Table 2.4.8: Summary of Skeletal Morbidity Rate (risk set definition) of any SRE (-HCM) up to Month 9, by Stratum and Treatment Group (Sponsor Analysis)

	N	Skeletal morbidity rate (no. of events per year)		P-values* for the between treatment comparison	
		Mean ± SD	Median	Zol 4 mg	Zol 8/4 mg
Lung Cancer					
Placebo	130	2.37 ± 4.102	0	0.307	0.012
Zol 4 mg	134	2.62 ± 11.815	0		0.117
Zol 8/4 mg	139	1.36 ± 3.279	0		
Other Solid Tumors					
Placebo	120	2.67 ± 6.039	0	0.116	0.147
Zol 4 mg	123	1.82 ± 4.707	0		0.849
Zol 8/4 mg	127	1.75 ± 4.300	0		
Total					
Placebo	250	2.52 ± 5.115	0	0.069	0.005
Zol 4 mg	257	2.24 ± 9.124	0		0.309
Zol 8/4 mg	266	1.55 ± 3.798	0		

The time to multiple occurrences of SREs was also analyzed by the sponsor using Anderson-Gill approach. In this analysis every counted occurrence of an SRE was followed by a 20-day period during which no other occurrence of an SRE was counted. Time to each counted occurrence of an SRE was counted from the 22nd day of the last counted occurrence of an SRE to the onset day. Per sponsor analysis the difference between placebo and zoledronate 4 mg group was statistically significant.

Reviewer's Comments:

1. All secondary efficacy analyses can only be considered as exploratory and supportive of a positive primary efficacy analysis. In this study per sponsor and protocol specified primary efficacy analysis the treatment (zoledronate 4 mg) is not statistically significantly different from placebo.
2. The agency had recommended that the time to first occurrence of an SRE to be evaluated as a primary efficacy variable. The results of this analysis have already been discussed in the previous section (section 2.3.8.2, Reviewer's comment 3).
3. As stated before (section 2.3.8.2, Reviewer's comments), the estimates of the treatment effect may be biased due to high drop out rate and less than optimum method used for evaluation of missing data (last observation carried forward).
4. Per sponsor analysis there is no statistically significant difference between the placebo and zoledronate 4 mg with respect to skeletal morbidity rate (Table 2.4.8).
5. The sponsor's multiple event analysis has not been verified by the reviewer at this time.

6. This reviewer conducted exploratory multivariable Cox regression analyses of the time to first SRE data with treatment (placebo=0, zoledronate=1), prior history of skeletal events (no=0, yes=1), time from initial diagnosis of cancer to bone metastases (in months), and time from first bone metastases to Visit 2 of the study (in months). The results of these analyses are presented in Tables 2.4.9a - 2.4.9c. In all of the models treatment effect was statistically significant. The point estimate of hazard ratio for placebo versus treatment was consistent among all the models and the upper 95% confidence limit of the hazard ratio was less than 1. Exploratory models comparing placebo with zoledronate 8/4 mg groups are presented in Appendix (Appendix 4.2).

Table 2.4.9a: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) as Co-variate

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment Overall	0.733 (0.557, 0.965)	0.027
Treatment Lung Cancer Group	0.785 (0.544, 1.132)	0.194
Treatment Other Solid Tumors Group	0.664 (0.438, 1.009)	0.055

Table 2.4.9b: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) and prior history of SRE (Yes or No) as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.741 (0.563, 0.976)	0.033
Prior SRE	1.437 (1.050, 1.965)	0.023

Table 2.4.9c: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) and Prior History of SRE (Yes or No), Time from Initial Diagnosis of Cancer to Bone Metastases, and Time from First Bone Metastases to Visit 2 of the Study as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.722 (0.548, 0.952)	0.021
Prior SRE	1.535 (1.116, 2.110)	0.008
Time from Initial Dx. of Ca. To Bone Met.	0.994 (0.989, 0.999)	0.015
Time from First Bone Met. to Study Entry	0.986 (0.969, 1.003)	0.102

2.1.19.4 Safety Analyses

2.1.19.4.1 Survival Analysis

Because the zoledronate treatment was not expected to improve survival, it was evaluated as part of safety analysis. The following is the survival analysis results of FDA analysis using the ITT population (instead of safety population used by sponsor). There were no statistically significant differences in survival between zoledronate 4 mg and placebo groups, or between zoledronate 8 mg and placebo groups as presented in Figures 2.4.1-2.4.3 and Table 2.4.10. All other safety analyses are presented in the clinical review of the application.

Figure 2.4.1: Kaplan-Meier Survival Analysis of Over All Survival in ITT Population (FDA Analysis)

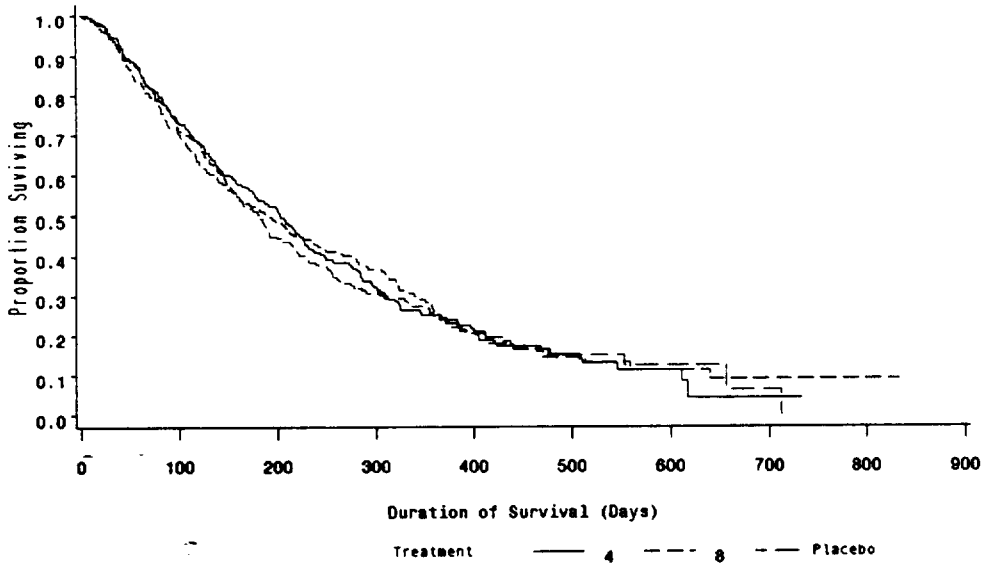

Figure 2.4.2: Kaplan-Meier Survival Analysis of Zoledronate 4 mg versus Placebo groups in ITT Population (FDA Analysis)

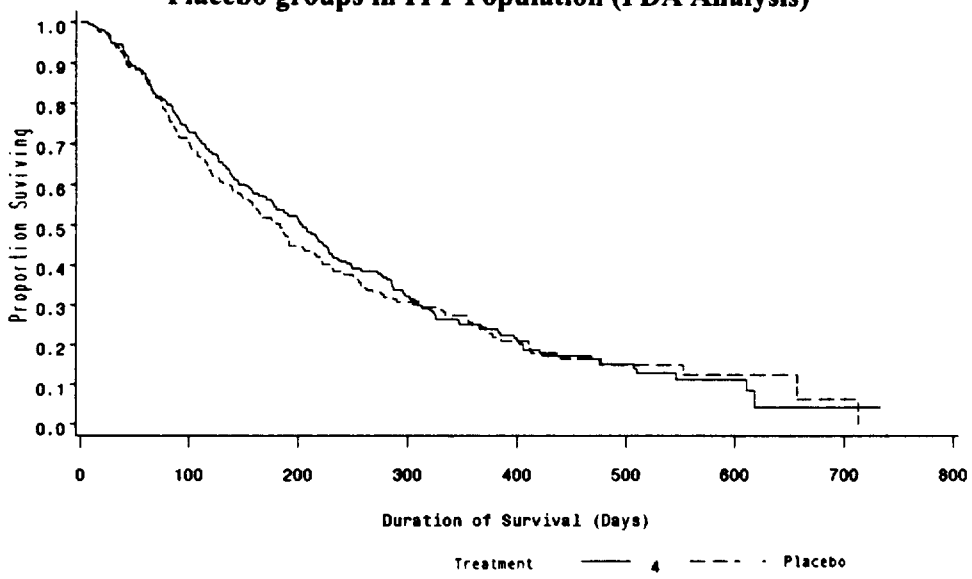

Figure 2.4.3: Kaplan-Meier Survival Analysis of Zoledronate 8/4 mg versus Placebo Groups in ITT Population (FDA Analysis)

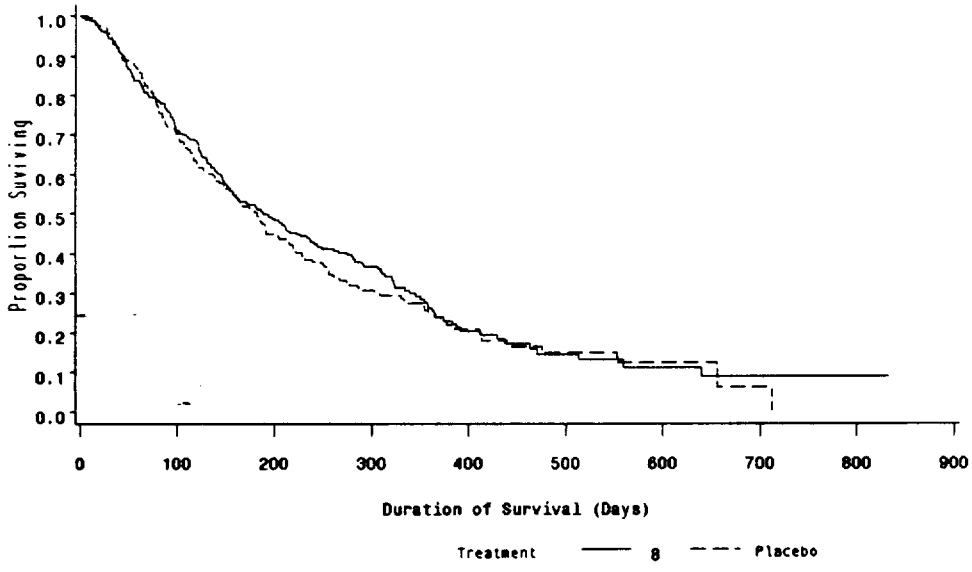

Table 2.4.10: Summary of Survival Analyses Results (FDA Analysis)

	N	Number of Events	Median (95% C.I.) in days	Hazard Ratio (95% C.I.)	P-values (Treatment versus Placebo, Log-rank test)
Placebo	250	188	183 (155, 205)		
Zol 4 mg	256	199	203 (175, 228)	0.632 (0.780, 1.163)	0.63
Zol 8/4 mg	266	191	189 (154, 237)	0.923 (0.755, 1.129)	0.44

2.1.20 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Study 011 was a randomized, double-blind, multicenter, parallel-group, placebo controlled Phase III study conducted in a total of 773 patients aged 18 years or over with ECOG performance status ≤ 2 and bone metastases from solid tumors other than breast or prostate cancer. The primary objective of this study was to assess the efficacy of zoledronate therapy (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone, in preventing skeletal-related events in patients with any cancer with bone metastases other than breast cancer, multiple meyeloma or prostate cancer. Skeletal-related events (SREs) were defined as radiation therapy to bone, surgery to bone, spinal cord compression, and pathologic fracture events. The primary efficacy endpoint was the proportion of patients with any SRE exclusive of tumor induced hypercalcemia by month 9.

1. The sample size calculations were based on that zoledronate would be considered more efficacious than placebo if either of the two comparisons (4 mg versus placebo or 8 mg versus placebo) was statistically significant at a 2-sided p-value < 0.025. During the study, the design was amended to treat all patients on study in the 8 mg group at 4 mg dose level because of the observed renal toxicity with 8 mg group. In lieu of this, the protocol was amended (Amendment 6) which stated that zoledronate 4 mg will be considered more efficacious than placebo if the comparison for the primary efficacy outcome is statistically significant at 0.05 level (2-sided) favoring zoledronate 4 mg. It should be noted that the original design and calculation of sample size was based on comparing 4 mg versus placebo group at 0.025 level. Dropping a treatment arm (in this case 8 mg group) could potentially inflate the overall type I error rate.
2. Although there appears to be no imbalance between the treatment arms there are significant differences between the two stratum (lung versus other solid tumors) with respect time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study (study start day). It is not clear as to how this difference in time between the two strata translates to differences or lack of differences with respect to skeletal related events. These patients were also receiving concomitantly anticancer therapy and this

is a confounding factor with the study drug in estimating the reduction in skeletal related events attributable to the study drug in each stratum and treatment group.

3. The study has failed to demonstrate efficacy of 4 mg zoledronate over placebo treated group in reducing the proportion of SREs at 9 months per protocol specified analysis (P-value=0.127). The protocol specified estimates of the proportion of SREs (Table 2.4.2) may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 9 months (Table 2.4.4). There appears to be a statistically significant difference between the Zoledronate 4 mg group and placebo group (p=0.026, 2-sided log-rank test) by this analysis.
4. Multivariate analyses of time to first occurrence suggest that the results are consistent and the zoledronate 4 mg treatment appears to have efficacy.
5. Patients on the study were receiving varying anticancer therapy, which could potentially be confounding efficacy of the study drug in estimating the reduction in skeletal related events in each stratum and treatment group.

Study 039 (Prostate cancer patients with metastatic bone lesions)

2.1.21 Background

Prostate cancer is one of the most common cancers among men. The vast majority of patients with advanced prostate cancer have skeletal metastases. Skeletal complications due to metastatic disease include, bone pain, spinal cord compromise, and pathological fractures. The purpose of this clinical study was to determine if zoledronate would be an effective treatment to decrease the occurrence of skeletal-related complications associated with metastatic bone disease in prostate cancer patients. In this study, zoledronate treatment in addition to antineoplastic therapy versus antineoplastic therapy alone, was to be administered to prostate cancer patients who have developed biochemical progression of disease (a rising serum prostate-specific antigen (PSA) level) while on first-line hormonal therapy for metastatic bone disease. Skeletal-related events were to include pathologic bone fracture event, spinal cord compression events, surgery to bone, radiation therapy to bone (including the use of radioisotopes) and a change of antineoplastic therapy to treat bone pain.

Study 039 was a international, multicenter, randomized, double-blind, placebo-controlled, parallel study conducted in prostate cancer patients with a history of metastatic bone disease who have a rising serum PSA concentration despite treatment with first-line hormonal therapy for meatastatic disease. Patients were randomized in a double-blind fashion to receive either zoledronate 4 mg intravenously, or zoledronate 8 mg intravenously, or a placebo intravenous infusion every three weeks in addition to their antineoplastic therapy. The randomized treatment assignment ratio was to be 1:1:1. In addition all patients were to receive 500 mg of calcium orally and multivitamin tablet (containing 400-500 I.U. of vitamin D) daily throughout the study.

2.1.22 Data Analyzed and Sources

Data used for this review was obtained from the electronic submission dated 8/21/2001. The network path is "\\Cdsesub1\n21386\N_000\2001_08_21\CRT\datatsets\039" in the EDR. The following volumes were reviewed: 1, 106, 107, 109, 112, 114, and 115.

2.1.23 Study Objectives

The primary objective of this study was to assess the efficacy of zoledronate treatments (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone to prevent skeletal-related events (SREs) in prostate cancer patients with a history of metastatic bone disease who have developed biochemical progression of disease. SREs were defined as pathologic bone

fracture events, spinal cord compression events, surgery to bone, and radiation therapy to bone (including the use of radioisotopes).

2.1.24 Efficacy Endpoints

The primary efficacy variable in this study was the proportion of patients having at least one skeletal-related event.

The secondary efficacy variables included: (1) skeletal morbidity rate (SMR), (2) time to the first occurrence of a SRE, (3) time to disease progression in bone, (4) time to disease progression, (5) pain scores (BPI), (6) analgesic scores, (7) performance status (ECOG), (8) quality of life (FACT-G and EURO QOL EQ-5D), (9) objective bone lesion response from radiological studies, and (10) biochemical variables.

Reviewer's Comments:

FDA reviewer of the IND protocol had conveyed to the sponsor that the if the drop-out rate is relatively high, then the primary endpoint, SRE proportion estimate may be biased and had also suggested that the time to the first SRE be used as the co-primary endpoint.

2.1.25 Sample Size Considerations

This trial was designed to have 80% power to detect a 16% difference in the proportion of patients reporting any SRE during the first 15 months of the trial (Phase I) between the two dose level (4 mg and 8 mg) of zoledronate and placebo. Based on the bonferroni's adjustment, the sample size was calculated, assuming a 40% incidence rate on placebo; a 24% incidence rate on either dose level of zoledronate, with an overall Type I error rate of 0.05 (two-sided). The total sample size was determined to be 519 patients (173 on each arm). It was recommended that 550 patients be enrolled to account for the noise introduced by the use of intent-to-treat (ITT) population.

Reviewer's Comments:

1. A total of 643 patients were enrolled into the study (208 in placebo group, 214 in the zoledronate 4 mg group and 221 in the zoledronate 8/4 mg group) instead of the planned total of 550 patients.
2. The sample size calculations were based on that zoledronate would be considered more efficacious than placebo if either of the two comparisons (4 mg versus placebo or 8 mg versus placebo) was statistically significant at a 2-sided p-value < 0.025.

3. During the study, the design was amended (Amendment 4) to treat all patients on study in the 8 mg group at 4 mg dose level because of the observed renal toxicity with 8 mg group. In lieu of this, in the Amendment 6 (Volume 112, Page 8-181), it was stated that zoledronate 4 mg will be considered more efficacious than placebo if the comparison for the primary efficacy outcome is statistically significant at 0.05 level (2-sided) favoring zoledronate 4 mg. It should be noted that the original design and calculation of sample size was based on comparing 4 mg versus placebo group at 0.025 level. Dropping a treatment arm (in this case 8 mg group) could potentially inflate the overall type I error rate. (Reference: Tsong, Y, Hung HMJ, Wang SJ, et. al.. Dropping a treatment arm in clinical trial with multiple arms, JSM Proceedings, 1997).

2.1.26 Stratification

The randomization was stratified by prostate cancer history (no metastatic disease present at the time of the initial diagnosis of prostate cancer versus metastatic disease present at the time of the initial diagnosis), after Amendment 1 of the protocol (Volume 112, page 8-99).

2.1.27 Interim Analysis

No interim analysis was planned for this study. However, at an interim time point the 8 mg zoledronate arm was dropped due to renal toxicity concerns. The sponsor claimed there was no efficacy analyses conducted at the interim look.

2.1.28 Efficacy Analysis Methods

The primary efficacy endpoint of proportion of patients with any SRE during the first 15 months of the study, was originally planned to be compared between treatment and placebo groups using chi-squared test. This plan was amended after Amendment 1 of the protocol (Volume 112, page 8-119) to compare the treatment and placebo groups using the Cochran-Mantel-Haenzel test statistic. 95% CI for the proportion of patients reporting any SRE by treatment group was also to be presented. In the Amendment 1 the analysis also included evaluation of the influence of stratum and previous experience of SREs using logistic regression analyses.

One of the secondary efficacy variables, skeletal morbidity rate (SMR) defined as the ratio of the number of occurrences of any SRE, allowing one event per assessing period (3 weeks), divided by the time at risk, was originally planned to be compared between treatment groups using Wilcoxon rank sum test, which was later amended (Amendment 1, Volume 112, page 8-120) to analyze using Cochran-Mantel-Haenzel test statistic with modified ridit scores.

Time to first occurrence of a SRE was planned to be compared between the treatment groups using survival analysis methods, including Kaplan-Meier product limit estimates and the log-rank test. Death not related to SRE would be considered as censored observation. Multiple events analysis, allowing one event every assessing period would be explored using Anderson-Gill approach.

For each particular type of SRE, the proportion of patients with the SRE, the SMR of the SRE, at month 3, 6, 9, 12 and 15 and the time to first occurrence of the SRE was planned to be similarly analyzed using the method for the respective variable with any SRE.

Change from baseline in BPI composite score was planned to compared between the treatment groups using analysis of covariance with baseline value as a covariate and the treatment group as a factor at 3, 6, 9, 12, and 15 months. Change from baseline in mean analgesic use and performance status were planned to be compared between the treatment groups using the Cochran-Mantel-Haenzel (CMH) test statistic with modified ridit scores (originally planned to use Wilcoxon rank sum test) at 3, 6, 9, 12, and 15 months. Change from baseline in FACT-G total scores and the 4 subscales were planned to be compared between the treatment groups using analysis of covariance with baseline value as a covariate and treatment groups as a factor, at 3, 6, 9, 12, and 15 months. Change from baseline in EURO QOL-5D was planned to be analyzed similarly.

Time to progression of disease and time to progression of bone lesions were planned to be compared between treatment groups using Kaplan-Meier product limit estimates and log-rank test.

Percent change from baseline of biochemical variables were planned to be compared between the treatment groups using the CMH test statistics with modified ridit scores.

Reviewer's Comments:

1. Early dropouts and missing assessments were not considered in the above planned analyses.
2. The infusion time was amended (Amendment 3) from 5 minutes to 15 minutes during the study.
3. After the enrollment was completed in all the three treatment arms, the dose was reduced in the 8 mg arm to 4 mg (Amendment 4) because of renal toxicity. In this Amendment it was also stated that the 8/4 mg arm would not be evaluated for efficacy. However, it should be noted that by the time of this Amendment, majority of the patients had completed the phase I (15 months) or had dropped out of the study.

4. The definition of ITT population was modified (Amendment 6) to include all randomized patients who had evidence of bone metastases at study entry.

2.1.29 Sponsor's Results and Reviewer's Findings/Comments

2.1.29.1 Baseline Characteristics

A total of 643 patients were randomized as follows: 214 patients were randomized to zoledronate 4 mg, 221 patients to the zoledronate 8 mg group, and 208 patients to the placebo group. At the time of randomization, patients were stratified by the their history of prostate cancer (presence or absence of metastatic disease at the time of their initial diagnosis of prostate cancer). Several patients in each stratum were randomized to the incorrect stratum as follows: 30 patients were incorrectly assigned to the stratum of patients with no metastases at the time of initial diagnosis, and 27 patients were incorrectly assigned to the stratum of patients with metastases at the time of initial diagnosis. Thirty one patients were withdrawn from the study prematurely. One patient in the zoledronate 4 mg group was discovered to never have had bone lesions. Table 2.5.1a describes the baseline characteristics as presented by the sponsor in the safety population (Sponsor's Table 7-3, 7-4, 7-5, Volume 106, pages 8-56 to 8-58).

Table 2.5.1a: Baseline Characteristics (Sponsor's Analysis – Safety Population)

	Total		
	Zol 4 mg N=214	**Zol 8/4 mg N=218**	**Placebo N=208**
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
Age n (%)			
≤ 60	19 (8.9%)	19 (8.7%)	98 (7.2%)
> 60	195 (91.9%)	199 (91.3%)	149 (92.8%)
Race n (%)			
Caucasian	178 (83.2%)	184 (84.4%)	172 (82.7%)
Black	24 (11.2%)	18 (8.3%)	19 (9.1%)
Other	12 (5.6%)	16 (7.3%)	17 (8.2%)
Weight (kg)			
N	212	217	207
Mean ± SD	82.7±14.15	82.2±14.50	83.4±16.08
Median	81.9	81.0	80.2
Metastases other than bone at initial diagnosis n (%)			
Lung	4 (.9%)	1 (0.5%0	1 (0.5%0
Liver, Brain, Skin, and Eye	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pleura	0 (0.0%)	1 (0.5%)	0 (0.0%)
Distant lymph nodes	19 (8.9%)	9 (4.1%)	9 (4.3%)
Other	2 (0.9%)	4 (1.8%)	4 (1.9%)
Serum creatinine n (%)			
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%)
Previous SRE n (%)			
Yes	66 (30.8%)	70 (32.1%)	78 (37.5%)
No	148 (69.2%)	148 (67.9%)	130 (62.5%)
Prostate Specific Antigen			
Mean ± SD	276.5 ± 737.10	354.0 ± 1156.54	211.1 ± 464.89
Median	81.7	88.5	61.0
Time from initial diagnosis of cancer to bone metastases (month)			
N	214	217	207
Mean ± SD	39.1±47.98	41.7±46.00	38.4±47.72
Median	19.6	26.6	19.6
Time from bone metastases to Visit 2 (month)			
N	214	217	207
Mean ± SD	23.5±25.77	25.5±31.33	28.4±30.70
Median	16.1	15.5	17.8
ECOG status n (%)			
ECOG 0-1	197 (92.1%)	199 (91.3%)	190 (91.3%)
ECOG ≥ 2	17 (7.9%)	18 (8.3%)	18 (8.7%)
Analgesic score n (%)			
0	93 (43.5%)	73 (33.5%)	77 (37.0%)
1	70 (32.7%)	83 (38.1%)	77 (37.0%)
2	9 (4.2%)	11 (5.0%)	9 (4.3%)
3	40 (18.7%)	48 (22.0%)	41 (19.7%)
4	2 (0.9%)	3 (1.4%)	3 (1.4%)
BPI composite pain score			
N	193	198	191
Mean ± SD	2.0±1.98	2.5±2.10	2.1±2.04
Median	1.8	2.3	1.8

	Total		
	Zol 4 mg N=214	Zol 8/4 mg N=218	Placebo N=208
FACT-G total score			
N	193	192	187
Mean ± SD	81.0±15.36	81.2±13.69	82.2±14.57
Median	82.5	82.1	82.8

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Table 2.5.1b: Baseline Characteristics (FDA Analysis – ITT population)

	No Metastasis at Initial Diagnosis			Metastases at Initial Diagnosis			Total		
	Zol 4 mg N=115	Zol 8/4 mg N=134	Placebo N=116	Zol 4 mg N=99	Zol 8/4 mg N=87	Placebo N=92	Zol 4 mg N=214	Zol 8/4 mg N=221	Placebo N=208
Age (years)									
N	115	134	116	99	87	92	214	221	208
Mean ± SD	72.6±0.8	70.8±0.7	73.0±0.7	70.9±0.8	71.7±0.9	71.3±0.9	71.8±0.5	71.2±0.5	72.2±0.5
Median	73	71	74	71	72	73	72	72	73
Age									
≤ 60	9 (7.8%)	11 (8.2%)	6 (5.2%)	10 (10.1%)	8 (9.2%)	9 (9.8%)	19 (8.9%)	19 (8.6%)	15 (7.2%)
> 60	106 (92.2%)	123 (91.8%)	110 (94.8%)	89 (89.9%)	79 (90.8%)	83 (90.2%)	195 (81.2%)	202 (91.4%)	193 (92.8%)
Race n (%)									
Caucasian	102 (88.7%)	116 (86.6%)	93 (80.2%)	76 (76.8%)	70 (80.5%)	79 (85.9%)	178 (83.2%)	186 (84.2%)	172 (82.7%)
Black	8 (7.0%)	10 (7.5%)	11 (9.5%)	16 (16.2%)	9 (10.3%)	8 (8.7%)	24 (11.2%)	19 (8.6%)	19 (9.1%)
Other	5 (4.3%)	8 (5.9%)	12 (10.3%)	8 (7.0%)	8 (9.2%)	5 (5.4%)	12 (5.6%)	16 (7.2%)	17 (8.2%)
Weight (kg)									
N	114	133	116	98	87	91	212	220	207
Mean ± SD	83.8±1.3	82.3±1.3	83.9±1.5	81.5±1.5	81.9±1.6	82.8±1.7	82.8±1.0	82.1±1.0	83.4±1.1
Median	82.3	81.0	79.7	81.4	79.8	82.0	82.0	81.0	80.2
Serum creatinine									
Normal (< 1.4 mg/dL)	92 (80.0%)	101 (75.4%)	96 (82.8%)	81 (81.8%)	72 (82.8%)	79 (85.9%)	173 (80.8%)	173 (78.3%)	175 (84.1%)
Abnormal (≥ 1.4 mg/dL)	23 (20.0%)	33 (24.6%)	20 (17.2%)	18 (18.2%)	15 (17.2%)	13 (14.1%)	41 (19.2%)	48 (21.7%)	33 (15.9%)
Previous SRE									
Yes	30 (26.1%)	42 (31.6%)	44 (37.9%)	36 (36.7%)	29 (33.3%)	34 (37.0%)	66 (31.0%)	71 (32.3%)	78 (37.5%)
No	85 (73.9%)	91 (68.4%)	72 (62.1%)	62 (63.3%)	58 (66.7%)	58 (63.0%)	147 (69.0%)	149 (67.7%)	130 (62.5%)
Prostate Specific Antigen									
N	115	132	113	97	86	87	212	218	200
Mean ± SD	261.2±63.4	382.3±109.4	164.1±38.8	294.7±82.6	302.8±104.1	272.2±55.9	276.5±50.6	350.9±77.8	211.1±32.9
Median	89.4	90.9	56.0	76.7	87.2	69.7	81.7	88.2	61.0
Time from initial diagnosis of cancer to bone metastases (month)									
N	115	133	115	99	87	92	214	220	207
Mean ± SD	64.7±4.5	64.4±3.7	63.8±4.6	8.1±2.2	7.9±2.7	6.6±1.8	38.5±3.3	42.0±3.1	38.4±3.3
Median	60.8	58.3	53.0	0.2	0.3	0.2	19.2	28.6	19.6
Time from bone metastases to Visit 2 (month)									
N	115	133	115	99	87	92	214	220	207
Mean ± SD	15.0±2.1	13.6±1.4	20.0±2.4	33.9±2.6	44.5±4.2	39.0±3.5	23.8±1.8	25.8±2.1	28.4±2.1
Median	6.5	6.5	12.3	26.2	31.3	32.3	16.1	16.1	17.8

	No Metastasis at Initial Diagnosis			Metastases at Initial Diagnosis			Total		
	Zol 4 mg N=115	Zol 8/4 mg N=134	Placebo N=116	Zol 4 mg N=99	Zol 8/4 mg N=87	Placebo N=92	Zol 4 mg N=214	Zol 8/4 mg N=221	Placebo N=208
ECOG status n (%)									
ECOG 0-1	106 (92.2%)	124 (92.5%)	104 (89.7%)	91 (91.9%)	78 (90.7%)	86 (93.5%)	197 (92.1%)	202 (91.8%)	190 (91.3%)
ECOG ≥ 2	9 (7.8%)	10 (7.5%)	12 (10.3%)	8 (8.1%)	8 (9.3%)	6 (6.5%)	17 (7.9%)	18 (8.2%)	18 (8.7%)
Analgesic score n (%)									
0	56 (48.7%)	46 (34.6%)	44 (38.3%)	38 (38.4%)	27 (31.4%)	33 (35.9%)	94 (43.9%)	73 (33.3%)	77 (37.2%)
1	32 (27.8%)	49 (36.8%)	39 (33.9%)	37 (37.4%)	35 (40.7%)	38 (41.3%)	69 (32.2%)	84 (38.4%)	77 (37.2%)
2	4 (3.5%)	6 (4.5%)	6 (5.2%)	5 (5.0%)	5 (5.8%)	3 (3.3%)	9 (4.2%)	11 (5.0%)	9 (4.4%)
3	23 (20.0%)	31 (23.3%)	25 (21.7%)	17 (17.2%)	17 (19.8%)	16 (17.4%)	40 (18.7%)	48 (21.9%)	41 (19.8%)
4	0 (0.0%)	1 (0.8%)	1 (0.9%)	2 (2.0%)	2 (2.3%)	2 (2.2%)	2 (0.9%)	3 (1.4%)	3 (1.5%)
BPI composite pain score									
N	107	124	110	86	75	81	193	199	191
Mean ± SD	2.2±0.2	2.3±0.2	2.2±0.2	1.9±0.2	2.8±0.3	2.0±0.2	2.0±0.1	2.5±0.1	2.1±0.1
Median	1.8	2.0	1.9	2.0	2.8	1.8	1.8	2.3	1.8
FACT-G total score									
N	107	120	107	86	73	80	193	193	187
Mean ± SD	80.7±1.5	81.1±1.2	81.2±1.4	81.3±1.6	81.9±1.7	83.6±1.6	81.0±1.1	81.4±1.0	82.2±1.1
Median	80.2	80.0	82.0	83.0	83.0	83.4	82.5	82.2	82.8

Reviewer's Comments:

1. Table 2.5.1b above describes the baseline characteristics of the ITT population as analyzed by this reviewer.
2. Both by the Sponsor's description (Table 2.5.1a) and FDA description (Table 2.5.1b) there appears to be imbalance between treatment groups favoring zoledronate 4 mg group with respect to age group, serum creatinine, previous SRE, time from initial diagnosis of cancer to bone metastases, performance status, analgesic score and BPI composite pain score.
3. There are significant differences between the two stratum (no metastases at initial diagnosis of prostate cancer versus metastases at initial diagnosis of prostate cancer) with respect to time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study (study start day). As in Study 011, in this study also, it is not clear as to how this difference in time between the two strata translates to differences or lack of differences with respect to skeletal related events. These patients were also receiving concomitantly anticancer therapy and this is a confounding factor with the study drug in estimating the reduction in skeletal related events attributable to the study drug in each stratum and treatment group.

2.1.29.2 Primary Efficacy Analyses

The primary efficacy variable was the proportion of patients experiencing at least one SRE (-HCM). Per sponsor analysis by month 15 both the zoledronic acid 4 mg and 8/4 mg groups had a lower proportion than the placebo group. There was statistically significant difference between 4 mg and placebo groups (p=0.021), where as there was no statistically significant difference between 8/4 mg and placebo groups (p=0.222), as presented below in Table 2.5.2 (Sponsor Table 9-1, Volume 106, page 8-61).

Table 2.5.2: Proportion of Patients Having SRE (-HCM) up to Month 15 by Stratum and Treatment Group (ITT patients) – Sponsor's Analysis

		95% C.I. and P-value for the difference	
	Proportion	Zol 4 mg	Zol 8/4 mg
No Initial Metastases			
Placebo	54/116 (47%)	(-24.4%,0.9%), p=0.069	(-21.5%,3.0%), p=0.140
Zol 4 mg	40/115 (35%)	-	(-9.4%,14.5%), p=0.679
Zol 8/4 mg	50/134 (37%)	-	-
With Initial Metastases			
Placebo	38/92 (41%)	(-23.6%,3.6%), p=0.152	(-15.5%,13.3%), p=0.884
Zol 4 mg	31/99 (31%)	-	(-4.9%,22.7%), p=0.206
Zol 8/4 mg	35/87 (40%)	-	-
Total			
Placebo	92/208 (44%)	(-20.3%,-1.8%), **p=0.021**	(-15.1%,3.6%), p=0.222
Zol 4 mg	71/214 (33%)	-	(-3.7%, 14.3%), p=0.255
Zol 8/4 mg	85/221 (38%)	-	-

Reviewer's Comments:

1. Since the decision was made to drop 8/4 mg zoledronate arm for toxicity, the efficacy comparison between 8/4 mg arm and placebo arm is not appropriate and may result in type I error adjustment.
2. The estimates of the proportion of SREs presented in Table 2.5.2 may be biased estimates because of high dropout rate (approximately only 35% were treated at 15 months) as presented below in Table 2.5.3. In the least conservative approach, if the total number of events at 15 months in each of the treatment groups are subtracted from the total number of patients that were randomized, then 84/143 patients (58.7%) in zoledronate 4 mg group, 63/136

patients (46.3%) in zoledronate 8/4 mg group, and 66/116 patients (56.9%) in the placebo group received treatment at 15 months. Therefore the dropout rate was at least 46%.

Table 2.5.3: Number of Patients Treated up to 15 Months (FDA Analysis)

	No Initial Metastases			With Initial Metastases			Total		
	Zol 4 mg	Zol 8/4 mg	Placebo	Zol 4 mg	Zol 8/4 mg	Placebo	Zol 4 mg	Zol 8/4 mg	Placebo
Study Start (Visit 2)	115	134	116	99	87	92	214	221	208
3 months	99	117	108	80	69	79	179	186	187
6 months	75	94	84	67	57	64	142	151	148
9 months	65	69	62	54	51	48	119	120	110
12 months	54	50	43	50	36	41	104	86	84
15 months	42 (36.5%)	36 (26.9%)	35 (30.2%)	42 (42.4%)	27 (31.0%)	31 (33.7%)	84 (39.3%)	63 (28.5%)	66 (31.7%)

3. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 15 months (Table 2.5.4). Data beyond 15 months was confounded because of cross over of patients to zoledronate treatment group from placebo group. The Kaplan-Meier estimates of the proportion of skeletal event rate at 15 months are larger than the estimates presented in Table 2.5.2 (protocol specified analysis). There is significant difference between the zoledronate 4 mg group and placebo group (p=0.009, 2-sided log rank test). Kaplan-Meier estimates of proportion of SREs at 3, 6, and 9 months respectively are presented in Table 2.5.4b.

Table 2.5.4a: Analysis of Time to First Skeletal Related Event Truncated at 15 Months Using Kaplan-Meier Estimation Procedure (ITT Population FDA Analysis)

	Event Rate at 9 Months	N	Median Time to Event in days (95% C.I.)	P-value (Comparison to Placebo using Log-rank test)
No Initial Metastases				
Placebo	59.6%	116	304 (198, *)	
Zol 4 mg	45.6%	115	* (291, *)	0.058
Zol 8/4 mg	50.7%	134	419 (251, *)	0.270
With Initial Metastases				
Placebo	54.0%	92	335 (244, *)	
Zol 4 mg	44.4%	99	* (364, *)	0.085
Zol 8/4 mg	57.0%	87	346 (209, *)	0.709
Total				
Placebo	57.2%	208	321 (252, *)	
Zol 4 mg	44.9%	214	* (383, *)	0.009
Zol 8/4 mg	53.2%	221	363 (255, *)	0.541

* = Not Reached

Table 2.5.4b: Analysis of Time to First Skeletal Related Event Truncated at 3, 6, 9, 12 and 15 Months Using Kaplan-Meier Estimation Procedure (ITT population FDA Analysis)

Total	At 3 Months		At 6 Months		At 9 Months		At 12 Months		At 15 Months	
	Event Rate	*Diff. in Event Rate	Event Rate	*Diff. in Event Rate	Event Rate	*Diff. in Event Rate	Event Rate	*Diff. in Event Rate	Event Rate	*Diff. in Event Rate
Placebo	16.5%		31.6%		42.7%		52.8%		57.2%	
Zol 4 mg	9.1%	7.4%	21.8%	9.8%	30.0%	12.7%	36.9%	15.9%	43.7%	13.5%
Zol 8/4 mg	16.7%	-0.2%	29.6%	2.0%	42.0%	0.7%	46.5%	6.3%	53.2%	4.0%

* Difference in event rates between placebo and treatment groups - not for comparison.

4. The α penalty for dropping a treatment group (8/4 group) with respect to type I error rate is debatable because although the treatment group was dropped for safety reasons, the decision to drop the treatment arm from efficacy analysis was made after all the patients were enrolled into the 8 mg group and had received a significant amount of treatment. Table 2.5.5 lists the occurrence of events during the 15 months study period. More than 50% of the SREs had occurred by 3 months evaluation in the two zoledronate treatment groups, at which time majority (99%) of the patients in the 8 mg treatment group had received the treatment per original protocol at 8 mg dose level (Table 2.5.6).

Table 2.5.5: Number of SREs by Stratum, Treatment, and Evaluation Times (FDA Analysis)

	3 months	6 months	9 months	12 months	15 months	Total up to 15 months
No Initial Metastases						
Placebo	29	11	8	3	3	54
Zol 4 mg	15	13	6	5	1	40
Zol 8/4 mg	28	9	9	3	1	50
With Initial Metastases						
Placebo	18	7	7	5	1	38
Zol 4 mg	10	8	3	6	4	31
Zol 8/4 mg	20	6	3	5	1	35
Total						
Placebo	47	18	15	8	4	92
Zol 4 mg	25	21	9	11	5	71
Zol 8/4 mg	48	15	12	8	2	85

Table 2.5.6: Number of Patients in the Zoledronate 8 mg Group Who Were Treated at Reduced Dose of Zoledronate 4 mg up to 3 Months

Visit #:	2 (start)	3	4	5	6 (3 months)
# of patients treated at Zol 4 mg	1/219	1/208	1/199	2/188	1/178

2.1.29.3 Secondary Efficacy Analyses

The sponsor evaluated several parameters (as listed in section 2.5.3) as secondary efficacy variables. Here we will present analyses of only two of the secondary efficacy variables.

Time to first occurrence of an SRE was evaluated by the sponsor as a secondary efficacy parameter as specified in the protocol (Table 2.5.7) (Table 9-2, page 8-62, Volume 106). By this analysis zoledronate 4 mg group was significantly different from placebo group (p=0.011) and there was no difference between the zoledronate 8/4 mg and placebo groups (p=0.491). However, there appears to border line significant difference between zoledronate 4 mg and 8/4 mg groups (p=0.059).

Table 2.5.7: Summary of Time to the First SRE (-HCM) up to Month 15, by Stratum and Treatment Group (Sponsor Analysis)

					P-values* for the between treatment comparison	
	N	Event rate at day 252	25% Quartile (days)	Median (days)	Zol 4 mg	Zol 8/4 mg
No Initial Metastases						
Placebo	116	59.6%	109	304	0.045	0.225
Zol 4 mg	115	45.6%	175	Not Reached	-	0.398
Zol 8/4 mg	134	50.7%	133	419	-	-
With Initial Metastases						
Placebo	92	54.0%	140	335	0.110	0.709
Zol 4 mg	99	44.4%	222	Not Reached	-	0.052
Zol 8/4 mg	87	57.0%	105	346	-	-
Total						
Placebo	208	57.2%	122	321	0.011	0.491
Zol 4 mg	214	44.9%	182	Not Reached	-	0.059
Zol 8/4 mg	221	53.2%	127	363	-	-

* P-values from Cox-regression with factor treatment stratified by the strata

Skeletal morbidity rate defined as the number of SREs divided by the time at risk in years was analyzed by the sponsor as presented below in Table 2.5.8. (Sponsor's Table 9-3, page 8-63, Volume 106).

Table 2.5.8: Summary of Skeletal Morbidity Rate (risk set definition) of any SRE (-HCM) up to Month 15, by Stratum and Treatment Group (Sponsor Analysis)

		Skeletal morbidity rate (no. of events per year)		P-values* for the between treatment comparison	
	N	Mean ± SD	Median	Zol 4 mg	Zol 8/4 mg
No Initial Metastases					
Placebo	116	1.32 ± 2.19	0.00	0.068	0.132
Zol 4 mg	115	0.91 ± 1.70	0.00	-	0.730
Zol 8/4 mg	134	0.95 ± 1.86	0.00	-	-
With Initial Metastases					
Placebo	92	1.70 ± 4.38	0.00	0.040	0.627
Zol 4 mg	99	0.67 ± 1.70	0.00	-	0.109
Zol 8/4 mg	87	1.23 ± 2.62	0.00	-	-
Total					
Placebo	208	1.49 ± 3.33	0.00	0.006	0.143
Zol 4 mg	214	0.80 ± 1.70	0.00	-	0.191
Zol 8/4 mg	221	1.06 ± 2.19	0.00	-	-

The time to multiple occurrences of SREs was also analyzed by the sponsor using Anderson-Gill approach. In this analysis every counted occurrence of an SRE was followed by a 20-day period during which no other occurrence of an SRE was counted. Time to each counted occurrence of an SRE was counted from the

22nd day of the last counted occurrence of an SRE to the onset day. Per sponsor analysis the difference between placebo and zoledronate 4 mg group was statistically significant.

Reviewer's Comments:

1. The agency had recommended that the time to first occurrence of an SRE to be evaluated as a primary efficacy variable. The results of this analysis have already been discussed in the previous section (section 2.5.8.2, Reviewer's comment 1).
2. Per sponsor analysis there is statistically significant difference between the placebo and zoledronate 4 mg groups with respect to skeletal morbidity rate (Table 2.5.8). However these estimates of the treatment effect may be biased because of high drop out rate.
3. The sponsor's multiple event analysis has not been verified by the reviewer at this time. It should be noted that the Anderson-Gill approach assumes the multiple events are independent of each other. However the skeletal related events being considered here are likely to be highly correlated.
4. This reviewer conducted exploratory multivariable Cox regression analyses of the time to first SRE data with treatment (placebo=0, zoledronate=1), prior history of skeletal events (no=0, yes=1), time from initial diagnosis of cancer to bone metastases (in months), time from first bone metastases to Visit 2 of the study (in months), $\log_e$ of baseline PSA and baseline analgesic scores. The results of these analyses are presented in Tables 2.5.9a - 2.5.9c. Although in all of the models considered here zoledronate 4 mg treatment effect was statistically significant, when the factors identified with imbalance in section 2.5.8.1, Reviewer comment, the p-value increased. The point estimate of hazard ratio for placebo versus zoledronate 4 mg treatment was consistent among all the models and the upper 95% confidence limit of the hazard ratio was less than 1. Exploratory models comparint placebo with zoledronate 8/4 mg groups are presented in Appendix (Appendix 4.3).

Table 2.5.9a: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) as Co-variate

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment Overall	0.661 (0.484, 0.903)	0.009
Treatment No Metastases at Initial Dx.	0.673 (0.446, 1.016)	0.06
Treatment With Metastases at Initial Dx.	0.658 (0.408, 1.063)	0.088

Table 2.5.9b: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) and prior history of SRE (Yes or No) as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.670 (0.490, 0.916)	0.012
Prior SRE	1.450 (1.055, 1.992)	0.022

Table 2.5.9c: Cox Regression Model with Treatment (Placebo vs. Zol 4 mg) and prior history of SRE (Yes or No), time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.680 (0.491, 0.941)	0.020
Prior SRE	1.374 (0.984, 1.919)	0.063
Time from Initial Dx. of Ca. To Bone Met.	0.999 (0.996, 1.003)	0.725
Time from First Bone Met. to Study Entry	0.993 (0.986, 1.000)	0.042
Log_e (baseline PSA)	1.154 (1.047, 1.272)	0.004
Baseline Analgesic Score	1.214 (1.056, 1.396)	0.007

2.1.29.4 Safety Analyses

2.1.29.4.1 Survival Analyses

Because the zoledronate treatment was not expected to improve survival, it was evaluated as part of safety analysis. The following is the survival analysis results of FDA analysis using the ITT population (instead of safety population used by sponsor). There were no statistically significant differences in survival between zoledronate 4 mg and placebo groups, or between zoledronate 8 mg and placebo groups as presented in Figures 2.5.1-2.5.3 and Table 2.5.10. All other safety analyses are presented in the clinical review of the application.

Figure 2.5.1: Kaplan-Meier Survival Analysis of Over All Survival in ITT Population (FDA Analysis)

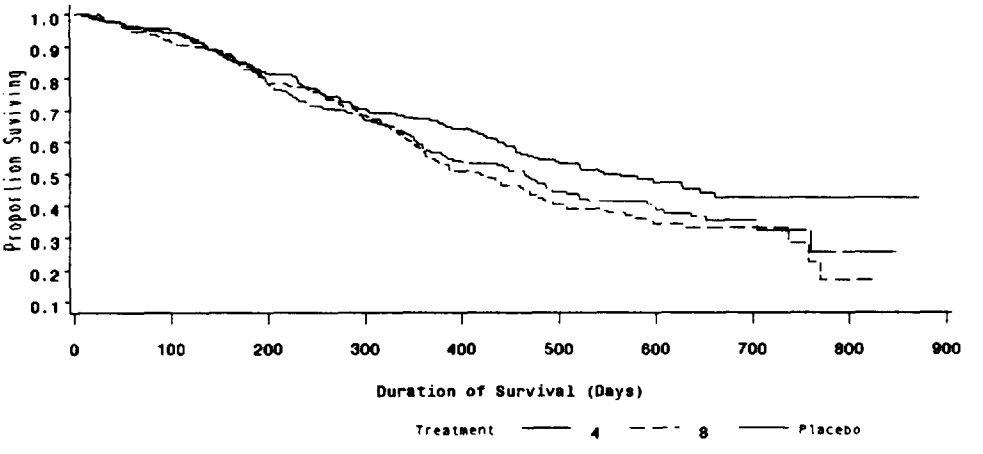

Figure 2.5.2: Kaplan-Meier Survival Analysis of Zoledronate 4 mg versus Placebo in ITT Population (FDA Analysis)

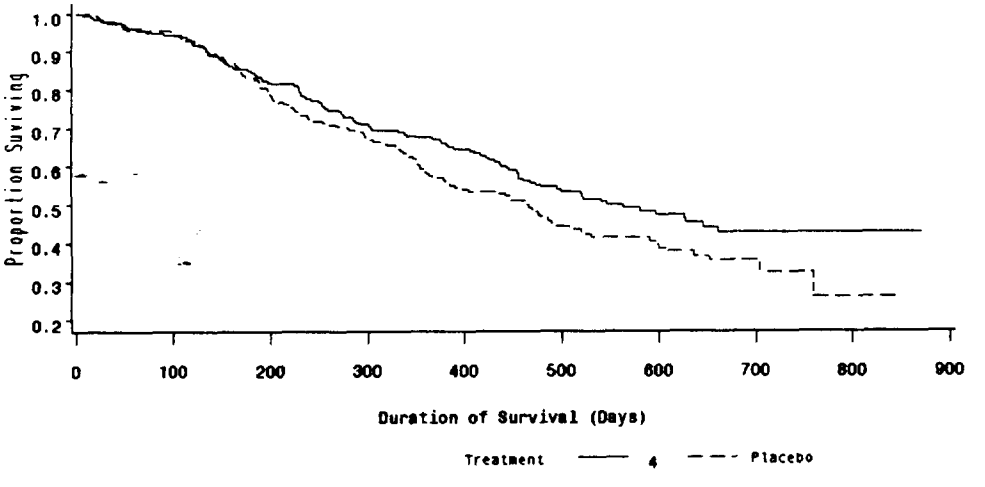

Figure 2.5.3: Kaplan-Meier Survival Analysis of Zoledronate 8/4 mg versus Placebo in ITT Population (FDA Analysis)

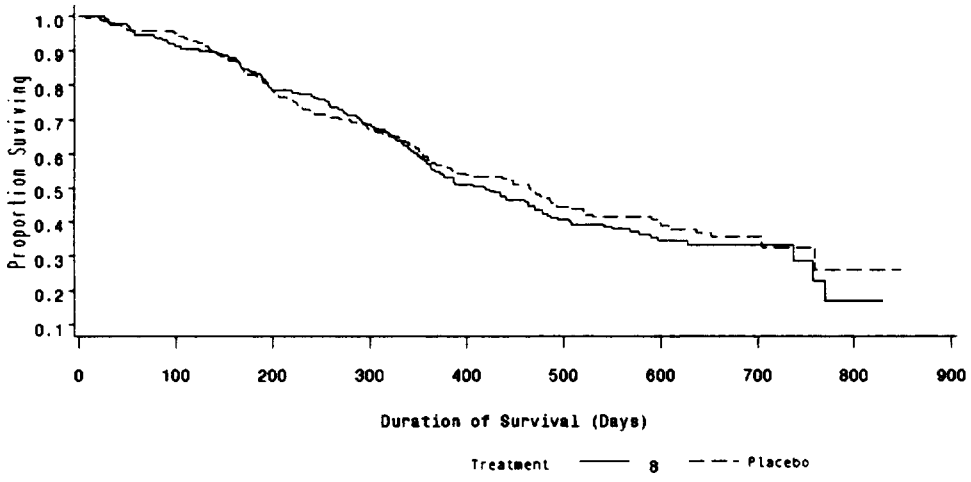

Table 2.5.10: Summary of Survival Analyses Results (FDA Analysis)

	N	Number of Events	Median (95% C.I.) in days	Hazard Ratio (95% C.I.)	P-values (Treatment versus Placebo, Log-rank test)
Placebo	208	122	464 (379, 521)		
Zol 4 mg	214	107	546 (461, *)	0.792 (0.611, 1.027)	0.078
Zol 8/4 mg	221	138	419 (363, 478)	1.083 (0.849, 1.382)	0.521

Reviewer's Comments:

It appears from the survival analysis of the time to death that the zoledronate 8/4 mg was slightly worse than the placebo group. It is not clear if this is because of inherent not apparent differences in baseline prognostic factors, or because of chance mechanism.

2.1.30 Sponsor's Conclusions and Reviewer's Conclusions/Comments

Study 039 was a international, multicenter, randomized, double-blind, placebo-controlled, parallel study conducted in prostate cancer patients with a history of metastatic bone disease who have a rising serum PSA concentration despite treatment with first-line hormonal therapy for meatastatic disease. A total of 643 patients were enrolled into the study (208 in placebo group, 214 in the zoledronate

4 mg group and 221 in the zoledronate 8/4 mg group). The primary objective of this study was to assess the efficacy of zoledronate treatments (4 or 8 mg) in addition to antineoplastic therapy, compared to antineoplastic therapy alone to prevent skeletal-related events (SREs) in prostate cancer patients with a history of metastatic bone disease who have developed biochemical progression of disease. SREs were defined as pathologic bone fracture events, spinal cord compression events, surgery to bone, and radiation therapy to bone (including the use of radioisotopes). The primary efficacy endpoint of this study was the proportion of patients having at least one skeletal-related event by month 15.

1. A total of 643 patients were enrolled into the study instead of the planned total of 550 patients. No explanation is provided for the increase in sample size.
2. The sample size calculations were based on that zoledronate would be considered more efficacious than placebo if either of the two comparisons (4 mg versus placebo or 8 mg versus placebo) was statistically significant at a 2-sided p-value < 0.025. During the study, the design was amended (Amendment 4) to treat all patients on study in the 8 mg group at 4 mg dose level because of the observed renal toxicity with 8 mg group. In lieu of this, it was stated that zoledronate 4 mg will be considered more efficacious than placebo if the comparison for the primary efficacy outcome is statistically significant at 0.05 level (2-sided) favoring zoledronate 4 mg (Amendment 6). It should be noted that the original design and calculation of sample size was based on comparing 4 mg versus placebo group at 0.025 level. Dropping a treatment arm (in this case 8 mg group) could potentially inflate the overall type I error rate. It should also be noted that by the time of this Amendment, majority of the patients had completed the phase I (15 months) or had dropped out of the study.
3. There appears to be imbalance between treatment groups favoring zoledronate 4 mg group with respect to age group, serum creatinine, previous SRE, time from initial diagnosis of cancer to bone metastases, performance status, analgesic score and BPI composite pain score.
4. There are significant differences between the two stratum (no metastases at initial diagnosis of prostate cancer versus metastases at initial diagnosis of prostate cancer) with respect to time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study (study start day).
5. There is statistically significant difference between zoledronate 4 mg and placebo groups ($p=0.021$). The per protocol estimates of the proportion of SREs may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure,

truncating the maximum follow up time at 15 months. There is statistically significant difference between the zoledronate 4 mg group and placebo group (p=0.009, 2-sided log-rank test).

6. Multivariate analyses of time to first occurrence adjusting for some of the covariates which appear to be imbalanced among the treatment groups suggest that the results are consistent and the zoledronate 4 mg treatment appears to have efficacy, although the strength of evidence is not as significant.
7. It appears from the survival analysis of the time to death that the zoledronate 8/4 mg was slightly worse than the placebo group. It is not clear if this is because of inherent differences in baseline prognostic factors, or because of chance mechanism.

3 Statistical Evaluation of Collective Evidence

Zometa® or zoledronate (zoledronic acid for injection) is proposed to be used for the treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy in cancer patients. Sponsor has submitted efficacy data and results from three double-blind studies (Studies 010, 011, and 039). In all the three studies patients were randomized in a double-blind fashion to receive either zoledronate 4 mg intravenously, or zoledronate 8 mg intravenously, or an active control/placebo intravenous infusion every three weeks in addition to their antineoplastic therapy. The randomized treatment assignment ratio was to be 1:1:1. The primary efficacy endpoint in all the three studies was the proportion of patients experiencing at least one SRE, defined as radiation therapy to bone, surgery to bone, pathologic bone fracture or spinal cord compression.

Study 010 was a multicenter, double-blind, randomized, controlled, Phase III parallel comparative trial of i.v. zoledronic acid (Zometa, 4 mg or 8 mg) versus iv. Aredia (90 mg) (pamidronate) as an adjunct to standard therapies in a total of 1640 patients with multiple myeloma and breast cancer with cancer related bone lesions. The "non-inferiority" test in Study 010 demonstrates marginal effectiveness (p=0.052) with respect to proportion of SREs at 12 months of zoledronate 4mg arm, using a margin of 3.65% which is defined as preserving 50% of the lower limit of the 95% CI of the point estimate of the Aredia effect. The original selection of 8% margin is not acceptable based on the current understanding because it tends to be liberal.

Study 011 was a randomized, double-blind, multicenter, parallel-group, placebo controlled Phase III study conducted in a total of 773 patients with bone metastases from solid tumors other than breast or prostate cancer. The study has failed to demonstrate efficacy of 4 mg zoledronate over placebo treated group in reducing the proportion of SREs at 9 months per protocol specified analysis (p=0.127). The protocol specified estimates of the proportion of SREs (Table 2.4.2) may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 9 months (Table 2.4.4). There appears to be a statistically significant difference between the Zoledronate 4 mg group and placebo group (p=0.026, 2-sided log-rank test) by this analysis.

Study 039 was an international, multicenter, randomized, double-blind, placebo-controlled, parallel study conducted in 643 prostate cancer patients with a history

of metastatic bone disease who have a rising serum PSA concentration despite treatment with first-line hormonal therapy for meatastatic disease. There was statistically significant difference between zoledronate 4 mg and placebo groups (p=0.021) with respect to the proportion of SREs at 15 months as defined in the protocol. However, the per protocol estimates of the proportion of SREs may be biased estimates because of high dropout rate. The sponsor was advised by the agency during the protocol development stage to consider time to first SRE as the primary efficacy parameter, which can take into account censoring of observations during the course of the study. Therefore, in order to account for the early censoring of the observations, this reviewer conducted time to first SRE analysis using Kaplan-Meier estimation procedure, truncating the maximum follow up time at 15 months. There is statistically significant difference between the zoledronate 4 mg group and placebo group (p=0.009, 2-sided log-rank test).

In these reviewers' opinion the results of Studies 11 and 39 support efficacy of zoledronate 4 mg given intravenously versus placebo given intravenously in patients with bone metastases from solid tumors other than breast cancer, and the study results of Study 10 suggest marginal effectiveness of zoledronate 4 mg given intravenously in patients with bone metastases from breast cancer and multiple myeloma based on a "non-inferiority" test using Aredia as the active control .

References:

1. Gang Chen, George Chi, Mark Rothmann, Ning Li (2001), Active Control Trials - Hypotheses and Issues. ASA Proceedings.

2. Mark Rothmann, Ning Li, Gang Chen, George Chi and Hsiao-Hui Tsou (2001), Non-inferiority Methods for Mortality Trials, ASA Proceedings.

3. Ning Li, Mark Rothmann, Gang Chen, George Chi, (2001), Application of non-infweriority analysis methods in oncology NDA, ASA Proceedings.

STATISTICAL REVIEW AND EVALUATION

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This review consists of 76 pages of text
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4 APPENDICES

APPENDIX 1 - STUDY 010 - Zol. 8/4 mg versus Aredia

Skeletal related Event (SRE) rate

The sponsor provided data for SRE for Zole 8/4 mg arm. The Zole 8/4 mg arm was the original 8 mg arm but changed the dosage due to renal toxicity. The exploratory analysis results are summarized in Table 4.1.1 and 4.1.2.

Table 4.1.1: SRE Event Rate (Intent-to-Treat Patients) over study period

Treatment	N	3 month	6 month	9 month	12 month
Myeoloma:					
Aredia 90 mg	167	42 (25%)	66 (40%)	75 (45%)	82 (49%)
Zometa 8/4 mg	160	50 (31%)	62 (39%)	72 (45%)	78 (49%)
Breast (Chemo):					
Aredia 90 mg	181	49 (27%)	64 (35%)	72 (40%)	78 (43%)
Zometa 8/4 mg	172	43 (25%)	62 (36%)	65 (38%)	81 (47%)
Breaset(Hormonal)					
Aredia 90 mg	207	58 (28%)	79 (38%)	86 (42%)	97 (47%)
Zometa 8/4 mg	192	44 (23%)	63 (33%)	77 (40%)	74 (43%)
Overall:					
Aredia 90 mg	555	149(27%)	209(38%)	233(42%)	257 (46%)
Zometa 8/4 mg	524	137(26%)	187(36%)	214(41%)	233 (44%)

Table 4.1.2: Proportion of SRE to Month 13 by Stratum

	Zometa (8/4mg)	Aredia	Difference Δ (95% CI)*	p-value*
Myeloma	49% (79/160)	49% (82/167)	0% (-10.6%,11.1%)	0.961
Breast (Chemo)	47% (80/172)	43% (78/181)	4% (-7%, 13.8%)	0.519
Breast	43%	47%	-4%	0.467

(Hormonal)	(83/192)	(97/207)	(-13.4%, 6.1%)	
Total	**46% (242/524)**	**46% (257/555)**	**0% (-6.1%, 5.8%)**	**0.963**

*Δ=Zometa-Aredia

Reviewer's Comments:

1. The analysis shows that the proportions were 46% and 46% for the zoledronic acid 8/4 mg group and the Aredia 90 mg group, respectively. The upper limit of the 95% confidence interval of the difference was 5.8%, which was less than the non-inferiority margin of 8% specified in the protocol before dose amendment. In the stratum of breast cancer patients receiving hormonal therapy, the difference in the proportions between the zoledronic acid 8/4 mg group and the Aredia 90 mg group was –4%, while in the stratum of breast cancer patients receiving chemotherapy, the difference in the proportions between the zoledronic acid 8/4 mg group and the Aredia 90 mg group was +4% with an upper bound of 13.8%, implying 13.8% worse than Aredia is possible.
   Preservation of active control effect: The preservation of active treatment effect using the SRE rates can be determined by (7.3%-5.8%)/7.3%=20.5%. Hence, the current trial arm 8/4 mg arm demonstrated a 20.5% retention of Aredia vs. a placebo effect if we believe that the constant assumption holds.

Time to First SRE

Tables 4.1.3 and 4.1.4 summarize the results for study 010 by comparing Zole 8/4 mg with Aredia.

Table 4.1.3: K-M Estimated Event Rate (Intent-to-Treat Patients) Over Study Period

Treatment	N	9 month	Difference in Event Rate	12 month	p-value
Myeloma:					
Aredia 90 mg	167	44.9%		47.3%	
Zometa 8/4 mg	160	44.4%	0.5%	48.7%	0.46
Breast (Chemo):					
Aredia 90 mg	181	39.2%		42.5%	
Zometa 8/4 mg	172	38.4%	0.8%	44.8%	0.90
Breast (Hormonal)					
Aredia 90 mg	207	40.6%		43.5%	

Zometa 8/4 mg	192	39.1%	6.6%	41.7%	0.65
Overall:					
Aredia 90 mg	555	41.4%		44.3%	
Zometa 8/ 4 mg	524	40.5%	0.9%	44.9%	0.90

Table 4.1.4: Time to First SRE by Stratum and Treatment Arm

	N	Median (95%CI)	Hazard Ratio (95% CI)	p-value*
Myeloma				0.58
Aredia	167	301(191, ---)	1.09(.80, 1.49)	
Zol 8/4 mg	160	283(196, ---)		
Breast(CT)				0.87
Aredia	181	366(259, ---)	1.03(0.75, 1.4)	
Zol 8/4 mg	172	351(262, ---)		
Breast(HT)				0.44
Aredia	207	370(258, ---)	.89(.67, 1.20)	
Zol 8/4 mg	192	381 (275, --)		
Total				**0.90**
Aredia	**555**	**363(273, 399)**	**.99(.83, 1.18)**	
Zol 8/4 mg	**524**	**353(283, —))**		

*Log-rank test

Figure 4.1.1 is the K-M curve for the time to first SRE comparing overall Aredia with Zol 8/4 mg arm.

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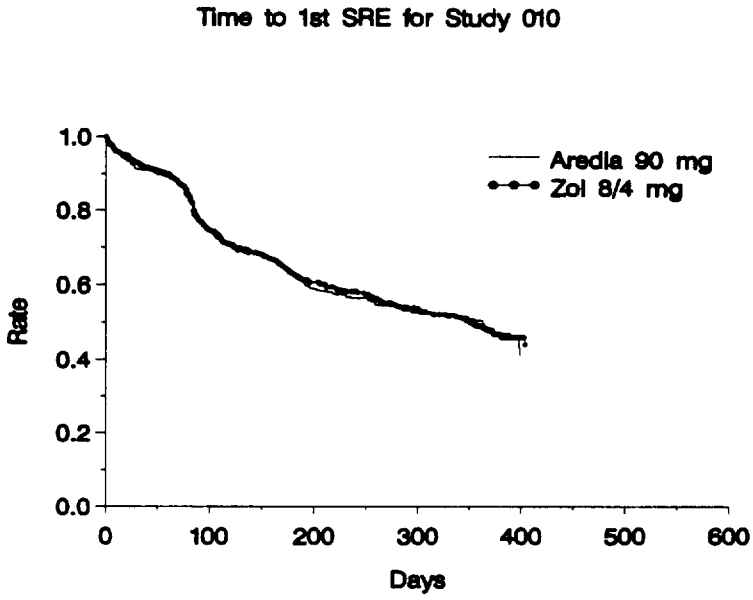
Figure 4.1.1



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APPENDIX 2 - STUDY 011 - Zol. 8/4 mg versus Placebo

Table 4.2.1: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) as Co-variate

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment Overall	0.743 (0.563, 0.980)	0.036
Treatment Lung Cancer Group	0.673 (0.459, 0.987)	0.043
Treatment Other Solid Tumors Group	0.826 (0.553, 1.234)	0.351

Table 4.2.2: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) and prior history of SRE (Yes or No) as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.745 (0.565, 0.983)	0.038
Prior SRE	1.359 (0.991, 1.864)	0.057

Table 4.2.3: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) and prior history of SRE (Yes or No), time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.722 (0.547, 0.954)	0.022
Prior SRE	1.486 (1.077, 2.051)	0.016
Time from Initial Dx. of Ca. To Bone Met.	0.996 (0.991, 1.000)	0.062
Time from First Bone Met. to Study Entry	0.981 (0.963, 1.000)	0.047

In addition the following pooled exploratory analysis was conducted and presented to the Advisory Committee:

Table 4.2.4: Proportion of Patients Having SRE (-HCM) up to Month 9 Treatment Group (4 mg + 8/4 mg) versus Placebo (ITT Patients)

	Proportion	95% C.I. for the Difference	P-value
Placebo	111/250 (44%)	-0.08 (-0.15, - 0.01)	0.027
Zol 4 mg + 8/4 mg	189/523 (44%)		

Table 4.2.5 Analysis of Time to First SRE Truncated at 9 Months Using K-M Estimation Procedure of 4 mg + 8/4 mg Treatment Arm versus Placebo

	N	Hazard Ratio (95% C.I.)	P-value (Log-rank Test)
Placebo	250	0.739 (0.584, 0.935)	0.012
4 mg + 8/4 mg	523		

APPENDIX 3 - STUDY 039 - Zol. 8/4 mg versus Placebo

Table 4.3.1: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) as Co-variate

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment Overall	0.912 (0.679, 1.226)	0.541
Treatment No Metastases at Initial Dx.	0.805 (0.547, 1.185)	0.272
Treatment With Metastases at Initial Dx.	1.091 (0.689, 1.728)	0.709

Table 4.3.2: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) and prior history of SRE (Yes or No) as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.926 (0.689, 1.245)	0.611
Prior SRE	1.534 (1.135, 2.073)	0.005

Table 4.3.3: Cox Regression Model with Treatment (Placebo vs. Zol 8/4 mg) and prior history of SRE (Yes or No), time from initial diagnosis of cancer to bone metastases, and time from first bone metastases to Visit 2 of the study as Co-variates

Co-variate	Hazard Ratio (95% C.I.)	P-value
Treatment	0.868 (0.638, 1.182)	0.368
Prior SRE	1.468 (1.059, 2.036)	0.021
Time from Initial Dx. of Ca. To Bone Met.	1.000 (0.996, 1.003)	0.901
Time from First Bone Met. to Study Entry	0.995 (0.989, 1.000)	0.073
Log_e (baseline PSA)	1.175 (1.070, 1.290)	0.0007
Baseline Analgesic Score	1.020 (0.888, 1.172)	0.777

In addition the following pooled exploratory analysis was conducted and presented to the Advisory Committee:

Table 4.3.4: Proportion of Patients Having SRE (-HCM) up to Month 15 Treatment Group (4 mg + 8/4 mg) versus Placebo (ITT Patients)

	Proportion	95% C.I. for the Difference	P-value
Placebo	92/208 (44%)	-0.08 (-0.161, - 0.001)	0.041
Zol 4 mg + 8/4 mg	156/435 (36%)		

Table 4.3.5: Analysis of Time to First SRE Truncated at 15 Months Using K-M Estimation Procedure of 4 mg + 8/4 mg Treatment Arm versus Placebo

	N	Hazard Ratio (95% C.I.)	P-value (Log-rank Test)
Placebo	208	0.781 (0.603, 1.012)	0.061
4 mg + 8/4 mg	435		

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/s/ [redacted]

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2/8/02 05:15:36 PM
BIOMETRICS
Dr. Ning Li is a joint statistical reviewer of this application

Ning Li
2/11/02 11:39:48 AM
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Gang Chen
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George Chi
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