

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-080

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER MEMO

NDA#: 22-080

Sponsor: Novartis Pharmaceuticals, Inc

Drug: Reclast (zoledronic acid), 5mg

Indication: Treatment of postmenopausal osteoporosis

Date of Submission: October 16, 2006

Primary Medical Reviewer: Bill Lubas, M.D., Ph.D.

I. Introduction and Background

Novartis Pharmaceuticals, Inc. has submitted this new drug application for zoledronic acid (Reclast) 5 mg for infusion, seeking approval for the treatment of osteoporosis in postmenopausal women. The basis for approval is protocol ZOL446H2301 (study 2301), a randomized, double-blind, placebo-controlled, 3-year study of zoledronic acid injection 5mg once yearly in the treatment of postmenopausal osteoporosis (PMO). Supportive data include the Phase II dose-finding Study 0041, a placebo-controlled 12 month trial evaluating the BMD response of five different intermittent doses of zoledronic acid in 351 postmenopausal women; Study ZOL446H2313 (2313), an active-controlled trial evaluating the safety and tolerability of intravenous zoledronate 5 mg once yearly compared to oral alendronate in postmenopausal patients with osteoporosis and at least one year exposure to oral alendronate; and Study ZOL446H2315 (2315), a 24-week active-controlled trial evaluating the rapidity of onset of action, as assessed by suppression of bone turnover markers, of intravenous zoledronic acid compared to alendronate in treatment-naive postmenopausal women with osteoporosis.

Zoledronic acid is currently approved in the United States as Zometa (4 mg for intravenous infusion) for treatment of hypercalcemia of malignancy, treatment of patients with multiple myeloma, and patients with documented bone metastases from solid tumors; and Reclast (5 mg for intravenous infusion) for treatment of Paget's disease of bone.

Zoledronic acid is a bisphosphonate agent for intravenous use whose specificity for bone allows dosing once yearly for the treatment of osteoporosis. Current therapies available for the treatment of osteoporosis in postmenopausal women include the bisphosphonates: alendronate sodium (Fosamax tablet, Fosamax oral solution, Fosamax Plus D tablet), risedronate sodium (Actonel tablet, Actonel with Calcium (copackaged)), and ibandronate sodium (Boniva tablet and Boniva for intravenous injection); the estrogen-agonist /antagonist raloxifene (Evista); the PTH anabolic agent teriparatide (Forteo subcutaneous injection); and salmon calcitonin nasal sprays (Miacalcin, Fortical).

Other currently approved and marketed bisphosphonate agents not indicated for the treatment of osteoporosis include etidronate (Didronel and generics - oral dosage form, intravenous product discontinued), pamidronate (Aredia and generics - intravenous administration), and tiludronate (Skelid, oral administration).

Important safety signals associated with bisphosphonates include gastrointestinal adverse events, predominantly associated with orally administered bisphosphonates; acute phase reaction;

hypocalcemia; inflammatory eye events; risk of renal insufficiency, primarily associated with intravenous bisphosphonates; osteonecrosis of the jaw; and musculoskeletal pain.

II. Clinical Efficacy

The sponsor has submitted one pivotal fracture study, Study ZOL446H2301 (2301) to support approval of zoledronic acid for the treatment of osteoporosis in postmenopausal women.

II.a Study ZOL446H2301: This is a multicenter, double-blind, randomized, placebo-controlled, study to assess safety and efficacy of zoledronic acid injection 5mg once yearly in the treatment of postmenopausal osteoporosis (PMO). The co-primary endpoints of the study were the proportion of subjects with at least one new vertebral fracture and the time to first hip fracture.

Study population: Subjects enrolled in the study were age 65 to 89 years, with diagnosed osteoporosis. Osteoporosis was defined as a femoral neck bone mineral density T-score below -2.5 or a femoral neck BMD T-score below -1.5 with radiologic evidence of prevalent vertebral fractures. Women with a history of metabolic bone disease, hypercalcemia, active parathyroid disease, hypocalcemia, renal insufficiency, diabetic nephropathy or retinopathy, or uncontrolled seizure disorder were excluded from the study. Subjects were stratified based on concomitant osteoporosis therapy use at or prior to randomization. The allowable concomitant therapies included hormone replacement therapy, raloxifene, calcitonin, tibolone, tamoxifen, ipriflavone, dehydroepiandrosterone(s) and medroxyprogesterone. Stratum I consisted of subjects who were on no concomitant osteoporosis therapy at enrollment. Patients in Stratum II started on a concomitant therapy; were continued on their osteoporosis therapy; or did not meet the wash-out time criteria for their prior osteoporosis therapy. Subjects previously on bisphosphonate therapy could be enrolled in the study only after a wash-out period. They could not be enrolled in the study without meeting the wash-out time criteria. For subjects on other osteoporosis therapies, they could be enrolled in Stratum I if they fulfilled the wash-out criteria and did not continue on the other therapy. If they wanted to continue on the other osteoporosis therapy concomitant with study drug, or they did not meet the wash-out criteria, they could be enrolled in Stratum II.

Study treatments: Eligible subjects were randomized 1:1 to receive zoledronic acid 5 mg infusion over 15 minutes once yearly or placebo infusion over 15 minutes once yearly. All subjects were to receive daily calcium (1000 - 1500 mg) and vitamin D (400 - 1200 IU) supplementation. The calcium and vitamin D supplements were not provided by the Company, they were procured by the investigator or patient.

Efficacy measures: This study had two co-primary and twenty secondary endpoints. The co-primary endpoints were the proportion of subjects with at least one new vertebral fracture and the time to first hip fracture. A closed testing procedure was performed to maintain the overall significance level at 5%. The proportion of patients with new morphometric vertebral fractures at Month 36 from Stratum I was analyzed first at a 4.96% level of significance. If a statistically significant result was obtained, a confirmatory analysis of time to first hip fracture was to be performed at the 4.06% level. For all secondary endpoints, a closed testing procedure was also implemented and endpoints were evaluated at a 0.0500 level of significance.

Lateral spine x-rays were performed at baseline and Months 12, 24 and 36 for patients in Stratum I, and at baseline and Month 36 for patients in Stratum II. All lateral spine x-rays were assessed by a quantitative morphometry (QM) reading. If the QM reading indicated a fracture (vertebral height reduction ≥ 4 mm and 20%), the assessment was confirmed by a semi-quantitative reading. For hip and other clinical fractures, patients were queried at their quarterly telephone follow-up.

If the patient reported a fracture, a copy of the x-ray, the x-ray report or the surgical procedure notes were required. Only confirmed fractures were included in the analyses.

Bone density measurements at the hip, determined by dual x-ray absorptiometry (DXA), were obtained on all patients at baseline, and Months 6, 12, 24, and 36. Bone density measurements at the spine and distal radius were obtained on a subset of patients at baseline and Months 6, 12, 24, and 36. DXA were evaluated by a central reading facility. Laboratory measurements of bone turnover markers included serum bone specific alkaline phosphatase - BSAP (bone formation) and serum c-telopeptides - CTx (bone resorption) were obtained on a subset of subjects at baseline and Months 6, 12, 24, and 36. In addition, the bone formation marker PINP was evaluated in a subset of patients at baseline and Months 12, 24, and 36.

Results:

Disposition: A total of 7736 subjects were enrolled into the study, 6084 (3045 zoledronic acid, 3039 placebo) in Stratum I and 1652 (3045 zoledronic acid, 3039 placebo) in Stratum II. As outlined in the table below, 84% of the enrolled population completed the study. Of the 1219 (16%) subjects who withdrew from the study, the most common reason for withdrawal was the withdrawal of consent by 581 (8%) subjects. Adverse events leading to withdrawal occurred in 392 (5%) subjects (210 in the zoledronic acid group and 182 in the placebo group). There was comparable subject disposition between the strata and treatment groups.

Study 2301: Patient Disposition						
	Stratum I		Stratum II		All	
	zole	plac	zole	plac	zole	plac
N, enrolled	3045	3039	830	822	3875	3861
Discontinued	500 (16)	451 (15)	127 (15)	141 (75)	627(16)	592 (15)
Death	108 (3.6)	90 (3.0)	22 (2.6)	22 (2.7)	130 (3.4)	112 (2.9)
Adverse Event	66 (2.2)	56 (1.8)	14 (1.7)	14 (1.7)	80 (2.1)	70 (1.8)
Abnormal lab or test	1 (<0.1)	5 (0.2)	5 (0.6)	1 (0.1)	6 (0.2)	6 (0.2)
Unsatisfac. response	2 (0.1)	4 (0.1)	0 (0.0)	3 (0.4)	2 (<0.1)	7 (0.2)
Lost to follow-up	57 (1.9)	51 (1.7)	25 (3.0)	24 (2.9)	82 (2.1)	75 (1.9)
Withdrew consent	251 (8.2)	222 (7.3)	46 (5.5)	62 (7.5)	297 (7.7)	284 (7.4)
Protocol violation	6 (0.2)	11 (0.4)	5 (0.6)	4 (0.5)	11 (0.3)	15 (0.4)
Administrative	9 (0.3)	11 (0.4)	10 (1.2)	11 (1.3)	19 (0.5)	22 (0.6)
Other	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
N, completed	2545 (84)	2588 (85)	703 (85)	681 (83)	3248 (84)	3269 (85)
N, ITT					3875 (100)	3861 (100)
N, mITT	2822 (73)	2853 (74)				
N, safety					3862	3852

Demographics: As outlined in the table below, baseline subject demographics were generally well balanced across the strata and treatment groups. The average age of enrollees was approximately 73 years. Overall 63% of the enrolled population had at least one prevalent fracture at baseline and 72% of the population had osteoporosis as diagnosed by femoral neck BMD less than -2.5. Approximately 14% of enrolled subjects had previously used bisphosphonates.

Study 2301: Patient Demographics						
	Stratum I		Stratum II		All	
	zole	plac	zole	plac	zole	Plac
N	3045	3039	830	822	3875	3861
Age (yrs, mean ± SD)	73 ± 5.3	73 ± 5.4	73 ± 5.5	72 ± 5.3	73 ± 5.3	73 ± 5.45
Age range	64 – 89	64 – 89	64 – 89	64 – 89	64 – 89	64 – 89
Race, n (%)						
White	2336 (77)	2337 (77)	718 (86)	718 (87)	3054 (79)	3055 (79)
Asian	496 (16)	497 (16)	66 (8)	62 (8)	562 (14)	559 (14)
Black	13 (0.4)	13 (0.4)	2 (0.2)	4 (0.5)	15 (0.4)	17 (0.4)
Hispanic	185 (6)	179 (6)	41 (5)	36 (4)	226 (61)	215 (6)
Other	15 (0.5)	13 (0.4)	3 (1)	2 (1)	18 (0.5)	15 (0.4)
Height (cm, mean)	153 ± 7.1	154 ± 7.1	154 ± 7.7	154 ± 7.3	153 ± 7.2	154 ± 7.1
Weight (kg, mean)	60 ± 11.1	60 ± 11.4	60 ± 11.2	61 ± 11.0	60 ± 11.1	61 ± 11.3
BMI (mean)	25 ± 4.3	25 ± 4.3	25 ± 4.5	25 ± 4.3	25 ± 4.3	25 ± 4.3
Prevalent Fx						
0	1140 (37)	1103 (36)	317 (38)	280 (34)	1457 (38)	1383 (36)
1	872 (29)	868 (29)	221 (27)	208 (25)	1093 (28)	1076 (28)
≥ 2	1031 (34)	1068 (35)	292 (35)	333 (40)	1323 (34)	1401 (36)
Missing	2 (0.1)	0 (0)	0 (0)	1 (0.1)	2 (<0.1)	1 (<0.1)
FN BMD (gm/cm ²)	0.532	0.531	0.535	0.544	0.533	0.534
FN BMD T score*						
> -1.5, n (%)	28 (1)	28 (1)	7 (0.8)	10 (1)	35 (0.9)	38 (1)
-1.5 to -2.5, n (%)	795 (26)	814 (27)	207 (25)	259 (32)	1002 (26)	1073 (28)
< -2.5, n (%)	2201 (73)	2185 (72)	613 (74)	549 (68)	2814 (73)	2734 (71)
Missing, n (%)	21 (0.7)	12 (0.4)	0 (0.4)	4 (0.5)	24 (0.6)	16 (0.4)

*WHO definitions: normal = T score > -1.0; osteopenia = T score -1.5 to -2.5; osteoporosis T score < -2.5

Concomitant medications: Patients in Stratum II were allowed to continue or begin other osteoporosis therapies except bisphosphonate or anabolic agents, which were not allowed. As outlined in the table below, approximately 82% of subjects in Stratum II were taking other osteoporosis therapies during the trial. Estrogen and estrogen agonist/antagonists were the predominant therapies used. Although other bisphosphonate therapies were not allowed, 38 subjects in the zoledronic acid group and 61 subjects in the placebo group in Stratum II received other bisphosphonate therapy during the trial. Concomitant osteoporosis therapy was not allowed in Stratum I. However, 596 subjects in Stratum I did receive other osteoporosis therapy during the trial. There was disparity between the treatment groups with 248 (8%) subjects in the zoledronic acid group and 348 (12%) subjects in the placebo group receiving other therapies. The largest differences were seen in the therapies currently approved for treatment of osteoporosis: raloxifene, calcitonin, alendronate and risedronate. In both strata combined, 64 subjects in the zoledronic acid group and 146 subjects in the placebo group received other bisphosphonate therapy during the trial. Initiation of treatment in the placebo group should diminish any treatment difference between zoledronic acid and placebo. In other words, this imbalance in concomitant osteoporosis therapies is not expected to bias the results in favor of zoledronic acid.

Study 2301: Concomitant Osteoporosis Therapies				
	Stratum I		Stratum II	
	zole	plac	zole	plac
N	3045	3039	830	822
Number using concomitant osteoporosis therapies; n (%)	248 (8)*	348 (12)	672 (81)	672 (82)
Estrogen	90	80	231	205

Study 2301: Concomitant Osteoporosis Therapies				
	Stratum I		Stratum II	
	zole	plac	zole	plac
Raloxifene	49	82	369	374
Tamoxifen	10	6	9	13
Medroxyprogesterone	2	3	28	28
Tibolone	2	3	4	8
Calcitonin	59	83	39	34
Alendronate	38	92	19	31
Risedronate	21	48	11	26
Clodronate	3	2	0	0
Etidronate	0	1	1	2
Ibandronate	0	1	3	1
Pamidronate	1	7	2	1
Zoledronic acid	1	1	2	3
Strontium ranelate	1	2	0	0

Morphometric Vertebral Fracture: The proportion of subjects in Stratum I with at least one new vertebral fracture over the three years of the trial was one of the co-primary endpoints of the study. The modified ITT population was used to analyze this co-primary endpoint. As outlined in the table below, 92/2822 (3.3%) subjects in the zoledronic acid group and 310/2853 (10.9%) subjects in the placebo group sustained at least one new morphometric vertebral fracture during the three years of the trial. The absolute risk reduction is 7.6% with a relative risk reduction of 70% ($p < 0.0001$). The proportion of patients in Stratum I with at least one new vertebral fracture over 1 and 2 years were secondary endpoints. Subgroup analyses including age, geographic location, BMI, race, baseline T-score, prevalent fracture, baseline creatinine clearance and prior bisphosphonate use revealed similar results.

The proportion of subjects with at least one new vertebral fracture in Stratum II was not included in the primary analysis. In Stratum II, spinal x-rays were evaluated only at Year 3. Overall, 27/689 (3.9%) subjects in the zoledronic acid group and 59/669 (8.8%) subjects in the placebo group sustained a morphometric vertebral fracture during the trial. The absolute risk reduction is 4.9% with a relative risk reduction of 56% ($p = 0.0006$).

Study 2301: Subjects with At Least One New Morphometric Vertebral Fracture, MITT				
	Stratum I		Stratum II	
	zole	plac	zole	plac
N	3045	3039	830	822
N, MITT	2822	2853	689	669
n (%), fracture through Year 3	92 (3.3)	310 (10.9)	27 (3.9)	59 (8.8)
RR (95% CI)	0.30 (0.24, 0.38)		0.44	
p-value	<0.0001		0.0006	
n (%), fracture through Year 2	63 (2.2)	220 (7.72)	-----	-----
RR (95% CI)	0.29 (0.22, 0.38)		-----	
p-value	<0.0001		-----	
n (%), fracture through Year 1	42 (1.5)	106 (3.7)	-----	-----
RR (95% CI)	0.40 (0.28, 0.57)		-----	
p-value	<0.0001		-----	

Hip Fracture: The time to first hip fracture was the second co-primary endpoint of the trial. The analysis of hip fracture included Stratum I and Stratum II. Over the three-year treatment period,

140 subjects (52 in the zoledronic acid group and 88 in the placebo group) sustained a hip fracture. Based on Kaplan-Meier estimates, the three-year event rates for hip fracture were 1.4% for the zoledronic acid group and 2.5% for the placebo group, with a hazard ratio of 0.59 (95% CI 0.42 to 0.83, p=0.0024).

Clinical fracture: The time to the first clinical fracture, clinical vertebral fracture, and non-vertebral clinical fracture were all secondary endpoints. Clinical fractures were divided into clinical vertebral fracture and non vertebral fracture. Nonvertebral fractures included all fractures except finger, toe and facial bones. As outlined in the table below, treatment with zoledronic acid resulted in a significantly lower incidence of all clinical fractures.

Study 2301: Clinical Fractures at 3 Years, All Subjects (ITT)		
	zole	plac
N, ITT	3875	3861
Any clinical fracture	308 (8.4)	456 (12.3)
Hazard ratio (95% CI)	0.67 (0.58, 0.77)	
p-value	<0.001	
Clinical vertebral fracture	19 (0.5)	84 (2.6)
Hazard ratio (95% CI)	0.23 (0.14, 0.37)	
p-value	<0.001	
Non-vertebral fracture	292 (8.0)	388 (10.7)
Hazard ratio (95% CI)	0.75 (0.64, 0.87)	
p-value	<0.001	

Bone Mineral Density: Bone mineral density of the lumbar spine, hip and distal radius was evaluated at Months 6, 12, 24 and 36. Hip BMD was evaluated in the entire treatment population while lumbar spine and distal radius BMD were evaluated in a small subset. As outlined in the table below, significant increases in BMD at the lumbar spine, total hip, femoral neck and distal radius were observed with zoledronic acid treatment compared to placebo at Years 1, 2 and 3.

Study 2301: Percent Change in BMD, ITT				
	Zole	Plac	LS Mean Difference	p value
Lumbar Spine				
N, ITT	223	212		
Month 6	2.93	0.54	2.39 (1.81, 2.96)	<0.0001
Month 12	3.88	0.22	3.66 (2.99, 4.33)	<0.0001
Month 24	5.76	-0.14	5.90 (5.09, 6.71)	<0.0001
Month 36	6.95	0.24	6.71 (5.69, 7.74)	<0.0001
Total Hip				
N, ITT	3061	3077		
Month 6	2.18	0.25	1.93 (1.76, 2.09)	<0.0001
Month 12	2.83	-0.00	2.83 (2.65, 3.01)	<0.0001
Month 24	3.72	-0.98	4.70 (4.48, 4.92)	<0.0001
Month 36	4.15	-1.87	6.02 (5.77, 6.28)	<0.0001
Femoral Neck				
N, ITT	3067	3083		
Month 6	2.17	0.60	1.58 (1.36, 1.80)	<0.0001
Month 12	2.70	0.53	2.17 (1.94, 2.41)	<0.0001
Month 24	3.38	-0.50	3.89 (3.62, 4.16)	<0.0001
Month 36	3.92	-1.13	5.06 (4.76, 5.36)	<0.0001
Distal Radius				

Study 2301: Percent Change in BMD, ITT				
	Zole	Plac	LS Mean Difference	p value
N, ITT	215	193		
Month 6	0.77	0.43	0.34 (-0.21, 0.90)	0.2263
Month 12	0.78	-0.69	-1.47 (0.81, 2.13)	<0.0001
Month 24	0.65	-1.18	1.82 (1.14, 2.50)	<0.0001
Month 36	1.04	-2.17	3.21 (2.42, 4.00)	<0.0001

Biochemical Markers of Bone Turnover: Secondary endpoints in study 2301 included the relative change from baseline in the biochemical markers of bone resorption [serum C-telopeptide (CTx)] and bone formation [serum bone specific alkaline phosphatase (BSAP)] at each scheduled pre- and post- infusion visit. Levels were analyzed at baseline, 6 months post-infusion and pre-dose in a subset of 605 subjects. The bone formation marker, serum PINP, was also evaluated at baseline and Months 12, 24 and 36 in a larger subset of 1246 subjects. As outlined in the figures below, serum CTx levels decreased in patients receiving zoledronic acid. Levels remained stable and although there was a slight trend toward increasing activity prior to the next dose, levels remained well below placebo-treated levels. Levels for PINP followed a similar pattern. At Month 36, the relative treatment effect of zoledronic acid compared to placebo was 0.45 (95% CI 0.40, 0.51, p<0.0001) for b-CTX; 0.71 (95% CI: 0.66, 0.76, p<0.0001) for BSAP and 0.48 (95% CI: 0.45, 0.51, p<0.0001) for PINP.

Fig 1: Study 2301, Mean serum CTx

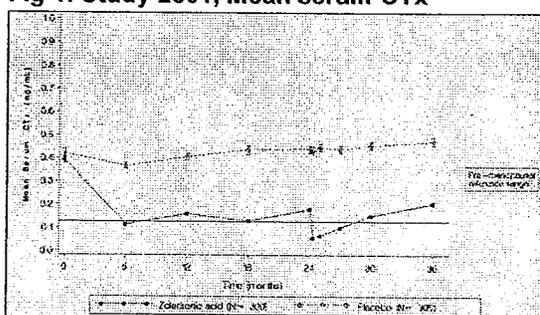
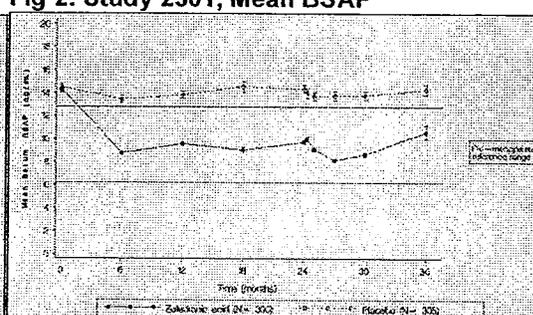


Fig 2: Study 2301, Mean BSAP



II.c. Efficacy Conclusions:

Treatment with zoledronic acid 5 mg once yearly is efficacious in reducing the occurrence of new morphometric vertebral fractures with an absolute risk reduction of 7.6% and a relative risk reduction of 70% (p<0.0001). Treatment with zoledronic acid 5 mg once yearly is efficacious in reducing hip fractures. Based on Kaplan-Meier estimates, the three-year event rates for hip fracture were 1.4% for the zoledronic acid group and 2.5% for the placebo group, with a hazard ratio of 0.59 (95% CI 0.42 to 0.83, p=0.0024). In addition to these two co-primary endpoints, zoledronic acid 5 mg once yearly is efficacious for all twenty secondary endpoints including reduction in the incidence of new or worsening vertebral fractures; reduction in the incidence of clinical vertebral fractures; reduction in the incidence of all clinical osteoporotic fractures; increasing total hip, femoral neck, and lumbar spine bone mineral density; and reduction in the markers of bone turnover.

III. Clinical Safety

III.a. Study ZOL446H2301: This is a multicenter, double-blind, randomized, placebo-controlled, study of zoledronic acid injection 5mg once yearly in the treatment of postmenopausal osteoporosis (PMO).

Safety Events and exposure: As noted in the table below, there were comparable adverse event rates between the zoledronic acid and placebo treatment groups.

Study 2301: Patient Disposition						
	Stratum I		Stratum II		All	
	zole	plac	zole	plac	zole	plac
N, enrolled	3045	3039	830	822	3875	3861
N, safety	3035	3031	827	821	3862	3852
Discontinued	500 (16.5)	451 (14.9)	127 (15.4)	141 (17.2)	627 (16.2)	592 (15.4)
N, completed	2545 (83.9)	2588 (85.4)	703 (85.0)	681 (82.9)	3248 (84.1)	3269 (84.9)
Death	108 (3.6)	90 (3.0)	22 (2.6)	22 (2.7)	130 (3.4)	112 (2.9)
Serious Adverse Event	865 (28.5)	873 (28.8)	264 (31.9)	288 (35.1)	1129 (29.2)	1161 (30.1)
Withdrawal due to AE	66 (2.2)	56 (1.8)	14 (1.7)	14 (1.7)	80 (2.1)	70 (1.8)
Study Drug Permanently Discontinued due to AE	171 (5.6)	151 (5.0)	38 (4.6)	36 (4.4)	209 (5.4)	187 (4.8)
Adverse Event	2897 (95.4)	2837 (93.6)	791 (95.6)	779 (94.9)	3688 (95.5)	3616 (93.9)

All patients were to receive intravenous zoledronic acid or placebo once yearly for three doses. In addition, all patients were to take daily calcium and vitamin D supplements. As outlined in the table below, 3086 (80%) of zoledronic acid-treated patients and 3174 (82%) placebo-treated subjects received all doses of study drug. Compliance with vitamin D and calcium supplementation was not recorded.

Study 2301: Compliance and Exposure						
	Stratum I		Stratum II		All	
	zole	plac	zole	plac	zole	plac
N, enrolled	3045	3039	830	822	3875	3861
N, no study drug administered	10 (0.3)	8 (0.3)	3 (0.4)	1 (0.1)	13 (0.3)	9 (0.2)
N, one dose received	324 (10.6)	253 (8.3)	108 (13.0)	66 (8.0)	432 (11.1)	319 (8.3)
N, two doses received	280 (9.2)	271 (8.9)	64 (7.7)	88 (10.7)	344 (8.9)	359 (9.3)
N, all doses received	2431 (79.8)	2507 (82.5)	655 (78.9)	667 (81.1)	3086 (79.6)	3174 (82.2)

Deaths: Through the three years of the trial, 242 subjects (130 (3%) in the zoledronic acid group and 112 (3%) in the placebo group) died. As outlined in the table below, the most common System/Organ/Class (SOC) were cardiac disorders, neoplasms and nervous system disorders. Of

these, the following occurred with at least a twofold higher incidence in the zoledronic acid group versus the placebo group: cerebrovascular accident (13 (0.3%) in the zoledronic acid group and 5 (0.1%) in the placebo group), cardio-respiratory arrest (9 (0.2%) in the zoledronic acid group and 2 (0.05%) in the placebo group), acute myocardial infarction (7 (0.2%) in the zoledronic acid group and 1 (0.03%) in the placebo group), and pneumonia (4 (0.1%) in the zoledronic acid group and 1 (0.03%) in the placebo group). Although there appears to be an imbalance in death due to acute myocardial infarction, all myocardial infarction events (preferred terms acute myocardial infarction and myocardial infarction) leading to death occurred in 14 (0.36%) patients in the zoledronic acid group and 9 (0.23%) patients in the placebo group. These findings would suggest that there is not an imbalance in the death rate due to myocardial infarction. This is further supported by the lack of a difference in the occurrence of myocardial infarction serious adverse events which were reported in 36 (0.93%) patients in the zoledronic acid group and 37 (0.96%) patients in the placebo group.

Study 2301 : Deaths		
	All Subjects	
	zole	plac
N, safety	3862	3852
All deaths	130 (3.4)	112 (2.9)
Cardiac disorders	39 (1.0)	33 (0.9)
cardiorespiratory arrest	9 (0.2)	2 (0.05)
acute myocardial infarction	7 (0.2)	1 (0.03)
myocardial infarction	7 (0.2)	8 (0.2)
Gastrointestinal disorders	4 (0.1)	4 (0.1)
General disorders	11 (0.3)	11 (0.3)
Hepatobiliary disorders	0 (0.0)	1 (0.03)
Infections and infestations	14 (0.4)	11 (0.3)
pneumonia	4 (0.1)	1 (0.03)
Injury, poisoning, procedural compl	1 (0.03)	3 (0.1)
Metabolism and nutrition	1 (0.03)	1 (0.03)
Musculoskeletal and connective tissue	1 (0.03)	0 (0.0)
Neoplasms	23 (0.6)	23 (0.6)
Nervous system disorders	22 (0.6)	12 (0.3)
cerebrovascular accident	13 (0.3)	5 (0.1)
Psychiatric disorders	1 (0.03)	0 (0.0)
Renal and urinary disorders	2 (0.05)	0 (0.0)
Respiratory, thoracic, mediastinal	10 (0.3)	10 (0.3)
Vascular disorders	1 (0.03)	3 (0.1)

Serious adverse events: A total of 2284 subjects experienced at least one SAE during this three-year trial: 1126 (29%) in the zoledronic acid group and 1158 (30%) in the placebo group. As outlined in the table below, the most common adverse events were pneumonia, atrial fibrillation, osteoarthritis, cerebrovascular accident and myocardial infarction. The only SAE with a notable imbalance between the treatment groups was atrial fibrillation, occurring in 50 (1.3%) subjects in the zoledronic acid group and 20 (0.5%) subjects in the placebo group. This finding is discussed in depth below. Other events with at least a twofold higher incidence in the zoledronic acid group compared to the placebo group include basal cell carcinoma (30 (0.8%) in the zoledronic acid group and 14 (0.4%) in the placebo group), and anemia (23 (0.6%) in the zoledronic acid group and 11 (0.3%) in the placebo group).

Study 2301 : Serious Adverse Events		
	All Subjects	
	zole	plac
N, safety	3862	3852
All SAEs	1126 (29.2)	1158 (30.1)
Blood and lymphatic disorders	34 (0.9)	23 (0.6)
Cardiac disorders	228 (5.9)	192 (5.0)
atrial fibrillation	50 (1.3)	20 (0.5)
myocardial infarction	36 (0.9)	37 (1.0)
Congenital, familial and genetic	7 (0.2)	4 (0.1)
Ear and labyrinth disorders	21 (0.5)	18 (0.5)
Endocrine disorders	9 (0.2)	10 (0.3)
Eye disorders	44 (1.1)	43 (1.1)
Gastrointestinal disorders	159 (4.1)	150 (3.9)
General disorders	75 (1.9)	70 (1.8)
Hepatobiliary disorders	34 (0.9)	45 (1.2)
Immune system disorders	5 (0.1)	2 (0.05)
Infections and infestations	191 (5.0)	180 (4.7)
pneumonia	51 (1.3)	55 (1.4)
Injury, poisoning, procedural compl*	186 (4.8)	297 (7.7)
Investigations	16 (0.4)	14 (0.4)
Metabolism and nutrition	44 (1.1)	32 (0.8)
Musculoskeletal and connective tissue	148 (3.8)	156 (4.0)
osteoarthritis	47 (1.2)	50 (1.3)
Neoplasms	185 (4.8)	167 (4.3)
Nervous system disorders	162 (4.2)	175 (4.5)
cerebrovascular accident	39 (1.0)	34 (0.9)
Pregnancy, puerperium, prenatal	1 (0.03)	0 (0.0)
Psychiatric disorders	25 (0.6)	23 (0.6)
Renal and urinary disorders	43 (1.1)	36 (0.9)
Reproductive and breast disorders	26 (0.7)	24 (0.6)
Respiratory, thoracic, mediastinal	94 (2.4)	95 (2.5)
Skin and subcutaneous disorders	8 (0.2)	12 (0.3)
Social circumstances	1 (0.03)	0 (0.0)
Surgical and medical procedures	6 (0.2)	8 (0.2)
Vascular disorders	67 (1.7)	66 (1.7)
*including fracture		

Comment: It is highly unusual to see an adverse event listed under SOC "pregnancy, puerperium, perinatal conditions" in a trial where the enrolled population is postmenopausal women. The Sponsor has clarified that there were no pregnancies during this trial and this event of "perineal hematoma" is incorrectly classified.

Adverse events leading to withdrawal from study: A total of 150 subjects (80 (2.1%) from the zoledronic acid group and 70 (1.8%) from the placebo group) withdrew from the study because of adverse events.

Adverse events leading to study drug discontinuation: Overall, 396 subjects (209 (5.4%) from the zoledronic acid group and 187 (4.8%) from the placebo group) discontinued study drug due to adverse events.

Adverse events: Overall, 7304 subjects (3688 (96%) from the zoledronic acid group and 3616 (94%) from the placebo group) reported at least one adverse event. The most common (> 10% incidence) adverse events were back pain, arthralgia, pyrexia, hypertension, headache, urinary tract infection, myalgia, pain in extremity and nasopharyngitis. Adverse events occurring at least 2% 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%). Many of these adverse events can most likely be attributed to the acute phase reaction-like syndrome associated with intravenous bisphosphonate use.

Adverse events of special interest

Hypocalcemia: Bisphosphonate use, most notably intravenous bisphosphonates, has been associated with hypocalcemia. Studies in Paget's disease of bone evidenced a concerning signal of hypocalcemia following zoledronic acid treatment in patients with Paget's disease. Currently, the Reclast label recommends that all patients with Paget's disease receive 1500 mg calcium and 800 IU vitamin D daily in divided doses, particularly in the 2 weeks following treatment. The enrolled population for study 2301 is postmenopausal women with osteoporosis. This is considered a population at lower risk of hypocalcemia because of the lower rates of bone turnover compared to active Paget's disease. In study 2301, subjects with a baseline calcium level < 8.0 mg/dL or > 11.0 mg/dL were excluded from study entry. There were no specific inclusion or exclusion criteria related to vitamin D levels. Study participants were to take 1000 – 1500 mg calcium and 400 – 1200 IU vitamin D daily. The baseline mean serum calcium level was 9.6 mg/dL.

Overall, there were 11 (0.3%) subjects in the zoledronic acid group and 5 (0.1%) subjects in the placebo group who had an adverse event of hypocalcemia (defined as calcium < 7.5 mg/dL). There were no hypocalcemia serious adverse events reported and no subjects discontinued from the study due to a hypocalcemia.

Calcium levels at the presumed nadir of 9-11 days post injection were evaluated in the renal safety substudy of study 2301. Following the first study drug dose, the incidence of serum calcium levels less than 8.3 mg/dL (lower limit of the reference range) was 49/2114 (2.3%) of subjects in the zoledronic acid group and 1/2491 (<0.1%) of subjects in the placebo group.

In the entire study cohort, 9 (0.2%) subjects in the zoledronic acid group and 5 (0.1%) subjects in the placebo group had markedly abnormal low calcium levels (below 7.5 mg/dL) and 8 (0.2%) subjects in the zoledronic acid group and 8 (0.2%) subjects in the placebo group had markedly abnormal high calcium levels (above 11.6 mg/dL). In the zoledronic acid group, the mean calcium level was 9.57 mg/dL at baseline; 9.60 mg/dL at Month 12; 9.64 mg/dL at Month 24; and 9.76 mg/dL at Month 36. In the placebo group, the mean calcium level was 9.57 mg/dL at baseline; 9.66 mg/dL at Month 12; 9.68 mg/dL at Month 24; and 9.79 mg/dL at Month 36. At the end of the study, 5 (0.2%) patients in the zoledronic acid group and no patients in the placebo group shifted from normal to low calcium levels while 32 (1.1%) patients in the zoledronic acid group and 88 (2.9%) subjects in the placebo group shifted from normal to high calcium levels.

The Sponsor proposes to include language in the Contraindications section of the product label regarding patients with preexisting risk factor for hypocalcemia and in the Precautions section of the product label regarding mineral metabolism.

Atrial fibrillation: In study 2301, cardiac arrhythmias were reported as serious adverse events in 109 (2.8%) of subjects in the zoledronic acid group and 77 (2.0%) of subjects in the placebo group. Atrial fibrillation accounted for the imbalance and was reported at a much higher rate in subjects treated with zoledronic acid: 50 (1.3%) of subjects in the zoledronic acid group and 20 (0.5%) of subjects in the placebo group. There was no difference in other arrhythmias between groups. In order to further evaluate these findings, the Sponsor convened an expert adjudication panel. The panel evaluated cardiovascular events through to March 31, 2006. The expert adjudication panel confirmed the atrial fibrillation events for all but one placebo-treated subject: 48 (1.2%) of subjects in the zoledronic acid group and 16 (0.4%) of subjects in the placebo group.

The overall incidence of atrial fibrillation events at study completion was 94 (2.4%) in the zoledronic acid group and 73 (1.9%) in the placebo group. The event rates were similar for each year of the trial. In the ECG substudy, the incidence of atrial fibrillation was 2.2% in the zoledronic acid group and 2.8% in the placebo group.

The timing of the events in relation to dose administration was investigated. The majority of the atrial fibrillation SAEs occurred more than 30 days after dosing. This would suggest that the occurrence of atrial fibrillation is not an acute event related to infusion of study drug.

Risk factors associated with the occurrence of atrial fibrillation are well recognized and include male sex, age, diabetes, hypertension, congestive heart failure, valvular heart disease, and history of myocardial infarction. Of the subjects with confirmed atrial fibrillation, 35 (73%) of zoledronic acid treated subjects and 14 (88%) placebo-treated subjects had underlying medical conditions that could contribute the event. Risk factors associated with the occurrence of atrial fibrillation were evaluated using a logistic regression model. Based on an analysis provided by the Sponsor and outlined in the table below, age and active tachyarrhythmia at randomization were the risk factors that characterized patients at greatest risk of an atrial fibrillation event. While treatment did have an odds ratio of 1.3, it was not statistically significant.

Study 2301: Risk factors Associated with Atrial fibrillation			
Factor	Estimate (SE)	Adjusted OR	p-value
Treatment	0.2594 (0.1598)	1.296	0.1044
Stratum	-0.1884 (0.1843)	0.828	0.3068
Age	0.0572 (0.0142)	1.059	<0.0001
Active tachyarrhythmia at randomization	1.3214 (0.2060)	3.749	<0.0001
Active cardiomyopathy at randomization	0.7730 (0.3188)	2.166	0.0153

As outlined in Dr. Lubas's review, the occurrence of risk factors for atrial fibrillation was evaluated specifically for the atrial fibrillation serious adverse event group. There was a subtle and consistent pattern of 10 to 20% greater occurrence of atrial fibrillation/flutter, congestive heart failure, diabetes and valvular heart disease in the zoledronic acid group. While the increased number of patients considered at risk is not large, it does approximate the number of patients who presented with serious atrial fibrillation. However, it is concerning that of the patients who developed serious atrial fibrillation, 9 (18%) in the zoledronic acid group compared to none in the placebo group had no preexisting risk factor for atrial fibrillation.

At the time of publication of the results of study 2301 in the New England Journal of Medicine, principal investigators for the alendronate Fracture Intervention Trial (FIT) published a letter to the editor reporting a similar pattern of atrial fibrillation coded as serious adverse events in one

study cohort.¹ In the combined cohort of the 4-year FIT (3236 subjects in the alendronate group and 3223 subjects in the placebo group, mean age 69 years), atrial fibrillation serious adverse events were reported in 47 (1.5%) subjects in the alendronate group and 31 (1.0%) subjects in the placebo group. Any atrial fibrillation (serious and nonserious cases) event was reported in 81 (2.5%) subjects in the alendronate group and 71 (2.2%) subjects in the placebo group. For further investigation, the data from the pivotal 3-year fracture trials of other bisphosphonate agents was reviewed. In the risedronate hip fracture study (3093 subjects in the risedronate 2.5 mg daily group, 3104 subjects in the risedronate 5 mg daily group, 3134 subjects in the placebo group, mean age 78 years) atrial fibrillation serious adverse events were reported in 21 (0.7%) subjects in the risedronate 2.5 mg daily group, 22 (0.7%) subjects in the risedronate 5.0 mg daily group and 18 (0.6%) subjects in the placebo group. Any atrial fibrillation event was reported in 58 (1.9%) subjects in the risedronate 2.5 mg daily group, 49 (1.6%) subjects in the risedronate 5.0 mg daily group and 51 (1.6%) subjects in the placebo group. In the 3-year oral ibandronate fracture study (977 subjects in the ibandronate 2.5 mg daily group, 977 subjects in the ibandronate 20 mg intermittent dosing group, 975 subjects in the placebo group, mean age 69 years) atrial fibrillation serious adverse events were reported in 10 (1.0%) subjects in the ibandronate 2.5 mg daily group, 6 (0.5%) subjects in the ibandronate 20 mg intermittent dosing group and 5 (0.5%) subjects in the placebo group. Any atrial fibrillation event was reported in 12 (1.2%) subjects in the ibandronate 2.5 mg daily group, 7 (0.7%) subjects in the ibandronate 20 mg intermittent dosing group and 10 (1.0%) subjects in the placebo group. In the 3-year intravenous ibandronate fracture study (950 subjects in the ibandronate 0.5 mg q3months group, 961 subjects in the ibandronate 1.0 mg q 3months group, 949 subjects in the placebo group, mean age 67 years) atrial fibrillation serious adverse events were reported in 3 (0.3%) subjects in all three treatment groups. Any atrial fibrillation event was reported in 11 (1.2%) subjects the ibandronate 0.5 mg q3months group, 7 (0.7%) subjects the ibandronate 1.0 mg q3months group, and 8 (0.8%) subjects in the placebo group. Based on the data available at present, there is not a consistent pattern noted for the approved bisphosphonate agents. These include both oral and intravenous agents.

I agree with Dr. Lubas 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. More, in-depth analyses need to be conducted to evaluate the causality of the serious atrial fibrillation adverse event findings with all bisphosphonate agents.

Renal Adverse Events: Intravenous zoledronic acid 4 mg has been associated with increased renal toxicity, most notably when comparing a 5 minute infusion to a 15 minute infusion. Zoledronic acid 8 mg was associated with increased renal toxicity regardless of infusion time _____

_____ In study 2301, subjects with a baseline calculated creatinine clearance < 30 mL/min, urine dipstick protein \geq 2+, or an increase in serum creatinine > 0.5mg/dL between the two screening visits were excluded from the study.

In Study 2301, 358 subjects (190 (4.9%) in the zoledronic acid group and 168 (4.4%) subjects in the placebo group) experienced an adverse event associated with a change in renal function. Renal failure (including acute renal failure) was reported in 41 (1.0%) subjects in the zoledronic acid group and 29 (0.8%) subjects in the placebo group. Of the 41 zoledronic-acid subjects experiencing renal failure, there was no temporal relationship to dose infusion. Eighteen of the 40 zoledronic-acid treated subjects had resolution of their renal failure during the study. Renal impairment was reported in 34 (0.9%) subjects in the zoledronic acid group and 32 (0.8%)

¹ Cummings SR, et.al. N Engl J Med. 2007 May 3. 356 (18):1895-6.

subjects in the placebo group. Increased blood creatinine was reported in 29 (0.8%) subjects in the zoledronic acid group and 10 (0.3%) subjects in the placebo group.

Study 2301 included a renal substudy which closely evaluated the effects of zoledronic acid infusion on renal function. A total of 4708 subjects were enrolled in this substudy. Creatinine clearance at baseline was below 60 mL/min for 45% of the population. Overall, 31 (1.8%) subjects in the zoledronic acid group and 19 (0.8%) subjects in the placebo group exhibited an increase in serum creatinine > 0.5 mg/dL when measured 9 – 11 days post infusion. When evaluated based on baseline creatinine clearance, the largest imbalance was seen in subjects with a baseline creatinine clearance less than 35 ml/min (5/47 subjects in the zoledronic acid group and 2/65 subjects in the placebo group).

When evaluated for long-term changes in renal function at end of study, 88 (2.4%) subjects in the zoledronic acid group and 94 (2.6%) subjects in the placebo group developed a creatinine clearance change to < 30 ml/min; 25 (0.7%) subjects in the zoledronic acid group and 27 (0.7%) subjects in the placebo group exhibited an increase in serum creatinine > 0.5 mg/dL relative to baseline and 5 (0.1%) subjects in the zoledronic acid group and 11 (0.3%) subjects in the placebo group developed proteinuria (> 2+ protein on dipstick) at some time during the study.

The Sponsor proposes to include language in the Warnings and Precautions section of the product label regarding renal dysfunction. I agree with Dr. Lubas that there is no data to support the need for zoledronic acid dose adjustments in postmenopausal osteoporosis patients with a creatinine clearance less than 60 mL/min.

Acute Phase Reaction: Symptoms consistent with acute phase reaction have been reported with intravenous bisphosphonate use. Symptoms considered possibly related to an acute phase reaction include flu-like symptoms such as fatigue, fever, chills, myalgia, arthralgia, pain and generalized body aches, occurring within 3 days of i.v. dosing and lasting less than 7 days. As previously noted, the most common adverse events reported in patients receiving zoledronic acid were symptoms attributable to the acute phase reaction-like syndrome associated with intravenous bisphosphonate use including 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 events occurred much more frequently after the first dose of study drug (44.7% in the zoledronic acid group and 14.7% in the placebo group) compared to the second (16.7% in the zoledronic acid group and 10.3% in the placebo group) and third (10.2% in the zoledronic acid group and 8.6% in the placebo group) injections.

Study 2407 evaluated the body temperature excursions and symptom profile following zoledronic acid injection in postmenopausal women. A total of 481 subjects were randomized into one of four treatment arms: zoledronic acid 5 mg plus placebo (zol+plac); zoledronic acid 5 mg plus 1000 mg acetaminophen four hours after infusion (zol+apap), then 1000 mg every 6 hours for 3 days; zoledronic acid 5 mg plus ibuprofen 400 mg four hours after infusion, then 400 mg every 6 hours for 3 days (zol+ibu); or placebo plus placebo (plac+plac). The mean age of the study population was 60 years. A clinically significant increase in temperature (defined as an increase of at least 1 C to a value above 37.5 C in the three day period after study drug administration) was observed in 11% subjects in the plac+plac group 64% of subjects in the zol+plac group, 37% of subjects in the zol+apap group, and 37% of subjects in the zol+ibu group. Additional anti-inflammatory medication was used by no subjects in the plac+plac group, 22% of subjects in the zol+plac group, 10% of subjects in the zol+apap group, and 10% of subjects in the zol+ibu group.

Osteonecrosis of the Jaw: Both intravenous and oral bisphosphonates have been associated with osteonecrosis of the jaw. In order to evaluate maxillofacial adverse events, a blinded adjudication committee comprised of 5 dental experts reviewed all adverse event reports pertaining to the jaw. A total of 50 preferred terms were predefined for selection of cases requiring adjudication. The predefined criteria for osteonecrosis of the jaw were an area of exposed bone for longer than 6 weeks with delayed healing despite adequate medical therapy.

Overall, including data up to March 31, 2006, a total of 101 (2.6%) subject cases in the zoledronic acid group and 127 (3.3%) subject cases in the placebo group were referred to the Committee for adjudication. After review, two subjects were noted to have findings consistent with osteonecrosis of the jaw: a 70-year-old woman in Stratum I receiving zoledronic acid, and a 67 year-old woman in Stratum I receiving placebo.

Inflammatory Eye Disease: An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. In order to evaluate inflammatory ocular findings in study 2301, a blinded ophthalmologist predefined criteria for evaluation for defining pertinent ocular AEs. These criteria included the preferred terms blepharitis, conjunctivitis, diplopia, episcleritis, eye irritation, eye pain, iridocyclitis, iritis, lacrimation increased, ocular icterus, orbital oedema, photophobia, scleritis, uveitis and vision blurred. Based on these criteria, 233 subjects (130 (3.4%) in the zoledronic acid group and 103 (2.7%) in the placebo group) experienced an inflammatory ocular adverse reaction. One notable omission from the preferred term list was eye inflammation. With the addition of eye inflammation, inflammatory ocular adverse events occurred in 136 (3.5%) subjects in the zoledronic acid group and 107 (2.8%) subjects in the placebo group. Overall, there is a small (0.7% absolute and 30% relative) increased risk in bisphosphonate associated ocular events in zoledronic acid treated patients compared to placebo.

Musculoskeletal Pain: An increased incidence of muscular and bone pain has been reported with bisphosphonate use. Overall, musculoskeletal pain symptoms occurred in 4062 subjects (2156 (55.8%) in the zoledronic acid group and 1906 (49.5%) in the placebo group). Specifically, the preferred term "bone pain" occurred in 222 (5.7%) subjects in the zoledronic acid group and 87 (2.3%) subjects in the placebo group.

Gastrointestinal disorders: Oral, nitrogen-containing bisphosphonates are well known to cause gastroesophageal irritation. Intravenous bisphosphonates have not been specifically associated with gastrointestinal adverse events. Overall, 951 (24.6%) subjects in the zoledronic acid group and 822 (21.3%) subjects in the placebo group experienced upper gastrointestinal adverse events symptoms.

Laboratory evaluations: Adverse events related to laboratories were reported in 458 subjects (219 (5.7%) in the zoledronic acid group and 239 (6.2%) in the placebo group). The most commonly reported laboratory adverse events were related to renal function abnormalities (112 (2.9%) zoledronic acid group and 110 (2.9%) placebo group), liver function abnormalities (36 (0.9%) zoledronic acid group and 45 (1.2%) placebo group) and mineral and electrolyte abnormalities (30 (0.8%) zoledronic acid group and 19 (0.5%) placebo group).

Vital Signs: Overall, adverse events related to vital signs were reported by 327 subjects (209 (5.4%) in the zoledronic acid group and 118 (3.1%) in the placebo group). The most common adverse events related to vital signs were weight decreased (71 (1.8%) subjects in the zoledronic acid group and 48 (1.2%) subjects in the placebo group) and blood pressure increased (58 (1.5%) subjects in the zoledronic acid group and 46 (1.2%) subjects in the placebo group). As noted in

the table below, there were no notable differences between the two treatment groups in the incidence of clinical significant changes in vital signs.

Study 2301 : Clinically Significant Changes in Vital Signs		
	All Subjects	
	zole	plac
N, safety	3862	3852
Pulse (bpm)		
> 120 and increased > 15	2 (0.06)	4 (0.1)
< 50 and decreased > 15	10 (0.3)	15 (0.4)
Systolic BP (mm Hg)		
> 180 and increased > 20	57 (1.6)	49 (1.3)
< 90 and increased > 20	8 (0.2)	5 (0.1)
Diastolic BP (mm Hg)		
> 105 and increased > 15	25 (0.7)	21 (0.6)
< 50 and decreased > 15	7 (0.2)	10 (0.3)
Body Weight (kg)		
Increase > 7%	510 (13.8)	438 (11.9)
Decrease > 7%	616 (17.0)	661 (18.0)

Bone histomorphometry: Bone safety was evaluated by bone biopsy with histomorphometry with double tetracycline labeling and microCT. Bone biopsies were obtained at any time between Months 33 and 36 in 153 subjects. Analysis by microCT was performed prior to quantitative histomorphometry on 143 bone biopsy samples. Qualitative histomorphometry assessment was performed on 152 biopsy specimens. A total of 111 specimens were adequate for quantitative histomorphometry (59 in the zoledronic acid group and 52 in the placebo group). Of those 111 specimens, 86 (38 in the zoledronic acid group and 48 in the placebo group) were evaluable for all histomorphometric parameters.

Osteoid thickness (OTh): Osteoid thickness can be used a marker of bone formation. The mean osteoid thickness was below the normal range for the zoledronic acid group. This is an expected finding, given the anti-resorptive nature of bisphosphonate drugs. Increases in osteoid thickness would be expected in the setting of a mineralization defect.

Osteoid volume/ Bone volume (OV/BV): Osteoid volume represents the percentage of bone volume that is non-mineralized osteoid. A clear increase in OV/BV would support the hypothesis of impaired mineralization. The mean OV/BV is within the normal range for the zoledronic acid group.

Osteoid surface / Bone surface (OS/BS): The osteoid surface/bone surface ratio reflects bone remodeling. The zoledronic acid group exhibits a mean OS/BS ratio significantly lower than the placebo group and below the normal range. This is an expected finding given the anti-resorptive nature of zoledronic acid. No subject had complete suppression of bone remodeling (OS/BS of 0). The lowest level of OS/BS was 0.35% in the zoledronic acid group and 2.24% in the placebo group.

Mineral apposition rate (MAR): The mineral apposition rate is an indicator of mineralized bone accrual at remodeling sites. A clear reduction in MAR during treatment in comparison with normal could indicate impairment of mineralization and the potential of a drug to induce osteomalacia. In this study, the mean MAR was at the high end of the normal range for the zoledronic acid group.

Mineralization Lag Time (MLT): Mineralization lag time represents the mean time interval between deposition of osteoid and its mineralization, and is the most sensitive index of abnormalities in mineralization. Frequently, it is the earliest change at the onset of osteomalacia. The mean MLT was in the normal range for both treatment groups. However, outliers are also present. Overall, 9/38 (24%) subjects in the zoledronic acid group and 4/48 (8%) subjects in the placebo group had a MLT greater than 80 days while three (8%) subjects in the zoledronic acid group and three (6%) subjects in the placebo group had a MLT greater than 100 days.

One subject in the zoledronic acid group, a 71-year-old woman from Mexico had a MLT of 224 days. Her baseline with a baseline femoral neck T-score was -2.39. She exhibited an 8.6% increase in FN BMD at Month 24 and then a 1.2% decrease in FN BMD at Month 36. One subject in the Stratum I placebo group, a 77-year-old woman from New Zealand had a MLT of 207 days. Her baseline with a baseline femoral neck T-score was -2.50. She exhibited a 5.6% increase in femoral neck BMD at Month 36.

Overall, there was no evidence of marrow fibrosis, woven bone or osteomalacia on qualitative histomorphometry. Quantitative measures revealed no evidence of impaired mineralization. MicroCT analysis revealed normal bone architecture.

Study 2301: Bone Histomorphometry				
Parameter	Normal Range	Zole	Placebo	p-value
		mean ± SD	mean ± SD	
N		38	48	
Osteoid Thickness (µm)	5.5 – 12.0	5.27 ± 0.16	5.82 ± 0.17	0.0094
Osteoid Volume (%)	0.30 – 3.10	0.70 ± 0.08	2.14 ± 0.19	<0.0001
Osteoid Surface (%)	7.0 – 25.0	6.71 ± 6.07	18.73 ± 9.50	<0.0001
Mineral Apposition Rate (µm/d)	0.360 – 0.630	0.62 ± 0.15	0.51 ± 0.08	0.0002
Mineralizing Surface (%)	1.0 – 13.5	1.18 ± 1.67	6.53 ± 5.58	<0.0001
Adjusted Apposition Rate (µm/d)	NA	0.17 ± 0.14	0.19 ± 0.12	0.1389
Mineralization Lag Time (days)	24 – 80	56 ± 40	46 ± 37	0.0958
Formation Period (years)	0.16 – 0.70	0.88 ± 0.67	0.71 ± 0.64	0.1381
Bone Volume (%)	14.0 – 30.0	17.0 ± 6.8	14.5 ± 4.3	0.0455
Trabecular Thickness (µm)	93 - 185	138 ± 39	133 ± 30	0.9317
Activation Frequency (per yr)	NA	0.13 ± 0.12	0.44 ± 0.37	<0.0001
Cortical Thickness (µm)	NA	656 ± 268	594 ± 271	0.2054

Electrocardiograms: Abnormal ECG findings were reported as adverse events in 20 subjects (14 in the zoledronic acid group and 6 in the placebo group). None of these reports identified atrial fibrillation as the abnormality.

In the ECG substudy, 559 patients (278 in the zoledronic acid group and 281 in the placebo group) had at least one ECG assessment at Month 24 during the study as well as before and 9 to 11 days after their third study drug dose. There were no notable differences between treatment groups concerning electrophysiological parameters. The incidence of atrial fibrillation was 6 (2.2%) subjects in the zoledronic acid group and 8 (2.5%) subjects in the placebo group, compared to the AE report rates of 2.4% in the zoledronic acid group and 1.9% in the placebo group.

III.b. Safety Conclusions

The large three-year pivotal fracture trial, Study 2301 provides sufficient data on the safety of zoledronic acid 5 mg administered as a 15 minute infusion once yearly for the treatment of postmenopausal osteoporosis to allow for an acceptable safety assessment.

In Study 2301, 130 (3%) subjects in the zoledronic acid group and 112 (3%) subjects in the placebo group died during the three years of the trial. Causes of death occurring with at least a twofold higher incidence in the zoledronic acid group included cerebrovascular accident, cardio-respiratory arrest, acute myocardial infarction, and pneumonia. Serious adverse events occurred in approximately 30% of the population in both treatment groups with pneumonia, atrial fibrillation, osteoarthritis, cerebrovascular accident and myocardial infarction reported most frequently. There was a notable imbalance between the treatment groups in the incidence of atrial fibrillation occurring in 50 (1.3%) subjects in the zoledronic acid group and 20 (0.5%) subjects in the placebo group. The increased incidence of atrial fibrillation serious adverse events was an unexpected finding. The overall incidence of atrial fibrillation events at study completion did not have a comparable imbalance (94 (2.4%) subjects in the zoledronic acid group and 73 (1.9%) subjects in the placebo group). The incidence of atrial fibrillation in the ECG substudy was 2.2% in the zoledronic acid group and 2.5% in the placebo group, again without evidence of an imbalance between treatment groups. The majority of the atrial fibrillation SAEs occurred more than 30 days after treatment, suggesting that the occurrence of atrial fibrillation is not an acute event related to infusion of study drug. There was a subtle and consistent pattern of 10 to 20% greater occurrence of atrial fibrillation/flutter, congestive heart failure, diabetes and valvular heart disease in the zoledronic acid group. There is not a consistent pattern noted for the approved oral and intravenous bisphosphonate agents. While similar findings of increased incidence of atrial fibrillation serious adverse events were seen in one cohort of one fracture study for another bisphosphonate, no imbalance was noted for two other bisphosphonate agents including a second intravenous agent. Additional in-depth analyses need to be conducted to evaluate the causality of the serious atrial fibrillation adverse event findings with all bisphosphonate agents.

Most of the notable clinical safety issues from Study 2301 are adverse events known to occur with bisphosphonate use.

Bisphosphonate use, most notably intravenous bisphosphonates, has been associated with hypocalcemia. Studies in Paget's disease of bone evidenced a concerning signal of hypocalcemia following zoledronic acid treatment. In study 2301, the baseline mean serum calcium level was 9.6 mg/dL. Study participants were to take 1000 – 1500 mg calcium and 400 – 1200 IU vitamin D daily. Following the first study drug dose, the incidence of serum calcium levels less than 8.3 mg/dL 2.3% in the zoledronic acid group and less than 0.1% in the placebo group 9-11 days post injection. Over the 36 month study period, mean serum calcium levels increased and the occurrence of marked hypocalcemia (< 7.5 mg/dL) was rare. The postmenopausal osteoporosis population is considered at lower risk of hypocalcemia because of the lower rates of bone turnover compared to active Paget's disease. Currently, hypocalcemia is a contraindication to zoledronic acid use and the label recommends that patients should have low blood calcium levels normalized. No new labeled warnings are necessary.

Symptoms considered possibly related to an acute phase reaction including flu-like symptoms such as fatigue, fever, chills, myalgia, arthralgia, pain, and generalized body aches, occurring within 3 days of i.v. dosing and lasting less than 7 days were reported in 45% of zoledronic acid-treated patients and 15% of placebo-treated patients following the first dose of study drug. The incidence was much lower with subsequent doses.

Intravenous zoledronic acid 4 mg has been associated with increased renal toxicity, most notably when comparing a 5 minute infusion to a 15 minute infusion. Zoledronic acid 8 mg was associated with increased renal toxicity regardless of infusion time. Based on findings in oncology subjects, it is recommended that the dose of zoledronic acid (Zometa) be lowered in patients with renal impairment. Study 2301 included a renal substudy which closely evaluated the effects of zoledronic acid infusion on renal function. All patients received 5 mg zoledronic acid infused over 15 minutes. Creatinine clearance at baseline was below 60 mL/min for 45% of the population. Overall, 1.8% of the zoledronic acid group and 0.8% of the placebo group exhibited an increase in serum creatinine > 0.5 mg/dL when measured 9 – 11 days post infusion. When evaluated for long-term changes in renal function at end of study, 2.4% of the zoledronic acid group and 2.6% of the placebo group developed a creatinine clearance change to < 30 ml/min; while 0.7% of both treatment groups exhibited an increase in serum creatinine > 0.5 mg/dL relative to baseline. These data suggest that there is not a need to require zoledronic acid dose adjustment based on creatinine clearance.

Both intravenous and oral bisphosphonates have been associated with osteonecrosis of the jaw. In study 2301, two subjects, one in each treatment group, were noted to have findings consistent with osteonecrosis of the jaw. These are the first episodes of ONJ reported in the clinical trial setting with postmenopausal osteoporosis patients.

An increased incidence of muscular and bone pain has been reported with bisphosphonate use. There was a three-fold increase in bone pain with zoledronic acid treatment, occurring in 6% of zoledronic acid-treated patients and 2% of placebo-treated patients.

An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. In study 2301, inflammatory ocular adverse events occurred in 3.5% of the zoledronic acid group and 2.8% of the placebo group. Overall, there is a small (0.7% absolute and 30% relative) increased risk in bisphosphonate associated ocular events in zoledronic acid treated patients compared to placebo.

Bone safety was evaluated bone biopsy with qualitative and quantitative histomorphometry, with double tetracycline labeling and microCT. There was no evidence of marrow fibrosis, woven bone or osteomalacia. Quantitative measures revealed no evidence of impaired mineralization. MicroCT analysis revealed normal bone architecture.

Overall, the safety database reveals a safety profile of zoledronic acid treatment in postmenopausal women with osteoporosis that is similar to other bisphosphonates. Although the finding is present, there is no clear evidence to suggest that zoledronic acid is causally responsible for the higher reporting rate of serious atrial fibrillation.

IV. Pharmacology/Toxicology

As outlined in Dr. Wange's review, Pharmacology/Toxicology is recommending Approval of this supplemental NDA. Nonclinical studies supporting this current application were initially submitted in support of NDA 21-817 (Reclast 5 mg for treatment of Paget's disease of bone). The main toxicities noted in the nonclinical studies are renal and gastrointestinal toxicities, with adequate safety margins. Safety pharmacology studies indicated that there were no effects on CNS, cardiovascular or respiratory systems. Bone pharmacology studies in ovariectomized rats and rhesus monkeys demonstrated marked suppression of bone turnover and bone remodeling activation with a dose-dependent increase in bone mineral density and bone strength. Bone marrow was normal. Bone tissue was also normal and without evidence of a mineralization defect, accumulation of osteoid or woven bone.

V. Clinical Pharmacology

As outlined in Dr. Lau's review, the Clinical Pharmacology team focused on zoledronic acid's in vitro plasma protein binding data and a pharmacometric analysis of renal data from Study 2301. Zoledronic acid use is associated with renal impairment (even suspected renal failure) in cancer patients and dose adjustment per baseline renal function is recommended for the treatment of multiple myeloma and bone metastases of solid tumors. Due to the potential that zoledronic acid may cause renal impairment in the PMO patient population, the Pharmacometrics group was consulted to analyze the pivotal Phase 3 clinical study's renal safety data. Based on the data from 2320 PMO patients, there was no trend in the incidence of renal deterioration with once yearly repeated dosing of zoledronic acid as compared to placebo dosed patients.

VI. Chemistry, Manufacturing and Control (CMC)

As outlined in Dr. Markofsky and Dr. Al-Hakim's reviews, ONDQA is recommending Approval of the application. The CMC information for the previously approved Reclast NDA for treatment of Paget's disease of bone (NDA 21-817), referencing the drug substance (zoledronic acid) and CMC information for the approved NDA 21-223 (Zometa, zoledronic acid 4 mg), supports this NDA submission. The CMC data in this submission has been revised with additional stability data, and updated categorical exclusion from preparing an Environmental Assessment; and a new acceptable Establishment Inspection report for the CMC related facilities. The Drug Product and the Drug Substance are acceptable and the proposed 36 month expiry date is adequately supported.

As outlined in Dr. Metcalfe's review, no microbiology deficiencies were identified. The drug product is manufactured under sterile conditions and is lacking in any preservative.

VII. Other Regulatory Requirements

VII.a. Financial Disclosure

Dr. Lubas has reviewed the financial disclosure information and found them acceptable.

VII.b. Pediatrics

The proposed indication in this sNDA is restricted to women after the onset of menopause. The PREA pediatric study requirements for the indication proposed in this sNDA were waived.

VII.c. Clinical Audits/Inspections

A DSI audit was conducted for this submission. Site selection was based on subject enrollment and two sites in the United States were inspected. Overall, the data from these sites were considered acceptable to support the application.

In study 2301, the Sponsor terminated one study site (site 0196) located in Mexico where it was determined that there were data reliability issues identified during monitoring visits and data review. The 29 enrolled patients from this site were excluded from all safety and efficacy analyses.

VIII. Conclusions and Recommendations

VIII.a. Conclusions

Treatment with zoledronic acid 5 mg once yearly is efficacious in reducing the occurrence of new morphometric vertebral fractures with an absolute risk reduction of 7.6% and a relative risk reduction of 70% ($p < 0.0001$) and in reducing hip fractures with three-year event rates of 1.4% for the zoledronic acid group and 2.5% for the placebo group, with a hazard ratio of 0.59 (95% CI 0.42 to 0.83, $p = 0.0024$). In addition to these two co-primary endpoints, zoledronic acid 5 mg once yearly is efficacious for all twenty secondary endpoints including reduction in the incidence of new or worsening vertebral fractures; reduction in the incidence of clinical vertebral fractures; reduction in the incidence of all clinical osteoporotic fractures; increasing total hip, femoral neck, and lumbar spine bone mineral density; and reduction in the markers of bone turnover.

The large three-year pivotal fracture trial, Study 2301 provides sufficient data on the safety of zoledronic acid 5 mg administered as a 15 minute infusion once yearly for the treatment of postmenopausal osteoporosis to allow for an acceptable safety assessment. Most of the notable clinical safety issues from Study 2301 are adverse events known to occur with bisphosphonate use including hypocalcemia, acute phase reaction following drug administration, renal toxicity, osteonecrosis of the jaw, inflammatory eye disease, and musculoskeletal pain symptoms. The risk of hypocalcemia is lower in the postmenopausal population as compared to Paget's disease. Adequate calcium and vitamin D intake is the cornerstone of osteoporosis therapy, which will further reduce the risk of hypocalcemia. There is a high incidence of acute phase reaction-like symptoms, especially following the first dose. Symptoms may be mitigated by pretreatment with acetaminophen or ibuprofen.

Renal toxicity has been a prevailing concern with zoledronic acid therapy in the oncology population necessitating a dose reduction based on creatinine clearance. Careful evaluation of the data by the Clinical Pharmacology, Pharmacometrics and Clinical teams indicate that the level of renal toxicity seen in the oncology population is not observed in the postmenopausal osteoporosis population. Although language regarding renal impairment remains in the Warnings and Precautions section of the product label, further requirements of a dose adjustment based on creatinine clearance is not necessary.

The occurrence of osteonecrosis of the jaw has been reported postmarketing for both intravenous and oral bisphosphonates. Although more commonly reported in the oncology population, there have been reports in the osteoporosis population. Two subjects, one each in the zoledronic acid and placebo groups, met criteria consistent with the definition of ONJ during the pivotal fracture trial. These are the first episodes of ONJ reported in the clinical trial setting with postmenopausal osteoporosis patients. The risk of ONJ and pertinent risk factors have been clearly outlined in the label and the company has agreed to expedited safety reports for any cases of ONJ during the first year of marketing for the osteoporosis indication.

Overall, the robust efficacy findings are compelling. The safety database reveals a safety profile of zoledronic acid treatment in postmenopausal women with osteoporosis that is similar to other bisphosphonates. Many of these safety concerns can be mitigated by appropriate selection of the patient needing treatment and symptom monitoring. Although the finding is present, there is no clear evidence to suggest that zoledronic acid is causally responsible for the higher reporting rate of serious atrial fibrillation. Further investigations into the causal relationship of the bisphosphonate class of drugs and atrial fibrillation is ongoing.

VIII.b. Recommendation

Approve

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/s/

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8/17/2007 01:37:35 PM
MEDICAL OFFICER

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CLINICAL REVIEW

Application Type sNDA
Submission Number 22-080/N_000
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Reviewer Name William Lubas, M.D., Ph.D.
Review Completion Date August 16, 2006

Established Name zoledronic acid
(Proposed) Trade Name Reclast®
Therapeutic Class Bisphosphonate
Applicant Novartis Pharmaceuticals Corp.

Priority Designation S

Formulation 5mg/100mL solution
for IV infusion
Dosing Regimen once yearly
Indication Treatment of Postmenopausal
Osteoporosis
Intended Population Postmenopausal Women

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The pivotal trial 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, therefore, an Approval action is recommended.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 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.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zoledronic acid (4mg) is currently approved for the treatment of hypercalcemia of malignancy as a single dose, and for the treatment of patients with multiple myeloma and documented bone metastases from solid tumors, as multiple doses given once every 3 to 4 weeks, in conjunction with standard antineoplastic therapy under the trade name Zometa. Zoledronic acid (5mg) was recently approved (16-Apr-2007) for the treatment of patients with Paget's disease under the trade name Reclast, as a single dose with the possibility of retreatment as dictated by medical practice. The sponsor is now seeking a new indication, for once-yearly dosing of women with post menopausal osteoporosis.

1.3.2 Efficacy

The study enrolled patients who were not to receive additional osteoporosis therapies other than calcium and vitamin D or who had adequately washed out prior osteoporosis medications prior to the start of the trial into Stratum I (n=6,084), whereas women who were to receive certain hormone-related osteoporosis therapies or did not adequately meet wash out criteria from prior use of certain osteoporosis medications were enrolled into Stratum II (n=1,652). The primary efficacy objectives of this study were to show that the proportion of new vertebral fractures, over 36 months, in Stratum I patients was significantly lower for zoledronic acid-treated patients relative to placebo-treated patients and that the time to first hip fracture, over 36 months, in Stratum I and II patients was significantly longer for zoledronic acid-treated patients relative to placebo-treated patients. 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%, $p < 0.0001$). 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% reduction in the risk of hip fractures ($p = 0.0032$). These study results support the efficacy of once yearly dosing with zoledronic acid (5mg) for the treatment of women with post menopausal osteoporosis.

1.3.3 Safety

Intravenous zoledronic acid infusion was associated with the high occurrence of short-term flu-like symptoms including: nausea, pyrexia and chills, headaches, arthralgias, myalgias, bone pain, and asthenia. These events were transitory in nature and could be adequately treated with supportive therapy.

Adverse events that had been previously seen with other bisphosphonates, include: hypocalcemia, eye findings, and osteonecrosis of the jaw.

Hypocalcemia has been associated with bisphosphonate use especially with intravenous bisphosphonates and particularly in patients with Paget's disease, who have an increased rate of bone turnover. Use of zoledronic acid in patients with Paget's disease had been previously reviewed (see NDA 21-817), and it was determined that supplementation with adequate amounts of calcium and vitamin D was effective at attenuating the risk for developing hypocalcemia in this higher risk patient population. To avoid placing subjects with PMO at risk of severe hypocalcemia, women with baseline calcium levels < 2.0 mmol/L (8mg/dL) were excluded and all patients were provided with calcium (1000mg-1500mg/day) and vitamin D (400-1200IU/day) supplementation throughout the 3 year study. 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, with continued adequate dietary calcium and vitamin D intake, patients who have normal calcium and Vitamin D levels at the start of therapy do not need additional monitoring of serum calcium levels following infusions.

Ocular adverse events were observed at the low rate of about 3% with most symptoms described as transitory, reversible and responsive to appropriate management. Since most cases are associated with the short-term flu like symptoms following the infusions, _____

Risk factors that may increase the risk of osteonecrosis of the jaw in patients that receive bisphosphonate therapy include cancer, dental extraction, periodontal disease, dental trauma, concomitant therapies, corticosteroids and administration of cytotoxic agents. 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 risk of osteonecrosis with once yearly intravenous zoledronic acid for the treatment of PMO is low, but physicians will need to continue to make case by case risk benefit assessments for their individual patients.

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. There is an increase in serum creatinine from baseline to 9-11 days post infusion in the zoledronic acid group compared to the placebo group after each of the three infusions. 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 9-11 days 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. Also there was no difference in the mean final creatinine values (0.8mg/dL) or the distribution of final creatinine values between the treatment groups.

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Therefore, the exclusion criteria of creatinine clearance $> 30\text{mL/min}$ and urine $> 2+$ appears to be adequate in identifying subjects at risk of worsening renal function. While there is a slightly higher risk for developing an increase in creatinine of $>0.5\text{mg/dL}$ in patients with baseline creatinine clearance values between 30 and 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. Therefore, there is no evidence to suggest a need for dose adjustment in patients with baseline creatinine clearance values between 30 and 60mL/min .

Atrial fibrillation is an adverse event that had not been previously associated with bisphosphonates. 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 $70/3852=1.8\%$. 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 is statistically significant ($p<0.001$). 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. This increase in atrial fibrillation adverse events 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 patient 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 pivotal study 2301. At present there is no clear evidence to suggest that zoledronic acid is causally responsible for the higher reporting rate of serious atrial fibrillation, but it would be prudent to continue to monitor for this adverse event in ongoing studies including zoledronic acid and other intravenous bisphosphonates

1.3.4 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.

1.3.5 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- or other divalent cation-containing solutions because of the potential for chelation which would limit its effectiveness.

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1.3.6 Special Populations

No clinical studies in pediatric patients, patients with hepatic insufficiency or renal insufficiency (creatinine clearance $< 30\text{mL}/\text{min}$) 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 $60\text{mL}/\text{min}$ and urine dipstick $< 2+$, therefore there is no need for dose adjustment in this patient population.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zoledronic acid, trade named Zometa and proposed trade name Reclast, is a third generation nitrogen containing bisphosphonate which acts as an inhibitor of osteoclastic bone resorption and is intended for intravenous use. This current application seeks approval for zoledronic acid (proposed trade name Reclast) 5 mg injection once yearly for the treatment of PMO. Reclast (NDA 21-817) was approved April 16, 2007 for the single dose treatment of Paget's disease. Re-treatment may be considered for patients who relapse. Zoledronic acid is also marketed for oncology indications, e.g. the treatment of hypercalcemia of malignancy, multiple myeloma and bone metastases, since Feb. 22, 2002 under the brand name Zometa (NDA 21-386) for repeat dosing as a 4 mg dose, given no more frequently than every 7 days.

Zometa is available in Europe and world-wide in over 90 countries under the trade name Zometa for the treatment of the oncology indications and in 51 countries not including the US and Australia under the trade name Aclasta for the treatment of Paget's disease.

2.2 Currently Available Treatment for Indications

Drug products currently approved for the treatment of Paget's disease of bone include salmon calcitonin injection (Miacalcin), the injectable bisphosphonate pamidronate disodium (Aredia) and the oral bisphosphonates alendronate sodium (Fosamax), etidronate disodium (Didronel and generic Etidronate), risedronate sodium (Actonel), and tiludronate sodium (Skelid).

2.3 Availability of Proposed Active Ingredient in the United States

Zoledronic acid (5 mg injection) is currently approved for the treatment of Paget's disease under the trade name Reclast. Zoledronic acid (4mg injection) is currently approved for the treatment of hypercalcemia of malignancy, multiple myeloma and bone metastases, in conjunction with standard antineoplastic therapy under the trade name Zometa.

2.4 Important Issues With Pharmacologically Related Products

An increased risk of osteonecrosis of the jaw has been observed for intravenous bisphosphonates. see Oncology Drugs Advisory Committee meeting in 2005. Such information has been added to the label for Zometa and Aredia. Other safety concerns that have occurred more frequently in clinical trials with intravenous bisphosphonates include acute phase reactions, hypocalcemia and worsening of renal function. The risk of deterioration in renal function was significantly increased when zoledronic acid was infused over 5 minutes compared with the same dose infused over 15 minutes. In addition, the risk of deteriorating renal function was significantly increased with the 8 mg dose, regardless of the 15 minute infusion time.

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Other concerns that have emerged with post-marketing data include the occurrence of eye inflammation, and bone pain, whereas gastrointestinal adverse events occur primarily with oral bisphosphonate therapy. Class labeling for bisphosphonates regarding the use of these drugs in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug has recently been implemented.

2.5 Presubmission Regulatory Activity

The initial NDA submission sent in 16-Oct-2006 included an interim study report for study 2301 dated 27-Sep-2006 including all efficacy and safety data based on a cut-off date of 31-Mar-2006 as agreed to between the Agency and the sponsor. The sponsor also agreed to submit partially blinded safety information from the ongoing prevention of recurrent fracture trial 2310 concerning cardiovascular adverse events.

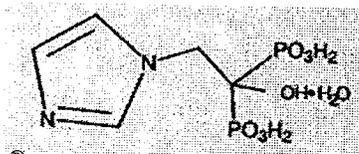
2.6 Other Relevant Background Information

The pivotal study 2301 was completed as planned with a last patient last visit date of 15-Jun-2006, and a database lock of 18-Aug-2006. This clinical study report was updated and final safety and efficacy information collected and submitted in the 12-Feb-2007 submission along with the 120 day Safety Update. It was agreed that the original cut-off date would be considered adequate to support the submission of zoledronic acid in the PMO indication. As a result, the efficacy analyses presented in the interim report are considered final and the efficacy data provided in the final study report are considered as supportive, and will not be used to reflect efficacy in the label. The final updated datasets were sent in the 27-Jun-2007 submission.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Zoledronic acid monohydrate is chemically designated as (1-hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate. Its structural formula is:



Reclast® (zoledronic acid) Injection is available as a sterile solution in bottles for intravenous infusion. One bottle with 100 mL solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis. Inactive Ingredients include mannitol, USP, _____ and sodium citrate, USP, _____ and water for injection, USP.

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Dr. Markofsky's CMC review recommended approval of this submission since the drug substance and drug product are identical to the approved drug substance and drug product from the Paget's disease submission, NDA 21-817, approved this past April. In addition, NDA 22-080 provided "a satisfactory up-dated Categorical Exclusion from preparing an Environmental Assessment, and a new acceptable Establishment Inspection report ... for the relevant CMC related facilities". Please refer to Dr. Markofsky's review for more detailed comments about the chemistry submission.

3.2 Animal Pharmacology/Toxicology

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Please see Dr. Wange's review for an analysis of the Pharmacology/Toxicology items included in this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The pivotal trial supporting the indication for the treatment of women with PMO is study CZOL446H2301, i.e. study 2301. It was originally submitted electronically on 16-Oct-2006. This submission included an interim study report for study 2301 dated 27-Sep-2006 including all efficacy and safety data based on a cut-off date of 31-Mar-2006. Additional lab datasets requested by this medical reviewer were submitted in the 05-Feb-2007 submission. The final updated report dated 29-Nov-2007 including the final study data was submitted on 12-Feb-2007 along with the 4-month safety update. The final study datasets were included in the 27-Jun-2007 and 03-Jul-2007 submissions. Additional baseline medical history information requested by this medical reviewer was submitted on 29-Jun-2007.

The sponsor also agreed to submit partially blinded cardiovascular adverse events safety information from the ongoing prevention of recurrent fracture trial, study 2310. This study report dated 11-May-2007 was included in the 14-May-2007 submission.

4.2 Tables of Clinical Studies

Dose Finding Studies

Study No.	Study objective/ Population	No. of patients ¹	Study duration	Medication, dosing scheme	Primary efficacy endpoint(s)
0041	Phase II, double-blind, randomized, placebo-controlled, dose-ranging study in postmenopausal women with osteopenia or osteoporosis	351	12 months	4 × 0.25 mg/3 months Zol 4 × 0.5 mg/3 months Zol 4 × 1 mg/3 months Zol 2 × 2 mg/6 months Zol 1 × 4 mg/12 months Zol (5-minute IV infusion) Placebo	Percent change from baseline in lumbar spine BMD at Month 12

Placebo-Controlled Studies

Study No.	Study objective/ Population	No. of patients ¹	Study duration	Medication, dosing scheme	Primary efficacy endpoint(s)
2301	Phase III, double-blind, randomized, placebo-controlled efficacy/safety study in postmenopausal women with osteoporosis	7736	36 months	3 × 5 mg Zol/12 months (15-minute IV infusions) Placebo	(a) Proportion of patients with at least 1 new vertebral fracture over 36 months in Stratum I patients ² (b) Time to first hip fracture over time in Strata I and II patients

¹ Randomized

² 7736 patients were actually included in the intent-to-treat patient population for efficacy and safety due to the exclusion of patients from Center 0106 [Section 4.2 Report Study 2301]

³ Stratum I: patients taking calcium and vitamin D only and no additional concomitant osteoporosis medications. Stratum II: patients taking calcium and vitamin D and additional concomitant osteoporosis medications (but not bisphosphonates).

Appears This Way
 On Original

Active-Controlled Trials

Study No.	Study objective/ Population	No. of patients ¹	Study duration	Medication, dosing scheme	Primary efficacy endpoint(s)
2313	Phase IIIb, double-blind, randomized, active-controlled safety study in postmenopausal women with moderate/severe osteopenia or osteoporosis who received at least 1 year of treatment with alendronate immediately prior to randomization	225	12 months	1 x 6 mg Zol (single 15-minute IV infusion) 70 mg alendronate/week (12 months)	Percent change from baseline in lumbar spine BMD at Month 12
2315	Phase IIIb, double-blind, randomized, active-controlled efficacy/safety study in postmenopausal women with moderate/severe osteopenia or osteoporosis	129	24 weeks	1 x 6 mg Zol (single 15-minute IV infusion) 70 mg alendronate/week (24 weeks)	Relative change from baseline in urinary NTx value at Week 1

¹ Randomized

Key: BMD = bone mineral density, IV = intravenous, NTx = cross-linked N-telopeptide of type I collagen, Zol = zoledronic acid (ZOL446)

4.3 Review Strategy

This medical reviewer independently reviewed pivotal trial 2301 for safety and efficacy, and reviewed 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. Dr. Liu, from biometrics, independently reviewed trial 2301 for efficacy. Dr. Lau, from clinical pharmacology, independently reviewed zoledronic acid's *in vitro* plasma protein binding data from trial R0400374, the phase 2 dosing study 0041 and the renal safety data from pivotal trial 2301. The clinical, biometrics and clinical pharmacology teams collaborated on their independent findings before making final recommendations.

4.4 Data Quality and Integrity

A DSI consult was requested to review two US study sites: 540, (Dr. Michael Lillestol, _____) and _____ These sites were chosen because had the _____ number of reported AEs in the US i.e. 861 and _____ respectively, and they had the third and _____ number of patients enrolled at a US study site, i.e. 48 and _____ patients, respectively.

No significant deviations from FDA regulations were observed at Dr. Michael Lillestol's site. However, 7 out of the _____ subjects enrolled at _____ site did not meet washout requirements for previous osteoporosis therapy required for Stratum I participation. The subjects are:

0580-00004 (did not meet washout requirement for SERMS),

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0580-00006 (did not meet washout requirement for HRT),
0580-00010 (did not meet washout requirements for bisphosphonates, HRT, and calcitonin),
0580-00012 (did not meet washout requirement for HRT),
0580-00019 (did not meet washout requirement for calcitonin),
0580-00022 (did not meet washout requirement for calcitonin), and
0580-00023 (did not meet washout requirement for SERMS).

Four of these patients were randomized to zoledronic acid and three were randomized to the placebo group. The net effect of an inadequate wash out period would likely be to limit the loss in BMD expected in the absence of treatment. Since this effect was distributed almost equally between treatment groups, due to randomization, it seems unlikely that this would have substantial affect on the observed efficacy.

Subject 0580-00100, a patient randomized to the placebo group, initiated the use of a prohibited concomitant medication (a bisphosphonate) during the study. This should have resulted in a decrease in the observed treatment effect for zoledronic acid in this study.

Subjects 0580-00128, a patient randomized to the zoledronic acid group, and 0580-00129, a patient randomized to the placebo group, were infused with the wrong study treatments in May 2004. These changes would also have resulted in a decrease in the observed treatment effect for the study medication.

The 10 study violations reported at study site 580 would not be expected to significantly affect the study results ($10/7765=0.1\%$). Therefore this medical reviewer agrees with DSI's overall assessment that data from both of these sites was acceptable for support of the current application.

4.5 Compliance with Good Clinical Practices

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

PROTOCOL VIOLATIONS

Prohibited medications, such as other bisphosphonates, PTH, sodium fluoride, strontium, anabolic steroids or other investigational medications, were used more frequently in the placebo group ($200/3,861=5.2\%$) than in the zoledronic acid group ($87/3,875=2.3\%$, relative risk 2.3). This occurred most likely as placebo patients who suffered a fracture sought alternative therapy. Vertebral or clinical fractures were experienced in 708 placebo-treated compared to 405 zoledronic acid-treated patients. Of these, 78 (11%) patients in the placebo and 15 (3.7%) in zoledronic acid took at least one prohibited medication during the study. The general association between fracture events and the use of prohibited concomitant medications was statistically significant for both treatment groups with $p=0.036$ for zoledronic acid and $p<0.0001$ for placebo, evaluated using the Cochran-Mantel-Haenszel test.

Slightly more patients randomized to zoledronic acid did not take the study drug compared to the placebo group (13/2,875=0.3% vs. 9/3,861=0.2%). Whereas the wrong study drug being dispensed during the entire study or a switch of study treatment during the study occurred in a similar number of patients (zoledronic acid 6/3,875=0.2%, placebo 8/3,861=0.2%).

Medical officer's comment-

These protocol violations were included as patients in the ITT analysis but were excluded from the protocol analyses for hip or vertebral fractures. The higher use of prohibited medications such as bisphosphonates, fluoride, strontium or PTH in this study in the placebo group would have been expected to decrease the observed treatment effect, unless they were started after a fracture event had already occurred. The mistakes in the randomization of patients or study drug dispensation occurred in a small numbers of patients and occurred in similar frequency between groups making it unlikely that these violations would have affected the integrity of the study results.

PROTOCOL AMENDMENTS

A total of six protocol amendments dated between 25-March-2002 and 26-Feb-2006 were submitted to the original protocol (22-Oct-2001) and were implemented prior to the data cut for the final study report (31-March-2006). None of the changes affected the integrity of the analyses of the primary endpoints. Most of the changes included clarification of inclusion/exclusion criteria, additional testing or adjudication of adverse events for safety reasons or the addition of additional patients to study secondary efficacy endpoints. A list of some of the more relevant changes include:

Amendment 1 (25-March-2002)

- Clarification made to vertebral fracture criterion: "radiological evidence of an existing vertebral fracture. . ." to "radiological evidence of at least two mild or one moderate existing vertebral fracture . . ."
- Exclusion criterion added excluding patients using systemic corticosteroids within the last year of the study.

Amendment 2 (26-Nov-2002)

- Hypocalcemia and increase in serum creatinine between Visit 1 and Visit 2 ≥ 0.5 mg/dL were added as exclusion criteria.
- Tibolone was removed, and strontium was added to the list of excluded concomitant medications.

Amendment 3 (25-Nov-2003)

- ECG testing was added for 400 Stratum I patients.
- Blood collection for bone markers was expanded.
- Quality of life and health economics assessments were added.

Amendment 4 (18-Dec-2003)

- Additional bone marker sample times were added.

Amendment 5 (9-Sept-2005)

- Early stopping rules added for efficacy and safety after interim analysis.
- Additional bone marker sampling was added.
- Introduction of special follow-up forms and description of an Independent Adjudication Committee who would review and adjudicate information related to AEs of interest from the following: ocular, renal, maxillofacial, hypocalcemia and joint related avascular necrosis, was added.
- Addition of a 24-hour urine measurement to verify renal function at study close out in patients with protocol defined renal laboratory abnormalities and a subset of approximately 300 control patients.

Amendment 6 (28-Feb-2006)

- Adjudication for skeletal events including fracture nonunion or delayed healing of the fracture site at appendicular locations was added.
- Adjudication for cardiovascular and cerebrovascular events was added.

4.6 Financial Disclosures

All 254 principal investigators who enrolled patients into the pivotal Study 2301 responded to the financial disclosure request from the sponsor. In addition, 747/755=99% of the sub-investigators also responded. No principal investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. Only two principle investigators had financial arrangements and interests to report. _____ had less than \$5,000 worth of common stock in his spouse's name, and _____ had stock options of undisclosed value. These two center's enrolled _____ patients, respectively, or less than _____ of the entire study population. Therefore, it is unlikely that the outcome of this trial was affected by these financial arrangements.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Studies showed a high affinity of zoledronic acid for bone tissue, with rapid binding and slow elimination from this site. The level of bone accumulation was proportional to cumulative dose. Drug in circulation was rapidly eliminated via renal excretion, and there was transient accumulation of drug in the kidney. There was no evidence that the drug is metabolized. Compound was poorly retained in soft tissues such as thymus, kidney, lung, heart, liver, GI tract, compared to bone. See Dr. Wange's review for a detailed explanation of these findings.

5.2 Pharmacodynamics

Zoledronate inhibited *in vitro* osteoclastogenesis, induced rabbit osteoclast apoptosis and altered osteoblast production of OPG and RANKL. The ratio between the IC50 for calcium incorporation and the IC50 for calcium release in murine calvaria cultures was 15,000. This suggests that for bone resorption inhibition indications there is very high therapeutic margin with regard to inhibition of bone mineralization.

In vivo bone pharmacology studies in ovariectomized (OVX) rats (up to 12-months) and rhesus monkeys (16-month study) demonstrated a dose-dependent increase in bone mineral density and bone strength parameters in OVX animals. Bone turnover and bone remodeling activation frequency were markedly suppressed in trabecular and Haversian bone. There were no clinical adverse effects in the studies. Bone and bone marrow tissue and cells were normal, and there was no evidence of a mineralization defect, accumulation of osteoid or woven bone. In the 8-month bone quality study in OVX rats, one single dose of 0.8, 4, 8, 20, 100, 500 ug/kg showed dose-dependent bone protective effects that were transient at the lower doses but persisted for the entire study duration at 100 and 500 ug/kg. See Dr. Wange's review for a detailed explanation of these findings.

Both bone resorption markers b-CTx and BSAP and bone formation marker PINP decreased to premenopausal levels by 12 months, in the zoledronic acid group and were maintained at this level for the total 36 months of pivotal study 2301. 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. For a more detailed review of these findings see Efficacy Findings section 6.1.4, secondary endpoints.

5.3 Exposure-Response Relationships

Serum calcium and phosphate levels were decreased in the single dose and 13-week intermittent infusion studies in dogs at <10 times human exposure (AUC). See Dr. Wange's review for a detailed explanation of these findings.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Treatment of postmenopausal osteoporosis (PMO)

6.1.1 Methods

The efficacy review was confined to pivotal trial 2301.

1 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

The primary efficacy objectives of this study were to show that the proportion of new vertebral fractures, over 36 months, in Stratum I patients was significantly lower for zoledronic acid-treated patient relative to placebo-treated patients and the time to first hip fracture, over 36 months, in Stratum I and II patients was significantly longer for zoledronic acid-treated patients relative to placebo-treated patients. A closed testing procedure was performed to maintain the overall significance level at 5%. The proportion of patients with new morphometric vertebral fractures at Month 36 from Stratum I was analyzed first at a 4.96% level of significance. If a statistically significant result was obtained, a confirmatory analysis of time to first hip fracture was to be performed at the 4.06% level. The significance levels were adjusted to these values to account for a previously conducted interim efficacy analysis using data up to a cut-off date of 6-Aug-2005. Missing data was replaced using a last-observation-carried-forward (LOCF) approach.

All secondary endpoints were evaluated at a 0.0500 level of significance and all confidence intervals were 2-sided at a 95% confidence level, unless otherwise specified. A closed testing procedure was implemented for the interim analysis with a 31-Mar-2006 cutoff to evaluate the

6.1.3 Study Design

Study 2301 was a phase 3, multi-center, prospective, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of once a year dosing of zoledronic acid in the treatment of osteoporosis in postmenopausal women taking calcium and vitamin D. 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). A total of 7,736 patients were stratified into two different strata depending on baseline and ongoing additional osteoporosis treatments (see strata definitions below) and then randomized 1:1 to receive zoledronic acid (5mg) or placebo intravenously over 15 minutes 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.

Visits 1 and 2	Visit 3	Visit MV3A ¹	Visit MV3B ²	Visit 4	Visits 5 and 6 ³	Visits MV5A and MV6A ¹	Visit 7
Maximum of 2 months prior to Visit 3	Day 0	9-11 days after Visit 3	1 month	6 months/ Day 180	12 and 24 months/Days 365 and 730	9-11 days after Visit 5 and Visit 6	36 months/ Day 1095
Screening /Eligibility	Randomization/ Dose Administration 5.0 mg zoledronic acid or placebo	Renal function testing	Renal function testing	Safety evaluation	Dose administration 5.0 mg zoledronic acid or placebo	Renal function testing	Safety evaluation

¹ MV3A (Monitoring Visit 3A), MV5A, and MV6A were to be performed on a cohort of 3500 patients 9 to 11 days after dosing, counting the day of dosing as Day 0. This cohort was to include the first 600 patients enrolled into the study plus 2900 additional patients from selected clinical sites enrolled throughout the course of the trial.
² Laboratory results for the first 600 patients in the 3500 patient renal monitoring cohort were to be reviewed and if a patient was found to have renal impairment at MV3A, MV3B was to be done at 1 month. Subsequent monitoring was to be done, if needed, at 3 months (MV3C) and 6 months after the first dose.
³ Up to 3 weeks prior to dosing at Visits 5 and 6, an additional visit was required to perform laboratory tests. This visit could be done up to 3 weeks prior to dosing. Laboratory results must have been available and reviewed prior to dosing the patient.

Source: [Study 2301, Figure 3-1]

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Visit Schedule

Examination	Screening			Dose administration/ Evaluation							7
	1	2	3	MV3A ^a	MV3B ^a	4	5	MV5A ^b	6	MV5A ^a	
Visit	Maximum of 2 months prior to V3			0	9-11 days after V3			9-11 days after V5		5-11 days after V5	
Day											
Month					1 month after V3	6	12		24		-1 month prior to biopsy
Informed consent(s)	X										
Medical history	X										
Inclusion/exclusion criteria	X	X									
Adverse experiences ¹			X	X	X	X	X	X	X	X	X
Concomitant medications ¹	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X						X		X		X
Physical examination including height (stadiometer, where available at clinical sites) and weight	X (Visit 1 or 2)						X (rx & wt only)		X (rx & wt only)		X
Central Laboratory (hematology, biochemistry, urinalysis)	X						X		X	X ^a	X
Study drug administration (zoledronic acid or placebo)			X				X		X		
Serum C-telopeptides (CTX), BSAP ²			X			X	X		X		X
PINP and other indicators of bone turnover ²			X				X		X		X
Urine and blood collection (stored for future analysis, 500 patients, at least 400 in Stratum I)			X			X	X		X		X
Calculated creatinine clearance ^a	X	X					X		X		
Examination	Screening			Dose administration/ Evaluation							
Visit	1	2	3	MV3A ^a	MV3B ^a	4	5	MV5A ^b	6	MV5A ^a	7
Day	Maximum of 2 months prior to V3			0	9-11 days after V3			9-11 days after V5		5-11 days after V5	
Month					1 month after V3	6	12		24		-1 month prior to biopsy
VRQ call	X	X	X			X	X		X		X
Renal monitoring: serum creatinine, BUN, electrolytes, calcium, magnesium, phosphorus and urinalysis ^a	X	X		X	X			X		X ^a	
DXA measurements hip (all patients)	X (Visit 1 or 3)					X	X		X		X
DXA measurements spine & distal radius (400 patients, at least 200 patients in Stratum I)			X			X	X		X		X
Lateral vertebral x-rays	X (Visit 1 or 2)						X ^a		X ^a		X
QCT of hip and spine (300 patients, at least 150 patients in Stratum I)			X								X
Blood collection for pharmacogenetics (pre-dose)			X								
Electrocardiogram (400 Stratum I patients)									X	X	
Bone biopsy informed consent									X		
Tetracycline dispensed to patients who agreed to bone biopsy											X
Urine samples for bone biopsy patients											X
Bone biopsy (approximately 200 patients)											X
Quartely Back Pain Questionnaire ³			X			X	X		X		X
Back Function Questionnaire ⁴			X				X		X		X
MiniOQLQ ^{5,6}			X				X		X		X
Health Care Resource Utilization Questionnaire ⁷						X	X		X		X
Collect data on clinical fractures						X	X		X		X
Days of Disability After Fracture ⁷						X	X		X		X
Termination											X

ASAP = bone specific alkaline phosphatase; miniOQLQ = Mini Osteoporosis Quality of Life Questionnaire
Also to be completed during the quarterly telephone contact.
Subset of 500 (placebo) randomized patients (at least 300 patients in Stratum 1) at selected clinical sites.
Subset of approximately 2500 (placebo) selected randomized patients at selected sites.
Must be calculated prior to dosing. See section 3.5.3, under Renal Monitoring for further details.
In addition to 2 baseline measurements for all screened patients, a subset of 3500 (placebo) randomized patients were to have assessment of serum creatinine, BUN and urinalysis performed by a central laboratory at 9 through 11 days after each dose (Visits 2, 5 and 6). For MV6A (9 through 11 days after the 3rd dose, Visit 6), a full chemistry panel was to be performed.
Results of MV3A will be reviewed for each of the first 600 patients of the 3500 (placebo) patient group being monitored for renal safety. If the 9 through 11 day (MV3A) assessment shows an impairment of renal function, then MV3B will not be required. But if the 9 through 11 day visit shows evidence of impaired renal function, then follow-up will be required. A 1-month post-dose assessment will be done (MV3B). If renal impairment is still seen at MV3B, further monitoring Visits will be required until resolution (e.g. MV3C at 3 months).
Performed for Stratum 1 patients only.
Completed by patients in native English speaking countries only.
Only the 3300 (placebo) patients in the renal safety cohort will have a full chemistry panel and urinalysis instead of a renal chemistry panel and urinalysis.

All the participants were required to meet the following washout schedule for prior bisphosphonate use:

Oral bisphosphonates:

- At least 2-year washout prior to randomization (if used for 48 weeks or longer)
- At least 1-year washout prior to randomization (if used for greater than 8 weeks but less than 48 weeks)
- At least 6-month washout prior to randomization (if used for greater than 2 weeks less than or equal to 8 weeks)
- At least 2-month washout prior to randomization (if used less than or equal to 2 weeks)

Intravenous bisphosphonates:

- At least 2-year washout prior to randomization regardless of the duration of use

Stratum 1 subjects (n=6,084) consisted of women who would not receive additional osteoporosis therapies other than calcium and vitamin D and had been adequately washed out from any prior therapies they may have received.

Stratum 2 subjects (n=1,652) consisted of women who were to receive any of the list of approved additional osteoporosis therapies [HRT, SERMs (raloxifene), calcitonin, tibolone, tamoxifen, ipriflavone, dehydroepiandrosterone(s), medroxyprogesterone] either starting or continuing at randomization or who did not adequately meet the wash out schedule listed for Stratum 1 subjects.

The reason for enrolling patients into these two strata was derived from the ethical concern of encouraging women with osteoporosis to enroll in a placebo-controlled study lasting for 3 years. By giving women enrolled in the study the option of starting the additional osteoporosis therapies permitted in Stratum 2, they could be guaranteed even if they ended up in the placebo group to get at least one currently approved drug for the treatment and/or prevention of osteoporosis. The efficacy endpoint of morphometric vertebral fracture was assessed only in the Stratum 1 patients as the additional osteoporosis therapies allowed in Stratum 2 have already been approved for this indication. The efficacy endpoint of hip fracture was assessed in the combined strata as additional osteoporosis therapies allowed in Stratum 2 have not been demonstrated to reduce the risk of hip fractures.

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Inclusion criteria included but not limited to:

- Postmenopausal women 65 through 89 years of age.
- Radiological evidence of at least 2 mild or moderate existing vertebral fractures and a femoral neck BMD T-score ≤ -1.5 or a femoral neck BMD T-score ≤ -2.5 with or without an existing vertebral fracture
- Ambulatory with or without an assistive device (e.g. cane, walker)

Exclusion criteria included but not limited to:

- Use of intravenous bisphosphonates in the past two years.
- Use of oral bisphosphonates without an adequate washout period
- Use of strontium formulations at any time
- Use of PTH for more than 1 week, or with ≤ 6 month washout if used for ≤ 1 week
- Use of sodium fluoride for >3 months and/or a total dose of elemental fluoride >1500 mg at any time; or with a ≤ 2 -year washout if prior use of sodium fluoride for ≤ 3 months and/or total dose of elemental fluoride ≤ 1500 mg
- Use of anabolic steroids or growth hormone within 6 months of entry in the trial
- Use of oral or intravenous systemic corticosteroids within the last year
- With a history of iritis or uveitis, except when secondary to trauma, and must have resolved > 2 years prior to randomization
- History of osteogenesis imperfecta, multiple myeloma, or Paget's disease
- Uncontrolled seizure disorders associated with falls
- Active primary hyperparathyroidism
- Self-reported history of diabetic nephropathy or retinopathy
- Abnormal baseline serum calcium > 2.75 mmol/L (11.0mg/dL) or < 2.0 mmol/L (8mg/dL)
- Baseline calculated creatinine clearance < 30 mL/min, urine dipstick $\geq 2+$ protein or increase in serum creatinine of > 0.5 mg/dL between baseline Visits 1 & 2.

The intent-to-treat (ITT) population is comprised of all 7,736 randomized patients.

The modified intent-to-treat (mITT) population is comprised of all randomized patients in Stratum I who had evaluable radiographs over the period being analyzed for at least 1 vertebra.

The per-protocol population (PP) was used for the analysis of time to the first hip fracture and included patients in the ITT population who did not have any major protocol violation(s) that would potentially bias the analysis in either stratum.

The renal safety population included a subset of 4,982 patients from the safety population who had a baseline serum-creatinine result and at least 1 renal monitoring measurement for serum creatinine or proteinuria (urine dipstick).

The ECG safety cohort included a subset of 559 patients monitored before and 9 to 11 days after their third study infusion.

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The bone biopsy subset included 131 patients. A spine/distal radius subset of 549 patients were analyzed by dual x-ray absorptiometry (DXA).

A C-telopeptides (CTx) and bone specific alkaline phosphatase (BSAP) (bone resorption markers) subset included 605 patients. A PINP (bone formation marker) subset included 1246 patients.

6.1.4 Efficacy Findings

Primary endpoint

New morphometric vertebral fractures, the first part of the coprimary 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 9% and a relative risk reduction of 70% (95% CI: 62% to 76%, $p < 0.0001$). Similar results were observed in the Per Protocol (PP) population with an event rate of 3.5% in the zoledronic acid group compared to 11.6% in the placebo group for a relative risk reduction of 70% (95% CI: 61% to 76%, $p < 0.0001$). At 36 months patients in the zoledronic acid group consistently had statistically fewer 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/m²), 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).

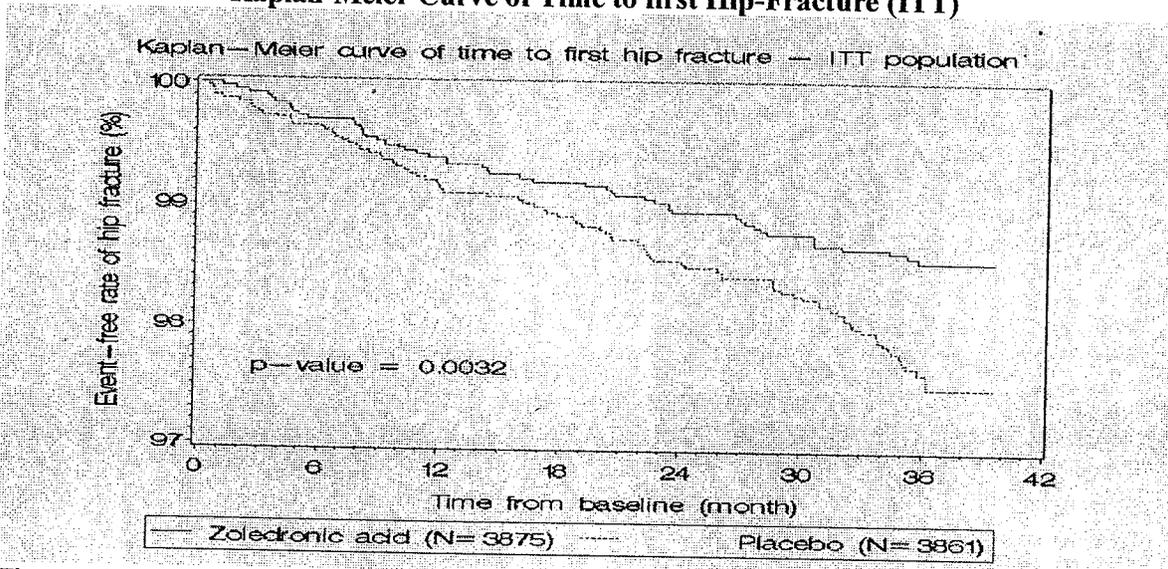
Medical officer's comment-There were too few black subjects enrolled in this study to draw any conclusions about efficacy in this subgroup (e.g. 1/11 black placebo patients and 0/11 black ZA patients had at least one new vertebral fracture).

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% reduction in the risk of hip fractures ($p = 0.0032$). Similar results were observed in the Per Protocol (PP) population with an event rate of 1.46% in the zoledronic acid group compared to 2.40% in the placebo group for a hazard ratio of 0.63 (95% CI: 0.44 to 0.90, $p=0.01$). The curves are seen to start to diverge within the first few months of treatment (see Figure 1). Whereas the hazard ratios were similar for the two strata, 0.60 and 0.58 for Stratum I and II respectively, the data from Stratum II alone was not statistically significant ($p < 0.009$ Stratum I vs. $p=0.17$, Stratum II) because of the smaller number of patients in Stratum II (n=1,652) compared to Stratum I (n=6,084). At 36 months patients in the zoledronic acid group consistently had trends for fewer fractures than placebo patients in the following 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/m²), femoral neck BMD T-score designations (≤ -2.5 and

> -2.5), prevalence of vertebral fractures at baseline (0, 1, \geq 2), baseline creatinine clearance (< 60 and \geq 60 mL/min), and prior use of bisphosphonates (yes/no). However, statistically significant differences were observed only in the following subgroups: age <70 and 70-74, Caucasian race, BMI >25 kg/m², femoral neck BMD T-score designations (\leq -2.5 and > -2.5), prevalence of 1 vertebral fracture at baseline, baseline creatinine clearance (< 60 and \geq 60 mL/min), and prior use of bisphosphonates (yes/no).

Figure 1

Kaplan-Meier Curve of Time to first Hip-Fracture (ITT)



The p-value came from a stratified log-rank test analyzed by study population stratum.

Secondary endpoints

All 20 secondary endpoints were found to be statistically significant with p-values ranging from 0.008 to 0.00001, well below the 0.05 level limit proposed in the closed testing procedure. A review of each of the twenty secondary endpoints is provided:

- 1) Proportion of patients with at least one new vertebral fracture over 12 months in Stratum I (Measured at 0-1, 0-2 and 0-3 years, mITT population)- Measurements of at least one new vertebral fracture were statistically significant compared to placebo over 0-12 months, 0-24 months and 0-36 months in the mITT population. The relative risk reduction seems to plateau around 70% at 24 months.

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Table 2
 Between-treatment comparison of the proportion of patients with at least one 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	42	1.5	106	3.7	0.40	<0.0001
0-24 months	63	2.2	220	7.7	0.29	<0.0001
0-36 months	92	3.3	310	10.9	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.

- 2) Proportion of patients with at least one new and/or worsening vertebral fracture over 36 months in Stratum I, (mITT population)- Measurements of at least one new and/or worsening vertebral fracture were statistically significant compared to placebo over 0-12 months, 0-24 months and 0-36 months in the mITT population, even though only the 36 month time point was chosen as a secondary endpoint. The relative risk reductions were slightly less for new and/or worsening fractures than for new fractures alone seen in Table 2, suggesting that zoledronic acid is slightly less effective at preventing worsening fractures than new fractures, but the number of fractures are too small to draw any clear conclusions in this regard.

Table 3
 Between-treatment comparison of the proportion of patients with at least one new and/or worsening vertebral fracture in Stratum I (mITT population)

Period	Zoledronic Acid n=2822		Placebo n=2853		Relative Risk	p-value
	n	%	n	%		
0-12 months	48	1.7	115	4.0	0.42	<0.0001
0-24 months	75	2.7	239	8.4	0.32	<0.0001
0-36 months	107	3.8	333	11.7	0.32	<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.

- 3) Proportion of patients with at least one moderate to severe new vertebral fracture over 36 months in Stratum I (mITT population)- Measurements of at least one moderate to severe new vertebral fracture were statistically significant compared to placebo over 0-12 months, 0-24 months and 0-36 months in the mITT population, even though only the 36 month time point was chosen as a secondary endpoint. The relative risk reduction seems to plateau around 70% at 24 months.