table 5-6. Incidence of patients requiring dialysis in phase 3 bone metastases studies (010, 011, and 039)

	Pre-15-minutes Amendment			Post 15-minute Amendment		
Treatment group	# patients	# renal events	Percent	# patients	# renal events	Percent
Study 010*						
Zol 4 mg	272	6	2.2	272	2	0.7
Zol 8 mg	240	3	1.3	263	6	2.3
Aredia	270	1	0.4	268	0	0.0
Total	782	10	1.3	803	8	1.0
Study 011*						
Zol 4 mg	61	0	0.0	165	1	0.6
Zol 8 mg	55	0	0.0	181	3	1.7
Placebo	54	0	0.0	163	0	0.0
Total	170	0	0.0	509	4	0.8
Study 039*						
Zol 4 mg	111	3	2.7	92	0	0.0
Zol 8 mg	120	4	3.3	87	2	2.3
Placebo	121	1	0.8	78	0	0.0
Total	352	8	2.3	257	2	0.8

* Includes extension/phase 2 data

No new cases of patients requiring dialysis are reported for study 011 or study 039. For post 15-minute infusion amendment patients, no zoledronate 4 mg patients in study 039 and 1 patient in study 011 required dialysis prior to the ISS report. One patient with multiple myeloma, who was treated with zoledronate 4 mg infused over 15 minutes in the extension study to 010, has required dialysis since the ISS. Four additional patients with multiple myeloma in study 010E also required dialysis since the ISS report. Of these, 2 patients were in the pre 15-minute infusion amendment receiving zoledronate 4 mg and 2 patients were in the post amendment group receiving zoledronate 8/4 mg.

There have been no additional deaths due to renal disorders since the ISS was published. One (0.1%) patient in the zoledronate 4 mg group died of renal disorders, compared with 10 (1.0%) of patients in the 8/4 mg group and no patients in the other treatment groups.

Zoledronate is marketed for the treatment of hypercalcemia of malignancy in the U.S. and internationally. Novartis estimates at least 27, 000 patients were treated through August 15, 2001. Eleven SAEs were reported, of which 3 included renal failure. Two of these patients, both with multiple myeloma, had been switched to zoledronate after 2 to 3 years of therapy with Aredia.

7.5 Safety Update: Late Renal Safety Data

The Applicant provided additional renal safety data, per FDA request, on January 18, 2002, and, following spontaneous Adverse Event reporting, on February 12, 2002.

7.5.1 January 2002 Update

The Applicant provided an analysis of the time course and degree of reversibility of renal deterioration for patients treated with zoledronate (as well as placebo and Aredia patients). Information was also provided regarding the need for dialysis in patients who experienced renal deterioration while on study. This document included data from the 120-day safety update. This extended the data collection to 19 months for study 010 (breast and multiple myeloma), 15 months for study 011 (solid tumors), and 21 months for study 039 (prostate cancer).

The incidence of grade 3 and 4 creatinine values was low (usually 0-1%) for patients treated with zoledronate 4 mg in most disease categories. For post 15-minute infusion amendment patients with myeloma, the incidence of grade 3 post-baseline serum creatinine was 1% for zoledronate 4 mg patients, 5% for 8/4 mg patients, and 5% for Aredia patients. The incidence of baseline grade 3 creatinine elevations in these patients was 0%, as was the incidence of baseline and post-baseline grade 4 creatinine elevations.

In all studies combined, 30 patients required dialysis. The majority of these patients had myeloma or prostate cancer (23 of 30).

With discontinuation of therapy, for those patients for whom follow-up creatinine was available at $\geq$ 84 days, renal deterioration seemed to be reversible for most patients.

Reviewer's Comment: The higher incidence of serious renal outcomes, such as need for dialysis, is not unexpected in patients with myeloma and prostate cancer with exposure to a potentially nephrotoxic drug. These diseases, particularly myeloma, may be associated with renal dysfunction.

7.5.2 February 2002 Update

The February 12, 2002 update includes spontaneous safety reports subsequent to the 120-day Safety Update provided in December 2001. At this time, Novartis estimated that more than [redacted], of zoledronate. An additional 11 reports for renal SAEs were provided, for a total of 14 from April 2001 to February 8, 2002. Of the 14 reports, 10 are for patients with multiple myeloma and 4 for hypercalcemia of malignancy. Deaths and renal failure are reported in 3 patients; dialysis and renal failure are reported in 3 patients.

The Applicant observed that 6 of the multiple myeloma patients with renal AEs were taking thalidomide. For this reason, they performed an analysis of the myeloma patients in study 010 who had deterioration of renal function, identifying patients who were also taking thalidomide.

Of the 186 patients receiving zoledronate 4 mg, 7 or 3.8%, experienced renal SAEs, similar to the incidence for those receiving Aredia 90 mg (5.4%), but less than those receiving zoledronate 8/4 mg (8.12%).

The incidence of renal function deterioration for myeloma patients not receiving thalidomide was 13.9% for the zoledronate 4 mg group, 27.3% for the 8/4 mg group, and 11.0% for the Aredia group. When patients were treated with thalidomide, the incidence of renal deterioration was markedly higher in the 8/4 mg group (n= 7 of 15=46.7%). For the Aredia group, the incidence was somewhat higher (4 of 26=15.4%). The incidence for zoledronate 4 mg was 3 of 27 (11.1%) which is slightly less than for patients *not* treated with thalidomide.

Reviewer's Comment: The data suggests the possibility that thalidomide may increase the risk of renal AEs in patients with myeloma, particularly for the 8/4 mg patients, but the effect was not obvious in the 27 myeloma patients taking thalidomide in the 4 mg arm of study 010.

7.6 Adequacy of safety testing

Zoledronate has been tested adequately for safety for the population studied. The randomized trials have established safety in a broad spectrum of malignancies for long-term therapy.

7.7 Summary of critical safety findings and limitations of data

Zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks has an acceptable safety profile, and is comparable in toxicity to Aredia 90 mg i.v. over 2 hours every 3-4 weeks as an adjuvant to standard anticancer therapy in patients with bone metastases from breast cancer and lesions of multiple myeloma. Zoledronate 4 mg i.v. over 15 minutes every 3 weeks has an acceptable safety profile, but is more toxic than placebo when used as an adjuvant to standard anticancer therapy in patients with prostate cancer and other solid tumors.

The risk of renal deterioration with Zoledronate is greater than placebo, but similar to Aredia. It must be infused over not less than 15 minutes in a volume of 100ml, and clinical monitoring of serum creatinine should be done before each dose to minimize renal risk. The risk of renal toxicity increases with duration of therapy (# of infusions). Caution is indicated for patients with elevated baseline creatinine, particularly since the study population excluded patients with creatinine > 3.0 and the drug is excreted unchanged by the kidneys. The study population did not have extensive concomitant exposure to other potentially nephrotoxic drugs. As the treatment population is expanded, it will be necessary to monitor for possible synergistic nephrotoxic drug effects.

8 Dosing, Regimen, and Administration Issues

The recommended dose of zoledronate in patients with multiple myeloma and metastatic bone lesions from solid tumors is 4 mg infused over 15 minutes every three or four weeks. Patients should take an oral calcium supplement (500 mg) and a multivitamin containing vitamin D 400 IU daily. Serum creatinine should be measured before each dose of zoledronate and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as an increase in creatinine of 0.5 mg/dL for patients with baseline creatinine less than 1.4 mg/dL or an increase of 1.0 mg/dL for patients with baseline creatinine of 1.4 mg/dL or higher. Zoledronate was held until return of the creatinine to within 10% of baseline.

The studies were amended twice because of renal toxicity. The duration of infusion was increased from 5 minutes to 15 minutes and the infusion volume was increased from 50 to 100 ml, with improvement of the toxicity profile. Subsequently, after all patients were accrued, the dose was reduced for those patients in the 8 mg arms to 4 mg (8/4 mg arm), with further decrease in renal toxicity.

Patients were excluded from the bone metastases trials for serum creatinine greater than 3.0 mg/dL. Patients were excluded from the hypercalcemia of malignancy (HCM) trials for creatinine greater than 4.5 mg/dL. For HCM, therapy would ordinarily be short-term, and patients would be less likely exposed to the cumulative risk of renal deterioration over time associated with long-term therapy with zoledronate.

Safety and pharmacokinetic data are limited in patients with severe renal impairment. At this time, there is no clinical data available to permit dose modification for patients with severe renal impairment, who were excluded from the clinical trials.

WARNINGS must emphasize that single doses of zoledronate should not exceed 4 mg; the duration of infusion should be no less than 15 minutes; baseline creatinine should be obtained and patients with severe renal impairment excluded (see above); serum creatinine should be assessed before each dose and the dose held for renal deterioration.

9 Use in Special Populations

9.1 Evaluation of Evidence for Gender, Age, Race, or Ethnicity Effects on Safety or Efficacy

- Gender. Gender has no apparent effect on safety or efficacy of Zoledronate. Efficacy was established in tumors that occur only in men (prostate cancer), predominantly in women (breast cancer), and in both (multiple myeloma and other solid tumors).

- Age. In the bone metastases trials, more than 50% of the patients treated with zoledronate were older than age 60. As shown in the following table, clinical studies in multiple myeloma and bone metastases showed similar for older patients for younger patients. Smaller number of patients preclude conclusions on statistical grounds.

Table 62: Overall proportion of patients with any SRE in patients 65 years and older

Study	Control	Zol. 4 mg	Zol. 8/4 mg
010	91/198 46%	94/201 47%	99/181 55%
011	43/115 37%	43/116 37%	28/108 26%
039	80/183 44%	52/173 30%	68/171 40%

The pharmocokinetics of zoledronate were not affected by age in patients who ranged from 38 to 84 years. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

- Race. The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer bone metastases.

9.2 Evaluation of Pediatric Program

The safety and effectiveness of Zoledronate in pediatric patients have not been established.

The Applicant requested and received a waiver from the requirement to do pediatric zoledronate studies due to small numbers of pediatric patients with bone metastases and the potential for added risk of zoledronate treatment in children. Multiple myeloma, a disease of adults, is the only hematologic malignancy to be included in the proposed indication. Per the Applicant, the incidence of non-hematological malignancies in patients less than 15 years of age is 3,500/year. Considering the requirement that patients also have bone metastasis, the small numbers of pediatric patient's with bone metastases from solid tumors would prohibit an adequately sized trial. Furthermore, because of long-term retention of zoledronate in bone, there is the additional risk in children of zoledronate interfering with bone remodeling and bone growth.

9.3 Comments on Data Available or Needed in Other Populations

Renal impairment. Safety and pharmacokinetic data are limited in patients with severe renal impairment. The bone metastases trials excluded patients with serum creatinine greater than 3.0 mg/dL. At this time there is inadequate clinical data to permit dose modification for patients with severe renal impairment. Zoledronate is excreted unchanged by the kidneys and clearance is related to the patient's creatinine clearance. The risk of renal deterioration is correlated with Area Under the Curve (AUC). AUC was increased in the limited number of patients studied with mild to severe renal impairment compared to patients with normal renal function.

Reviewer Comment: Consideration could be given to a Phase IV pharmacokinetic, safety and efficacy study of patients with renal dysfunction more severe than those included in the randomized trials. Adjusted dose zoledronate could be studied in patients with multiple myeloma or other suitable population. I would not favor expanding this to the "other solid tumor" population, where the benefit-risk ratio would be expected to be less due to their very short survival.

Hepatic impairment. Animal studies suggest that zoledronate is not metabolized or excreted by the liver. No studies have been done in patients with hepatic impairment.

Pregnancy and Nursing Mothers. Zoledronate should not be used during pregnancy. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an i.v. dose of 4 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations. Zoledronate is excreted in human milk. Because many drugs are excreted in human milk, and because Zoledronate binds to bone long-term, Zoledronate should not be administered to a nursing woman.

10 Conclusions

Conclusions are discussed for each of the studies, and then collectively.

Prostate cancer

The patients entering Study 039 had prostate cancer with PSA progression while on first-line hormonal therapy for metastatic disease. Efficacy analyses showed significantly less skeletal morbidity on the zol 4 arm than on the placebo arm both by the protocol-specified primary analysis of proportions of patients with at least one SRE (33% vs. 44%, respectively, p = 0.021) and by the FDA-preferred analysis of time to first SRE (p = 0.011). By both analyses, however, the zol 8/4 arm failed to demonstrate a statistically significant difference from placebo (Proportions: 38% vs. 44%, respectively, p = 0.222. Time to SRE: p = 0.491).

The study was a well-conducted, well controlled trial. The major problems that were debated internally, and were also presented to ODAC, were:

- Unsupportive evidence provided by efficacy analyses of the 8/4 mg arm.
- Prostate Cancer produces predominantly osteoblastic metastases, where as the only prior approval of a bisphosphonate was for Aredia in Breast cancer and Multiple Myeloma. In these diseases, the bone metastases are predominantly osteolytic. The question arose whether results from studies 010 and 011 could support the finding in the Zol. 4 mg arm.
- Lack of clinical data in published literature to support the efficacy of the Zol. 4 mg arm in this new indication

Several minor problems were discussed in this review:

- Asymptomatic vertebral compression fractures and changes in chemotherapy, events of questionable clinical meaning, were included as elements of the SRE endpoint. Because there were few such events on the study, this was not a significant problem.
- Unblinding of patients to treatment arm was noted in about 5% of patients, but was equally distributed among study arms.

The ODAC voted that Zol. 4 mg demonstrated "substantial evidence of efficacy" for the following reasons:

- Osteoclast activation appears to be the underlying mechanism of action for both osteolytic and osteobastic metastases.
- The overall efficacy results in the three studies were similar to each other.
- The exploratory analyses such as the pooled analysis of Zol. 4 mg + Zol. 8/4 mg suggested efficacy of Zoledronate.

For these reasons, zoledronate is being recommended for approval for prostate cancer.**Other Solid Tumors**

In Study 011, patients with a variety of solid cancers metastatic to bone were randomized 1:1:1 to treatment with zoledronate 4 mg, zoledronate 8/4 mg, or placebo to evaluate zoledronate's effect on SREs. The proportion of patients with an SRE was lower on the 4 mg arm than placebo, but the difference was not statistically significant (37% versus 44%, respectively, p = 0.106). The comparison of the 8/4 mg group to placebo showed a significant difference (35% versus 44% respectively, p = 0.044). Time to first SRE was 67 days longer in the 4mg arm than placebo (230 days versus 163 days respectively, p = 0.026) and was also significantly longer for the 8/4 mg arm. These data provide substantial evidence that Zoledronate 4mg was efficacious in the population in study 011.

However, FDA considered two important issues regarding Study 011:

- whether the study design assumption was valid that zoledronate efficacy observed in Study 011 study could be extrapolated to treatment of all solid tumors
- the lack of statistical significance for the primary analysis (proportions of patients with SRE) of Zol 4 versus placebo

The ODAC committee members voted that there was "substantial evidence" that Zol 4 mg is effective in the population studied. Even though results from the Zol 4 mg arm failed to achieve statistical significance relative to placebo for the primary endpoint (proportion of patients with SRE, 37% versus 44% respectively, p = 0.106), there was a statistically significant finding in the closely related secondary endpoint (time to SRE), there were statistically significant findings from the Zol 8/4 mg arm in prostate cancer for both the primary and secondary efficacy analyses, and there was support from trials in multiple myeloma, breast cancer, and prostate cancer. We concur with these findings by the ODAC.

Myeloma and Breast Cancer

Study 010 was an international, multicenter, stratified, double-blind, study that randomized patients 1:1:1 to zoledronate 4 mg, zoledronate 8mg, or Aredia 90 mg i.v. every 3-4 weeks for 12 months. The primary analysis was to be a non-inferiority analysis of the proportion of patients with at least one SRE, performed after 13 months (12 months of treatment and one month of followup)

Results by FDA using conservative non-inferiority demonstrate that zoledronate retains at least 49.3% of the Aredia-versus-placebo effect.

Before accepting the results of this non-inferiority analysis, FDA evaluated the *constancy assumption,* a determination that the active control drug (Aredia) would have shown efficacy in the new study or current setting, and it also requires an estimation of the size of the effect that Aredia would have shown in the current setting. FDA reviewers evaluated important differences between the hisorical Aredia trial and the current Zoledronate study . Although some differences were found in the study populations, careful evaluation of the differences suggest that the constancy assumption is valid.

We concur with the ODAC that these results represent substantial evidence of efficacy for zoledronate in the treatment of myeloma and bone metastases from breast cancer.

11 Recommendations

We recommend approval of zoledronate for treatment of patients with multiple myeloma and bone metastases from all solid tumors.

12 Other Relevant Materials

There were no large randomized trials in literature evaluating skeletal related events.

13 Individual More Detailed Study Reviews

None.

14 Appendix 1 Review of Zoledronate Safety in Prostate Cancer, Study 039

Study # CGP 42446-03-039: "A randomized, double-blind, placebo-controlled, multicenter, comparative, safety and efficacy study of intravenous zoledronate (4 and 8 mg) in prostate cancer patients with metastatic bone lesions receiving antineoplastic therapy."

This is a multicenter (136 sites), international study from June 22, 1998, until January 26, 2001. The study duration was 96 weeks, of which Phase 1, the 60-week Safety and Efficacy portion, is the subject of this review. Phase 2 was a 36-week Extension phase.

The study population consists of men with rising serum prostate specific antigen (PSA) while on hormonal therapy for prostate cancer metastatic to bone. No prior chemotherapy was allowed, although patients could receive antineoplastic therapy concomitant with the study, which could be hormonal or chemotherapy. Three sequentially rising PSA's were required, within 8 weeks of visit 1, and patients had to demonstrate castrate levels of testosterone. The creatinine was to be ≤ 3. Corrected serum calcium was required to be in the range of 8.0-11.6 mg/dL. Patients were stratified according to the presence or absence of metastatic disease at time of initial diagnosis.

Patients were randomized to receive zoledronate 4 mg or 8 mg or placebo by intravenous (i.v.) infusion q 3 weeks for 24 months. Initially zoledronate or placebo was given as a 5 minute i.v. infusion in 50 ml every 3 weeks. After Amendment 3, on June 24, 1999, the infusion time and volume were increased to 15 minutes and 100 ml, respectively. This was instituted in response to SAEs of renal failure in 3 patients receiving 8 mg dosing of zoledronate. By recommendation of the Data Safety Monitoring Board (DSMB) and the Renal Advisory Board (RAB), Amendment 4 was instituted on June 7, 2000. This required that all patients who received zoledronate would receive only 4 mg. Serum creatinine would be measured before each dose, and zoledronate held for worsening of creatinine, until the level was within 10% of the baseline creatinine. (Prior to the amendment, chemistries were required only at 3 weeks, 3months and then at 6 week intervals.)

The primary efficacy analysis was at the end of the study (month 15). The main efficacy endpoint was the "proportion of patients having at least one skeletal related event (SRE), which were defined as "pathologic bone fractures, spinal cord compression, surgery to

bone, radiation therapy to bone and change in antineoplastic therapy to treat bone pain." Hypercalcemia (HCM) was not included as an SRE.

Applicant assessment and analysis of safety

Adverse events, serious adverse events, laboratory studies and survival data were the main safety variables. Baseline and end of study physical examination, EKG, and laboratory evaluations were done, including hematology, blood chemistry, urine. Interim physical examination, vital signs, assessment for adverse events and laboratory studies were repeated every 3 weeks, except urine studies were approximately every 3 months. Serum creatinine was measured prior to each dose of study drug per amendment 4 (June 7, 2000). The time to discontinuation of study drug and duration of survival were assessed.

"For laboratory and adverse event analysis, data were cut at the end of the study drug period," either the end of phase 1 or the last date of study medication plus 28 days. For time to death and renal deterioration analysis, all available data was included, up to the date of data base lock For other safety parameters, the last visit date was used.

Renal toxicity was assessed by the number of patients experiencing "a renal adverse event using selected terms and the number of patients who met the predefined criteria of renal function deterioration." Kaplan-Meier curves were used to define the time course of renal function deterioration.

Study population

There were 643 patients randomized to the following groups:

Zometa 4 mg	# 214
Zometa 8/4 mg	# 222
Placebo	# 208

"The safety evaluable population included all patients who were randomized and received study drug." The number of patients in each arm is shown in applicant's table 7-2. Three of the randomized patients did not receive study drug and were not included in the safety analysis. One patient was randomized to the 4 mg group and 2 patients were randomized to the 8/4 mg group. One patient was randomized to the 8/4 mg group but actually received 4 mg for all treatments. This patient (USA/1891/11002) was included in the 8/4 mg group for efficacy, but was included in the 4 mg dose for safety analysis.

Applicant Table 7-2

	Number (%) of patients in analysis populations by treatment group		
Populations	**Zol 4 mg**	**Zol 8/4 mg**	**Placebo**

Randomized	214 (100)	221 (100)	208 (100)
ITT population	214 (100)	221 (100)	208 (100)
Safety evaluable population	214	218	208

Source: Post-text table 7.1-1.

Reviewer Note: From data provided by the applicant, for patients assigned to the 8/4 mg group, 247 of 2400 administrations of zoledronate were actually 4 mg rather than 8 mg, or approximately 10%.

The following is an abbreviated, composite version of the applicant's table 7-3, "Demographic summary by treatment group" and table 7-5, "Baseline disease specific variable by treatment":

Table 63: Abbreviated, composite version of applicant's table 7-3

	Zol 4 mg	**Zol 8/4 mg**	**Placebo**
Age (years)			
N	214	218	208 Mean ±
SD	71.8±7.91	71.2±8.04	72.2±7.89
Median	72.0	72.0	73.0 Min-max
	45-90	43-90	37-90
Age			
<= 60	19 (8.9)	19 (8.7)	15 (7.2)
>60	195 (91.1)	199 (91.3)	193 (92.8)
Serum creatinine			
Normal (< 1.4 mg/dL)	173 (80.8%)	168 (77.1%)	170 (81.7%)
Abnormal (≥ 1.4 mg/dL)	41 (19.2)	47 (21.6)	33 (15.9)
Missing	0 (0.0)	3 (1.4)	5 (2.4)

Patient factors which might increase susceptibility to renal toxicity of zoledronate are baseline renal function, age (which may relate to renal function reserve), and exposure to other nephrotoxic therapy. The above tables suggest similar age and baseline serum creatinine for the treatment groups. The applicant states that concomitant medication was similar for all treatment groups, and this seem to be the case (Post-text tables 8.2-1,2,3,4), with patients experiencing little exposure to potentially nephrotoxic drugs.

Overall Exposure

The applicant's table 8-1 demonstrates the overall exposure to study drug by treatment group for the safety evaluable patients.

Applicant table 8-1

For patients who did not present with metastatic disease at diagnosis,

Table 8-1. Overall exposure to study drug by treatment group (safety evaluable patients)

Stratum	Exposure (months)	Zol 4 mg	Zol 8/4 mg	Placebo
No metastases	N	114	133	116
	Mean	9.12	8.85	9.09
	SD	5.68	5.12	5.21
	Median	9.93	9.00	9.04
	Range			
Metastases	N	100	85	92
	Mean	9.77	8.64	8.90
	SD	6.02	5.58	5.54
	Median	11.61	9.04	9.07
	Range			
Total	N	214	218	208
	Mean	9.42	8.77	9.00
	SD	5.84	5.29	5.35
	Median	10.48	9.02	9.04
	Range			

Source: Post-text table 8.1-1.

the exposure (in months) to study drug is similar, particularly for the 4 mg and placebo treatment groups. For patients who presented at diagnosis with metastatic disease, the duration of exposure was greater for zoledronate 4 mg than for placebo or zoledronate 8/4 mg groups. The mean and median exposure was greater for the 4 mg group when the exposure for both strata was totaled.

For patients who did not present with metastatic disease at diagnosis, the exposure (in months) to study drug is similar, particularly for the 4 mg and placebo treatment groups. For patients who presented at diagnosis with metastatic disease, the duration of exposure was greater for zoledronate 4 mg than for placebo or zoledronate 8/4 mg groups. The mean and median duration exposure was greater for the 4 mg group when the exposure for both strata was totaled.

The following table, applicant table 8-2, demonstrates exposure to the study drug by treatment group, separating pre and post 15-minute infusion amendment patients. Data includes core (Phase 1) and extension (Phase 2) treatment periods. "The distribution of duration from randomization was similar before and after the amendment."

Applicant table 8-2

Table 8-2. Overall exposure to study drug by duration and treatment group for pre 15-minute infusion amendment patients and post 15-minute infusion amendment patients (Safety evaluable patients)

	Zol 4 mg N=214	Zol 8/4 mg N=218	Placebo N=208
Pre 15-minute infusion amendment patients			
Number of patients	117 (100.0%)	125 (100.0%)	124 (100.0%)
Duration from randomization (months)			
<= 3	20 (17.1%)	20 (16.0%)	15 (12.1%)
>3 to <= 6	23 (19.7%)	20 (16.0%)	27 (21.8%)
>6 to <=9	8 (6.8%)	22 (17.6%)	16 (12.9%)
>9 to <= 12	11 (9.4%)	22 (17.6%)	19 (15.3%)
>12 to <= 15	14 (12.0%)	18 (14.4%)	14 (11.3%)
>15 to <= 18	41 (35.0%)	23 (18.4%)	32 (25.8%)
>18 to <= 21	0 (0.0%)	0 (0.0%)	1 (0.8%)
Post 15-minute infusion amendment patients			
Number of patients	97 (100.0%)	93 (100.0%)	84 (100.0%)
Duration from randomization (months)			
<= 3	19 (19.6%)	19 (20.4%)	22 (26.2%)
>3 to <= 6	16 (16.5%)	17 (18.3%)	10 (11.9%)
>6 to <=9	12 (12.4%)	11 (11.8%)	12 (14.3%)
>9 to <= 12	7 (7.2%)	10 (10.8%)	10 (11.9%)
>12 to <= 15	15 (15.5%)	13 (14.0%)	6 (7.1%)
>15 to <= 18	28 (28.9%)	22 (23.7%)	24 (28.6%)
>18 to <= 21	0 (0.0%)	1 (1.1%)	0 (0.0%)

Includes all available data of core (Phase 1) and extension (Phase 2).
Source: Post-text table 8.1-2A and 8.1-2B.

Overall incidence and severity of adverse events

Clincal study reports used the IMN dictionary to code adverse events but the data for Study 039 is presented using the MedDRA dictionary. Adverse events were mapped from IMN preferred terms to the corresponding MedDRA terms, prior to pooling of data for analysis.

Almost all patients in each study group experienced at least one adverse event. The applicant's Table 10-2 lists the frequency of AEs with an incidence of at least 15% in each treatment group. Bone pain, nausea, constipation, and fatigue were noted most often. Fatigue, anemia, myalgia, pyrexia, and lower limb edema were more frequent in patients receiving zoledronate versus placebo, but there was no apparent correlation with dose. Nausea, anorexia and vomiting were more common in the zoledronate 8/4 mg group. Bone pain was less in the 4 mg group. Dizziness was higher in the 4 mg group (17.8%) compared with the 8/4 mg group (10.1%) and placebo (11.5%). The significance of these differences is uncertain, and there may be no direct relationship with treatment.

Applicant table 10-2

Table 10-2. Number of patients with most frequently occurring (≥15% in any treatment group) adverse events by treatment (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients	214	218	208
Total no. with an AE	206 (96.3)	216 (99.1)	199 (95.7)
Bone pain	108 (50.5)	133 (61.0)	127 (61.1)
Nausea	77 (36.0)	115 (52.8)	77 (37.0)
Constipation	72 (33.6)	85 (39.0)	72 (34.6)
Fatigue	70 (32.7)	67 (30.7)	53 (25.5)
Anemia NOS	57 (26.6)	60 (27.5)	37 (17.8)
Myalgia	53 (24.8)	53 (24.3)	37 (17.8)
Vomiting NOS	46 (21.5)	64 (29.4)	43 (20.7)
Weakness	45 (21.0)	50 (22.9)	40 (19.2)
Anorexia	43 (20.1)	55 (25.2)	36 (17.3)
Pyrexia	43 (20.1)	48 (22.0)	27 (13.0)
Edema lower limb	41 (19.2)	48 (22.0)	27 (13.0)
Dizziness (exc vertigo)	38 (17.8)	22 (10.1)	24 (11.5)
Diarrhea NOS	36 (16.8)	35 (16.1)	32 (15.4)
Weight decreased	36 (16.8)	38 (17.4)	26 (12.5)

Source: Post-text tables 10.1-1, 10.1-2.

Adverse events were thought to be study drug-related in 41.6%, 50.5% and 21.6% (Post-text table 10.1-5).

The incidence of grade 4 events was similar, 27.1%, 32.1%, and 25.0% for the 4 mg, 8/4 mg and placebo groups, respectively (Post-text table 10.1-4, volume 109).

Table 64: Selected (more frequent) grade 4 adverse events by body system and treatment group

Body system	Preferred term	Zol 4 mg N(%)	Zol 8/4 mg N(%)	Placebo N(%)
Any	Total	58 (27.1)	70 (32.1)	52 (25.0)
Blood and lymph	Total	8 (3.7)	9 (4.1)	5 (2.4)
	Anemia	6 (2.8)	6(2.8)	2 (1.0)
Cardiac	Total	10 (4.7)	10 (4.6)	8 (3.8)
GI	Total	8 (3.7)	3 (1.4)	6 (2.9)
Metab and Nutrit	Total	7 (3.3)	13 (6.0)	7 (3.4)
	Dehydration	4 (1.9)	2 (0.9)	2 (1.0)
Musculoskeletal	Bone pain	3 (1.4)	4 (1.8)	5 (2.4)
Neoplasms	Aggravated mal	10 (4.7)	14 (6.4)	6 (2.9)
Nervous system	Total	6 (2.8)	7 (3.2)	7 (3.4)
Renal, urinary	Total	7 (3.3)	15 (6.9)	7 (3.4)
	RF Acute	6 (2.8)	6 (2.8)	1 (0.5)

There is no clear signal suggesting a relation of grade 4 events to treatment arm, except for renal adverse events.

Renal adverse events

A Renal Advisory Board (RAB) was established in November of 1999 to monitor the renal safety of zoledronate, because of concerns about renal dysfunction associated with treatment. Amendment 3 had been instituted June 24, 1999, in response to SAEs of renal failure in 3 patients receiving 8 mg zoledronate. This changed administration volume from 50 ml to 100 ml and administration time from 5 minutes to 15 minutes. The pre-amendment data (applicant's table 10-4), suggests a possible dose-related renal toxicity for overall events, "renal failure acute," " renal impairment NOS," and "blood creatinine increased." Also of interest is the marked increase in "urinary retention" in the zoledronate 8/4 group, which could have exaggerated the apparent renal-toxic effect of study drug. One would anticipate that urinary retention is disease-, rather than drug-related.

Table 65:.**Selected renal AEs by preferred term and treatment group for pre 15-minute infusion amendment patients**

	Zol 4 mg	Zol 8/4 mg	Placebo
	N (%)	N (%)	N (%)
Total # patients	117	125	124
Total # with renal AE	36 (30.8)	54 (43.2)	33 (26.6)
RF, Acute	6 (5.1)	9 (7.2)	4 (3.2)
Renal impair, NOS	6 (5.1)	8 (6.4)	3 (2.4)
Urinary retention	5 (4.3)	18 (14.4)	11 (8.9)
Blood creatinine increased	4 (3.4)	6 (4.8)	0

The following table demonstrates renal AEs following amendment 3. The incidence of "Acute renal failure" is still higher for the zoledronate patients compared with placebo. However, "renal failure NOS" and "increased creatinine" are no longer reported in the 4 mg group. "Renal impairment NOS" is highest in the 4 mg group, with the 8/4 mg and placebo groups being similar.

Applicant table 10-5

Table 10-5. Renal AEs by preferred term and treatment group for post 15-minute infusion amendment patients (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Total no. of patients	97	93	84
Total no. of patients with a renal related AE	30 (30.9)	35 (37.6)	26 (31.0)
Hematuria	15 (15.5)	10 (10.8)	11 (13.1)
Renal impairment NOS	7 (7.2)	3 (3.2)	3 (3.6)
Urinary frequency	6 (6.2)	8 (8.6)	5 (6.0)
Urinary retention	6 (6.2)	10 (10.8)	7 (8.3)
Renal failure acute	5 (5.2)	4 (4.3)	0.0
Hematuria present	4 (4.1)	1 (1.1)	2 (2.4)
Hydronephrosis	2 (2.1)	4 (4.3)	2 (2.4)
Urethral obstruction	2 (2.1)	0.0	1 (1.2)
Calculus renal NOS	1 (1.0)	3 (3.2)	1 (1.2)
Calculus ureteric	1 (1.0)	0.0	0.0
Obstructive uropathy	1 (1.0)	4 (4.3)	0.0
Anuria	0.0	1 (1.1)	0.0
Blood creatinine increased	0.0	4 (4.3)	3 (3.6)
Difficulty in micturition	0.0	2 (2.2)	4 (4.8)
Hyperuricemia	0.0	0.0	1 (1.2)
Micturition urgency	0.0	1 (1.1)	1 (1.2)
Proteinuria present	0.0	1 (1.1)	0.0
Pyelonephritis NOS	0.0	0.0	2 (2.4)
Renal failure NOS	0.0	1 (1.1)	0.0
Renal failure chronic	0.0	1 (1.1)	0.0
Renal injury NOS	0.0	1 (1.1)	0.0
Urethral disorder NOS	0.0	0.0	2 (2.4)
Urinary tract disorder NOS	0.0	1 (1.1)	1 (1.2)

Source: Post-text table 10.1-7B.

Reviewer comment: Amendment 3 may have resulted in some slight improvement in the renal toxicity profile, but the important analysis of safety is for patients who were randomized following amendment 3 and amendment 4 (see below). Also note that the number of patients with urinary retention is less disproportionately distributed to the 8/4 mg group compared with the pre-third amendment patients.

The following table (applicant table 10-7) summarizes events which the applicant suggests are associated with bisphosphonates as a class. Electrolyte abnormalities are increased in zoledronate patients compared with placebo, possibly in a dose-dependant way.

Applicant table 10-7

Table 10-7. Number of patients experiencing adverse events commonly associated with bisphosphonate therapy by treatment (Safety evaluable patients)

Preferred grouping	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Any body system	166 (77.6)	173 (79.4)	144 (69.2)
Infections	100 (46.7)	103 (47.2)	99 (47.6)
Arthralgia/Myalgias	87 (40.7)	85 (39.0)	72 (34.6)
Cytopenias	65 (30.4)	70 (32.1)	42 (20.2)
Fever	44 (20.6)	50 (22.9)	27 (13.0)
Electrolytes	24 (11.2)	31 (14.2)	8 (3.8)
Eye abnormalities	20 (9.3)	17 (7.8)	16 (7.7)
Injection site reactions	7 (3.3)	7 (3.2)	8 (3.8)

The AE preferred terms within each preferred grouping are listed in Post-text table 10.1-8.
Source: Post-text table 10.1-8.

Deaths and other serious and other significant adverse events:

Section 3.5.3.2 of the protocol, the applicant defines a serious adverse event (SAE) as an event which:

1. Is fatal or life threatening.
2. Requires or prolongs hospitalization
3. Is significantly or persistently disabling or incapacitating
4. Constitutes a congenital anomaly or a birth defect
5. Encompasses any other clinically significant event

Item 5 is not clearly explained. "Clinically significant AEs" are defined as events which were not SAEs, but "resulted in withdrawal of study drug or were considered to be clinically important and required concomitant therapy."

Applicant table 10-8 lists "patients who died, had other serious or clinically significant AEs or discontinued therapy because of them."