7.1.2.2 Renal Safety

Bisphosphonates can inhibit farnesylpyrophosphate synthase blocking the mevalonate pathway. This can result in a build-up of isopentenyl pyrophosphate which can initiate apoptosis and disregulation of the Ras, Rac, Rho and G-proteins which are important in multiple intracellular functions. Typically bisphosphonates accumulate in bone where they exert their effects on bone osteoclasts. However, as bisphosphonates are excreted, unmetabolized, they can also exert effects on the kidney. Renal toxicity is a function of the magnitude and duration of the elevated bisphosphonate levels in renal proximal tubule cells which are involved in the active secretion of the bisphosphonate into the nephron. Renal toxicity had been previously observed with intravenous zoledronic acid 8mg, regardless of the infusion time and with zoledronic acid 4mg with a 5 minute infusion compared to a 15 minute infusion.

Patients with a baseline calculated creatinine clearance of < 30mL/min, an increase in serum creatinine of > 0.5mg/dL between the two screening visits or urine dipstick protein ≥2+ were excluded from the study. Serum creatinine, age, urine specimens and weight were assessed at baseline (visits 1, 2) and at Month 12 (Visit 5), Month 24 (Visit 6), and Month 36 (Visit 7). In addition, a cohort of 5035 randomized patients was assessed for serum creatinine, blood urea nitrogen, electrolytes, and urinalysis 9–11 days after each infusion.

Renal AEs associated with a change in renal function were similar in both treatment groups with 190 patients (4.9%) in the zoledronic acid group compared to 168 patients (4.4%) in the placebo group (see Table 25). The only adverse events seen in more than two patients in the zoledronic acid group (>0.1%) which occurred at least two fold more frequently in the zoledronic acid group compared to placebo were an increase in creatinine 30 (0.8%) vs. 12 (0.3%) and azotemia 5 (0.1%) vs. 0 (0.0%).

Table 25
AEs associated with change in renal function in study 2301 (Safety population)

	Zoledronic acid N=3862	Placebo N=3852
Preferred term	**n (%)**	**n (%)**
Total	**190 (4.9)**	168 (4.4)
Creatinine renal clearance decreased	78 (2.0)	91 (2.4)
Renal impairment	35 (0.9)	33 (0.9)
Blood creatinine increased	30 (0.8)	12 (0.3)
Renal failure	29 (0.8)	23 (0.6)
Proteinuria	13 (0.3)	8 (0.2)
Renal failure acute	12 (0.3)	6 (0.2)
Azotemia	5 (0.1)	0 (0.0)
Nephritis	2 (0.05)	0 (0.0)
Glomerulonephritis	1 (0.03)	1 (0.03)

Table 25
AEs associated with change in renal function in study 2301 (Safety population)

	Zoledronic acid N=3862	Placebo N=3852
Preferred term	**n (%)**	**n (%)**
Glomerulonephritis acute	1 (0.03)	0 (0.00)
Glomerulonephritis membranoproliferative	1 (0.03)	0 (0.00)
Glomerulonephritis proliferative	1 (0.03)	0 (0.00)
Renal failure chronic	1 (0.03)	4 (0.10)
Scleroderma renal crisis	1 (0.03)	0 (0.00)
Acute prerenal failure	0 (0.00)	2 (0.05)
Nephrotic syndrome	0 (0.00)	1 (0.03)
Source: Sponsor's PT-Table 10.2-8 Revised Report		

Despite the almost 3-fold higher rates for increase in creatinine in the zoledronic acid group, this did not lead to a significantly higher rate in discontinuation of patients from the zoledronic acid group compared to the placebo group in this study (see Table 26).

Table 26
Discontinuation of study drug due to AEs associated with change in renal function in study 2301(Safety population)

	Zoledronic acid N=3862	Placebo N=3852
Preferred term	**n (%)**	**n (%)**
Total	30 (0.8)	29 (0.8)
Creatinine renal clearance decreased	18 (0.5)	15 (0.4)
Renal impairment	7 (0.2)	7 (0.2)
Renal failure	4 (0.1)	7 (0.2)
Blood creatinine increased	1 (0.03)	1 (0.03)
Source: Sponsor's PT-Table 10.2-5x Revised Report		

Nor were there substantially more serious renal safety AEs (see Table 27).

Table 27
Serious AEs associated with change in renal function in study 2301 occurring in at least 2 subjects in the zoledronic acid group (Safety population)

	Zoledronic acid N=3862	Placebo N=3852
Preferred term	**n (%)**	**n (%)**
Total	43 (1.1)	36 (0.9)
Urinary incontinence	6 (0.2)	3 (0.1)
Bladder prolapse	5 (0.1)	3 (0.1)
Renal impairment	7 (0.2)	7 (0.2)
Renal failure	4 (0.1)	7 (0.2)
Renal failure acute	4 (0.1)	3 (0.1)
Renal colic	3 (0.1)	1 (0.03)
Renal cyst	3 (0.1)	1 (0.03)
Calculus ureteric	2 (0.05)	4 (0.1)
Hematuria	2 (0.05)	3 (0.1)
Incontinence	2 (0.05)	0 (0.0)
Renal mass	2 (0.05)	0 (0.0)

Source: Sponsor's PT-Table 10.2-3 Revised Report

There is an increase in serum creatinine from baseline to 9-11days post infusion in the zoledronic acid (ZA) group compared to the placebo group after each of the three infusions, independent of whether the comparison is made to the prestudy baseline creatinine or to the preinfusion baseline creatinine (see Table 28).

Table 28 Increase from baseline in Cr >0.5mg/dL in study 2301 (Renal Safety Population)

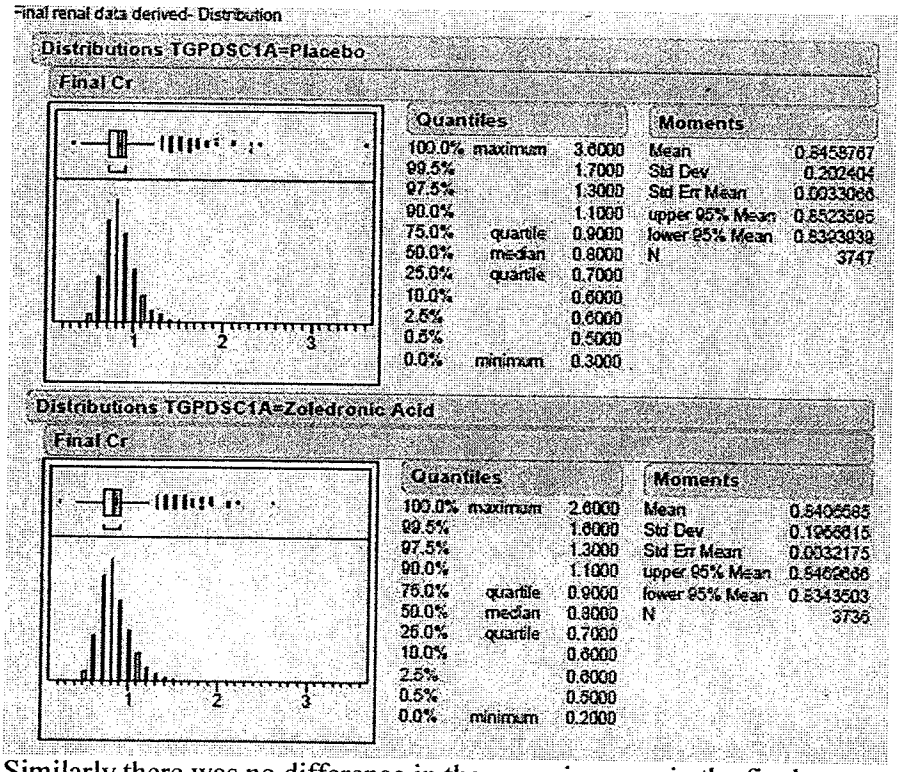
	Increase from prestudy baseline		Increase from preinfusion baseline	
	Zoledronic acid	Placebo	Zoledronic acid	Placebo
	n (%)	n (%)	n (%)	n (%)
Total N=2320 ZA N=2338 Placebo	42 (1.8)	19 (0.8)	31 (1.3)	10 (0.4)
Post 1st infusion n=2114 ZA N=2130 Placebo	13 (0.6)	6 (0.3)	13 (0.6)	6 (0.3)
Post 2nd infusion N=1663 ZA N=1721 Placebo	19 (1.1)	8 (0.5)	12 (0.7)	1 (0.06)
Post 3rd infusion N=1560 ZA N=1600 Placebo	15 (1.0)	7 (0.4)	8 (0.5)	3 (0.2)

Source: Sponsor's Table 10-14 & 10-15 Revised Report

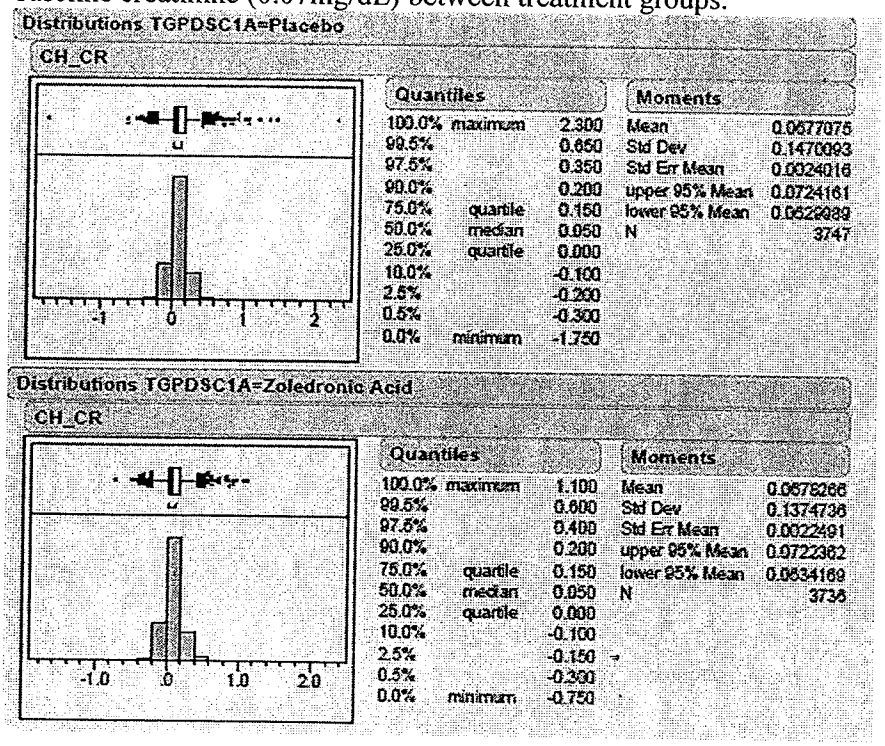
The absolute rate however is quite low (<1% per infusion) and there is no clear correlation with short term changes in creatinine and long term effects. Of the 31 patients in the zoledronic acid group with an increase of >0.5mg/dL at 9-11days post the latest preinfusion value, the serum creatinine values declined progressively over time, so that by 12 months post infusion, no patient still had an increase in serum creatinine >0.5 mg/dL relative to their preinfusion value. Whereas in the placebo group, only 8 of the original 10 patients with an increase in serum creatinine >0.5 mg/dL had the event resolved by 12 months.

While there was an increase in patients in the zoledronic acid treatment group who had an increase of >0.5mg/dL in creatinine relative to baseline at the 12 month time point, 19 (0.53%) vs. 9 (0.25%), there were no similar increases observed at 24 months, 16 (0.5%) vs. 20 (0.6%), or 36 months, 36 (1.0%) vs. 38 (1.2%) in the zoledronic acid and placebo groups, respectively, again suggesting that there is no long term effect on renal function. Whereas it is not possible to rule out that patients with worsening renal function were not selectively discontinued during the course of the trial, they should have been randomly discontinued from both treatment arms. Therefore the exclusion criteria of creatinine clearance > 30mL/min and urine > 2+ appears to be adequate in identifying subjects at risk of worsening renal function, as there was no relative increase in patients with worsening renal function in the zoledronic acid group during the second and third years of the trial.

Another way to look at long term safety data is to compare treatment groups by last observed value. This would attempt to compare patients who are at risk of study discontinuation because of worsening renal function. However, the datasets include only values from regularly scheduled visits and so would not identify patients who might have discontinued the trial because of abnormal creatinine values observed during an unscheduled hospitalization for some adverse event. There was no difference in the mean final creatinine values (0.8mg/dL) or the distribution of final creatinine values between the treatment groups.



Similarly there was no difference in the mean increase in the final serum creatinine from the baseline creatinine (0.07mg/dL) between treatment groups.



Two patients (<0.1%) in the zoledronic acid group had increases in serum creatinine >0.5 mg/dL after each of two separate infusions compared to no such patients in the placebo group, suggesting that very few patients were at risk for repeat changes in creatinine with subsequent dosing as long as renal function is adequately monitored prior to dosing.

The current Zometa label recommends dose adjustment for creatinine clearance levels between 30 and 60mL/min, whereas the pivotal study 2301 was performed with a single dose of 5mg for all patients with creatinine clearance values > 30mL/min. Study 2301 included an adequate number of patients with baseline values between 30 and 60 mL/min to confirm the safety of the 5mg yearly dose in this subpopulation without the need for dose adjustment. The data in Table 29 show that while there is a slightly higher risk for developing an increase in creatinine of >0.5mg/dL in patients with baseline creatinine clearance values < 60mL/min, the risk is similar in both treatment groups and therefore is likely a result of progression of the underlying renal disease and not related to the study medication.

Table 29

Changes of >0.5 in Creatinine from Baseline by Baseline Creatinine Clearance Categories in Study 2301 at the Patients Final Visit

		Placebo		Zoledronic Acid	
	Baseline CrCl (mL/min)	Total Patients	Patients with Inc of >0.5 in Cr from baseline at final visit N (%)	Total Patients	Patients with Inc of >0.5 in Cr from baseline at final visit N (%)
1	<30	3	1	0	0
2	≥30 <35	94	2 (2.1)	73	2 (2.7)
3	≥35 <40	149	1 (0.7)	167	2 (1.2)
4	≥40 ≤50	629	11 (1.7)	630	5 (0.8)
5	>50 ≤60	894	5 (0.6)	951	6 (0.6)
	≥30 ≤60	1766	19 (1.0)	1821	15 (0.8)
6	>60	2107	7 (0.3)	2068	9 (0.4)
	All patients	3876	27 (0.7)	3889	24 (0.6)

Data from derived a_renal.xpt from the 2006-10-16 submission analyzed using Jmp software. These data are slightly different from sponsor's PATIENT-Tale 10.6-1 from the Renal SpEER which measured values at the 9-11day post infusion visits, but the trends are similar.

Therefore, there is no evidence to suggest a need for dose adjustment in patients with baseline creatinine clearance values between 30 and 60mL/min.

7.1.2.3 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) defined as "exposed bone with delayed healing despite 6 weeks of appropriate medical care," is a rare finding seen primarily with intravenous bisphosphonates

used in immuno-compromised oncology patients, patients s/p radiation therapy to the jaw or in patients with preexisting mucosal lesions or oral pathology.

The American Dental Association estimates the incidence of new cases of ONJ in osteoporosis with oral bisphosphonates to be 0.7 cases per one hundred thousand person-years exposure[11]. Based on data from case report studies, there are estimates that the prevalence of ONJ in oncology patients receiving IV bisphosphonates can range from 0.8% to 10%. To help determine a more accurate prevalence of ONJ in a cancer patient population, Novartis ———————————————, to perform an independent retrospective chart review of 4026 patients that received IV bisphosphonates over a 10-year period as part of their chemotherapy at the MD Anderson Cancer Center. The study used a less stringent definition of ONJ as "non-healing exposed bone of ≥3 months duration." Overall, they found 33 cases of ONJ (0.8 % incidence) with the majority of cases associated with a previous dental extraction (17 patients) or periodontal disease (14 patients). Only two patients who developed ONJ had no documented dental or oral surgical procedures or pathology. On the basis of these reports, potential factors that may increase the risk of ONJ in patients that receive bisphosphonate therapy include cancer, dental extraction, periodontal disease, dental trauma, concomitant therapies, corticosteroids and administration of cytotoxic agents. Patients with multiple comorbidities may be at elevated risk.

There were 119/3862 (3.1%) of the patients in the zoledronic acid group and 149/3852 (3.9%) of the patients in the placebo group that had adverse events that met the adjudication criteria including 60 different Medra Preferred Terms used to identify maxillofacial events (see sponsor's Maxillofacil SpEER table 2-2, 2/12/07 submission). In the final study report there was only one adjudicated case of osteonecrosis of the jaw in the zoledronic acid group (0.03%) and one "possible" case in the placebo-treated group (0.03%). The patient in the zoledronic acid group (0311/00020) was a 70-year-old insulin-dependent diabetic with retinopathy and neuropathy who had never had regular dental care. She presented with an abscess in the residual root of a previous extraction 5 months after her second infusion of zolderonic acid. As the swelling decreased, but prior to complete resolution, 12 additional extractions and curettage were performed. Within a week the patient became extremely ill and was diagnosed with a periodontal infection. She refused hospitalization. The infection subsequently spread to the mandibular bone, resulting in osteomyelitis. The osteomyelitis resulted in necrosis of part of the mandible, which was confirmed radiographically. The patient was subsequently treated with antibiotics. Resolution of the infection with full healing was documented radiographically and with photographs taken 2 years after the initial presentation of symptoms. The sponsor's conclusion was that this patient's condition was most likely a combination of her underlying comorbidities, surgical extractions in an infected environment, and refusal of hospitalization, and it was not possible to determine what the contribution of bisphosphonate administration was to this patient's clinical course.

The patient in the placebo group (0601/00019) presented with a lesion in the region of the left maxilla that was inflamed and painful to palpation. Osteitis was diagnosed without any clinical

11 ADA Council on Scientific Affairs, Dental management of patients receiving oral bisphosphonate therapy, JADA August 2006, 137, 1144-1150

evidence of a soft tissue infection. Two debridements of the infected area and antibiotic therapy were performed as treatment for the condition. The time to resolution was approximately 8 months.

The sponsor's proposed labeling describes the risk of ONJ with the use of bisphosphantes under WARNINGS AND PRECAUTIONS and lists known risk factors to help treating physicians guide their management plan. It is this medical officer's opinion that the labeling provides adequate information to permit effective risk/benefit assessments for individual patients.

7.1.2.4 Ocular Adverse Events

Ocular adverse events are typically inflammatory in nature and associated with the acute phase flu-like syndrome seen within the first 72 hours after infusion of zoledronic acid. Transient post-dose symptoms, including the eye findings, are most common after the first infusion and occur less often with subsequent dosing. Overall there were 538 (14%) patients in the zoledronic acid group and 500 (13%) in the placebo group who had adverse events in the SOC, eye disorder. The number of patients with ocular adverse events decreased with repeated administration of zoledronic acid. There were 275 (7%) in the zoledronic acid group and 220 (6%) in the placebo group who had ocular adverse events between the first and second infusion, compared to 176 (5%) and 198 (6%), respectively, between the 2nd and 3rd infusions and 149 (5%) and 150 (5%), respectively, after the third infusion (Study 2301 PATIENT-Tables 10.1-2a-c). An expert review by an ophthalmologist, blinded to treatment assignment, was performed to identify ocular adverse events using 15 specific MedDRA terms for adjudication. Overall, the incidence of confirmed ocular adverse events was low about 3% and similar between treatment groups, except for eye pain (18 vs. 9), eye irritation (14 vs. 10), diplopia (7 vs. 2) and uveitis (6 vs. 0, but only 1 case was serious) which were higher in the zoledronic acid group (see Table 30).

Table 30

Patients with confirmed ocular adverse events in study 2301.

Preferred Term	Zoledronic acid N = 3862 n (%)	Placebo N = 3852 n (%)
Total	129 (3.34)	102 (2.65)
Conjunctivitis	54 (1.40)	48 (1.25)
Eye pain	18 (0.47)	9 (0.23)
Eye irritation	14 (0.36)	10 (0.26)
Vision blurred	13 (0.34)	16 (0.42)
Blepharitis	9 (0.23)	13 (0.34)
Diplopia	7 (0.18)	2 (0.05)
Lacrimation increased	7 (0.18)	8 (0.21)
Uveitis	6 (0.16)	0 (0.00)
Episcleritis	2 (0.05)	1 (0.03)
Photophobia	2 (0.05)	1 (0.03)
Iridocyclitis	1 (0.03)	1 (0.03)
Iritis	1 (0.03)	0 (0.00)

Source: [Safety Update Appendix Table 8.2-5]

A patient with multiple occurrences of the same AE is counted only once. Table 3-4 in SpEER of ocular AEs.

None of the ocular adverse events were vision threatening; all resolved with conservative management without sequelae. Conjunctivitis (n=54, 1.4%) probably occurs as part of an acute phase reaction, and can be treated with artificial tears or observation. Uveitis can be treated with topical steroid eye drops. No cases of scleritis, the most visually threatening event associated with bisphosphonates were observed in study 2301. The sponsor currently proposes to mention that cases of iritis/ uveitis/ episcleritis/ conjunctivitis have been seen with zoledronic acid treatment in the proposed labeling. It is this medical officer's opinion that it might also be useful to include in the labeling that symptoms typically present within a few weeks of the infusion.

7.1.3 Dropouts and Other Significant Adverse Events

The most common AEs occurring at a rate of at least 0.1% in any group and leading to a premature discontinuation from the study are listed in Table 31. Cerebrovascular accidents were more common in the zoledronic acid group compared to the placebo group 13 vs. 5. This is identical to the difference in stroke-related deaths which had been previously described under section 7.1.1. and probably refers to the same cases. Acute MIs (6 vs. 1) and cardiorespiratory arrests (4 vs. 1) were more common in the zoledronic acid group; cardiac arrest occurred at similar rates (5 vs. 6) and myocardial infarction occurred more commonly in the placebo group (3 vs. 8) for no net difference in cardiac events between groups (ZA 18 vs. Placebo 16). Renal failure was more common in the placebo group (7 vs. 4) suggesting that the transient effect on renal function observed following infusions with zoledronic acid did not result in an increase in long term renal morbidity. Chills (4 vs. 0) and arthralgias (4 vs. 0) were more common in the zoledronic acid group and are probably related to the short term flu-like syndrome observed following infusions with the bisphosphonate. Back pain was more common in the Placebo group (5 vs. 1) and is likely due to the protective effect of zoledronic acid on vertebral bone BMD.

Table 31

AEs leading to premature discontinuation from the study by primary PT occurring at a rate of at least 0.1% for any group (Safety population)

Preferred term	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Total no. of patients with an AE leading to discontinuation from study drug	209 (5.41)	187 (4.85)
Creatinine renal clearance decreased	18 (0.47)	15 (0.39)
Cerebrovascular accident	13 (0.34)	5 (0.13)
Renal impairment	7 (0.18)	7 (0.18)
Acute myocardial infarction	6 (0.16)	1 (0.03)
Breast cancer	6 (0.16)	2 (0.05)
Death	6 (0.16)	5 (0.13)
Cardiac arrest	5 (0.13)	6 (0.16)
Dementia	5 (0.13)	4 (0.10)
Arthralgia	4 (0.10)	0 (0.00)
Cardiac failure	4 (0.10)	4 (0.10)
Cardiac failure congestive	4 (0.10)	1 (0.03)
Cardiorespiratory arrest	4 (0.10)	1 (0.03)
Chills	4 (0.10)	0 (0.00)
Renal failure	4 (0.10)	7 (0.18)
Myocardial infarction	3 (0.08)	8 (0.21)
Back pain	1 (0.03)	5 (0.13)
Lung neoplasm malignant	1 (0.03)	4 (0.10)

Source Table10-10 Study 2301 Clinical Study Report 12-Feb-2007 submission.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

Adverse events occurring at greater than 5% of patients in study 2301 are listed in Table 32. Adverse events occurring at least 2% fold more frequently in the zoledronic acid group include arthralgia (23% vs. 20%), pyrexia (18% vs. 4%), headache (18% vs. 8%), myalgia (12% vs. 4%), influenza like illness (9% vs. 3%), nausea (8% vs. 5%), asthenia (6% vs. 3%), bone pain (6% vs. 2%), and chills (5% vs. 1%). These adverse events can most likely be attributed to the short-term flu-like syndrome commonly seen within the first few days following IV dosing with zoledronic acid.

Table 32
Common adverse events occurring at > 5% of the study population.

Preferred term	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Patients studied		
Total no. of patients	3862	3852
Total no. of patients with AEs	3686 (95.44)	3611 (93.74)
Preferred term		
Back pain	917 (23.74)	934 (24.25)
Arthralgia	895 (23.17)	763 (19.81)
Pyrexia	689 (17.84)	173 (4.49)
Hypertension	483 (12.51)	473 (12.28)
Headache	477 (12.35)	307 (7.97)
Urinary tract infection	458 (11.86)	443 (11.50)
Myalgia	448 (11.60)	141 (3.66)
Nasopharyngitis	434 (11.24)	424 (11.01)
Pain in extremity	416 (10.77)	364 (9.45)
Influenza	365 (9.45)	343 (8.90)
Osteoarthritis	348 (9.01)	367 (9.53)
Influenza like illness	342 (8.86)	103 (2.67)
Nausea	328 (8.49)	195 (5.06)
Dizziness	290 (7.51)	253 (6.57)
Constipation	284 (7.35)	290 (7.53)
Shoulder pain	248 (6.42)	205 (5.32)
Cataract	233 (6.03)	213 (5.53)
Diarrhea	228 (5.90)	212 (5.50)
Asthenia	222 (5.75)	127 (3.30)
Bone pain	216 (5.59)	83 (2.15)
Chills	206 (5.33)	38 (0.99)
Fatigue	206 (5.33)	136 (3.53)
Bronchitis	200 (5.18)	231 (6.00)

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings (Serum Calcium and the Risk for Hypocalcemia, Liver Function Tests, & Other Electrolytes)

7.1.7.1 Serum Calcium and the Risk for Hypocalcemia

Hypocalcemia has been associated with bisphosphonate use especially with intravenous bisphosphonates and particularly in patients with Paget's disease. Dr. Colman had previously reviewed the use of zoledronic acid in patients with Paget's disease and found that supplementation with adequate amounts of calcium and vitamin D adequately attenuated the risk for developing hypocalcemia in this patient population (see NDA 21-817).

To avoid placing subjects at risk of severe hypocalcemia in this study, patients with baseline calcium levels < 2.0 mmol/L (8mg/dL) were excluded. Baseline levels of vitamin D were not measured and no specific vitamin D inclusion or exclusion criteria were included, instead all patients were provided with calcium (1000mg-1500mg/day) and vitamin D (400-1200IU/day) supplementation throughout the 3 year study. Serum calcium values were corrected for albumin when the serum albumin was low-normal or low (e.g. albumin below 3.7 g/dL). Serum albumin levels were not part of the set of labs performed on the renal safety population at the monitoring visits conducted 9 to 11 days after each dose so corrected values were usually unavailable at this time point.

Since corrected calcium values were not available at each time point uncorrected serum calcium levels were compared between treatment groups (see Table 33). While the relative frequency of hypocalcemia was about 3-fold higher in the zoledronic acid group compared to the placebo the absolute incidence was low with the vast majority of cases of mild severity.

Table 33
Number Patients with Hypocalcemia by WHO Categories in the Safety Population in Study 2301

Serum Calcium	WHO Category	Zoledronic Acid N (%)	Placebo N (%)
Ca < 2.075mmol/L (8.3mg.dL)	Mild	66 (1.7)	21 (0.5)
Ca < 1.75mmol/L (7.0mg/dL)	Moderate	4 (0.1)	1 (0.03)
Ca < 1.525mmol/L (6.1mg/dL)	Severe	0 (0)	0 (0)
Data source A_elec SAS dataset from 20007-2-05 submission, Day_1N>0			

The presumed nadir for calcium levels following intravenous zoledronic acid infusion occurs at 9-11 days post-infusion. Calcium data from the safety population Vists 3.01, 5.01 and 6.01 showed that most of the hypocalcemia occurred following the initial infusion (see Table 34). Only four patients, all in the zoledronic acid treatment group, had a recurrence of hypocalcemia during a subsequent infusion.

Table 34
Number of Patients with Hypocalcemia (Ca < 2.075mmol/L) at 9-11 days Post Infusion in the Study 2301 Safety Population

	Total Pts	Zoledronic Acid N (%)	Placebo N (%)
After first infusion	ZA N=2129, Placebo N=2142	39 (1.8)	1 (0.05)
After second infusion	ZA N=1674, Placebo N=1731	4 (0.2)	2 (0.1)
After third infusion	ZA N=1582, Placebo N=1621	8 (0.5)	4 (0.2)
Data source A_elec SAS dataset from 20007-2-05 submission, Day_1N>0, Vis_Map=3.01, 5.01 or 6.01, Ca<2.075mmol/L			

A total of 11 (0.3%) patients in the zoledronic acid group and 5 (0.1%) patients in the placebo group had adverse events reported by the study investigators with the preferred term hypocalcemia. The adjudication review committee determined that 4 of the events in the zoledronic acid group and 2 of the events in the placebo group were clinically relevant events. In five of the cases, conditions that may have predisposed the patient to hypocalcemia included thyroidectomy with possible parathyroid compromise (n=4) or gastrointestinal tract resection that may have led to malabsorption of calcium (n=1). No treatment was required for any of these patients, and the study drug was continued in all cases except for one where the patient decided to remove her consent. None of the adverse events met serious criteria, nor did the events lead to the need for discontinuation from the study. All patients were asymptomatic, and the hypocalcemia resolved without need for any intervention. Therefore, it is this medical officer's conclusion that while it is imperative that all osteoporosis patients treated with bisphosphonates receive adequate dietary calcium and vitamin D and patients with baseline hypocalcemia be treated before starting therapy with zoledronic acid, there is no need to specifically continue monitoring serum calcium levels following infusions.

7.1.7.2 Liver Function Tests

Similar degrees of elevation in liver function tests (e.g. ALT, AST and alkaline phosphatase) were seen in patients in both the zoledronic acid and the placebo treatment groups (see Tables 35, 36 and 37). Very few patients (<0.1%) had elevations of 6xULN or greater or had multiple elevations ≥3xULN.

Table 35
Rate of ALT elevations in the treatment groups in study 2301

SGPT/ALT	Placebo		Zoledronic Acid	
	Events	Patient number † (%) n=3696	Events	Patient number† (%) n=3662
<ULN	16310	3836 (99.0)	16084	3843 (98.8)
≥1xULN & <3xULN	842	474 (12.2)	862	532 (13.7)
≥3xULN & <6xULN	29	25 (0.6)	21	20 (0.5)
≥6xULN & <9xULN	2	2 (0.05)	2	2 (0.05)
≥9xULN	2	2 (0.05)	4	3 (0.08)

Data from A_Liver.xpt dataset from 05 Feb 2007 submission. Day_1N>0, ULN=33U/L
† Patient number in each row calculated separately so the total in all rows can add up to over 100%.

Table 36
Rate of AST elevations in the treatment groups in study 2301

SGOT/AST	Placebo		Zoledronic Acid	
	Events	Patient number † (%) n=3692	Events	Patient number† (%) n=3660
<ULN	12364	3118 (84.4)	12189	3597 (98.2)
≥1xULN & <3xULN	676	405 (11.0)	641	402 (11.0)
≥3xULN & <6xULN	11	10 (0.3)	14	12 (0.3)
≥6xULN & <9xULN	1	1 (0.03)	2	2 (0.05)
≥9xULN	1	1 (0.03)	2	1 (0.03)

Data from A_Liver.xpt dataset from 05 Feb 2007 submission. Day_1N>0, ULN=35U/L
† Patient number in each row calculated separately so the total in all rows can add up to over 100%.

Table 37
Rate of Alkaline Phosphatase elevations in the treatment groups in study 2301

Alkaline phosphatase	Placebo		Zoledronic Acid	
	Events	Patient number † (%) n=3696	Events	Patient number† (%) n=3662
<ULN	16583	3839 (99.0)	16639	(99.3)
≥1xULN & <3xULN	702	402 (10.4)	424	299 (7.7)
≥3xULN & <6xULN	1	1(0.03)	1	1 (0.03)
≥6xULN & <9xULN	1	1 (0.03)	0	0 (0.0)
≥9xULN	1	1 (0.03)	1	1 (0.03)

Data from A_Liver.xpt dataset from 05 Feb 2007 submission. Day_1N>0, ULN=124U/L
† Patient number in each row calculated separately so the total in all rows can add up to over 100%.

7.1.7.3 Other Electrolytes

No consistent, clinically significant changes from baseline in potassium, sodium, chloride, creatinine, albumin, total protein or urea were seen in the zoledronic acid group compared to the placebo group (see Table 38).

Table 38

Laboratory results meeting clinically notable criteria in study 2301

Post-Text Table 10.2-6 (Page 1 of 2)
Laboratory results meeting clinical notable laboratories criteria for biochemistry panel by laboratory test
Safety population

Biochemistry

Laboratory test	Criterion	Zoledronic acid (N=3862) Total	n	%	Placebo (N=3852) Total	n	%
Albumin	< 25 g/L	3650	7	0.19	3683	1	0.03
	> 60 g/L	3650	0	0.00	3683	0	0.00
Potassium	> 6 mmol/l	3750	13	0.35	3766	13	0.35
	< 3 mmol/l	3750	23	0.61	3766	20	0.53
SGOT (AST)	< 0 U/L	3648	0	0.00	3678	0	0.00
	> 100 U/L	3648	16	0.44	3678	12	0.33
SGPT (ALT)	< 0 U/L	3650	0	0.00	3682	0	0.00
	> 110 U/L	3650	18	0.49	3682	17	0.46
Sodium	< 125 mmol/l	3751	7	0.19	3766	3	0.08
	> 154 mmol/l	3751	15	0.40	3766	15	0.40
Alkaline phosphatase, serum	< 0 U/L	3650	0	0.00	3682	0	0.00
	> 250 U/L	3650	8	0.22	3682	6	0.16

Post-Text Table 10.2-6 (Page 2 of 2)
Laboratory results meeting clinical notable laboratories criteria for biochemistry panel by laboratory test
Safety population

Biochemistry

Laboratory test	Criterion	Zoledronic acid (N=3862) Total	n	%	Placebo (N=3852) Total	n	%
Chloride	< 95 mmol/l	3751	4	0.11	3766	7	0.19
	> 119 mmol/l	3751	2	0.05	3766	1	0.03
Creatinine	< 18 mmol/l	3751	0	0.00	3766	0	0.00
	> 221 mmol/l	3751	4	0.11	3766	6	0.16
Calcium	< 1.87 mmol/l	3751	9	0.24	3766	5	0.13
	> 2.89 mmol/l	3751	8	0.21	3766	8	0.21
Total Protein (Serum)	< 42 g/L	3650	0	0.00	3683	0	0.00
	> 96 g/L	3650	2	0.05	3683	1	0.03
Urea	< 0.7 mmol/l	3751	0	0.00	3766	0	0.00
	> 14.3 mmol/l	3751	39	1.04	3766	44	1.17
Uric Acid	< 89 mmol/l	3650	3	0.14	3683	3	0.08
	> 595 mmol/l	3650	28	0.77	3683	47	1.28

- N = the number of patients with non-clinical notable baseline value and at least one post-baseline value.
- n= the number of patients meeting the criterion.
- (%)= n/N*100.

7.1.8 Vital Signs

No consistent, clinically significant changes from baseline in vital signs (e.g. systolic and diastolic blood pressure or pulse) were seen in the zoledronic acid group compared to the placebo group (see Table 39).

Table 39

Vital Sign and Body Weight Changes in the Safety Population

Post-Text Table 10.4-2 (Page 1 of 1)
Vital sign and body weight results meeting clinical notable criteria by parameter
Safety population

		Zoledronic acid			Placebo		
Parameter	Criteria	N	n	(%)	N	n	(%)
Pulse (bpm)	> 120 bpm & increase of > 15 bpm	3607	2	0.1	3644	2	0.1
	< 50 bpm & decrease of > 15 bpm	3607	8	0.2	3644	14	0.4
Systolic BP (mmHg)	> 180 mmHg & increase of > 20 mmHg	3616	52	1.4	3661	47	1.3
	< 90 mmHg & decrease of > 20 mmHg	3616	7	0.2	3661	4	0.1
Diastolic BP (mmHg)	> 105 mmHg & increase of > 15 mmHg	3615	24	0.7	3661	17	0.5
	< 50 mmHg & decrease of > 15 mmHg	3615	5	0.1	3661	9	0.2
Body Weight (kg)	Increase of > 7%	3634	461	12.7	3671	411	11.2
	Decrease of > 7%	3634	575	15.8	3671	610	16.6

7.1.9 Electrocardiograms (ECGs)

A total of 559 patients in the safety population had at least one ECG assessment, 278 in zoledronic acid and 281 in placebo. There were no major differences between treatment groups concerning electrophysiological parameters. An ECG sub-set of patients was evaluated before the third infusion and then 9 to 11 days after that infusion. At each evaluation, measurements of the RR, PR, QRS, and QT interval durations were performed.

There were no clinically relevant heart rate effects and effects on cardiac conduction. Data on cardiac repolarization showed no effect on central tendency and no evidence of any specific outliers. Under conditions used in this trial, there was no evidence of any on-treatment ECG effects demonstrated by zoledronic acid compared with placebo.

7.1.10 Immunogenicity

No immunogenicity data was submitted in this NDA.

7.1.11 Human Carcinogenicity

No human carcinogenicity data was submitted in this NDA.

7.1.12 Special Safety Studies

No special safety studies were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Therapy with bisphosphonates has not been previously associated with withdrawal or abuse potential, and no new data addressing these issues was submitted in this NDA.

7.1.14 Human Reproduction and Pregnancy Data

This is a Pregnancy D category drug. No new human reproduction or pregnancy data was included in this submission. However, since this is indication for post menopausal women this is a moot issue.

7.1.15 Assessment of Effect on Growth

Whereas there would be no expected effect on growth in the PMO population, zoledronic acid did show an affect at preserving height compared to placebo with an observed decrease in height measured at 3 years of 4.2mm in the zoledronic acid group compared to of 7.0mm in the placebo group. Measurements were performed annually using a stadiometer, and were statistically significant at both 2 and 3 years.

7.1.16 Overdose Experience

Clinical experience with acute overdosage of zoledronic acid is limited. Overdosage may cause clinically significant renal impairment, hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively. No new cases of overdosage were described in this NDA.

7.1.17 Postmarketing Experience

As of 30-Apr-2007 the world-wide exposure based on the amount of drug-substance sold and the defined doses is estimated at 11,373 patient-years. A search of the Novaritis database using the Medra PT search term, hypocalcemia and blood calcium decreased, identified only 12 cases, for a frequency of 0.11 per 100pt-years of exposure. Most cases occurred within the first two weeks of dosing: nine occurred between 1 and 12 days post dose, in two cases the time of onset was unknown and one case occurred at 84 days post dosing. Most patients were elderly: eight out of twelve were between 77 and 99 years old. The lowest reported values for serum calcium were 3.9, 5.5, 7.1, 7.4, 7.8, 7.9, 7.9, 8.1, 8.2, and 8.3. No cardiovascular complications or arrhythmias were reported including one patient who had a history of atrial fibrillation. All patients fully recovered with appropriate treatment.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study 2301 was a phase 3, multi-center, prospective, double-blind, randomized, placebo-controlled study in 7,736 women with postmenopausal osteoporosis. The study was conducted in 27 countries (240 centers) including: Argentina (6), Australia (7), Austria (6), Belgium (5), Brazil (6), Canada (11), China (2), Columbia (4), Finland (7), France (4), Germany (11), Hong Kong (1), Hungary (7), Israel (6), Italy (14), Korea (8), Mexico (6), New Zealand (1), Norway (8), Poland (6), Russia (20), Sweden (5), Switzerland (8), Taiwan (5), Thailand (6), the United Kingdom (5) and the United States (65). Patients were stratified into two different strata depending on baseline and ongoing additional osteoporosis treatments and then randomized 1:1 to receive zoledronic acid (5mg) or placebo at 0, 12 and 24 months. All participants also received 1000 to 1500 mg of elemental calcium and 400 to 1200 IU of vitamin D during the 3-year follow-up period. Chronic safety and efficacy was monitored at 0.5, 1, 2, and 3 years. An acute renal safety cohort of 4,982 subjects was monitored for renal safety at 9 to 11 days after each dose. An ECG safety cohort of 559 subjects was monitored before and 9 to 11 days after their third infusion.

7.2.1.2 Demographics

The baseline demographic characteristics of the patients in the ITT population were comparable for race (79% Caucasian, 6% Hispanic, 0.4% Black), mean age (73 ± 5 years), mean weight (60-61 ± 11 kg), and mean height (153-154 ± 7 cm) see Table 40. The baseline demographic characteristics were also similar between the two strata except that the percentage of Caucasian patients was slightly higher in Stratum II than in Stratum I (87% vs. 77%) while the percentage of Asian patients was half as large in Stratum II than in Stratum I (8% vs. 16%).

Table 40

Patient Demographics in Study 2301

Table 7-4 Baseline demographic characteristics (ITT population)

Demographic variables	Zoledronic acid N=3875	Placebo N=3861	Total N=7736
Race, n (%)			
Caucasian	3054 (78.81%)	3055 (79.12%)	6109 (78.97%)
Black	15 (0.39%)	17 (0.44%)	32 (0.41%)
Hispanic	226 (5.83%)	215 (5.57%)	441 (5.70%)
Japanese	9 (0.23%)	12 (0.31%)	21 (0.27%)
Other Asian and Pacific Islander	553 (14.27%)	547 (14.17%)	1100 (14.22%)
Other	18 (0.46%)	15 (0.39%)	33 (0.43%)
Age group (year), n (%)			
< 65	7 (0.18%)	8 (0.21%)	15 (0.19%)
65 – 74	2371 (61.19%)	2401 (62.19%)	4772 (61.69%)
75 – 84	1405 (36.26%)	1356 (35.12%)	2761 (35.69%)
≥ 85	92 (2.37%)	96 (2.49%)	188 (2.43%)
Age (year)			
n	3875	3861	7736
Mean (SD)	73.1 (5.34)	73.0 (5.40)	73.1 (5.37)
Min, Median, Max	64, 73.0, 89	64, 73.0, 89	64, 73.0, 89
Weight (kg)			
n	3872	3860	7732
Mean (SD)	59.9 (11.12)	60.6 (11.33)	60.3 (11.23)
Min, Median, Max	32, 59.0, 119	26, 60.0, 129	26, 59.5, 129
Height (cm) – Non-Stadiometer			
n	1890	1890	3780
Mean (SD)	153.4 (7.19)	153.6 (7.09)	153.5 (7.14)
Min, Median, Max	126, 153.0, 178	115, 153.0, 177	115, 153.0, 178
Height (mm) – Stadiometer			
n	2179	2165	4344
Mean (SD)	1551.1 (70.73)	1550.9 (69.42)	1551.0 (70.07)
Min, Median, Max	1295, 1550.5, 1790	1330, 1551.0, 1791	1295, 1550.5, 1791

Source: PT- Table 7.4-1

The baseline medical history characteristics of the patients in the ITT population were comparable for mean femoral neck BMD (0.53 g/cm^2), mean total hip BMD (0.65g/cm^2), femoral neck T-score [≤-2.5 (71 to 73%), >-2.5 to -1.5 (26 to 28%) and >-1.5 (1%)], number of vertebral fractures [n=1 (28%), and n ≥2 (34 to 36%)], mean BMI (25kg/m^2), % of stratum I (79%), % of stratum II (21%), current smoking history (91 to 92% nonsmokers), alcohol consumption [<1 drink/day (93%), 1-2 drinks/day (6%)] and years post menopause [>5-30 (78%), and >30 (22%)] see Table 41

Table 41

Patient Medical History in Study 2301

Table 7-5 Baseline disease and background characteristics (ITT population)

Background variables	Zoledronic acid N=3875	Placebo N=3861	Total N=7736
Stratum, n (%)			
I	3045(78.58%)	3039(78.71%)	6084(78.65%)
II	830(21.42%)	822(21.29%)	1652(21.35%)
Region, n (%)			
North America/ Oceania	766(19.77%)	765(19.81%)	1531(19.79%)
Latin America	625(16.13%)	622(16.11%)	1247(16.12%)
Western Europe	1160(29.94%)	1162(30.10%)	2322(30.02%)
Asia	550(14.19%)	540(13.99%)	1090(14.09%)
Eastern Europe	774(19.97%)	772(19.99%)	1546(19.98%)
Prior BP use, n (%)			
No	3293(84.98%)	3282(85.00%)	6575(84.99%)
Yes	565(14.58%)	557(14.43%)	1122(14.50%)
Unknown/Missing	17(0.44%)	22(0.57%)	39(0.50%)
# of yrs postmenopausal, n (%)			
≤ 5	1(0.03%)	3(0.08%)	4(0.05%)
>5 - 30	3005(77.55%)	3011(77.98%)	6016(77.77%)
> 30	858(22.14%)	833(21.57%)	1691(21.86%)
Missing	11(0.28%)	14(0.36%)	25(0.32%)
BMI (kg/m^2)			
n	3868	3856	7724
Mean (SD)	25.132 (4.3328)	25.377 (4.3093)	25.255 (4.3225)
Min, Median, Max	13.355, 24.671, 54.770	12.726, 24.990, 48.225	12.726, 24.806, 54.770
Femoral neck BMD (g/cm^2)			
n	3852	3846	7698
Mean (SD)	0.533 (0.0624)	0.534 (0.0644)	0.533 (0.0634)
Min, Median, Max	0.281, 0.537, 0.842	0.211, 0.539, 0.958	0.211, 0.538, 0.958
Total hip BMD (g/cm^2)			
n	3845	3840	7685
Mean (SD)	0.647 (0.0897)	0.648 (0.0908)	0.648 (0.0903)
Min, Median, Max	0.231, 0.648, 1.100	0.251, 0.651, 1.324	0.231, 0.650, 1.324
Femoral neck T-score, n (%)			
≤ -2.5	2815(72.65%)	2735(70.84%)	5550(71.74%)

Appears This Way
On Original

Background variables	Zoledronic acid N=3875	Placebo N=3861	Total N=7736
>-2.5 - -1.5	1002(25.86%)	1073(27.79%)	2075(26.82%)
> -1.5	35(0.90%)	38(0.98%)	73(0.94%)
Missing	23(0.59%)	15(0.39%)	38(0.49%)
Prevalent vertebral fracture, n (%)			
0	1455(37.55%)	1380(35.74%)	2835(36.65%)
1	1090(28.13%)	1074(27.82%)	2164(27.97%)
≥ 2	1323(34.14%)	1400(36.26%)	2723(35.20%)
Missing	7(0.18%)	7(0.18%)	14(0.18%)
Alcohol (drinks/day) n (%)			
<1	3622(93.47%)	3606(93.40%)	7228(93.43%)
1-2	237(6.12%)	240(6.22%)	477(6.17%)
≥ 3	16(0.41%)	14(0.36%)	30(0.39%)
Missing	0(0.00%)	1(0.03%)	1(0.01%)
Current smoker - n(%)			
Yes	344(8.88%)	316(8.18%)	660(8.53%)
No	3531(91.12%)	3544(91.79%)	7075(91.46%)
Missing	0(0.00%)	1(0.03%)	1(0.01%)

Source: PT-Table 7-4.3, PT-Table 7.4-3a

7.2.1.3 Extent of exposure (dose/duration)

Per protocol the duration of each infusion was expected to last 15 minutes. The actual mean durations of exposure was very close to that at approximately 17 ± 4min for each treatment group. Approximately 80% of patients in each treatment group received all three infusions (see Table 42).

Table 42

Cumulative exposure of study drug in trial 2301 (safety population)

	Zoledronic acid (N=3862)		Placebo (N=3852)		Total (N=7714)	
Cumulative exposure	n	(%)	n	(%)	n	(%)
1st infusion only	432	(11.19)	319	(8.28)	751	(9.74)
1st and 2nd infusion only	324	(8.35)	343	(8.90)	667	(8.65)
1st and 3rd infusion only	21	(0.54)	16	(0.42)	37	(0.48)
1st, 2nd, and 3rd infusions	3085	(79.88)	3174	(82.40)	6259	(81.14)

Source: PT-Table 8.1-3

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

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), were used to evaluate the relative risk of atrial fibrillation associated with the use of zoledronic acid. See section 7.1.2.1.

7.2.2.2 Postmarketing experience

See section 7.1.17.

7.2.2.3 Literature

Safety data from clinical trials in the literature comparing rates of atrial fibrillation associated with the use of other bisphosphonates were described in section 7.1.2.1.

7.2.3 Adequacy of Overall Clinical Experience

There is adequate clinical experience in the pivotal trial 2301 to confirm the efficacy and safety of zoledronic acid for the treatment of PMO.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Special animal and/or *in vitro* testing had been previously reviewed and found acceptable.

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing was adequate given the prior experience with this drug.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This information had been previously reviewed and found acceptable.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adverse events associated with the use of bisphosphonates have been well characterized with this and previous bisphosphonates. Bisphosphonates are associated with small but increased risks

of: hypocalcemia (especially in patients with Paget's Disease), ocular inflammation and ONJ. Oral bisphosphonates are specifically associated with esophagitis and esophageal erosions.

Adverse events that are specific for zoledronic acid include the acute phase reactions, hypersensitivity and dose related transient renal toxicity.

Serious cases of atrial fibrillation were seen more commonly in the zoledronic acid treatment group in trial 2301, but were not seen in other zoledronic acid studies nor with other bisphosphonates. At this time it is not clear if this represents a drug-related event or was a chance finding. It is recommended that atrial fibrillation continue to be monitored in all future clinical trials with zoledronic acid.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted and reviewed was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The safety update was submitted in the 2-Feb-2007 submission. The pertinent safety information was incorporated in the original safety review in section 7.1. No new safety concerns were identified in the safety update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Acute phase reactions are common drug related events due to zoledronic acid that are usually self limiting and can be partially ameliorated with premedication with acetaminophen or ibuprofen.

Ocular inflammation (e.g. iritis, uveitis, episcleritis, conjunctivitis) is an uncommon event which is likely drug-related typically occurring within a few weeks after the infusion and which responds well to conservative management.

Whereas ONJ is well documented as an adverse event associated with the use of zoledronic acid in the oncology population, it is much less common in the PMO population. There was one case of ONJ documented in the zoledronic acid treatment group in all of the studies submitted in this application. This case was confounded by the fact that the patient refused hospitalization and appropriate antibiotic therapy during the course of the chronic infection.

Renal toxicity, demonstrated by an increase in serum creatinine from baseline to 9-11days post infusion is an uncommon drug-related event occurring in about 1% of the study population relative to placebo. The current data support that there are no long term sequelae from this short term increase in serum creatinine as long as the drug is used only in patients with adequate renal function at baseline (creatinine clearance > 30mL/min, and <2+ urine protein), they are

adequately hydrated during the infusion and the infusion is given at a constant rate over no less than 15 minutes. Data on patients with creatinine clearance < 30mL/min is not available and the drug should not be used in this population because of the potential of more severe renal toxicity.

Serious cases of atrial fibrillation were seen more commonly in the zoledronic acid treatment group in trial 2301. At this time it is not clear if this represents a drug-related event or was a chance finding. It is recommended that atrial fibrillation continue to be monitored in all future clinical trials with zoledronic acid.

7.4 General Methodology

Only one dose of Reclast was used in these trials so no dose dependency for adverse events was available. It was noted however, that patients who received infusions in less than 15 minutes were more likely to develop acute phase reactions, including adverse events of arthralgia, pain in extremity, pyrexia, headache, nasopharyngitis, osteoarthritis, influenza-like illness, nausea, myalgia, chills, fatigue, neck pain, and diarrhea. In addition, acute phase reactions were less common in older patients, > 75 years of age, and were less likely to recur with repeat dosing. Data from study 2407 confirmed that the mean severity of acute phase symptoms could be decreased, but not eliminated by premedication with acetaminophen or ibuprofen. Acetaminophen and ibuprofen were equally effective at reducing the acute phase symptoms.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor proposes a single dosing regimen of 5mg IV to be infused over 15min, once yearly for the treatment of PMO. The same dose is currently approved for the treatment of Paget's disease, under the same trade name Reclast. A 4mg dose of zoledronic acid is also approved for the treatment of hypercalcemia of malignancy, treatment of patients with multiple myeloma or bone metastases from solid tumors, under the trade name Zometa.

8.2 Drug-Drug Interactions

No new drug interaction studies were submitted in this application for the treatment of PMO. Zoledronic acid is excreted in the urine unmetabolized and does not inhibit microsomal CYP450 enzymes *in vitro*, so is unlikely to result in drug-drug interactions.

Reclast should not come in contact with calcium containing solutions.

8.3 Special Populations

No patients with hepatic insufficiency or renal insufficiency (creatinine clearance < 30mL/min) were included in this submission. Adequate safety and efficacy was reported in the pivotal trial for patients < and ≥ 75 years of age. Adequate safety and efficacy was reported in the pivotal trial for patients with baseline creatinine clearance between 30 and 60mL/min and urine dipstick < 2+, therefore there is no need for dose adjustment in this patient population.

8.4 Pediatrics

No clinical studies in pediatric patients were submitted in this application.

8.5 Advisory Committee Meeting

There was no need for an advisory committee meeting to evaluate this NDA submission.

8.6 Literature Review

Relevant literature references were cited throughout the course of this review in footnotes at the bottom of the page.

8.7 Postmarketing Risk Management Plan

No risk management plan was submitted and no specific safety concern for which a risk management plan would be necessary was identified.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

Pivotal trial 2301 supports the efficacy of once yearly dosing of intravenous zoledronic acid (5mg) for the treatment of PMO. The efficacy of this treatment regime, especially in women who can not take the chronic oral bisphosphonate medication, outweighs the treatment-related safety concerns.

9.2 Recommendation on Regulatory Action

An Approval action is recommended.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

The sponsor is requested to continue close monitoring of all ongoing and future trials for the risk of atrial fibrillation and to submit data from individual trials in addition to cumulative data in all future study reports and annual updates.

9.4 Labeling Review

INDICATION AND USAGE SECTION
This section should be limited to indication and should not include any efficacy data.

DOSAGE AND ADMINISTRATION
This section should include information about adequate calcium and vitamin D supplementation and the usefulness of premedication with acetaminophen or ibuprofen to help prevent acute phase reaction symptoms.

CONTRAINDICATIONS
This section should include hypocalcemia and hypersensitivity. There are currently 10 cases in AERs datamart of reports of anaphylaxis following infusions with Zometa. Most cases were in oncology patients, but there were also a few cases of off label use in patients with osteoporosis and ankylosing spondylitis.

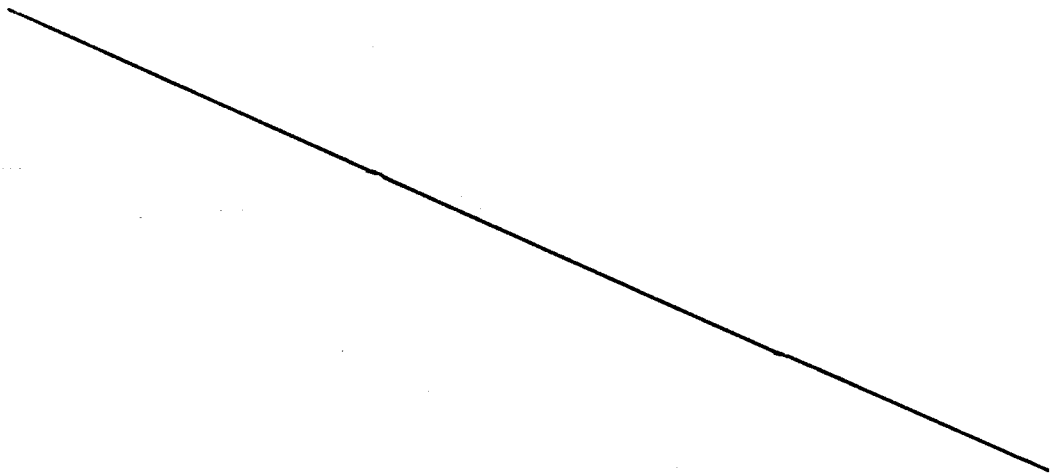
WARNINGS AND PRECAUTIONS
This section should recommend creatinine monitoring before dosing in all patients and should suggest interim monitoring of patients with impaired renal function as needed.

This section should recommend routine oral exams on all patients before dosing and recommend a preventative dental exam on all patients with the following risk factors: cancer, chemotherapy, use of corticosteroids, _____ or poor oral hygiene. This section should also mention that dental surgery in these patients may exacerbate the condition.

ADVERSE REACTIONS
The table of Adverse Reactions should list events occurring ≥2.0% of the study population. With almost 4000 patients in each treatment group there is adequate data to support listing numbers to the tenth decimal place.

The Atrial Fibrillation section should mention that over 90% of events occurred more that one month after the infusion and that an ECG substudy in 559 patients found no evidence for an increase in atrial fibrillation at 9-11days post infusion compared to baseline.

The Ocular Adverse Events section should list the frequency of iritis, uveitis, and episcleritis in the zoledronic acid and placebo treatment groups.



9.5 Comments to Applicant

None

10 APPENDICES

None

11 REFERENCES

ADA Council on Scientific Affairs, Dental management of patients receiving oral bisphosphonate therapy, JADA August 2006, 137, 1144-1150

Aviles 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.

Breen TL, Shane E. J Clin Oncol. 2004 Apr 15;22(8):1531-2

Cummings SR, Schwartz AV, Black DM. Alendronate and Atrial fibrillation N Engl J Med. 2007 May 3; 356(18):1895-6.

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.

Karam R, Camm J, McClung M N Engl J Med. 2007 August 16:357(7):712

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.

Rosen CJ, Brown S. N Engl J Med. 2003 Apr 10;348(15):1503-4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

William Lubas
8/16/2007 11:50:16 AM
MEDICAL OFFICER

Theresa Kehoe
8/16/2007 01:55:59 PM
MEDICAL OFFICER