Table 4
Between-treatment comparison of the proportion of patients with at least one moderate to severe new vertebral fracture in Stratum I (mITT population)

Period	Zoledronic Acid n=2822		Placebo n=2853		Relative Risk	p-value
	n	%	n	%		
0-12 months	35	1.2	89	3.1	0.40	<0.0001
0-24 months	54	1.9	185	6.5	0.30	<0.0001
0-36 months	79	2.8	267	9.4	0.30	<0.0001

Data source Table 9-5 Study 2301 Clinical Study Report, The p-value for between-treatment difference is from a logistic regression with treatment and baseline fracture status in the model using log-likelihood type approach.

4) Proportion of patients with at least one new vertebral fracture over 36 months in patients 75 years of age and older in Stratum I (mITT population)- Measurements of at least one new vertebral fracture over 36 months in the mITT population, were statistically significant compared to placebo in all three age subgroups (<70, 70-74 and ≥75), even though only the ≥75 years of age subgroup was chosen as a secondary endpoint. The relative risk reduction was somewhat less in the older patients, ≥75 years of age, at 60% compared to the younger patients at between 76 and 80%, as the background rate of total fractures was higher in the older group.

Table 5
Between-treatment comparison of the proportion of patients with at least one new vertebral fracture in Stratum I (mITT population) separated by age subgroup

Age	Zoledronic Acid		Placebo		Relative Risk	p-value
	n	%	n	%		
<70 years n=832 ZA, 852 P	17	2.0	85	10.0	0.20	<0.0001
70-74 years n=907 ZA, 923 P	23	2.5	96	10.4	0.24	<0.0001
≥75 years n=1083ZA, 1078P	52	4.8	129	12.0	0.40	<0.0001

Data source Table 9-6 Study 2301 Clinical Study Report, The p-value for between-treatment difference is from a logistic regression with treatment and baseline fracture status in the model using log-likelihood type approach..

4a) Reduction in new vertebral fractures in patients without baseline vertebral fractures over 36 months at the 0.05 level (see Table 6)

4b) Reduction in new vertebral fractures in patients with one baseline vertebral fracture over 36 months at the 0.05 level (see Table 6)

4c) Reduction in new vertebral fractures in patients with at least two baseline vertebral fractures over 36 months at the 0.05 level (see Table 6)

There was a statistically significant lower risk of new vertebral fractures in the zoledronic acid group compared to the placebo group independent of the number of baseline vertebral fractures (0, 1, ≥2). The relative risk reduction of new vertebral fractures was similar, between 64 to 72%, and also independent of the number of baseline vertebral fractures.

Table 6
Between-treatment comparison of the proportion of patients with at least one new vertebral fracture in Stratum I depending on baseline vertebral fracture history (mITT population)

# of Baseline vertebral fractures	Zoledronic Acid		Placebo		Relative Risk	p-value
	n	%	n	%		
0 n=1070 ZA, 1038 P	20	1.9	60	5.8	0.32	<0.0001
1 n=807 ZA, 815P	21	2.6	59	7.2	0.36	<0.0001
≥2 n=945ZA, 1000P	51	5.4	191	19.1	0.28	<0.0001

Data source Table 9.1-3 Study 2301 Clinical Study Report, The p-value for the subgroup and treatment interaction was computed from a logistic regression with treatment, baseline fracture status, subgroup, and the interaction of treatment and subgroup in the model using log-likelihood type approach.

5) Time to first clinical fracture over time in Stratum I and II (any clinical fracture) (3-yr event rates based on Kaplan-Meier estimates, ITT population)- (see Table 7)

6) Time to first clinical vertebral fracture over time in Stratum I and II (3-yr event rates based on Kaplan-Meier estimates, ITT population)- (see Table 7)

7) Time to first non-vertebral fracture over time in Stratum I and II (3-yr event rates based on Kaplan-Meier estimates, ITT population)- (see Table 7)
The incidence of first clinical fracture of any type, first clinical vertebral fracture and first clinical non-vertebral fractures were all statistically less common in the zoledronic acid group compared to the placebo treatment group. The greatest risk reduction of 77% was seen with vertebral fractures which accounted for only 13% of all clinical fractures.

Table 7
Between-treatment comparison of time to first clinical fractures in Stratum I+II (3-yr event rates based on Kaplan-Meier estimates, ITT population)

Age	Zoledronic Acid n=3875		Placebo n=3861		Relative Risk	p-value
	n	%	n	%		
First clinical Fx of any type (5)	308	8.4	456	12.8	0.67	<0.001
First clinical vertebral Fx (6)	19	0.5	84	2.6	0.23	<0.001
First clinical non-vertebral Fx (7)	292	8.0	388	10.7	0.75	<0.001

Data source Table 9-7 Study 2301 Clinical Study Report, The p-value is calculated from a stratified log-rank test by study population stratum.

8) Percentage change from baseline at Month 6 and 36 in total hip BMD in Stratum I+II, ITT population)-A statistically significant increase in BMD was seen with respect to placebo at 6, 12, 24 and 36 months, even though only the 6 and 36 months time points were chosen as secondary endpoints. There is a clear trend with increasing BMD with respect to time from the earliest time point measured at 6 months through to the final time point at 36 months, suggesting a beneficial effect on BMD with continued use.

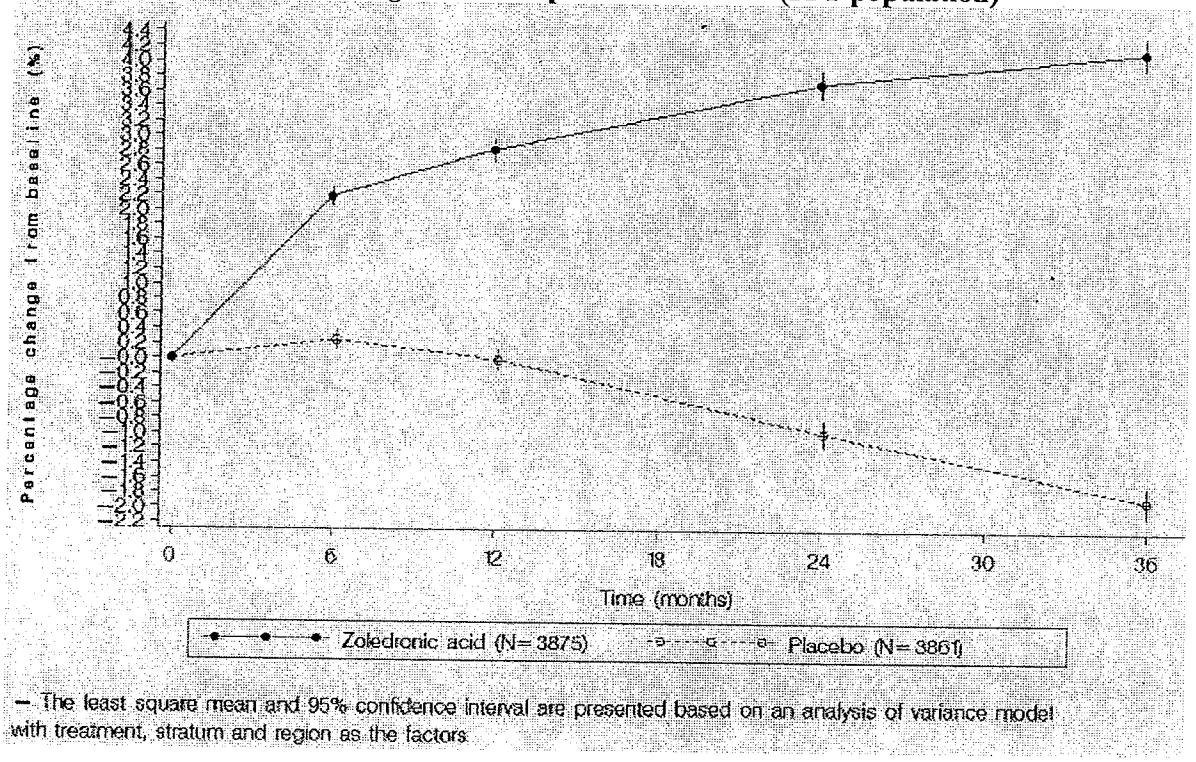
Table 8
Between-treatment comparison of percent change from baseline at Month 6 and 36 in total hip BMD (ITT population)

Age	Zoledronic Acid	Placebo	LS mean difference	p-value
	% LS mean[2]	% LS mean[2]		
Month 6 n=3515ZA, 3543P	2.18	0.25	1.93	<0.0001
Month 12 n=3516ZA, 3542P	2.83	0.00	2.83	<0.0001
Month 24 n=3228ZA, 3248P	3.72	-0.98	4.70	<0.0001
Month 36 n=3061ZA, 3077P	4.15	-1.87	6.02	<0.0001

Data source Table 9-8 Study 2301 Clinical Study Report, p-values are calculated from a three-way analysis of variance model with treatment, region and stratum in the model.

Figure 2

Mean % change in total hip BMD over time (ITT population)



– The least square mean and 95% confidence interval are presented based on an analysis of variance model with treatment, stratum and region as the factors

9) Percentage change from baseline at Month 6 and 36 in femoral neck BMD in Stratum I+II, ITT population)- The results seen at the femoral neck site were similar to the results seen in total hip BMD. A statistically significant increase in BMD was seen with respect to placebo at 6, 12, 24 and 36 months, even though only the 6 and 36 months time points were chosen as secondary endpoints. There is a clear trend with increasing BMD with respect to time from the earliest time point measured at 6 months through to the final time point at 36 months, suggesting a beneficial effect on BMD with continued use.

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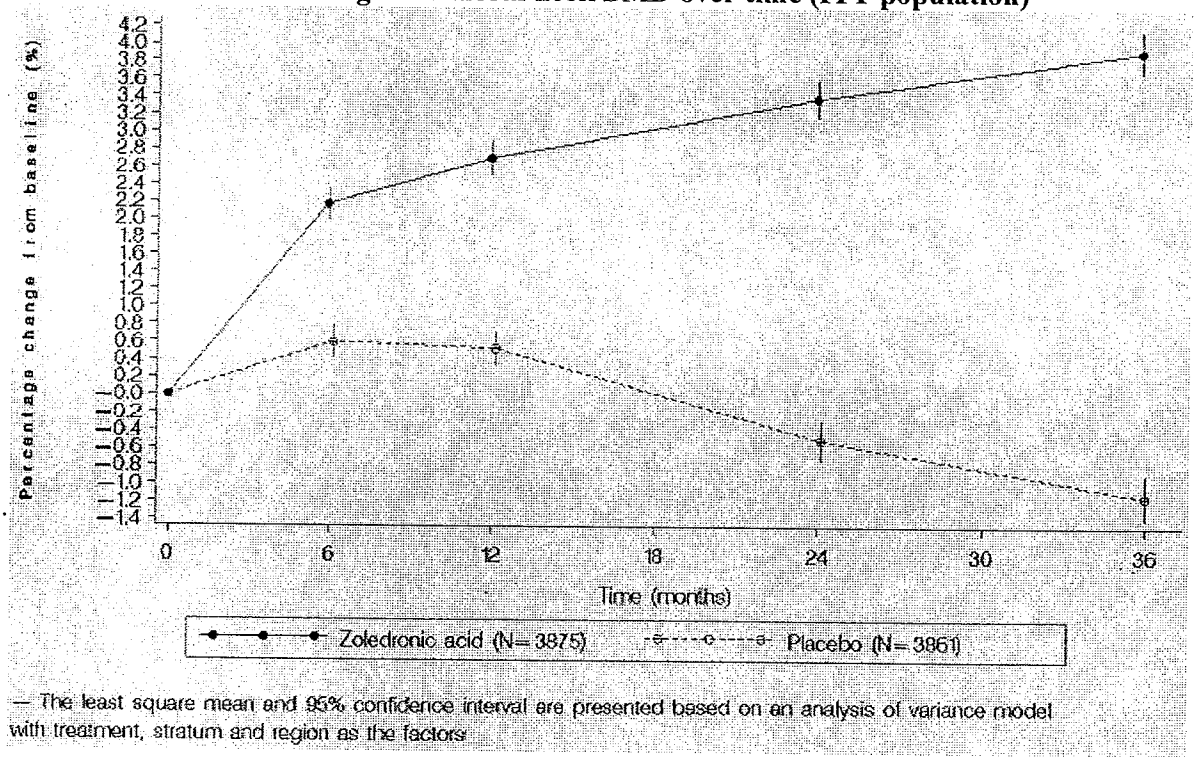
Table 9
Between-treatment comparison of percent change from baseline at Month 6 and 36 in femoral neck BMD (ITT population)

Age	Zoledronic Acid	Placebo	LS mean difference	p-value
	% LS mean[2]	% LS mean[2]		
Month 6 n=3522ZA, 3549P	2.17	0.60	1.58	<0.0001
Month 12 n=3522A, 3548P	2.70	0.53	2.17	<0.0001
Month 24 n=3234ZA, 3254P	3.38	-0.50	3.89	<0.0001
Month 36 n=3067ZA, 3083P	3.92	-1.13	5.06	<0.0001

Data source Table 9-8 Study 2301 Clinical Study Report, p-values are calculated from a three-way analysis of variance model with treatment, region and stratum in the model.

Figure 3

Mean % change in femoral neck BMD over time (ITT population)



10) Percentage change from baseline at Month 36 in lumbar spine BMD in Stratum I+II, ITT population)- The results seen at the lumbar spine site were similar to the results seen in total hip and femoral neck BMD. A statistically significant increase in BMD was seen with respect to

placebo at 6, 12, 24 and 36 months, even though only the 36 month time point was chosen as a secondary endpoint. There is a clear trend with increasing BMD with respect to time from the earliest time point measured at 6 months through to the final time point at 36 months, suggesting a beneficial effect on BMD with continued use.

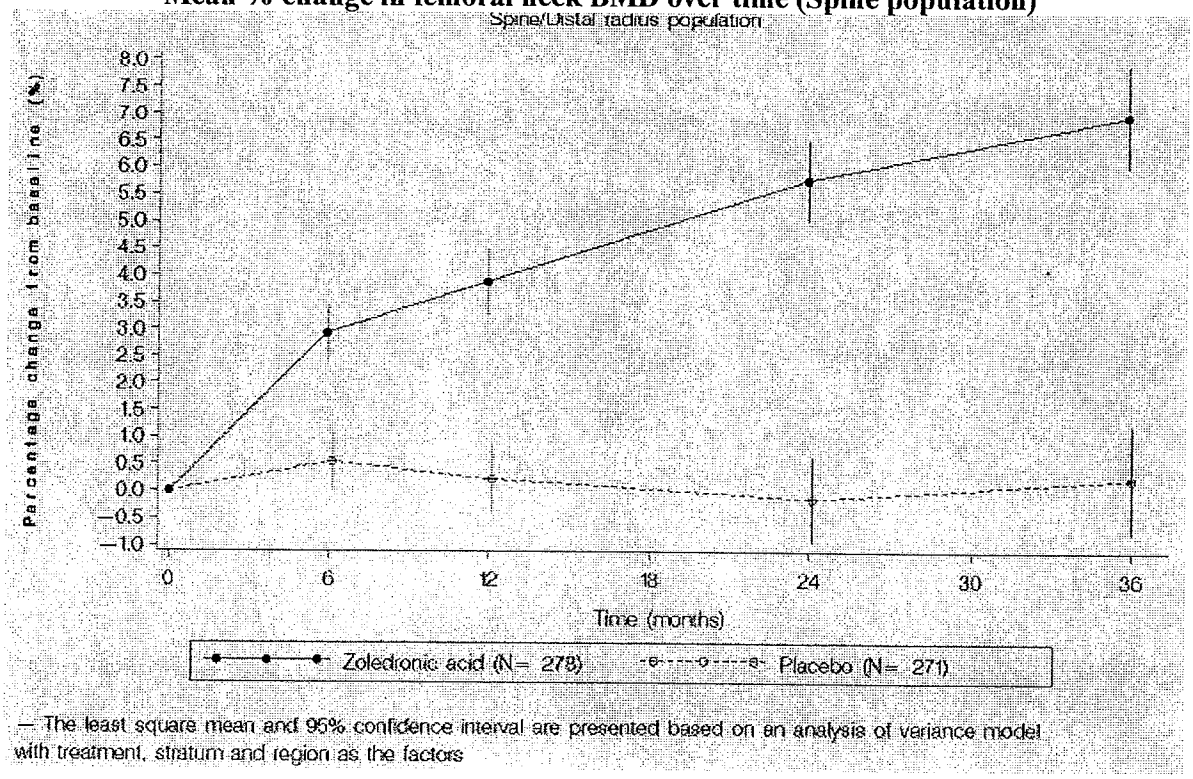
Table 10
Between-treatment comparison of percent change from baseline at Month 36 in lumbar spine BMD (Spine population)

Age	Zoledronic Acid	Placebo	LS mean difference	p-value
	% LS mean[2]	% LS mean[2]		
Month 6 n=268ZA, 265P	2.93	0.54	2.39	<0.0001
Month 12 n=262A, 258P	3.88	0.22	3.66	<0.0001
Month 24 n=236ZA, 226P	5.76	-0.14	5.90	<0.0001
Month 36 n=228ZA, 212P	6.95	0.24	6.71	<0.0001

Data source Table 9-8 Study 2301 Clinical Study Report, p-values are calculated from a three-way analysis of variance model with treatment, region (center was used for lumbar spine), and stratum in the model.

Figure 4

Mean % change in femoral neck BMD over time (Spine population)



– The least square mean and 95% confidence interval are presented based on an analysis of variance model with treatment, stratum and region as the factors

11) Relative change from baseline at Month 36 in biochemical markers of bone turnover (b-CTx, BSAP and P1NP) in Stratum I and II- Mean serum b-CTX and BSAP, markers of bone resorption, were statistically lower, and in the premenopausal range at the first measured time point of 6 months after the first infusion and were maintained at this same lower level during the total 36 months of the study. No further decrease in these markers was seen with the second and third infusions.

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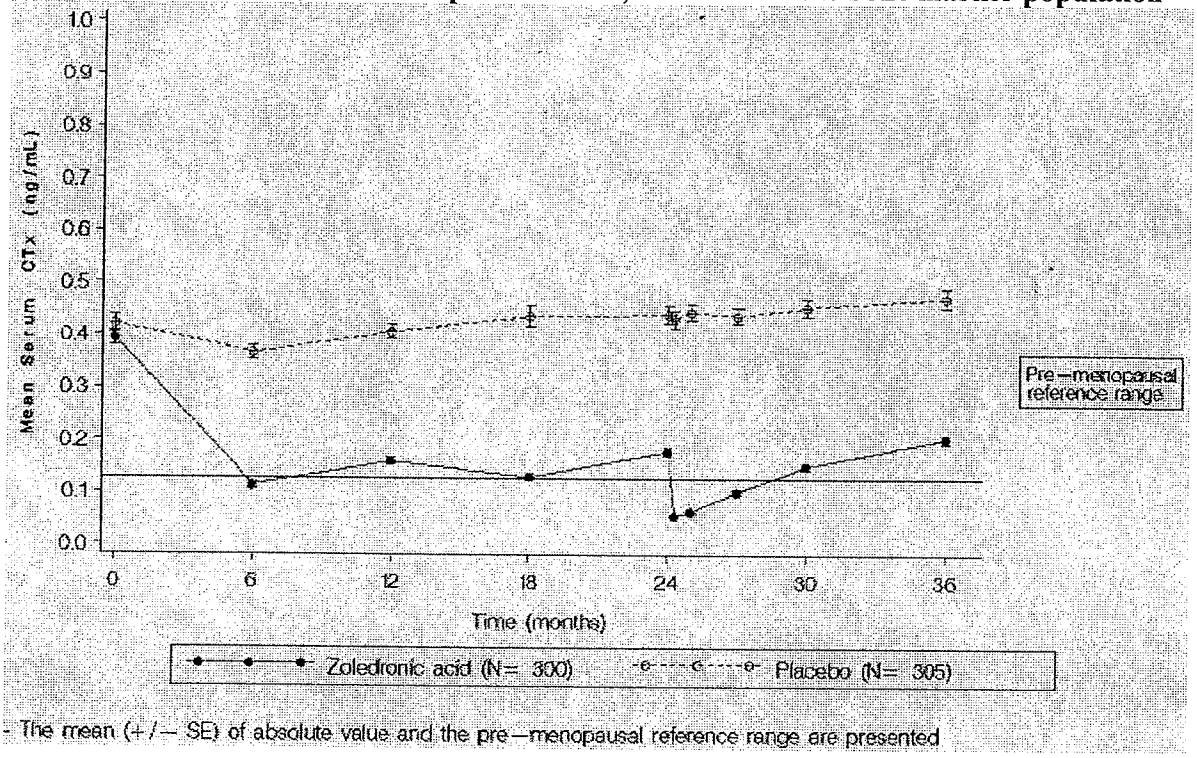
Figure 5

Mean serum b-CTx, bone resorption marker, over time in the bone marker population



- The mean (+/- SE) of absolute value and the pre-menopausal reference range are presented

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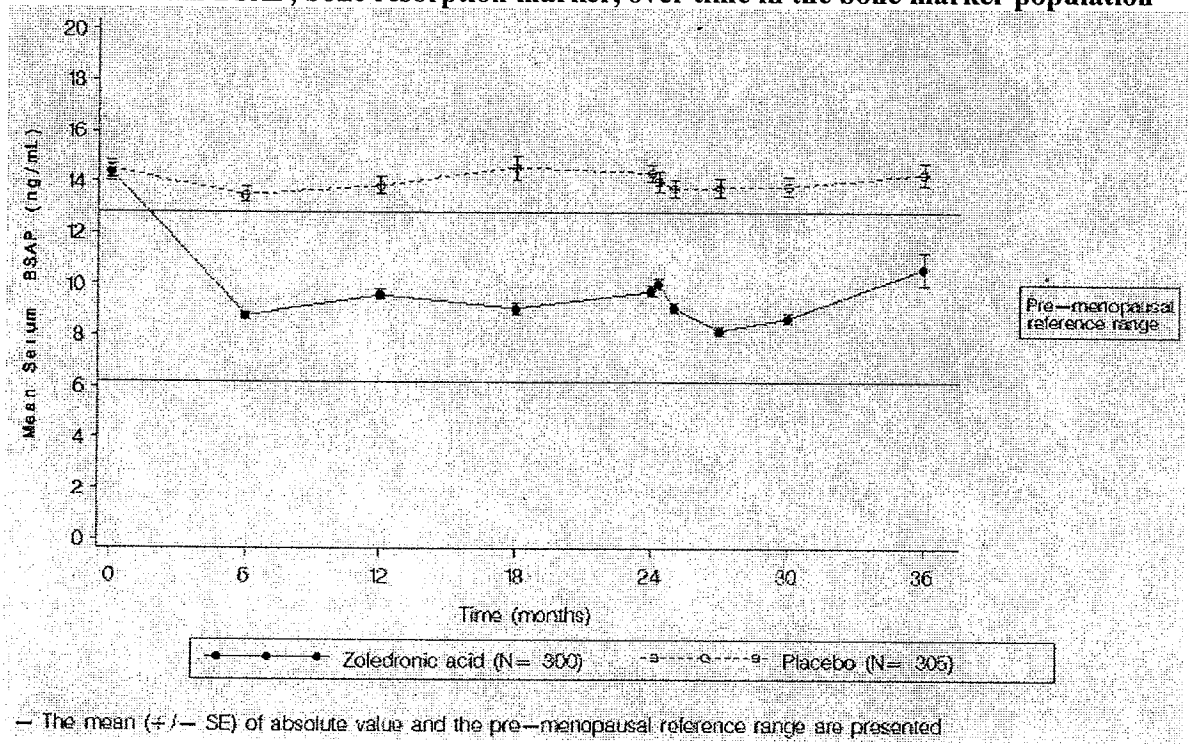
Figure 6

Mean serum BSAP, bone resorption marker, over time in the bone marker population



– The mean (+/– SE) of absolute value and the pre–menopausal reference range are presented

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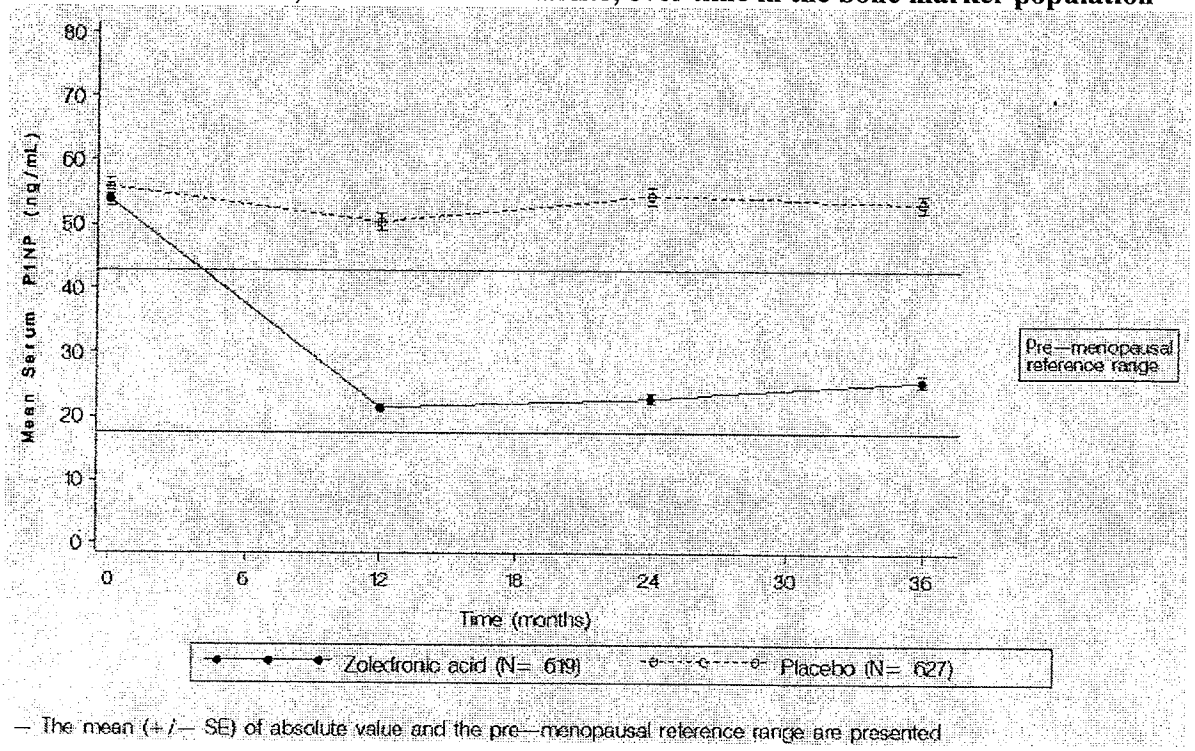
Mean serum P1NP, a markers of bone formation, was statistically lower, and in the premenopausal range at the first measured time point of 12 months after the first infusion and was maintained at this same lower level during the total 36 months of the study. No further decrease in this marker was seen with the second and third infusions.

Figure 7

Mean serum P1NP, bone formation marker, over time in the bone marker population



— The mean (+/— SE) of absolute value and the pre—menopausal reference range are presented

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12) Change from baseline at Month 36 in height in Stratum I and II
Both treatments groups lost height during the course of the trial, however the decrease in standing height from baseline was statistically lower in subjects treated with zoledronic acid compared to placebo at both 24 and 36 months. Only the 36 month time point was chosen as a secondary endpoint at the beginning of the study.

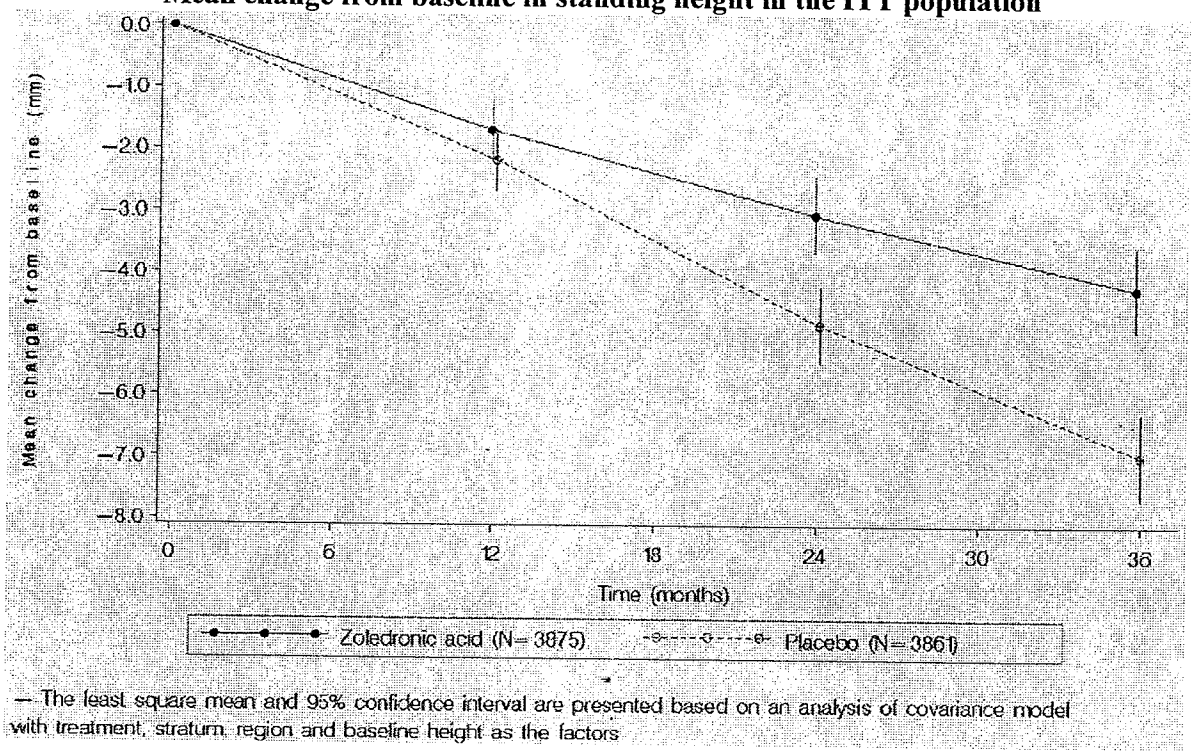
Table 11
Between-treatment comparison of change from baseline at Month 36 in stadiometric height (mm) in Stratum I+II (ITT population)

Age	Zoledronic Acid	Placebo	LS mean difference	p-value
	% LS mean[2]	% LS mean[2]		
Month 12 n=1955ZA, 1960P	-1.69	-2.18	0.49	ns
Month 24 n=1813ZA, 1801P	-3.05	-4.83	1.78	<0.0001
Month 36 n=1707ZA, 1686P	-4.24	-6.96	2.72	<0.0001

Data source Table 9-8 Study 2301 Clinical Study Report, p-values are calculated from a three-way analysis of covariance model with treatment, region, stratum, and baseline height in the model.

Figure 8

Mean change from baseline in standing height in the ITT population



– The least square mean and 95% confidence interval are presented based on an analysis of covariance model with treatment, stratum, region and baseline height as the factors

13) Total number of days with limited-activities during the study due to fracture, (ITT population)- The mean number of days with limited activities due to a fracture was statistically greater in the patients in the placebo group than in the zoledronic acid group.

Table 12
Between-treatment comparison of the total number of days with limited activities during the study due to fracture (ITT population)

Period	Zoledronic Acid n=3853	Placebo n=3846	p-value
Mean (days)	5.9	9.9	<0.001
SE	0.54	0.68	

Data source Post Text Table 9.2-24 Study 2301 Clinical Study Report, p-value for treatment differences is from the Wilcoxon rank-sum test

14) Total number of days with bed-rest during the study due to fracture, (ITT population)- The mean number of days with bed rest due to a fracture was statistically greater in the patients in the placebo group than in the zoledronic acid group.

Table 13
Between-treatment comparison of the total number of days of bed rest during the study due to fracture (ITT population)

Period	Zoledronic Acid n=3853	Placebo n=3846	p-value
Mean (days)	1.6	2.2	<0.001
SE	0.25	0.25	

Data source Post Text Table 9.2-24 Study 2301 Clinical Study Report, p-value for treatment differences is from the Wilcoxon rank-sum test

15) Total number of days with limited-activities during the study due to back pain, (ITT population)- The mean number of days with limited activities due to back pain was statistically greater in the patients in the placebo group than in the zoledronic acid group.

Table 14
Between-treatment comparison of the total number of days with limited activities during the study due to back pain (ITT population)

Period	Zoledronic Acid n=3861	Placebo n=3853	p-value
Mean (days)	60.5	71.9	0.008
SE	2.4	2.7	

Data source Post Text Table 9.2-25 Study 2301 Clinical Study Report, p-value for treatment differences is from the Wilcoxon rank-sum test

16) Total number of days with bed-rest during the study due to back pain, (ITT population)- The mean number of days with bed rest due to back pain was statistically greater in the patients in the placebo group than in the zoledronic acid group.

Table 15
Between-treatment comparison of the total number of days of bed rest during the study due to back pain (ITT population)

Period	Zoledronic Acid n=3853	Placebo n=3846	p-value
Mean (days)	8.2	9.2	<0.008
SE	0.73	0.76	

Data source Post Text Table 9.2-25 Study 2301 Clinical Study Report, p-value for treatment differences is from the Wilcoxon rank-sum test

Medical officer's comment- While the disability data are consistent with the fracture efficacy reported in this study, these endpoints have not been validated and as such would not be acceptable for labeling in the Package Insert.

Tertiary endpoints

Percentage change from baseline at Month 6, 12, 24 and 36 in distal radius BMD in Stratum I+II- The data show an increase in BMD in the zoledronic acid group at 6 months which remains stable for the 36 months of the study, in contrast to the placebo group, which after minimal change in BMD over the initial 6 months of the study shows a decline in BMD over the following 30 months. Statistically significant differences in BMD were seen with respect to placebo at 12, 24 and 36 months.

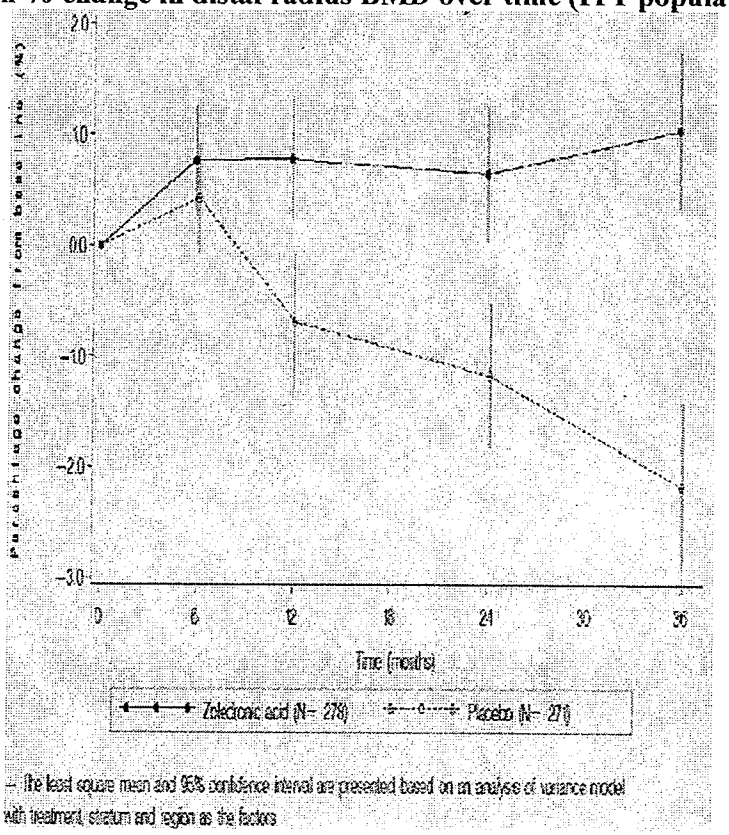
Table 16
Between-treatment comparison of percent change from baseline at Month 6, 12, 24 and 36 in distal radius BMD (Distal radius population)

Age	Zoledronic Acid	Placebo	LS mean difference	p-value
	% LS mean[2]	% LS mean[2]		
Month 6 n=253ZA, 242P	0.77	0.43	0.34	0.23
Month 12 n=250A, 235P	0.78	-0.69	1.47	<0.0001
Month 24 n=225ZA, 207P	0.65	-1.18	1.82	<0.0001
Month 36 n=215ZA, 193P	1.04	-2.17	3.21	<0.0001

Data source Post Text Table 9.2-15 Study 2301 Clinical Study Report. p-value was obtained from an analysis of variance on the percentage change from baseline with treatment, stratum, and center as explanatory variables

Figure 9

Mean % change in distal radius BMD over time (ITT population)



6.1.5 Clinical Microbiology

No clinical microbiology data was included in this submission.

A Product Quality Microbiology Review was performed by Dr. John Metcalfe, who found adequate sterility and bacterial endotoxin testing to recommend approval of this drug product.

6.1.6 Efficacy Conclusions

1) New morphometric vertebral fractures, the first part of the co-primary endpoint, occurred in 87/2260=3.8% of zoledronic acid treated patients compared to 300/2352=12.8% of placebo-treated patients over 36 months (mITT, Stratum I data). This corresponds to a statistically significant absolute risk reduction of 8.9% and a relative risk reduction of 70% (95% CI: 62% to 76%, $p < 0.0001$).

2) The three-year event rates of hip fractures based on Kaplan-Meier estimates, the second part of the co-primary endpoint, were 1.45% (n=52) for the zoledronic acid treated patients and 2.50% (n=87) for placebo-treated patients over 36 months (ITT, combined Stratum I and II data). The hazard ratio of 0.60 (95% CI: 0.43 to 0.85) for the zoledronic acid group versus the placebo group represents a 40% relative risk reduction in the risk of hip fractures ($p = 0.0032$).

3) There was a statistically significant decrease in new, new and/or worsening, and moderate to severe vertebral fractures in the zoledronic acid treatment group compared to the placebo group which was seen as early as 12 months and extended out for the entire 36 months of the study.

4) At 36 months patients in the zoledronic acid group consistently had statistically fewer vertebral fractures than placebo patients in all age categories (<70, 70-74, ≥ 75 years), all geographic regions, race groups of Caucasian, Asian, and Hispanic, all BMI categories (<19, 19-25, >25 kg/m^2), femoral neck BMD T-score designations (≤ -2.5 and > -2.5), prevalence of vertebral fractures at baseline (0, 1, ≥ 2), baseline creatinine clearance (< 60 and ≥ 60 mL/min), and prior use of bisphosphonates (yes/no).

5) At 36 months patients in the zoledronic acid group consistently had statistically fewer hip fractures than placebo patients in the following subgroups: age <70 and 70-74, Caucasian race, BMI >25 kg/m^2, femoral neck BMD T-score designations (≤ -2.5 and > -2.5), prevalence of 1 vertebral fracture at baseline, baseline creatinine clearance (≥ 60 mL/min), and prior use of bisphosphonates (yes/no).

6) The frequencies of first clinical fracture of any type, first clinical vertebral fracture and first clinical non-vertebral fractures, over the course of the 3-year study, were all statistically lower in the zoledronic acid group compared to the placebo treatment group. The greatest risk reduction of 77% was seen with vertebral fractures which accounted for only 13% of all clinical fractures.

7) A statistically significant increase in total hip, femoral neck, lumbar spine and distal radius BMD was seen in the zoledronic acid treatment group with respect to placebo at 12, 24 and 36 months. The difference in BMD with respect to time continues to increase from the earliest time point measured (e.g. 6 months) through to the final time point (e.g. 36 months), suggesting improved efficacy with continued use, however, the exact relationship between change in BMD and clinical efficacy is yet to be established.

8) Bone resorption markers b-CTx and BSAP and bone formation marker P1NP decreased to premenopausal levels by 12 months, in the zoledronic acid group and were maintained at this level for the total 36 months of the study. No further decrease in these markers was seen after the second and third infusions at 12 and 24 months. Bone markers, in the placebo group, were maintained at baseline levels throughout the 36 months of the study.

9) Patients in both zoledronic acid and placebo treatments groups lost height during the course of the trial. The decrease in standing height from baseline, although small, was statistically lower in subjects treated with zoledronic acid compared to placebo at both 24 and 36 months. The LS

mean difference at 36 months was 2.7 mm, with 95% confidence intervals between 1.9 and 3.5 mm.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review consisted primarily of findings from pivotal trial 2301 but also included safety data from the ongoing prevention of recurrent fracture trial, 2310, active control trials, 2313 and 2315, and oncology trials, ekr01, ZOL446E US24, and ZOL446G US 45, as they related to the risk for atrial fibrillation associated with the use of zoledronic acid.

7.1.1 Deaths

The total number of deaths was similar between the zoledronic acid (129/3862=3.3%) and placebo (109/3852=2.8%) treatment groups. An analysis by primary system organ class (SOC) found similar distributions by all organ classes except for the Nervous System Disorders class, where there was an approximately two-fold higher mortality rate in the zoledronic acid group, see Table 17).

Table 17

Causes of death by primary SOC (Safety population)

Primary system organ class affected	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Total no. of patients died	129(3.34)	109(2.83)
Cardiac disorders	39(1.01)	31(0.80)
Neoplasms benign, malignant and unspecified	23(0.60)	23(0.60)
Nervous system disorders	22(0.57)	12(0.31)
Infections and infestations	14(0.36)	11(0.29)
General disorders and administration site conditions	11(0.28)	11(0.29)
Respiratory, thoracic and mediastinal disorders	9(0.23)	9(0.23)
Gastrointestinal disorders	4(0.10)	4(0.10)
Renal and urinary disorders	2(0.05)	0(0.00)
Injury, poisoning and procedural complications	1(0.03)	3(0.08)
Metabolism and nutrition disorders	1(0.03)	1(0.03)
Musculoskeletal and connective tissue disorders	1(0.03)	0(0.00)
Psychiatric disorders	1(0.03)	0(0.00)
Vascular disorders	1(0.03)	3(0.08)
Hepatobiliary disorders	0(0.00)	1(0.03)

Source: PT-Table 10.2-2

Data source Table 10-8 Study 2301 Clinical Study report 16-Oct-2006 submission.

An analysis of the Nervous System Disorders class shows that this imbalance was primarily due to an increase in the Preferred Term (PT) cerebrovascular deaths 13/3862=0.34% vs. 5/3852=0.13%, see Table 18.

Table 18

Causes of death by primary SOC and PT (Safety population)

Nervous system disorders		
-Total	22(0.57)	12(0.31)
Cerebrovascular accident	13(0.34)	5(0.13)
Haemorrhage intracranial	2(0.05)	1(0.03)
Ischaemic stroke	2(0.05)	1(0.03)
Cerebral haemorrhage	1(0.03)	1(0.03)
Cerebral infarction	1(0.03)	0(0.00)
Parkinson's disease	1(0.03)	1(0.03)
Spinal epidural haemorrhage	1(0.03)	0(0.00)
Subarachnoid haemorrhage	1(0.03)	0(0.00)
Cerebrovascular disorder	0(0.00)	1(0.03)
Haemorrhagic stroke	0(0.00)	2(0.05)

Data source Post Text Table 10.2-2 Study 2301 Clinical Study report 16-Oct-2006 submission

Data from the 120 day SUR showed an additional 3 cerebrovascular deaths in the zoledronic acid group compared to one new case in the placebo group, with new cumulative event rates of 0.41% vs. 0.16%. The sponsor argues that this imbalance while concerning still represents event rates that are lower than expected for the study population and that most events occurred more than 30 days after study drug administration and so are not likely to be drug related.

A Jmp analysis, of the S_AEV_1 and S_AEV_2 final datasets submitted in the 26-Jun-2007 submission was performed by this medical reviewer and identified a similar number of patients with strokes (STXAE=1) in both the zoledronic acid 155/3862=4.0% and placebo treatment groups 151/3852= 3.9%. Since the number of stroke related deaths is only a small fraction of the total number of patients with stroke AEs it may represent an incidental finding as suggested by the sponsor.

The incidence of stroke-related AEs in study 2310, the hip fracture study, was also similar between the zoledronic acid group (62/1054=5.9%) and the placebo group (64/1057=6.1%). Following adjudication of the cause of death there were 7 patients in each treatment group for whom a cerebrovascular event contributed to their death for a rate of 0.66%, slightly higher than the event rates for stroke-related death seen in the pivotal trial 2301 (0.16% -0.41%). This also suggests that the difference in stroke-related deaths in study 2301 may be an incidental finding.

7.1.2 Other Serious Adverse Events (Atrial Fibrillation, Renal Safety, Osteonecrosis of the Jaw, & Ocular Adverse Events)

The frequency of serious adverse events was similar between the zoledronic acid and placebo groups, 29% and 30%, respectively. An analysis by primary SOC found similar distributions by all organ classes. An analysis by PT (see Table 19) showed a higher rate of atrial fibrillation 50/3862=1.3% in the zoledronic acid group compared to the rate of 20/3852=0.52% in the placebo group. While this difference was not statistically significant it will be discussed in more detail in section 7.1.2.1. Other PT terms that occurred at least twice more frequently in the zoledronic acid group include basal cell carcinoma 30 vs. 14, and anemia 23 vs. 11. It is not clear if these represent real findings or events that occurred by chance. In contrast, PT terms that occurred more commonly in the placebo group and are likely to be related to the protective effect of zoledronic acid include hip fracture 31 vs. 49, back pain 19 vs. 33, femur fracture 19 vs. 32, wrist fracture 14 vs. 23 and humerus fracture 7 vs. 20.

Table 19

Causes of Serious AEs by primary PT occurring at a rate of at least 0.5% for any group (Safety population)

Preferred term	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Total no. of patients with an SAE	1126 (29.16)	1158 (30.06)
Pneumonia	51 (1.32)	55 (1.43)
Atrial fibrillation	50 (1.29)	20 (0.52)
Osteoarthritis	47 (1.22)	50 (1.30)
Cerebrovascular accident	39 (1.01)	34 (0.88)
Myocardial infarction	36 (0.93)	37 (0.96)
Breast cancer	31 (0.80)	29 (0.75)
Hip fracture	31 (0.80)	49 (1.27)
Basal cell carcinoma	30 (0.78)	14 (0.36)
Angina pectoris	28 (0.73)	31 (0.80)
Cataract	25 (0.65)	23 (0.60)
Anemia	23 (0.60)	11 (0.29)
Cardiac failure	23 (0.60)	18 (0.47)
Abdominal pain	21 (0.54)	15 (0.39)
Cardiac failure congestive	21 (0.54)	13 (0.34)
Hypertension	21 (0.54)	22 (0.57)
Urinary tract infection	21 (0.54)	17 (0.44)
Arthralgia	19 (0.49)	20 (0.52)
Back pain	19 (0.49)	33 (0.86)
Femur fracture	19 (0.49)	32 (0.83)
Chronic obstructive pulmonary disease	18 (0.47)	27 (0.70)
Dyspnea	18 (0.47)	23 (0.60)
Cholelithiasis	16 (0.41)	20 (0.52)
Wrist fracture	14 (0.36)	23 (0.60)
Humerus fracture	7 (0.18)	20 (0.52)

Data source Table 10-9 Study 2301 Clinical Study report 12-Feb-2007 submission.

Special safety assessments were performed for atrial fibrillation, renal safety, osteonecrosis of the jaw and eye findings and are listed below in sections 7.1.2.1 through 7.1.2.4. Serum calcium levels and the risk for hypocalcemia are discussed under Laboratory Findings in section 7.1.7.1.

7.1.2.1 Atrial Fibrillation

Atrial fibrillation is an adverse event that had not been previously associated with bisphosphonates. The prevalence of atrial fibrillation can be estimated from the Cardiovascular

Health Study (CHS) in elderly women (>65y/o) as 1.4 per 100 person years[1]. Extrapolating these data to trial 2301 which lasted 3 years would predict an event rate of 4.2%.

In study 2301, there were more reports of adverse events of atrial fibrillation in the safety population, in the zoledronic group 91/3862= 2.4% compared to the placebo group 70/3852=1.8% (data source Post-Text Table 10.1-3 Medra preferred-term). This difference was not statistically significant p=0.11 using a Fisher Exact Test, and represents a small absolute risk. The total number of events occurring during the first 30 days following infusion was similar for both zoledronic acid (6/91, 6.59%) and placebo (5/70, 7.14%), and constituted only a fraction of the total events indicating that the occurrence of atrial fibrillation is not an acute event following the infusion.

A subset of 559 patients in the safety population had ECG measurements performed before and 9 to 11 days after the third infusion (278 in zoledronic acid and 281 in placebo). The incidence of atrial fibrillation was similar in both treatment groups in this subset of patients (6/278=2.2% zoledronic acid, 8/281=2.8% placebo). There was also no evidence of any other significant on treatment ECG effects between the two treatment groups, again suggesting the events were not related to the acute infusions.

The total number of events seen in the zoledronic acid group during the year following each infusion was essentially similar i.e. 1st year 30/3862=0.8%, 2nd year 33/3409=1.0% and 3rd year 34/3106=1.1% suggesting that while there may have been a slight trend for increased adverse events of atrial fibrillation with subsequent dosing there was no substantial greater risk with repeat dosing.

However, looking solely at serious adverse events of atrial fibrillation, while the total number of events is much lower, there are three times more events in the zoledronic acid group (48/3862=1.2%) compared to the placebo group (17/3852=0.4%) and this difference reaches statistical significance, p<0.001. Serious atrial-fibrillation adverse events were defined as events resulting in hospitalization or disability or judged to be life-threatening. A review of the individual case reports found that all the serious events resulted in hospitalization, and very few were also judged as life-threatening or resulting in a disability. The total number of serious events occurring during the first 30 days following infusion was also higher for zoledronic acid (3/3862, 0.08%) compared to the placebo (1/3852, 0.03%), but the total events is too low to draw any conclusions about the occurrence of serious atrial fibrillation as an acute event following the infusion. The single placebo patient was an 83 y/o women with a history of hypertension and MI, and no acute precipitating event was identified. The three patients in the zoledronic acid group included: a 71 y/o women with history of a dilated cardiomyopathy, mitral and tricuspid insufficiency and pulmonary hypertension with no acute precipitating event identified; a 69 y/o female who developed atrial fibrillation as part of an episode of anaphylactic shock following IV administration of aprotinin for chronic pancreatitis, and a 71 y/o diabetic asthmatic who

1 Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997 Oct 7;96(7):2455-61.

developed atrial fibrillation following administration of beta-agonists for an asthma attack. Again there is no data suggesting a substantial risk following acute infusions.

The number of cases of atrial fibrillation of mild and moderate severity were similar between groups (23 zoledronic acid vs. 20 placebo in the mild group, and 41 zoledronic acid vs. 41 placebo in the moderate severity group), while the number of cases of atrial fibrillation of severe severity was greater in the zoledronic group (26/3862=0.7%) compared to the placebo group (9/3852=0.2%, p=0.006). This is consistent with the observation that there were more serious adverse events of atrial fibrillation in the zoledronic acid group.

Recognized risk factors for atrial fibrillation include male sex, age, diabetes, hypertension, CHF, valvular heart disease, and h/o myocardial infarction[2]. A review of the past medical history of the patients in study 2301 suggested that at least part of the reason for the higher rate of serious atrial fibrillation AEs in the zoledronic acid group may be accounted for by the higher baseline rate of atrial fibrillation, diabetes mellitus, CHF and valvular heart disease in this group compared to the placebo group (see Table 20).

Table 20
Number of Patients with the following Past Medical History PT Events Noted at Visit 1 in the Safety Population

Preferred Term	Total (n=7765)	Placebo (n=3876)	Zoledronic Acid (n=3889)
Acute myocardial infarction	20	10	10
Angina pectoris	405	199	206
Aortic valve disease	3	2	1
Aortic valve disease mixed	1	0	1
Aortic valve incompetence	23	13	10
Aortic valve prolapse	1	0	1
Aortic valve repair	4	1	3
Aortic valve replacement	11	6	5
Aortic valve sclerosis	4	1	3
Aortic valve stenosis	7	2	5
Arrhythmia	250	127	123
Arteriosclerosis	29	15	14
Atherosclerosis	106	61	45
Atrial fibrillation	186	83	103
Atrial flutter	3	1	2
Atrial hypertrophy	2	1	1
Cardiac failure	111	59	52
Cardiac failure acute	1	1	0
Cardiac failure chronic	4	1	3
Cardiac failure congestive	51	20	31
Diabetes mellitus	355	159	196

2 Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997 Oct 7;96(7):2455-61.

Table 20
Number of Patients with the following Past Medical History PT Events Noted at Visit 1 in the Safety Population

Preferred Term	Total (n=7765)	Placebo (n=3876)	Zoledronic Acid (n=3889)
Diabetes mellitus insulin-dependent	6	4	2
Diabetes mellitus non-insulin-dependent	129	65	64
Essential hypertension	152	76	76
Heart valve insufficiency	4	1	3
Heart valve stenosis	1	0	1
Hypertension	3340	1681	1659
Hypertensive crisis	4	0	4
Hypertensive heart disease	8	5	3
Hypertrophic cardiomyopathy	1	0	1
Hypertrophic obstructive cardiomyopathy	2	1	1
Ischaemic cardiomyopathy	9	5	4
Labile hypertension	10	5	5
Mitral commissurotomy	2	2	0
Mitral valve calcification	2	1	1
Mitral valve disease	10	4	6
Mitral valve incompetence	58	23	35
Mitral valve prolapse	54	26	28
Mitral valve repair	4	1	3
Mitral valve replacement	7	4	3
Mitral valve stenosis	10	5	5
Myocardial infarction	187	93	94
Myocardial ischaemia	557	280	277
Myocarditis	12	7	5
Pericarditis	7	1	6
Systolic hypertension	3	2	1

Data taken from combined SAS datasets CND_S1 and CND_S2 using JMP software to identify individual patients with selected PT terms by treatment group.

As a result of these findings the sponsor was asked to submit past medical history rates for the following medical conditions: atrial fibrillation, CHF, diabetes and valvular heart disease. Novartis in conjunction with the cardiovascular adjudication committee at Duke University set up a list of all preferred terms that they felt best specified these medical conditions and the summary data is presented in Table 21.

Table 21
Past Medical History for Patients with Specific Medical Conditions from Study 2301 (Safety Population)

Medical Conditions	Placebo (n=3862)		Zoledronic Acid (n=3852)		Relative Ratio	Absolute Difference
	N	%	N	%	% ZA/% P	n(ZA)-n(P)
Atrial Fib/flutter	84	2.2	105	2.7	1.2	21
CHF	81	2.1	88	2.3	1.1	7

Table 21
Past Medical History for Patients with Specific Medical Conditions from Study 2301 (Safety Population)

Medical Conditions	Placebo (n=3862)		Zoledronic Acid (n=3852)		Relative Ratio	Absolute Difference
	N	%	N	%	% ZA/% P	n(ZA)-n(P)
Diabetes	242	6.3	278	7.2	1.1	36
Valvular Heart Disease	128	3.3	151	3.9	1.2	23

Data from June 18, 2007 Report in 29-Jun-2007 submission

Whereas the data show that the treatment groups were fairly well randomized using the pooled preferred terms for each specific medical condition, there was a consistent pattern of 10 to 20% greater risk of each of these medical conditions in the zoledronic acid group which accounted for between 7 to 36 more patients in the zoledronic acid group with each medical condition. While this may not seem like a larger difference, there were only 48 and 17 patients, in the zoledronic acid and placebo groups respectively, with serious atrial fibrillation AEs in the original data submission, or 50 and 22, respectively, in the final data set submitted in the 120-day safety update.

A review of all the case reports generated for patients with serious atrial fibrillation adverse events was performed by this medical officer. It identified that most patients had a preexisting arrhythmia, 77% in the placebo group and 46% in the zoledronic acid group. In addition all of the placebo patients had preexisting risk factors in the form or prior arrhythmia, history of cardiac disease or hypertension compared to only 82% of the zoledronic acid group (see Table 22).

Table 22
Past Medical History of Patient with Serious Atrial Fibrillation AEs

	Preexisting Arrhythmia		Preexisting Arrhythmia or Cardiac Disease		Preexisting Arrhythmia or Cardiac Disease or Hypertension		No history of (Preexisting Arrhythmia or Cardiac Disease or Hypertension)	
	n	%	n	%	n	%	n	%
Zoledronic acid n=50	22	46	35	70	41	82	9	18
Placebo n=22	17	77	22	100	22	100	0	0

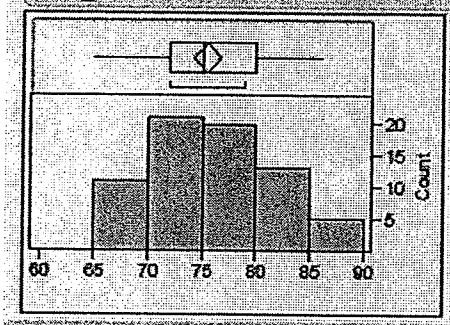
Data taken from individual case reports

Only 9/3852=0.2% of all the patients in the zoledronic acid group developed serious atrial fibrillation without a relevant documented past medical history so that actual risk is quite low. It is not clear with so few events if this actually represent a difference between the placebo and zoledronic acid groups or is a chance occurrence.

Age is another known risk factor for atrial fibrillation. The mean age of all atrial fibrillation cases in the study 2301 was identical in both the placebo and zoledronic acid groups (e.g. 75 years).

Distributions TGPDSC1A=Placebo

AGE_1N

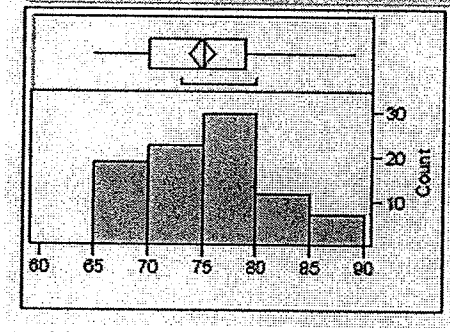


Quantiles		
100.0%	maximum	86.000
99.5%		86.000
97.5%		85.225
90.0%		83.000
75.0%	quartile	80.000
50.0%	median	75.000
25.0%	quartile	72.000
10.0%		67.000
2.5%		65.000
0.5%		65.000
0.0%	minimum	65.000

Moments	
Mean	75.414286
Std Dev	5.5128121
Std Err Mean	0.6589071
upper 95% Mean	76.728769
lower 95% Mean	74.099802
N	70

Distributions TGPDSC1A=Zoledronic Acid

AGE_1N



Quantiles		
100.0%	maximum	89.000
99.5%		89.000
97.5%		87.700
90.0%		81.800
75.0%	quartile	79.000
50.0%	median	75.000
25.0%	quartile	70.000
10.0%		67.000
2.5%		65.000
0.5%		65.000
0.0%	minimum	65.000

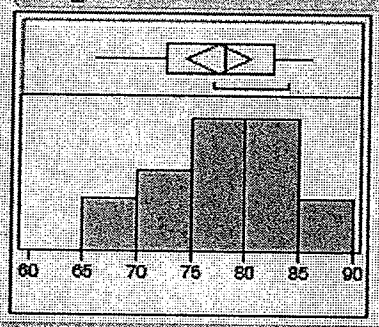
Moments	
Mean	74.813187
Std Dev	5.7250174
Std Err Mean	0.6001449
upper 95% Mean	76.005479
lower 95% Mean	73.620894
N	91

And looking at only the serious atrial fib events the mean age was slightly higher in the placebo group 77 compared to the zoledronic acid group 74. Therefore, advanced age did not account for the higher observed reporting rate of serious atrial fibrillation AEs in the zoledronic acid group seen in study 2301.

Serious Afib & Demog data- Distribution

Distributions TGPDSC1A=Placebo

AGE_1N

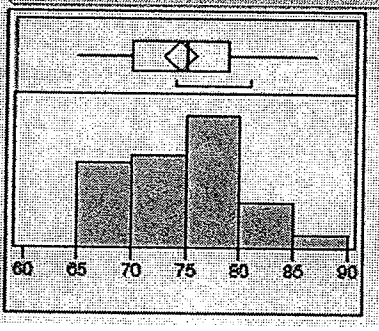


Quantiles		
100.0%	maximum	86.000
99.5%		86.000
97.5%		86.000
90.0%		85.200
75.0%	quartile	82.500
50.0%	median	78.000
25.0%	quartile	72.500
10.0%		69.400
2.5%		66.000
0.5%		66.000
0.0%	minimum	66.000

Moments	
Mean	77.352941
Std Dev	5.8942894
Std Err Mean	1.4295752
upper 95% Mean	80.383505
lower 95% Mean	74.322377
N	17

Distributions TGPDSC1A=Zoledronic Acid

AGE_1N



Quantiles		
100.0%	maximum	87.000
99.5%		87.000
97.5%		86.775
90.0%		81.000
75.0%	quartile	78.750
50.0%	median	75.000
25.0%	quartile	70.000
10.0%		67.000
2.5%		65.000
0.5%		65.000
0.0%	minimum	65.000

Moments	
Mean	74.395833
Std Dev	5.4136926
Std Err Mean	0.7813992
upper 95% Mean	75.967606
lower 95% Mean	72.823881
N	48

In contrast to study 2301, none of the other studies included in this submission in women treated for PMO showed a risk for atrial fibrillation that could be attributed to the use of the zoledronic acid.

In study 2313, a randomized, double-blind, double-dummy, 12-month study comparing zoledronic acid to alendronate in post-menopausal women the adverse event rate for atrial fibrillation was similar between treatment groups (zoledronic acid, 1/113=0.9% and alendronate 1/112=0.9%).

In study 2315, a randomized, double-blind, double-dummy, 24-week study comparing zoledronic acid to alendronate in post-menopausal women there was one adverse event rate of atrial fibrillation in the alendronate group compared to none in the zoledronic acid group (zoledronic acid, 0/69=0% and alendronate 1/59=1.7%).

In study 0041e2, a two-year, open-label, safety extension study of zoledronic acid in 119 post-menopausal women there were no cases of atrial fibrillation reported.

In study 2047, a randomized, double-blind, parallel-group study comparing acetaminophen, ibuprofen or placebo in post-menopausal women treated with a single dose of zoledronic acid and followed for one week, there were no cases of atrial fibrillation in the zoledronic acid and

ibuprofen group (0/137=0%) or the zoledronic acid and placebo group (0/137=0%) and only one case in the zoledronic acid and acetaminophen group (1/135=0.7%).

In study ZOL446L2310, a double-blind, randomized, placebo controlled, parallel group study assessing the efficacy of 5mg of zoledronic acid every 12 months in preventing subsequent osteoporotic fractures after a hip fracture, there were similar reporting rates for total atrial fibrillation events between the zoledronic acid (29/1054=2.8%) and placebo (27/1057=2.6%) treatment groups and for serious atrial fibrillation events between the zoledronic acid (12/1054=1.1%) and placebo (14/1057=1.3%) treatment groups. Following adjudication the total number of serious atrial fibrillation events was relatively unchanged with 11 in the zoledronic acid group and 13 in the placebo group. Of note, the atrial fibrillation reporting rates seen in study 2310 are in the same range as seen for the zoledronic acid group in study 2301 suggesting that the underestimation of the true placebo event rate in study 2301 may have been responsible for the observation that there was a relative increase in atrial fibrillation events seen in that study (see Table 23).

Table 23
Rates of Atrial fibrillation in Studies 2301 and 2310

	Study 2301		Study 2310	
	Placebo	Zoledronic Acid	Placebo	Zoledronic Acid
Total atrial fib AEs	1.8%	2.4%	2.6%	2.8%
Serious atrial fib AES	0.4%	1.2%	1.3%	1.1%

While there were slightly more hypocalcemia AEs in the zoledronic acid group (5/1054=0.5%) vs. the placebo group (0/1057=0%) as would be expected from the mechanism of action of the bisphosphonate, there were actually more serious arrhythmia AEs in the placebo group (56/1057=5.3%) compared to the zoledronic acid group 46/1054=4.4%) in study 2310, consistent with the fact that hypocalcemia was not part of the mechanism behind the occurrence of arrhythmias in this study.

Comparing the demographics of the patients in study 2310 to the pivotal study 2301 there were more Asian/Pacific Islanders in study 2301 (14% vs. 0.2%) and fewer Caucasians (79% vs. 91%). However, this did not contribute to the relative higher reporting rate of serious atrial fibrillation in the zoledronic acid group in study 2301 as the reporting rate was similar for Asian/Pacific Islanders in both the zoledronic acid group (3/48=6%) and the placebo group (1/17=6%).

The higher number of Asians in study 2301 and the fact that study 2301 was performed only in women whereas study 2310 had 24% men probably accounted for why the 2301 study population was shorter (mean height 153.5cm vs. 162.1cm) and weighed less (mean weight 60.3kg vs. 65.3kg) even though both populations had similar mean BMI values (25.3kg/m^2 vs. 24.8kg/m^2 for studies 2301 and 2310, respectively). In addition, only study 2301 enrolled patients from Asia (14%), whereas study 2310 had more patients from North America (29 vs. 20%), Western Europe (33 vs. 30%) and Eastern Europe (25 vs. 20%), and slightly fewer

patients from Latin America (12 vs. 16%). It is unclear if these demographic differences between the studies contributed to the difference in reporting rates of serious atrial fibrillation AEs.

The mean age for both studies was similar 73.1 (study 2301) vs. 74.5 (study 2310) but the age distribution was different so that there were both more younger and older patients in study 2310 (see Table 24). The higher percentage of very elderly patients, ≥85 years of age, in study 2310 may have contributed to the slightly higher reporting rate for total atrial fibrillation cases in study 2310 compared to 2301 as reported in Table 23 above. However, it is unclear if these demographic differences between the studies contributed to the difference in reporting rates of serious atrial fibrillation AEs.

Table 24
Age Distributions in Studies 2301 and 2310

Age group	Study 2301 (%) n=7736	Study 2310 (%) n=2127
<65	0.2	17
65-74	62	27
75-84	36	42
≥85	2	14

Similarly, none of the oncology studies in men with prostate cancer included in this submission showed an increased risk for atrial fibrillation that could be attributed to the use of the zoledronic acid that was above the background rate predicted using the CHS data.

In study ekr01, an open-label, ~24-week study in oncology patients with metastatic prostate cancer receiving 4mg of zoledronic acid every 3-4 weeks for a maximum of 6 doses, no adverse events of atrial fibrillation were reported in the 45 patients enrolled.

In study ZOL446E US24, an open-label, ~48-week study in oncology patients with metastatic prostate cancer receiving 4mg of zoledronic acid every 3 weeks for a maximum of 16 doses, 5 adverse events of atrial fibrillation were reported in the 257 (1.2%) patients enrolled of which only one case was considered serious. The one serious case included a 75 y/o patient with a h/o CHF who was diagnosed with atrial fibrillation nine days after the initial zoledronic acid infusion. During a work up for this event the patient's cardiologist determined that it was likely that the patient had been in atrial fibrillation for some time prior to the initial infusion and that the zoledronic acid was not suspected of precipitating this event.

In study ZOL446G US45, an open-label, ~52-week study in oncology patients with metastatic prostate cancer receiving 4mg of zoledronic acid every 3 months for a maximum of 5 doses, 3 adverse events of atrial fibrillation were reported in the 112 (2.7%) patients enrolled in the zoledronic acid group of which only one case was considered serious. The one serious case occurred in an 81 y/o diabetic male, with a h/o coronary heart disease, COPD, and chronic peripheral edema whose acute illness was precipitated by pneumonia and worsening CHF. There were no cases of atrial fibrillation reported in the placebo group of 110 patients (0%). The reporting rate of 2.7% at 52 weeks is similar to the prevalence of atrial fibrillation estimated

from the Cardiovascular Health Study in elderly men (>65y/o) i.e. 2.6 per 100 person years[3]. There were slightly more patients with a past medical history of atrial fibrillation randomized into the zoledronic acid group (9/112=8.0%) compared to the placebo group (6/110=5.5%) which may have accounted for part of the difference seen in this study (source Post-text Table 7.3-3, page 2 of 57, pg 110 of US45 report).

One possible explanation why no increase in atrial fibrillation had been seen in the oncology trials is that this is a rare event and these trials enrolled too few patients to see such a rare event. A recent reanalysis of the Fracture Intervention Trial (FIT)[4] which randomized 4,432 postmenopausal women to a different bisphosphonate, alendronate, or placebo also found no statistically significant increase in total atrial fibrillation adverse events in the alendronate treatment group 81 events (2.5%) versus the placebo group 71 events (2.2%) (relative hazard 1.14, 95% confidence interval [CI] 0.83 to 1.57, p = 0.42). Nor was there an increase in serious atrial fibrillation adverse events among patients receiving daily alendronate, 47 events (1.5%), compared to those receiving placebo, 31 events (1.0%) during the 4 year trial (relative hazard 1.51, 95% CI 0.97 to 2.40, p = 0.07), although the trend was greater in this case. No information is available from this report about the relative frequency of baseline atrial fibrillation and cardiac disease between the randomized groups in the FIT trial which may have accounted for part of the observed trend. Sumilarly, a letter to the editor in today's New England Journal of Medicine[5] found no increase in total (1.4% placebo vs. 1.3% 2.5mg and 1.4% 5mg risedronate) or serious (0.5% placebo vs. 0.5% 2.5mg and 0.6% 5mg risedronate) nonadjudicated atrial fibrillation adverse events in over 15,000 patients treated for up to 3 years with another oral bisphosphonate, risedronate, in phase 3, placebo-controlled, clinical trials. These varied findings in clinical trials with three different bisphosphonates suggest that the increase in serious atrial fibrillation events seen in the case of zoledronic acid is not a class effect and is more likely a chance finding.

Cummings speculates[4] that while there is no known biological explanation to account for an increase in atrial fibrillation in patients receiving bisphosphonates these drugs have been associated with the release of inflammatory cytokines[6] which have been associated with an increased risk for atrial fibrillation[7]. However such an explanation would not account for why >94% of the serious cases in pivotal trial 2301 were seen between 1 and 12 months after the IV infusion well after any predicted increase in cytokines which is associated with the acute phase response would have subsided. Such an explanation would be more reasonable with daily bisphosphonate therapy similar to what occurred in the FIT trial. As an aside, statins have been shown to mitigate the bisphosphonate cytokine release *in vitro* and it has been suggested that

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3 Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997 Oct 7;96(7):2455-61.
4 Cummings SR, Schwartz AV, Black DM. Alendronate and Atrial fibrillation N Engl J Med. 2007 May 3; 356(18):1895-6.
5 Karam R, Camm J, McClung M N Engl J Med. 2007 August 16:357(7):712
6 Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood γδ T cells in response to aminobisphosphonates is inhibited by statins. Clin Exp Immunol. 2005 Jan;139(1):101-11.
7Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial fibrillation. Circulation. 2003 Dec 16;108(24):3006-10. Epub 2003 Nov 17.

they may be useful clinically to prevent cytokine meditated adverse events[8]. A review of the concomitant meds, in pivotal study 2301, found similar low levels of statin use in this elderly female population 1261/3861=33% (placebo group) and 1373/3875= 35% (zoledronic acid group), suggesting no benefit from statin use at preventing the serious atrial fibrillation AEs. Similarly a higher percentage of patients in the zoledronic acid group who developed serious atrial fibrillation AEs were on a statin during the course of the study 15/48=31% compared to 2/17=12% in the placebo group, also demonstrating no benefit from statin use at preventing these AEs, but suggesting that the patients in the zoledronic acid treatment group may have had more clinically significant cardiac disease requiring the additional statin therapy. A more detailed analysis beyond the scope of this review would be needed to determine if the timing of the stain medication use (e.g. at the time of the infusion or at the time just prior to the arrhythmia) or the dose or brand of statin medication might still suggest a protective effect.

Another possible mechanism for the development of atrial fibrillation may be related to transient hypocalcemia affecting electrical depolarization in the heart. There are two reports in the literature of patients, who also had unsuspected Vitamin D deficiency, who developed abnormal cardiac rhythms after receiving IV bisphosphonates. One case report was a 52 year old woman with PMO s/p gastric stapling for morbid obesity who developed atrial fibrillation and tetany 3 weeks after IV pamidronate associated with hypocalcemia (4.8mg/dL) and vitamin D deficiency (7ng/mL, normal 9 to 55)[9]. The other case report was a 63 year old man s/p partial gastrectomy for gastric cancer treated with treated with zoledronic acid for metastatic prostate cancer, who developed a prolonged QT interval due to severe hypocalcemia (5.4mg/dL) 7 days after a single 4mg dose of zoledronate[10]. His admission 25-OH Vitamin D level was low at 9ng/dL (normal 10 to 68). Both of these patients were at risk for Vitamin D deficiency due to prior gastric surgery and required prolonged Ca and Vitamin D replacement therapy to normalize their calcium levels. Both of these cases occurred shortly after the initially course of therapy when hypocalcemia is most likely to occur and so would not explain the vast majority of cases of atrial fibrillation which occurred after the first month of therapy in study 2301. In addition, all patients in the pivotal study 2301 received 1000 to 1500mg of Ca, and 400 to 1200IU of Vitamin D during the three year follow up and so were less likely to be Vitamin D or calcium deficient. Also, none of the case narratives for the patients who developed serious atrial fibrillation in study 2301 described any abnormal calcium levels. There were only two patients who developed serious atrial fibrillation AEs in the zoledronic acid treatment group who had slightly low Ca levels in the sponsor's original dataset (8.1 and 8.2 mg/dL) which occurred during the first visit 9 to 10 days after the first drug dosing. But these values were not nearly as extreme as those reported in the two cases from the literature, and the atrial fibrillation events occurred five months after the first dose in one case and eight months after the second dose in the other patient, and so were not related to the time course of the reported hypocalcemia. Therefore, it seems unlikely that

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8 Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins.
Clin Exp Immunol. 2005 Jan;139(1):101-11.
9 Rosen CJ, Brown S. N Engl J Med. 2003 Apr 10;348(15):1503-4
10 Breen TL, Shane E. J Clin Oncol. 2004 Apr 15;22(8):1531-2

transient undocumented hypocalcemia could have explained any of the episodes of atrial fibrillation observed in study 2301.

Jo Wyeth from the Division of Drug Risk Evaluation (DDRE) was asked to consult on the risk of atrial fibrillation associated with bisphosphonate use to see if there was a signal in the AERS database for post marketing reports with the use of pamidronate or zoledronic acid. A total of 8,316 adverse event reports were identified in the database for these two medications through April 30, 2007. There were 18 world wide reports of atrial fibrillation for pamidronate (9 in the US), and 22 for zoledronic acid (14 in the US), for event rates of 0.5% and 0.4%, respectively. The median reported age was 74 years. Of the 40 combined reports 65% (n=26) had a history of atrial fibrillation or other risk factor in addition to age. Most were receiving the bisphosphonate for a cancer mediated indication (55%, n=22) while only a small group were being treated for osteoporosis (28%, n=11). No clear dose or exposure time associations were identified. Nor did the review suggest a group of bisphosphonate users who appeared to be at increased risk of atrial fibrillation. The final conclusion of the report was that given the characteristics and prevalence of atria fibrillation and the population using bisphosphonates, it is difficult to distinguish possible bisphosphonate-induced atrial fibrillation from age or other cause-associated atrial fibrillation using spontaneous reports and therefore the analysis was inconclusive regarding the effects of pamidronate and zoledronic acid on the risk of atrial fibrillation.

In summary, increased rates of serious and severe cases of atrial fibrillation were seen in elderly females treated for PMO with zoledronic acid compared to placebo in study 2301. This had not been seen previously with other bisphosphonates and was not observed in the other phase 3 trials included in this submission including study 2310 a 2000 patients hip fracture trial and oncology trials in which patients received 5 to 16 repeat doses of zoledronic acid within a one-year period compared to the once-a-year dosing in study 2301. Whereas the individual dose of zoledronic acid in study 2301 was slightly higher than the dose used in the oncology trials (5 vs. 4mg) which may have resulted in a slightly higher Cmax, as the drug was dosed over the same time period of 15 minutes, it seems less likely that this was responsible for the increased rate of atrial fibrillation seen in trial 2301 as most of the serious cases, i.e. 45/48=94%, occurred more than 30 days after the last infusion, well after the peak serum levels of the drug would have dissipated. At present there is no plausible mechanism to explain how zoledronic acid could be responsible for an increased risk of atrial fibrillation, as the known drug related transient adverse events, short-term flu-like symptoms, decreased renal function and hypocalcemia, occur during the first two weeks after treatment and well before > 94% of the serious atrial fibrillation cases reported in this study. A review of the past medical history of the patients in study 2301 suggests that most patients who developed serious atrial fibrillation AEs had preexisting risk factors including a preexisting arrhythmia, valvular heart disease or hypertension. At most 18% of the cases of serious atrial fibrillation in the zoledronic acid treatment group had no clear documented history of risk factors outside of age. In conclusion, it is this medical officer's opinion that there is no clear evidence to suggest that zoledronic acid was causally responsible for the higher reporting rate of serious atrial fibrillation observed in study 2301, but it would be prudent to continue to monitor for this adverse event in ongoing studies including zoledronic acid and other intravenous bisphosphonates.