Sponsor

Novartis

Generic Drug Name

Zoledronic acid

Trial Indication(s)

Osteoporosis

Protocol Number

CZOL446H2301

Protocol Title

A multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of zoledronic acid in the treatment of osteoporosis in postmenopausal women taking calcium and vitamin D

Clinical Trial Phase

Phase III

Study Start/End Dates

22-Jan-2002 to 15-Jun-2006.

Reason for Termination

Not applicable.

Study Design/Methodology

This was an international, multi-center, randomized, double-blind, placebo-controlled trial in postmenopausal women with osteoporosis. Participants were classified and placed into one of two strata for treatment based on their "usual care" concomitant osteoporosis medication use at or prior to randomization. "Usual care" was comprised of various medications that included hormone replacement therapy, selective estrogen receptor modulators (raloxifene), calcitonin, tibolone, tamoxifen, dehydroepiandrosterone(s), ipriflavone, or medroxyprogesterone. Those in Stratum I received calcium and vitamin D only in addition to their assigned study drug, but no additional concomitant osteoporosis medications were allowed. The "usual care" for women in Stratum II involved taking calcium and vitamin D, plus any one of the additional osteoporosis medications listed above. All participants (Stratum I and Stratum II) were required to meet washout criteria for prior bisphosphonate use.

Centers

240 centers in 27 countries: 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), United Kingdom (5), and United States (65).

Objectives:

Primary efficacy objective

- To assess the proportion of patients with at least one new vertebral fracture over 3 years in Stratum I (modified intent to treat [mITT])
- To assess the time to first hip fracture in all patients (Stratum I+II).

Secondary efficacy objectives

- To assess the proportion of patients in Stratum I with at least (a) one new vertebral fracture, and (b) one new and/or worsening vertebral fracture
- To assess the time to first clinical fracture, clinical vertebral fracture, and non-vertebral clinical fracture
- To assess the percent change in bone mineral density (BMD) over 36 months relative to baseline for the hip (all sites), lumbar spine, and distal radius
- To assess the relative change in the biochemical markers of bone formation over 36 months (N-terminal propeptide of type I collagen {P1NP} and bone specific alkaline phosphatase {BSAP})
- To assess the relative change in the biochemical marker of bone resorption (beta c-telopeptides {b-CTx}) over 36 months
- To assess the change in stadiometer height over 36 months relative to baseline
- To assess the number of days of disability during the study due to a fracture or back pain that cause limited activities and bed rest

Safety objectives

- The overall AE profile.
- Changes in laboratory parameters from baseline.
- Changes in renal function 9-11 days following each study drug infusion and over the course of the entire study in a subset of 5035 patients.
- Changes in ECG parameters after the third study drug infusion in a subset of 559 patients.
- Bone quality through histomorphometry measurements taken from bone biopsies at 36 months in a subset of 152 patients.

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational therapy was supplied as a solution (5 mg zoledronic acid in 5 mL of sterile water for infusion) and was further diluted with 100 mL of normal saline. In addition, a new dosage form consisting of a 5 mg/100 mL zoledronic acid in a ready-to-infuse plastic bottle was made available. Zoledronic acid was given as a single, slow, 15-minute intravenous infusion. Patients received a single 15-minute intravenous administration of zoledronic acid 5 mg once per year at 0 (Day 0), 12, and 24 months and were then monitored over a 3-year period.

Statistical Methods

With approximately 3700 patients per treatment group, a two-sided log-rank test for equality of survival curves had approximately 90% power at a significance level of 5% to detect a 50% reduction in the incidence of hip fractures. This assumed a placebo fracture rate of 1.8% over 3 years under an exponential model and an annual exponential dropout rate of 0.054. A 2-group continuity corrected chi-square test with a 5%, 2-sided significance level had approximately 90% power to detect a 50% reduction in the proportion of patients with a new morphometric vertebral fracture over 3 years with 1126 patients per treatment group. This assumed a placebo fracture rate of 1.9% per year. A 2-group continuity corrected chi-square test with a 5%, 2-sided significance level had approximately an 80% power to detect a difference in the proportion of patients with a new and/or worsening vertebral fracture at 1 year when the sample size in each group is 1479 patients. This assumes an incidence of new and/or worsening vertebral fracture of 2.25% over the first year of the study in the placebo group and a 60% reduction in the zoledronic acid group.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Females, between 65 and 89 years of age, inclusive (at randomization).
- With either one of the two following fracture criteria:
  - Radiological evidence of at least two mild or one moderate existing vertebral fracture(s) and a femoral neck BMD T-score ≤ -1.5 (a local reading of BMD was used)
  - Femoral neck BMD T-score ≤ -2.5 with or without evidence of an existing vertebral fracture (a local reading of BMD was used)
- Who could not take or decided not to take oral bisphosphonates, fluoride, strontium, or parathyroid hormone (PTH)
- Who were ambulatory or ambulatory with an assistive device (cane, walker, etc)
- Who had signed written informed consent

Exclusion criteria:

- With any prior use of intravenous bisphosphonate within the last 2 years
- Who used oral bisphosphonates except according to the washout schedule
  - At least 2 years (if used for 48 weeks or longer)
  - At least 1 year (if used for greater than 8 weeks but less than 48 weeks)
  - At least 6 months (if used for greater than 2 weeks but less than or equal to 8 weeks)
  - At least 2 months (if used less than or equal to 2 weeks)

- With prior use of strontium (all formulations)
- With prior use of PTH for more than 1 week; or with a ≤ 6-month washout if used for ≤ 1 week
- With prior 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
- With prior exposure to anabolic steroids or growth hormone within 6 months of entry in the trial
- With prior 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.
- With serum calcium greater than 2.75 mmol/L (11.0 mg/dL).
- With hypocalcemia (serum calcium less than 8 mg/dL or 2.0 mmol/L at Visit 1 and/or Visit 2).
- With a baseline renal insufficiency (calculated creatinine clearance < 30.0 mL/min) at Visit 1 or Visit 2, or urine dipstick ≥ 2+ protein without evidence of contamination or bacteriuria.
- With a serum creatinine increase between Visit 1 and Visit 2 of > 0.5 mg/dL.
- Who had bilateral hip replacement or bilateral hip surgery with implantation of an appliance.
- With a new diagnosis or active treatment for cancer less than or equal to 12 months prior to Visit 1; or those with known metastases (or by history). Those with the following were not excluded: basal cell or squamous cell carcinoma of the skin, colonic polyps with non-invasive malignancy which have been removed, ductal carcinoma in-situ (DCIS) that has been surgically removed, and carcinoma-in-situ (CIS) of the uterine cervix that has been surgically removed.
- With AST or ALT greater than twice the upper limit of normal.
- With alkaline phosphatase greater than twice the upper limit of normal.
- With a history of hypersensitivity to bisphosphonates.
- Who had used any investigational drug(s) and/or devices within 30 days prior to randomization.
- With any medical or psychiatric condition which, in the Investigator's opinion, would preclude the participant from adhering to the protocol or completing the trial per protocol.
- Who used hip protectors

Participant Flow Table

Patient disposition (ITT Population)

	Zoledronic acid N=3875 n (%)	Placebo N=3861 n (%)	Total N=7736 n (%)
Total no. of patients			
Completed	3248 (83.82)	3269 (84.67)	6517 (84.24)
Discontinued	627 (16.18)	592 (15.33)	1219 (15.76)
Reason for discontinuation			
Subject withdrew consent	297 (7.66)	284 (7.36)	581 (7.51)
Death	130 (3.35)	112 (2.90)	242 (3.13)
Lost to follow-up	82 (2.12)	75 (1.94)	157 (2.03)
Adverse Event(s)	80 (2.06)	70 (1.81)	150 (1.94)
Administrative problems	19 (0.49)	22 (0.57)	41 (0.53)
Protocol violation	11 (0.28)	15 (0.39)	26 (0.34)
Abnormal laboratory value(s)	4 (0.10)	5 (0.13)	9 (0.12)
Unsatisfactory therapeutic effect	2 (0.05)	7 (0.18)	9 (0.12)
Abnormal test procedure result(s)	2 (0.05)	1 (0.03)	3 (0.04)
Subject's condition no longer requires study drug	0 (0.00)	1 (0.03)	1 (0.01)

Baseline Characteristics

Demographic and disease background characteristics (All randomized patients)

Demographic variables	Zoledronic acid N=3875	Placebo N=3861	Total N=7736
Race, n (%)			
Caucasian	3054 (78.81%)	3055 (79.12%)	6109 (78.97%)
Black	15 (0.39%)	17 (0.44%)	32 (0.41%)
Hispanic	226 (5.83%)	215 (5.57%)	441 (5.70%)
Japanese	9 (0.23%)	12 (0.31%)	21 (0.27%)
Other Asian and Pacific Islander	553 (14.27%)	547 (14.17%)	1100 (14.22%)
Other	18 (0.46%)	15 (0.39%)	33 (0.43%)
Age group (year), n (%)			
< 65	7 (0.18%)	8 (0.21%)	15 (0.19%)
65 – 74	2371 (61.19%)	2401 (62.19%)	4772 (61.69%)
75 – 84	1405 (36.26%)	1356 (35.12%)	2761 (35.69%)
≥ 85	92 (2.37%)	96 (2.49%)	188 (2.43%)
Age (year)			
n	3875	3861	7736
Mean (SD)	73.1 (5.34)	73.0 (5.40)	73.1 (5.37)
Min, Median, Max	64, 73.0, 89	64, 73.0, 89	64, 73.0, 89

Demographic variables	Zoledronic acid N=3875	Placebo N=3861	Total N=7736
Weight (kg)			
n	3872	3860	7732
Mean (SD)	59.9 (11.11)	60.6 (11.33)	60.3 (11.23)
Min, Median, Max	32, 59.0, 119	26, 60.0, 129	26, 59.5, 129
Height (cm) – Non-Stadiometer			
n	1890	1890	3780
Mean (SD)	153.4 (7.19)	153.6 (7.09)	153.5 (7.14)
Min, Median, Max	126, 153.0, 178	115, 153.0, 177	115, 153.0, 178
Height (mm) – Stadiometer			
n	2179	2165	4344
Mean (SD)	1551.1 (70.73)	1550.9 (69.42)	1551.0 (70.07)
Min, Median, Max	1295, 1550.5, 1790	1330, 1551.0, 1791	1295, 1550.5, 1791

Summary of Efficacy

Primary Outcome Result

Between-treatment comparison of the proportion of patients with at least one new vertebral fracture over 36 months in Stratum I (mITT)

Treatment	N	n (%) [1]	Relative risk [2] 95% CI	p-value [3]
Zoledronic acid	2822	92 (3.26)	0.30 (0.24,0.38)	< 0.0001
Placebo	2853	310 (10.87)	---	---

[1]n is the number of patients with the event and % is calculated as n/N*100
[2]The relative risk is the likelihood of a vertebral fracture in the zoledronic acid group vs. the placebo group. A relative risk < 1 implies that zoledronic acid-treated patients have a lesser likelihood of having a vertebral fracture than placebo-treated patients
[3]The p-value comparing between-treatment differences in vertebral fracture rates is computed from a logistic regression with treatment and baseline fracture status as explanatory variables based on the likelihood ratio test.

Between-treatment comparison of the incidence of first hip fracture over time (ITT population)

Treatment	N	n [1]	Event rate(%) [2]	Hazard ratio(%) 95% CI [3]	p-value [4]
Zoledronic acid	3875	52	1.44	0.59	0.0024
Placebo	3861	88	2.49	(0.42, 0.83)	

[1]n is the number of patients with the event.
[2]The event rate is from Kaplan-Meier estimate at Month 36.
[3]The hazard ratio/95% CI of zoledronic acid vs. placebo is computed from a stratified Cox proportional hazards regression model with treatment as a factor and stratified by study population stratum. A hazard ratio < 1 implies that zoledronic acid-treated patients have a lower risk of having a hip fracture than placebo-treated patients.
[4]The p-value is calculated from a stratified log-rank test analyzed by study population stratum.

Between-treatment comparison of the incidence of first hip fracture over time by stratum (ITT population)

Stratum	Treatment	N	n [1]	Event rate (%) [2]	Hazard ratio(%) 95% CI [3]	p-value [4]
I	Zoledronic acid	3045	42	(1.48)	0.59 (0.41, 0.87)	0.0069
	Placebo	3039	71	(2.56)		
II	Zoledronic acid	830	10	(1.30)	0.58 (0.27, 1.27)	0.1686
	Placebo	822	17	(2.24)		

[1]n is the number of patients with hip fractures over time.
[2]The event rate is from Kaplan-Meier estimate at Month 36.
[3]The hazard ratio/95% CI of zoledronic acid vs. placebo is computed from a Cox proportional hazards regression model with treatment as a factor. A hazard ratio < 1 implies that zoledronic acid-treated patients have a lower risk of having a hip fracture than placebo-treated patients.
[4]The p-value is calculated from a log-rank test.

Secondary Outcome Results,

Between-treatment comparison of the proportion of patients with vertebral fracture in Stratum I (mITT population)

Endpoint	Period (months)	Treatment	N	n (%)	Relative Risk 95% CI [1,2]
At least one new vertebral fracture	0-12 †	Zoledronic acid	2822	42 (1.49)	0.40
		Placebo	2853	106 (3.72)	(0.28,0.57)***
	0-24	Zoledronic acid	2822	63 (2.23)	0.29
		Placebo	2853	220 (7.71)	(0.22,0.38)***
	0-36	Zoledronic acid	2822	92 (3.26)	0.30
		Placebo	2853	310 (10.87)	(0.24,0.38)***
At least one new/worsening vertebral fracture	0-12	Zoledronic acid	2822	48 (1.70)	0.42
		Placebo	2853	115 (4.03)	(0.30,0.59)***
	0-24	Zoledronic acid	2822	75 (2.66)	0.32
		Placebo	2853	239 (8.38)	(0.25,0.41)***
	0-36 †	Zoledronic acid	2822	107 (3.79)	0.32
		Placebo	2853	333 (11.67)	(0.26,0.40)***
At least one moderate/severe new vertebral fracture	0-12	Zoledronic acid	2822	35 (1.24)	0.40
		Placebo	2853	89 (3.12)	(0.27,0.59)***
	0-24	Zoledronic acid	2822	54 (1.91)	0.30
		Placebo	2853	185 (6.48)	(0.22,0.40)***
	0-36 †	Zoledronic acid	2822	79 (2.80)	0.30

Endpoint	Period (months)	Treatment	N	n (%)	Relative Risk 95% CI [1,2]
		Placebo	2853	267 (9.36)	(0.23,0.38)***
At least one moderate/severe new/worsening vertebral fracture	0-12	Zoledronic acid	2822	41 (1.45)	0.42
		Placebo	2853	98 (3.43)	(0.29,0.61)***
	0-24	Zoledronic acid	2822	66 (2.34)	0.32
		Placebo	2853	206 (7.22)	(0.25,0.43)***
	0-36	Zoledronic acid	2822	93 (3.30)	0.32
		Placebo	2853	293 (10.27)	(0.26,0.40)***
At least two new vertebral fractures	0-12 [3]	Zoledronic acid	N/A	N/A	N/A
		Placebo	N/A	N/A	N/A
	0-24	Zoledronic acid	2822	4 (0.14)	0.10
		Placebo	2853	41 (1.44)	(0.04, 0.27)***
	0-36	Zoledronic acid	2822	7 (0.25)	0.11
		Placebo	2853	66 (2.31)	(0.05, 0.23)***

†Corresponds to a secondary efficacy endpoint in the closed testing procedure specified for the interim analysis.
[1]The relative risk is the overall relative risk of zoledronic acid vs. placebo. A relative risk < 1 implies that zoledronic acid-treated patients have a lower chance of having the event than placebo-treated patients.
[2]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. ***p-value < 0.0001.
[3]Endpoint not analyzed and thus results not available.

Between-treatment comparisons of the proportion of patients in Stratum I with new vertebral fractures over 36 months in key subgroups (mITT population)

Subgroup	Category	Treatment	N	n (%)	Relative Risk 95% CI [1,2]
Age (years)	< 70	Zoledronic acid	832	17 (2.04)	0.20 (0.12, 0.34)***
		Placebo	852	85 (9.98)	
	70-74	Zoledronic acid	907	23 (2.54)	0.24 (0.16, 0.38)***
		Placebo	923	96 (10.40)	
	≥ 75 †	Zoledronic acid	1083	52 (4.80)	0.40 (0.29, 0.55)***
		Placebo	1078	129 (11.97)	
Prevalence of vertebral fractures at baseline	0 †	Zoledronic acid	1070	20 (1.87)	0.30 (0.20, 0.59)***
		Placebo	1038	60 (5.78)	
	1 †	Zoledronic acid	807	21 (2.60)	0.36 (0.22, 0.59)***
		Placebo	815	59 (7.24)	
	≥ 2 †	Zoledronic acid	945	51 (5.40)	0.28 (0.21, 0.38)***
		Placebo	1000	191 (19.10)	

†Subgroup included as one of the endpoints in the closed testing procedure specified for secondary efficacy variables (for interim analysis).
[1]The relative risk is the likelihood of a vertebral fracture in the zoledronic acid group vs. the placebo group within the subgroup. A relative risk < 1 implies that zoledronic acid-treated patients have a lesser likelihood of having the event than placebo-treated patients.
[2]The within subgroup p-value comparing the between-treatment difference for the subgroup is computed from the logistic regression with treatment and baseline fracture status in the model using log-likelihood type approach.
***p-value < 0.0001

Between-treatment comparisons of the incidence of first clinical fracture by fracture location (ITT population)

Location	Treatment	N	n	Event rate (%) [4]	Hazard ratio(%) 95% CI [5]	p-value [6]
Any clinical fracture [1]	Zoledronic acid	3875	308	8.42	0.67	<0.001
	Placebo	3861	456	12.83	(0.58, 0.77)	
Clinical vertebral fracture [2]	Zoledronic acid	3875	19	0.53	0.23	<0.001
	Placebo	3861	84	2.59	(0.14, 0.37)	
Non-vertebral fracture [1]	Zoledronic acid	3875	292	7.97	0.75	<0.001
	Placebo	3861	388	10.71	(0.64, 0.87)	
Hip	Zoledronic acid	3875	52	1.44	0.59	0.0024
	Placebo	3861	88	2.49	(0.42, 0.83)	
Wrist	Zoledronic acid	3875	97	2.68	0.81	0.1242
	Placebo	3861	120	3.32	(0.62, 1.06)	
Arm	Zoledronic acid	3875	41	1.13	0.58	0.0047
	Placebo	3861	71	1.95	(0.39, 0.85)	
Rib	Zoledronic acid	3875	35	0.93	1.06	0.8021
	Placebo	3861	33	0.95	(0.66, 1.71)	
Other [3]	Zoledronic acid	3875	92	2.53	0.76	0.0424
	Placebo	3861	122	3.36	(0.58, 0.99)	

[1]Excluding finger, toe, and facial bone fractures.
[2]Clinical vertebral fracture includes thoracic spine fracture and lumbar spine fracture.
[3]Other fracture excludes clinical vertebral, hip, wrist, arm, ribs, finger, toe, and facial bone fractures.
4 The event rate is from Kaplan-Meier estimate at Month 36.
[5] The hazard ratio/95% CI of zoledronic acid vs. placebo is computed from a stratified Cox proportional hazards regression model with treatment as a factor and stratified by study population stratum. A hazard ratio <1 implies that a zoledronic acid-treated patient has a lower risk of having the event than a placebo-treated patient.
[6] The p-value is calculated from a stratified log-rank test by study population stratum.
Note: Pathological fractures and fractures due to excessive trauma are excluded.

Between-treatment comparison of the percentage change from baseline in total hip BMD, femoral neck, and lumbar spine by visit (ITT population)

Location	Visit	Treatment	n [1]	LS mean [2]	LS mean difference 95% CI [2]
Total hip	Month 6 †	Zoledronic acid	3515	2.18	1.93 (1.76, 2.09)***
		Placebo	3543	0.25	
	Month 12	Zoledronic acid	3516	2.83	2.83 (2.65, 3.01)***
		Placebo	3542	-0.00	
	Month 24	Zoledronic acid	3228	3.72	4.70 (4.48, 4.92)***
		Placebo	3248	-0.98	
	Month 36 †	Zoledronic acid	3061	4.15	6.02 (5.77, 6.28)***
		Placebo	3077	-1.87	
Femoral neck	Month 6 †	Zoledronic acid	3522	2.17	1.58 (1.36, 1.80)***
		Placebo	3549	0.60	
	Month 12	Zoledronic acid	3522	2.70	2.17 (1.94, 2.41)***
		Placebo	3548	0.53	
	Month 24	Zoledronic acid	3234	3.38	3.89 (3.62, 4.16)***
		Placebo	3254	-0.50	
	Month 36 †	Zoledronic acid	3067	3.92	5.06 (4.76, 5.36)***
		Placebo	3083	-1.13	

Location	Visit	Treatment	n [1]	LS mean [2]	LS mean difference 95% CI [2]
Lumbar spine	Month 6	Zoledronic acid	268	2.93	2.39 (1.81, 2.96)***
		Placebo	265	0.54	
	Month 12	Zoledronic acid	262	3.88	3.66 (2.99, 4.33)***
		Placebo	258	0.22	
	Month 24	Zoledronic acid	236	5.76	5.90 (5.09, 6.71)***
		Placebo	226	-0.14	
	Month 36 †	Zoledronic acid	228	6.95	6.71 (5.69, 7.74)***
		Placebo	212	0.24	

†Corresponds to a secondary efficacy endpoint in the closed testing procedure specified for the interim analysis.
Note: The percentage change from baseline is defined as 100x (post-baseline value minus baseline value) divided by baseline value.
[1]n is the number of patients with evaluable measurements at both baseline and post-baseline visit, as determined by efficacy window.
[2]The LS mean is the least squares mean of the percentage change from baseline. The LS mean, the LS mean difference of zoledronic acid vs. placebo, 95% CI, and p-values are calculated from a three-way analysis of variance model with treatment, region (center was used for lumbar spine), and stratum in the model.
***p-value < 0.0001

Between-treatment comparison of serum b-CTx (ng/mL) by visit (Bone marker population [b-CTx and BSAP])

Visit	Treatment	n [1]	Mean (SE), Median	p-value
Baseline	Zoledronic acid	257	0.393 (0.015), 0.362	0.1337 [2]
	Placebo	260	0.421 (0.015), 0.370	
6 months post 1st infusion	Zoledronic acid	237	0.113 (0.006), 0.085	<0.0001 [3]
	Placebo	248	0.367 (0.013), 0.329	
2nd infusion (Month 12)	Zoledronic acid	201	0.160 (0.007), 0.141	<0.0001 [3]
	Placebo	214	0.406 (0.014), 0.380	
6 months post 2nd infusion	Zoledronic acid	136	0.130 (0.007), 0.105	<0.0001 [3]
	Placebo	156	0.437 (0.019), 0.414	
3rd infusion (Month 24)	Zoledronic acid	191	0.179 (0.008), 0.157	<0.0001 [3]
	Placebo	196	0.441 (0.017), 0.418	
9-11 days post 3rd infusion	Zoledronic acid	143	0.056 (0.004), 0.042	<0.0001 [3]
	Placebo	155	0.433 (0.017), 0.414	
1 month post 3rd infusion	Zoledronic acid	178	0.064 (0.004), 0.047	<0.0001 [3]
	Placebo	192	0.446 (0.016), 0.411	
3 months post 3rd infusion	Zoledronic acid	191	0.101 (0.006), 0.082	<0.0001 [3]
	Placebo	200	0.439 (0.015), 0.396	
6 months post 3rd infusion	Zoledronic acid	190	0.151 (0.007), 0.125	<0.0001 [3]
	Placebo	197	0.455 (0.016), 0.433	
Month 36 †	Zoledronic acid	174	0.205 (0.009), 0.174	<0.0001 [3]
	Placebo	170	0.473 (0.018), 0.460	

†Endpoint in closed testing procedure for secondary efficacy variables specified for the interim analysis.
[1]n is the number of patients with evaluable measurements at each visit, as determined by efficacy window
[2]The p-value for the between-treatment baseline comparison is from analysis of variance model on loge (baseline) with treatment, stratum, and center as explanatory variables.
[3] The p-value for the post-randomization between-treatment comparisons is obtained from the analysis of covariance model on loge (ratio) with treatment, stratum, center, and loge (baseline) as explanatory variables, where ratio is defined as the post-baseline value divided by the baseline value.

Between-treatment comparison of serum BSAP (ng/mL) by visit (Bone marker population [b-CTx and BSAP])

Visit	Treatment	n	Mean (SE), Median	p-value
Baseline	Zoledronic acid	299	14.37 (0.32), 13.03	0.8152
	Placebo	305	14.49 (0.35), 13.36	
6 months post 1st infusion	Zoledronic acid	288	8.78 (0.14), 8.45	<0.0001
	Placebo	295	13.48 (0.30), 12.67	
2nd infusion (Month 12)	Zoledronic acid	240	9.60 (0.19), 8.96	<0.0001
	Placebo	258	13.86 (0.32), 12.78	
6 months post 2nd infusion	Zoledronic acid	147	9.05 (0.22), 8.58	<0.0001
	Placebo	166	14.59 (0.46), 12.80	
3rd infusion (Month 24)	Zoledronic acid	230	9.75 (0.19), 9.23	<0.0001
	Placebo	237	14.35 (0.35), 13.46	
9-11 days post 3rd infusion	Zoledronic acid	158	10.03 (0.23), 9.54	<0.0001
	Placebo	168	14.02 (0.42), 13.14	
1 month post 3rd infusion	Zoledronic acid	202	9.08 (0.18), 8.65	<0.0001
	Placebo	220	13.75 (0.36), 12.69	
3 months post 3rd infusion	Zoledronic acid	213	8.18 (0.16), 7.80	<0.0001
	Placebo	227	13.78 (0.36), 12.80	
6 months post 3rd infusion	Zoledronic acid	211	8.69 (0.20), 8.31	<0.0001
	Placebo	223	13.83 (0.35), 12.82	
Month 36 †	Zoledronic acid	177	10.61 (0.62), 9.33	<0.0001
	Placebo	174	14.30 (0.44), 13.16	

†Endpoint in closed testing procedure for secondary efficacy variables specified for the interim analysis.
[1]n is the number of patients with evaluable measurements at each visit, as determined by efficacy window
[2]The p-value for the between-treatment baseline comparison is from analysis of variance model on loge (baseline) with treatment, stratum, and center as explanatory variables.
[3]The p-value for the post-randomization between-treatment comparisons is obtained from the analysis of covariance model on loge (ratio) with treatment, stratum, center, and loge (baseline) as explanatory variables, where ratio is defined as the post-baseline value divided by the baseline value.

Between-treatment comparison of serum P1NP (ng/mL) ratio by visit (P1NP population)

Visit	Treatment	n	Mean (SE), Median	p-value
Baseline	Zoledronic acid	619	53.98 (1.21), 49.95	0.6750
	Placebo	627	55.90 (1.28), 49.00	
2nd infusion (Month 12)	Zoledronic acid	553	21.35 (0.57), 18.12	<0.0001
	Placebo	579	50.38 (1.22), 46.18	
3rd infusion (Month 24)	Zoledronic acid	514	22.84 (0.75), 18.64	<0.0001
	Placebo	520	54.50 (1.38), 48.16	
Month 36 †	Zoledronic acid	411	25.65 (0.83), 21.86	<0.0001
	Placebo	401	53.43 (1.39), 48.88	

[†]Endpoint in closed testing procedure for secondary efficacy variables specified for the interim analysis.
1n is the number of patients with evaluable measurements at each visit, as determined by efficacy window
[2]The p-value for the between-treatment baseline comparison is from analysis of variance model on loge (baseline) with treatment, stratum, and center as explanatory variables.
[3]The p-value for the post-randomization between-treatment comparisons is obtained from the analysis of covariance model on loge (ratio) with treatment, stratum, center, and loge (baseline) as explanatory variables, where ratio is defined as the post-baseline value divided by the baseline value.

Between-treatment comparison of change from baseline in height (mm) by visit (ITT population)

Visit	Treatment	n [1]	LS mean [2]	LS mean difference 95% CI [2]
Month 12	Zoledronic acid	1955	-1.69	0.49 (-0.11, 1.09)
	Placebo	1960	-2.18	
Month 24	Zoledronic acid	1813	-3.05	1.78 (1.06, 2.50)***
	Placebo	1801	-4.83	
Month 36 †	Zoledronic acid	1707	-4.24	2.72 (1.92, 3.52)***
	Placebo	1686	-6.96	

†Endpoint in closed testing procedure for secondary efficacy variables specified for the interim analysis.
[1]n is the number of patients with evaluable measurements at both baseline and post-baseline visit, as determined by efficacy window.
[2]The LS mean is the least squares mean of the change from baseline. The LS mean, the LS mean difference of zoledronic acid vs. placebo, 95% CI, and p-values are calculated from a three-way analysis of covariance model with treatment, region, stratum, and baseline height in the model.
***p-value < 0.0001

Days of disability due to fracture during the study (ITT population)

			Zoledronic acid N=3875		Placebo N=3861	
Parameters	**Fracture**	**Days**	**n**	**(%)**	**n**	**(%)**
Bed Rest	Missing/Unknown	Missing	22	(0.57)	15	(0.39)
	Pt had no fracture	0	3433	(88.59)	3215	(83.27)
	Pt had a fracture	0	250	(6.45)	362	(9.38)
		1 -7	57	(1.47)	79	(2.05)
		8 - 14	29	(0.75)	45	(1.17)
		15 - 30	33	(0.85)	73	(1.89)
		31 - 60	27	(0.70)	40	(1.04)
		61 - 90	11	(0.28)	16	(0.41)
		> 90	13	(0.34)	16	(0.41)
Limited Activity	Missing/Unknown	Missing	22	(0.57)	15	(0.39)
	Pt had no fracture	0	3433	(88.59)	3215	(83.27)
	Pt had a fracture	0	89	(2.30)	154	(3.99)
		1 -30	132	(3.41)	155	(4.01)
		31 -60	86	(2.22)	111	(2.87)
		61 -90	54	(1.39)	90	(2.33)
		91 - 182	41	(1.06)	84	(2.18)
		> 182	18	(0.46)	37	(0.96)

Note: The fracture category is defined based on the quarterly CRF record on days of disability after fracture.

Days of disability due to back pain during the study (ITT population)

			Zoledronic acid N=3875		Placebo N=3861	
Parameters	**Back Pain**	**Days**	**n**	**(%)**	**n**	**(%)**
Bed Rest	Missing/Unknown	Missing	14	(0.36)	8	(0.21)
		0	14	(0.36)	12	(0.31)
	Pt had no back pain	0	491	(12.67)	456	(11.81)
	Pt had back pain	0	2778	(71.69)	2719	(70.42)
		1 -7	162	(4.18)	216	(5.59)
		8 -14	95	(2.45)	99	(2.56)
		15 -30	111	(2.86)	127	(3.29)
		31 - 182	169	(4.36)	175	(4.53)
		183 - 365	26	(0.67)	32	(0.83)
		> 365	15	(0.39)	17	(0.44)
Limited Activity	Missing/Unknown	Missing	14	(0.36)	8	(0.21)
		0	14	(0.36)	12	(0.31)
	Pt had no back pain	0	491	(12.67)	456	(11.81)
	Pt had back pain	0	1742	(44.95)	1682	(43.56)
		1 -91	986	(25.45)	987	(25.56)
		92 - 182	246	(6.35)	252	(6.53)
		183 - 273	113	(2.92)	125	(3.24)
		274 - 365	81	(2.09)	105	(2.72)
		366 - 547	91	(2.35)	100	(2.59)
		548 - 730	48	(1.24)	69	(1.79)
		> 730	49	(1.26)	65	(1.68)

Note: The back pain category is defined based on the quarterly CRF record on back pain questionnaire.

Summary of Safety

Safety Results

Adverse Events by System Organ Class

Most frequent adverse events (AEs) (at least 5.0% for any group) by primary system organ class (Safety population)

	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Patients studied		
Total no. of patients	3862	3852
Total no. of patients with AEs	3688 (95.49)	3616 (93.87)
Primary system organ class affected		
Musculoskeletal and connective tissue disorders	2515 (65.12)	2335 (60.62)
Infections and infestations	1968 (50.96)	1930 (50.10)
General disorders and administration site conditions	1669 (43.22)	853 (22.14)
Gastrointestinal disorders	1477 (38.24)	1359 (35.28)
Nervous system disorders	1271 (32.91)	1085 (28.17)
Injury, poisoning and procedural complications	1014 (26.26)	1200 (31.15)
Vascular disorders	768 (19.89)	750 (19.47)
Metabolism and nutrition disorders	581 (15.04)	567 (14.72)
Respiratory, thoracic and mediastinal disorders	557 (14.42)	591 (15.34)
Cardiac disorders	542 (14.03)	485 (12.59)
Eye disorders	538 (13.93)	500 (12.98)
Investigations	458 (11.86)	385 (9.99)
Psychiatric disorders	456 (11.81)	436 (11.32)

	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Skin and subcutaneous tissue disorders	408 (10.56)	429 (11.14)
Renal and urinary disorders	390 (10.10)	335 (8.70)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	298 (7.72)	279 (7.24)
Ear and labyrinth disorders	265 (6.86)	262 (6.80)
Blood and lymphatic system disorders	241 (6.24)	218 (5.66)

Most Frequently Reported AEs Overall by Preferred Term n (%)

Most frequent AEs (at least 5.0% for any group) by preferred term (Safety population) n)

Preferred term	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Patients studied		
Total no. of patients	3862	3852
Total no. of patients with AEs	3688 (95.49)	3616 (93.87)
Preferred term		
Back pain	933 (24.16)	963 (25.00)
Arthralgia	918 (23.77)	785 (20.38)
Pyrexia	693 (17.94)	176 (4.57)
Hypertension	492 (12.74)	477 (12.38)
Headache	478 (12.38)	310 (8.05)

Urinary tract infection	468 (12.12)	451 (11.71)
Myalgia	452 (11.70)	143 (3.71)
Pain in extremity	437 (11.32)	383 (9.94)
Nasopharyngitis	435 (11.26)	425 (11.03)
Influenza	365 (9.45)	343 (8.90)
Osteoarthritis	351 (9.09)	374 (9.71)
Influenza-like illness	341 (8.83)	103 (2.67)
Nausea	330 (8.54)	199 (5.17)
Dizziness	295 (7.64)	257 (6.67)
Constipation	285 (7.38)	294 (7.63)
Shoulder pain	267 (6.91)	214 (5.56)
Cataract	244 (6.32)	222 (5.76)
Diarrhea	232 (6.01)	215 (5.58)
Bone pain	222 (5.75)	87 (2.26)
Fatigue	209 (5.41)	135 (3.50)
Chills	206 (5.33)	38 (0.99)
Bronchitis	205 (5.31)	234 (6.07)
Asthenia	194 (5.02)	112 (2.91)

Serious Adverse Events and Deaths

Category	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Total	3436 (88.97)	3368 (87.44)
Death and SAEs		
Death	130 (3.37)	112 (2.91)
SAEs [1]	1126 (29.16)	1158 (30.06)
Other significant AEs		
Discontinuation from study drug		
SAEs	135 (3.50)	121 (3.14)
Non-serious AEs	75 (1.94)	70 (1.82)
AEs	209 (5.41)	187 (4.85)
Discontinuation from study		
AEs	80 (2.07)	70 (1.82)
Lab abnormalities	4 (0.10)	4 (0.10)
AEs requiring concomitant medications	3352 (86.79)	3282 (85.20)
Targeted AEs		
AEs associated with change in renal function	190 (4.92)	168 (4.36)
AEs of hypocalcemia	11 (0.28)	5 (0.13)

Qualitative ECG abnormalities pre-3rd infusion or post-3rd infusion (ECG Population)

ECG Findings	Abnormality	Zoledronic acid Total=278 n	Zoledronic acid Total=278 (%)	Placebo Total=281 n	Placebo Total=281 (%)
Arrhythmia	Total	43	(15.47)	42	(14.95)
	VPC	20	(7.19)	13	(4.63)
	APC	27	(9.71)	32	(11.39)
Conduction	Total	61	(21.94)	74	(26.33)
	First degree AV block	30	(10.79)	35	(12.46)
	RBBB	6	(2.16)	11	(3.91)
	IVCD	3	(1.08)	5	(1.78)
	LBBB	4	(1.44)	7	(2.49)
	Left anterior hemiblock	27	(9.71)	30	(10.68)
	IRBBB	1	(0.36)	2	(0.71)
	Prolonged QTc	4	(1.44)	2	(0.71)
MYOCARDIAL	Total	4	(1.44)	3	(1.07)
	Septal MI V1, V2, (V3)	2	(0.72)	1	(0.36)
	Antero septal MI V1-V4	1	(0.36)	0	(0.00)
	Inferior MI (2), 3, F	1	(0.36)	2	(0.71)

Qualitative ECG abnormalities pre-3rd infusion or post-3rd infusion (ECG Population) – continued…

ECG Findings	Abnormality	Zoledronic acid Total=278 n	Zoledronic acid Total=278 (%)	Placebo Total=281 n	Placebo Total=281 (%)
Rhythm	Total	35	(12.59)	27	(9.61)
	Sinus bradycardia	14	(5.04)	13	(4.63)
	Sinus tachycardia	7	(2.52)	1	(0.36)
	Atrial fibrillation	6	(2.16)	8	(2.85)
	Artificial Pacemaker	4	(1.44)	0	(0.00)
	Ventricular bigeminy	0	(0.00)	1	(0.36)
	Ventricular trigeminy	1	(0.36)	1	(0.36)
	Atrial bigeminy	4	(1.44)	1	(0.36)
	Ectopic Supraventricular Rhythm	1	(0.36)	2	(0.71)
	Other abnormal rhythm	1	(0.36)	1	(0.36)
ST segment	Total	4	(1.44)	6	(2.14)
	Depressed ST segment	4	(1.44)	6	(2.14)
T waves	Total	35	(12.59)	26	(9.25)
	Flat T waves	18	(6.47)	11	(3.91)
	Inverted T waves	16	(5.76)	14	(4.98)
	Biphasic T waves	8	(2.88)	2	(0.71)
U waves	Total	1	(0.36)	0	(0.00)
	U waves present	1	(0.36)	0	(0.00)

Other Relevant Findings

AEs associated with change in renal function (Safety population)

Preferred term	Zoledronic acid N=3862 n (%)	Placebo N=3852 n (%)
Total no. of patients with AEs associated with change in renal function	190 (4.92)	168 (4.36)
Creatinine renal clearance decreased	78 (2.02)	91 (2.36)
Renal impairment	35 (0.91)	33 (0.86)
Blood creatinine increased	30 (0.78)	12 (0.31)
Renal failure	29 (0.75)	23 (0.60)
Proteinuria	13 (0.34)	8 (0.21)
Renal failure acute	12 (0.31)	6 (0.16)
Azotemia	5 (0.13)	0 (0.00)
Nephritis	2 (0.05)	0 (0.00)
Glomerulonephritis	1 (0.03)	1 (0.03)
Glomerulonephritis acute	1 (0.03)	0 (0.00)
Glomerulonephritis membranoproliferative	1 (0.03)	0 (0.00)
Glomerulonephritis proliferative	1 (0.03)	0 (0.00)
Renal failure chronic	1 (0.03)	4 (0.10)
Scleroderma renal crisis	1 (0.03)	0 (0.00)
Acute prerenal failure	0 (0.00)	2 (0.05)
Nephrotic syndrome	0 (0.00)	1 (0.03)

Increase from baseline in serum creatinine more than 0.5 mg/dL and/or urinary protein dipstick more than 2+ by 9-11 day post-infusion visit (Renal safety population)

Visit / Criterion	Zoledronic acid N	Zoledronic acid n	Zoledronic acid (%)	Placebo N	Placebo n	Placebo (%)
9-11 day post 1st infusion						
Increase in serum creatinine > 0.5 mg/dL	2114	13	(0.61)	2130	6	(0.28)
Urinary protein – dipstick > 2+	2086	6	(0.29)	2101	3	(0.14)
9-11 day post 2nd infusion						
Increase in serum creatinine > 0.5 mg/dL	1663	19	(1.14)	1721	8	(0.46)
Urinary protein – dipstick > 2+	1644	5	(0.30)	1706	1	(0.06)
9-11 day post 3rd infusion						
Increase in serum creatinine > 0.5 mg/dL	1560	15	(0.96)	1600	7	(0.44)
Urinary protein – dipstick > 2+	1469	4	(0.27)	1514	0	(0.00)
Overall [1]						
Increase in serum creatinine > 0.5 mg/dL	2320	42	(1.81)	2338	19	(0.81)
Urinary protein – dipstick > 2+	2244	14	(0.62)	2262	4	(0.18)

Note: N is the number of patients with baseline and at least one post-baseline measurement at the specified visit, as determined by safety window. For protein urine dipstick, baseline urine dipstick ≤ 2+ is required.
Note: n is the number of patients who reported the event at least once at the specified visit, as determined by safety window.
[1]The overall indicates any 9-11 day post-infusion visit.

Increase from pre-infusion in serum creatinine more than 0.5 mg/dL by 9–11 day post-infusion visit (Renal safety population)

Visit	Zoledronic acid			Placebo		
Criteria	N	n	(%)	N	n	(%)
9-11 days post 1st infusion						
Increase in serum creatinine > 0.5 mg/dL	2114	13	(0.61)	2130	6	(0.28)
9-11 days post 2nd infusion						
Increase in serum creatinine > 0.5 mg/dL	1663	12	(0.72)	1721	1	(0.06)
9-11 days post 3rd infusion						
Increase in serum creatinine > 0.5 mg/dL	1560	8	(0.51)	1600	3	(0.19)
Overall [1]						
Increase in serum creatinine > 0.5 mg/dL	2320	31	(1.34)	2338	10	(0.43)

Note: N is the number of patients with baseline and at least one post-baseline measurement at the specified visit, as determined by safety window.
Note: n is the number of patients who reported the event at least once at the specified visit, as determined by safety window
[1]Overall indicates any 9–11 day post infusion visit.

Effect of active hypertension at baseline on increases from baseline in serum creatinine more than 0.5 mg/dL by visit (renal safety population)

Visit	Active hypertension	Zoledronic acid n/N (%)	Placebo n/N (%)
9-11 days post 1st infusion	Yes	10/917 (1.09)	3/941 (0.32)
	No	3/1197 (0.25)	3/1189 (0.25)
9-11 days post 2nd infusion	Yes	17/683 (2.49)	4/751 (0.53)
	No	2/980 (0.20)	4/970 (0.41)
9-11 days post 3rd infusion	Yes	11/644 (1.71)	6/686 (0.87)
	No	4/916 (0.44)	1/914 (0.11)

Renal laboratory data (Safety population)

Visit Criterion	Zoledronic acid N	n	(%)	Placebo N	n	(%)
Pre 2nd infusion (Month 12)						
Increase in serum creatinine > 0.5 mg/dL	3595	19	(0.53)	3624	9	(0.25)
Urinary protein – dipstick > 2+	3581	1	(0.03)	3606	3	(0.08)
Creatinine clearance < 30 mL/min	3574	49	(1.37)	3615	44	(1.22)
Pre 3rd infusion (Month 24)						
Increase in serum creatinine > 0.5 mg/dL	3289	16	(0.49)	3345	20	(0.60)
Urinary protein – dipstick > 2+	3277	3	(0.09)	3323	5	(0.15)
Creatinine clearance < 30 mL/min	3284	57	(1.74)	3337	63	(1.89)
Month 36						
Increase in serum creatinine > 0.5 mg/dL	3022	36	(1.19)	3066	38	(1.24)
Urinary protein – dipstick > 2+	2980	2	(0.07)	3021	5	(0.17)
Creatinine clearance < 30 mL/min	2994	97	(3.24)	3035	96	(3.16)
End of study visit [1]						
Increase in serum creatinine > 0.5 mg/dL	3752	36	(0.96)	3767	37	(0.98)
Urinary protein – dipstick > 2+	3749	5	(0.13)	3758	12	(0.32)
Creatinine clearance < 30 mL/min	3621	103	(2.84)	3658	106	(2.90)
During the study [2]						
Increase in serum creatinine > 0.5 mg/dL	3752	104	(2.77)	3767	77	(2.04)
Urinary protein – dipstick > 2+	3749	19	(0.51)	3758	19	(0.51)
Creatinine clearance < 30 mL/min	3621	160	(4.42)	3658	152	(4.16)

Note: N is the number of patients with baseline and at least one post-baseline measurement at the specified visit, as determined by safety window. For protein urine dipstick, baseline urine dipstick ≤ 2+ is required.
Note: n is the number of patients who reported the event at least once at the specified visit, as determined by safety window.
[1]Patients with abnormal renal lab data at the last assessment.
[2]Patients with abnormal renal lab data any time during the study. For patients in renal safety population, this includes the abnormality observed at the renal monitoring visits.

Mean changes in serum creatinine and calculated creatinine clearance from baseline over time (Safety population)

Lab parameter	Visit	Treatment	n	Mean change (SD)
Creatinine (umol/L)	Month 12	Zoledronic acid	3595	2.5 (10.30)
		Placebo	3624	2.5 (10.75)
	Month 24	Zoledronic acid	3289	4.3 (10.84)
		Placebo	3345	4.1 (11.94)
	Month 36	Zoledronic acid	3022	7.2 (12.27)
		Placebo	3066	6.9 (13.17)
	Last visit	Zoledronic acid	3752	6.6 (12.66)
		Placebo	3767	6.4 (13.14)
Creatinine clearance (mL/min)	Month 12	Zoledronic acid	3574	-3.05 (8.921)
		Placebo	3615	-3.35 (9.232)
	Month 24	Zoledronic acid	3284	-5.73 (8.986)
		Placebo	3338	-5.71 (9.498)
	Month 36	Zoledronic acid	2989	-8.75 (9.575)
		Placebo	3031	-8.67(9.625)
	Last visit	Zoledronic acid	3621	-8.28 (9.820)
		Placebo	3658	-8.19 (9.769)

Note: n is the number of patients with evaluable measurements at both baseline and the post-baseline visit, as determined by the safety window.

Adverse events of atrial fibrillation by year of dosing and time after dosing

Criteria	Zoledronic Acid	Placebo
Time after dosing	**n/N (%)**	**n/N (%)**
≤ 3 days		
Year 1	1/3862 (0.03)	0/3852 (0.00)
Year 2	0/3409 (0.00)	0/3517 (0.00)
Year 3	1/3107 (0.03)	1/3190 (0.03)
Cumulative	2/3862 (0.05)	1/3852 (0.03)
4-15 days		
Year 1	0/3862 (0.00)	0/3852 (0.00)
Year 2	2/3409 (0.06)	1/3517 (0.03)
Year 3	0/3107 (0.00)	1/3190 (0.03)
Cumulative	2/3862 (0.05)	2/3852 (0.05)
16-30 days		
Year 1	1/3862 (0.03)	1/3852 (0.03)
Year 2	0/3409 (0.00)	2/3517 (0.06)
Year 3	1/3107 (0.03)	0/3190 (0.00)
Cumulative	2/3862 (0.05)	3/3852 (0.08)
>30 days		
Year 1	29/3862 (0.75)	30/3852 (0.78)
Year 2	31/3409 (0.91)	21/3517 (0.60)
Year 3	35/3107 (1.13)	17/3190 (0.53)
Cumulative	90/3862 (2.33)	67/3852 (1.74)
Overall		
Year 1	31/3862 (0.80)	31/3852 (0.80)
Year 2	33/3409 (0.97)	24/3517 (0.68)
Year 3	37/3107 (1.19)	19/3190 (0.60)
Cumulative	94/3862 (2.43)	73/3852 (1.90)

Note: N = Number of patients who received a study drug infusion for that year in the trial; n = the number of patients who had atrial fibrillation over that time period.
Note: Patients are counted once in the overall and can be counted in multiple time periods in the event that they had more than 1 event.

Descriptive summary of quantitative bone biopsy parameters (Bone biopsy population)

Parameter (Code) (Unit)	Statistics	Zoledronic acid	Placebo	p-value
Micro-CT parameters				
Bone volume (BVTV) (%)	n	50	49	0.0200
	Median	16.620	12.810	
Connectivity density (CONND) ($1/mm^3$)	n	50	49	0.0617
	Median	4.400	3.300	
Trabecular number (TBN) (1/mm)	n	50	49	0.0081
	Median	1.360	1.220	
Trabecular spacing (TBSP) (mm)	n	50	49	0.0105
	Median	0.715	0.800	
Histomorphometry parameters				
Activation frequency (ACFSGL) (/ yr)	n	38	48	<0.0001
	Median	0.100	0.270	
Bone formation rate (BFRBVX) ($mm^2/mm^2/yr$)	n	38	48	<0.0001
	Median	0.048	0.152	

Parameter (Code) (Unit)	Statistics	Zoledronic acid	Placebo	p-value
Mineral appositional rate (MAR) (um/day)	n	38	48	0.0002
	Median	0.600	0.530	
Mineralizing surface (MS/BS) (%)	n	59	52	<0.0001
	Median	0.450	4.790	
Osteoid surface (OS/BS) (%)	n	59	52	<0.0001
	Median	5.020	17.750	
Osteoid thickness (OTH) (um)	n	59	52	0.0094
	Median	5.100	5.650	
Osteoid volume (OVBV) (%)	n	59	52	<0.0001
	Median	0.500	1.780	

Publications

Black, Dennis M., Delmas, Pierre D., Eastell, Richard, et al (2007) Once-Yearly Zoledronic Acid for treatment of postmenopausal Osteoporosis. The New England Journal of Medicine 2007; 356: 1809-21

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