Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Fracture risk and zoledronic acid therapy in men with osteoporosis

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Supplementary Appendix

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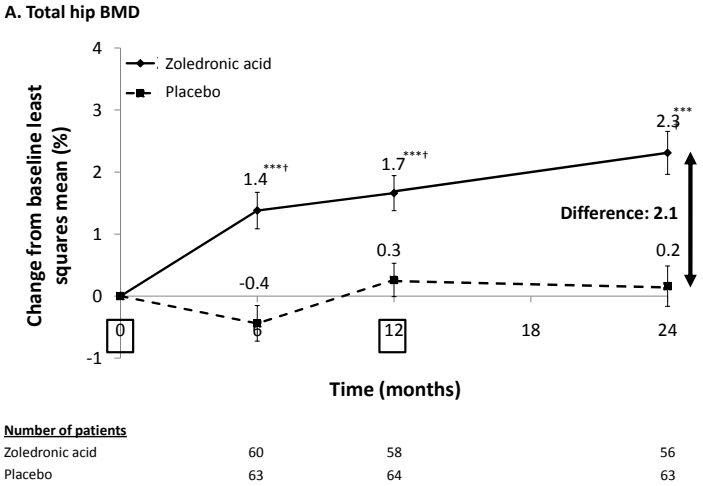
Overall responsibilities of the data monitoring committee (DMC)

The DMC periodically reviewed the safety data of the trial for unexpected large differences or toxicity between the treatment groups.

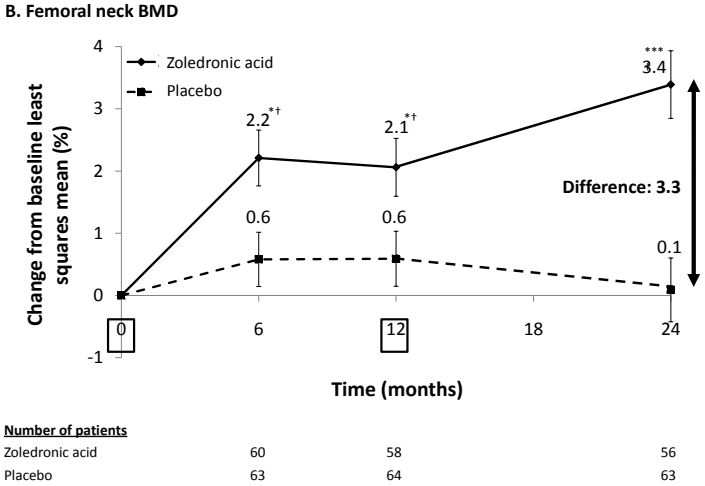
The DMC functioned independently of all other individuals associated with the conduct of this trial, including investigators, and the sponsor. It was responsible for assuring the safety of the trial participants and that the trial was being conducted with high scientific and ethical standards. The DMC was responsible for assessing the safety data as defined by the study protocol during the trial, for monitoring the overall conduct of the trial on a periodic basis, and for making recommendations to the sponsor on actions including:

- Discontinuation of the trial (with provisions for orderly discontinuation in accordance with good clinical practice)
- Suggestion of modifications to the trial protocol; modifications may include, but were not limited to: changes in inclusion/exclusion criteria, frequency of visits for safety monitoring, alterations in trial procedures or trial conduct
- Continuation of the trial according to the protocol and relevant amendments

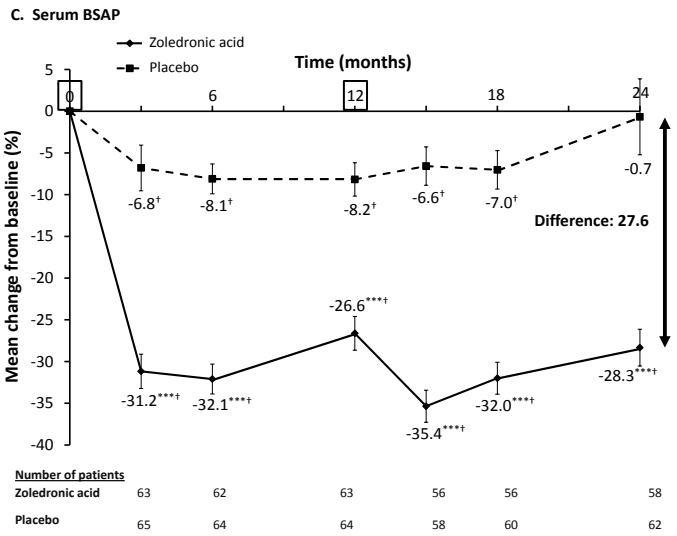
Figure S1: Percentage change from baseline in (A) total hip and (B) femoral neck BMD, and (C) BSAP in a subset of patients over time



Number of patients			
Zoledronic acid	60	58	56
Placebo	63	64	63



Number of patients			
Zoledronic acid	60	58	56
Placebo	63	64	63



Number of patients						
Zoledronic acid	63	62	63	56	56	58
Placebo	65	64	64	58	60	62

*p<0.05 vs. placebo;***, p<0.001 vs. placebo;†, p<0.05 vs. baseline.

Months in boxes indicate times when zoledronic acid or placebo were administered.
Error bars are standard error of the mean.
For Figure C, values shown are based on unadjusted mean percentage changes.
BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase.

Table S1: Baseline (I) bone mineral density (BMD) and (II) bone turnover markers (BTMs) in patients in the zoledronic acid and the placebo group, stratified by total testosterone levels using (a) 350 ng/dL or (b) 230 ng/dL threshold

(I) Baseline BMD levels

(a) In patients with total testosterone >350 or ≤350 ng/dL

	Zoledronic acid		Placebo	
BMD, g/cm^2	**Total testosterone ≤350 ng/dL, n=9**	**Total testosterone >350 ng/dL, n=55**	**Total testosterone ≤350 ng/dL, n=15**	**Total testosterone >350 ng/dL, n=50**
Total hip, mean (SE)	0.874 (0.034)	0.815 (0.014)	0.818 (0.029)	0.819 (0.015)
Femoral neck, mean (SE)	0.699 (0.043)	0.680 (0.013)	0.673 (0.030)	0.689 (0.015)
Lumbar spine, mean (SE)	0.872 (0.038)*	0.823 (0.012)	0.855 (0.043)*	0.836 (0.014)[†]

(b) In patients with total testosterone >230 or ≤230 ng/dL

	Zoledronic acid		Placebo	
BMD, g/cm^2	**Total testosterone ≤230 ng/dL, n=0**	**Total testosterone >230 ng/dL, n=64**	**Total testosterone ≤230 ng/dL, n=3**	**Total testosterone >230 ng/dL, n=62**
Total hip, mean (SE)	NA	0.823 (0.013)	0.876 (0.015)	0.816 (0.014)
Femoral neck, mean (SE)	NA	0.682 (0.012)	0.669 (0.046)	0.686 (0.014)
Lumbar spine, mean (SE)	NA	0.831 (0.012)[‡]	0.847 (0.057)[§]	0.840 (0.015)[‡]

(II) Baseline BTMs levels

(a) In patients with total testosterone >350 or ≤350 ng/dL

	Zoledronic acid		Placebo	
BTMs	**Total testosterone ≤350 ng/dL, n=10**	**Total testosterone >350 ng/dL, n=54**	**Total testosterone ≤350 ng/dL, n=15**	**Total testosterone >350 ng/dL, n=51**
β-CTx, µg/L, mean (SE)	0.324 (0.038)	0.372 (0.024)	0.364 (0.056)	0.402 (0.035)
PINP, ng/dL, mean (SE)	39.65 (3.71)	44.07 (2.27)	40.33 (4.38)	43.41 (2.94)
BSAP, µg/L, mean (SE)	10.84 (0.79)	12.35 (0.72)	12.83 (1.32)	11.89 (0.45)

(b) In patients with total testosterone >230 or ≤230 ng/dL

	Zoledronic acid		Placebo	
BTM	**Total testosterone ≤230 ng/dL, n=0**	**Total testosterone >230 ng/dL, n=64**	**Total testosterone ≤230 ng/dL, n=3**	**Total testosterone >230 ng/dL, n=63**
β-CTx, µg/L, mean (SE)	NA	0.365 (0.021)	0.350 (0.104)	0.395 (0.031)
PINP, ng/dL, mean (SE)	NA	43.38 (2.01)	35.33 (3.75)	43.06 (2.58)
BSAP, µg/L, mean (SE)	NA	12.11 (0.62)	10.64 (1.64)	12.17 (0.47)

Only results from patients with total testosterone measured by 12 noon are included in these tables.

*Zoledronic acid, n=10; Placebo, n=14.

[†]Placebo, n=49.

[‡]Zoledronic acid, n=65; Placebo, n=61.

[§]Placebo, n=2.

The conversion factor for total testosterone, from ng/dL to nmol/L, is 0.0347.

BSAP, bone-specific alkaline phosphatase; β-CTx, β-C-terminal telopeptide of type 1 collagen; NA, not applicable; PINP, procollagen I N-terminal propeptide; SE, standard error of the mean.

Table S2: New morphometric vertebral fracture rates at 12 and 24 months in patients receiving zoledronic acid or placebo, stratified by total testosterone levels using (a) 350 ng/dL or (b) 230 ng/dL as thresholds.

(a) New morphometric vertebral fractures in patients with total testosterone >350 or ≤350 ng/dL

Total testosterone, ng/dL	Treatment	Incidence rate, n/N (%)	RR (95%CI)	p-value	Interaction p-value
Primary endpoint: ≥1 new morphometric vertebral fracture over 24 months					
>350	Zoledronic acid	5/364 (1.4)	0.36 (0.13, 1.00)	0.0347	0.9499
	Placebo	13/341 (3.8)			
≤350	Zoledronic acid	2/108 (1.9)	0.33 (0.07, 1.52)	0.1333	
	Placebo	8/142 (5.6)			
Secondary endpoint: ≥1 new morphometric vertebral fracture over 12 months					
>350	Zoledronic acid	3/364 (0.8)	0.40 (0.10, 1.54)	0.1574	0.8898
	Placebo	7/341 (2.1)			
≤350	Zoledronic acid	1/108 (0.9)	0.26 (0.03, 2.22)	0.1712	
	Placebo	5/142 (3.5)			

(b) New morphometric vertebral fractures in patients with total testosterone >230 or ≤230 ng/dL

Total testosterone, ng/dL	Treatment	Incidence rate, n/N (%)	RR (95%CI)	p-value	Interaction p-value
Primary endpoint: ≥1 new morphometric vertebral fracture over 24 months					
>230	Zoledronic acid	6/450 (1.3)	0.34 (0.13, 0.84)	0.0111	0.9499
	Placebo	18/453 (4.0)			
≤230	Zoledronic acid	1/22 (4.5)	0.45 (0.05, 4.08)	NA	
	Placebo	3/30 (10.0)			
Secondary endpoint: ≥1 new morphometric vertebral fracture over 12 months					
>230	Zoledronic acid	4/450 (0.9)	0.34 (0.11, 1.03)	0.0393	0.8898
	Placebo	12/453 (2.6)			
≤230	Zoledronic acid	0/22 (0.0)	NA	NA	
	Placebo	0/30 (0.0)			

Only results from patients with total testosterone measured by 12 noon are included in these tables.
Between treatment p-value is obtained from a logistic regression model with treatment, prevalent vertebral fracture, and region as explanatory variables.
Interaction p-value is obtained from a logistic regression model with total testosterone and treatment by total testosterone interaction as additional explanatory variables.
The conversion factor for total testosterone, from ng/dL to nmol/L, is 0.0347.
CI, confidence intervals; NA, not applicable; RR, relative risk.

Table S3: Percentage change from baseline in lumbar spine BMD in patients receiving zoledronic acid or placebo, stratified by total testosterone levels using (a) 350 ng/dL or (b) 230 ng/dL as thresholds.

(a) Change in lumbar spine BMD in patients with total testosterone >350 or ≤350 ng/dL

	Total testosterone, ng/dL	Treatment	n	Least squares mean (SE), %	Treatment difference (95% CI), %	p-value (between zoledronic acid and placebo)	Interaction p-value
Month 12	>350	Zoledronic acid	51	5.55 (0.49)	4.51 (3.13, 5.90)	<0.0001	0.7498
		Placebo	48	1.04 (0.50)			
	≤350	Zoledronic acid	9	5.46 (1.04)	5.46 (2.67, 8.25)	0.0006	
		Placebo	14	0.00 (0.83)			
Month 24	>350	Zoledronic acid	49	7.65 (0.50)	5.99 (4.56, 7.42)	<0.0001	0.6322
		Placebo	47	1.66 (0.51)			
	≤350	Zoledronic acid	9	8.23 (1.22)	6.84 (3.57, 10.11)	0.0003	
		Placebo	14	1.39 (0.97)			

(b) Change in lumbar spine BMD in patients with Total testosterone >230 ng/dL

	Total testosterone, ng/dL	Treatment	n	Least squares mean (SE), %	Treatment difference (95% CI), %	p-value (between zoledronic acid and placebo)	Interaction p-value
Month 12	>230	Zoledronic acid	60	5.51 (0.44)	4.66 (3.43, 5.89)	<0.0001	0.7436
		Placebo	60	0.85 (0.44)			
Month 24	>230	Zoledronic acid	58	7.73 (0.46)	6.07 (4.78, 7.35)	<0.0001	0.5597
		Placebo	59	1.66 (0.46)			

Only results from patients with total testosterone measured before 12 noon are included in these tables.
Similar results were seen with BMD at total hip and femoral neck. For (b), between total testosterone subgroups comparison cannot be performed because no zoledronic acid-treated patient with serum total testosterone ≤230 ng/dL had BMD measurements.
Between treatment p-value is obtained from an analysis of covariance model with treatment and baseline value as explanatory variables.
Interaction p-value is obtained from the ANCOVA with total testosterone and treatment by Total testosterone interaction as additional explanatory variables.
The conversion factor for total testosterone, from ng/dL to nmol/L, is 0.0347.
NA, not applicable; SE, standard error of the mean.

Table S4: Between treatment comparison of log (e) CTx, PINP and BSAP ratio during the study, stratified by total testosterone status using (a) 350 ng/dL or (b) 230 ng/dL as thresholds.

(a) Bone turnover markers (BTMs) in patients with total testosterone >350 or ≤350 ng/dL

	Total testosterone, ng/dL	Treatment	n	Change from baseline, mean (SE), %	Relative effect (95% CI)	p-value (between zoledronic acid and placebo)	Interaction p-value
Serum β-CTx							
Month 12	>350	Zoledronic acid	53	-48.5 (3.90)	0.45 (0.39, 0.53)	<0.0001	0.4608
		Placebo	49	7.71 (6.71)			
	≤350	Zoledronic acid	10	-44.6 (10.8)	0.42 (0.23, 0.76)	0.0056	
		Placebo	15	6.86 (9.79)			
Month 24	>350	Zoledronic acid	46	-48.1 (3.96)	0.43 (0.37, 0.51)	<0.0001	0.2491
		Placebo	48	14.4 (6.81)			
	≤350	Zoledronic acid	9	-46.6 (7.46)	0.49 (0.33, 0.73)	0.0011	
		Placebo	14	1.83 (10.1)			
PINP							
Month 12	>350	Zoledronic acid	53	-45.8 (3.52)	0.56 (0.49, 0.64)	<0.0001	0.0103
		Placebo	49	-4.52 (5.39)			
	≤350	Zoledronic acid	10	-40.2 (5.51)	0.81 (0.58, 1.13)	0.2081	
		Placebo	15	-21.1 (6.61)			
Month 24	>350	Zoledronic acid	48	-47.1 (3.91)	0.49 (0.42, 0.57)	<0.0001	0.0095
		Placebo	48	7.90 (7.63)			
	≤350	Zoledronic acid	10	-30.8 (8.46)	0.74 (0.59, 0.93)	0.0107	
		Placebo	14	-9.90 (5.87)			
BSAP							
Month 12	>350	Zoledronic acid	53	-27.4 (2.18)	0.78 (0.73, 0.84)	<0.0001	0.1260
		Placebo	49	-8.01 (2.31)			
	≤350	Zoledronic acid	10	-22.8 (5.55)	0.81 (0.69, 0.94)	0.0095	
		Placebo	15	-8.70 (4.08)			
Month 24	>350	Zoledronic acid	48	-28.2 (2.52)	0.72 (0.65, 0.79)	<0.0001	0.2529
		Placebo	48	1.85 (5.71)			
	≤350	Zoledronic acid	10	-28.9 (4.41)	0.79 (0.65, 0.95)	0.0173	
		Placebo	14	-9.33 (4.27)			

(b) BTMs in patients with total testosterone >230 /dL

	Total testosterone, ng/dL	Treatment	n	Change from baseline, mean (SE), %	Relative effect (95% CI)	p-value (between zoledronic acid and placebo)	Interaction p-value
Serum β-CTx							
Month 12	>230	Zoledronic acid	63	-47.9 (3.67)	0.44 (0.38, 0.52)	<0.0001	0.6380
		Placebo	61	8.89 (5.77)			
Month 24	>230	Zoledronic acid	55	-47.9 (3.51)	0.45 (0.38, 0.52)	<0.0001	0.2843
		Placebo	59	12.0 (6.01)			
PINP							
Month 12	>230	Zoledronic acid	63	-44.9 (3.08)	0.59 (0.52, 0.66)	<0.0001	0.0406
		Placebo	61	-7.42 (4.51)			
Month 24	>230	Zoledronic acid	58	-44.3 (3.61)	0.53 (0.46, 0.60)	<0.0001	0.0149
		Placebo	59	4.44 (6.36)			
BSAP							
Month 12	>230	Zoledronic acid	63	-26.6 (2.03)	0.78 (0.73, 0.83)	<0.0001	0.2671
		Placebo	61	-7.76 (2.01)			
Month 24	>230	Zoledronic acid	58	-28.3 (2.21)	0.72 (0.66, 0.78)	<0.0001	0.3705
		Placebo	59	0.06 (4.69)			

Only results from patients with Total testosterone measured by 12 noon are included in these tables.
Similar log(e) β-CTx, PINP and BSAP ratios were seen at month 3, 6, 15 and 18.

For (b) between total testosterone subgroups comparison cannot be performed since no zoledronic acid-treated patient with serum total testosterone ≤230 ng/dL had BTM measurements.

Between treatment p-value is obtained from an analysis of covariance on log(e) (ratio) with treatment and log(e) (baseline value) as explanatory variables.
Interaction p-value is obtained from the ANCOVA with total testosterone and treatment by total testosterone interaction as additional explanatory variables.
The conversion factor for total testosterone, from ng/dL to nmol/L, is 0.0347.
BSAP, bone-specific alkaline phosphatase; β-CTx, β-C-terminal telopeptide of type 1 collagen; CI, confidence interval; PINP, procollagen I N-terminal propeptide; SE, standard error of the mean.

Table S5: Sensitivity analyses of primary endpoint results

	≥1 new morphometric vertebral fracture at Month 24, n/N (%)				
	Zoledronic acid	Placebo	RR (95% CI)	OR (95% CI)	p-value
Completers	9/523 (1.7)	20/534 (3.7)	0.46 (0.21, 1.00)	0.45 (0.19, 0.97)	0.0415
Single imputation	9/588 (1.5)	28/611 (4.6)	0.33 (0.16, 0.70)	0.32 (0.14, 0.66)	0.0017
Multiple imputation	9/588 (1.5)	28/611 (4.6)	NA	0.32 (0.15, 0.69)	0.0035

The 'completers' method included non-missing data only; subjects who had month 24 X-ray in the modified intent-to-treat population (patients who had baseline and ≥1 post-baseline assessment of the primary efficacy variable). The 'single imputation' method assigned 'no fracture' to all subjects who had undetermined fracture status at month 24 in the intent-to-treat population. The 'multiple imputation' method imputed undetermined fracture status at month 24 in the intent-to-treat population 200 times using a logistic regression model.

Table S6: (A) Relative risk of morphometric vertebral fracture incidence,(B) Incidence of clinical fractures in the two study groups and (C) Bayesian analysis of any clinical and nonvertebral fractures using the HORIZON-PFT[1] and -RFT[2] as historical data.

(A) Relative risk of fracture incidence (mITT population)

Type of fracture	No. of patients, n (%)		Relative risk (95% CI)
	Zoledronic acid, N=553	Placebo, N=574	
Primary endpoints			
≥1 new morphometric vertebral fracture over 24 months	9 (1.6)	28 (4.9)	0.33** (0.16–0.70)
Secondary endpoints			
≥1 new morphometric vertebral fracture over 12 months	5 (0.9)	16 (2.8)	0.32* (0.12–0.88)
≥1 new moderate–severe morphometric vertebral fracture over 12 months	2 (0.4)	11 (1.9)	0.19* (0.04–0.85)
≥1 new moderate–severe morphometric vertebral fracture over 24 months	6 (1.1)	17 (3.0)	0.37* (0.15–0.92)
≥1 new/worsening morphometric vertebral fracture over 12 months	7 (1.3)	16 (2.8)	0.45 (0.19–1.10)
≥1 new/worsening morphometric vertebral fracture over 24 months	11 (2.0)	28 (4.9)	0.41** (0.21–0.81)

(B) Incidence of clinical fractures (ITT population)

	Zoledronic acid, N=588	Placebo, N=611	Hazard ratio (95% CI)
Clinical fractures, n (%)	6 (1.0)	11 (1.8)	0.6 (0.2, 1.5)
Clinical vertebral fractures, n (%)	1 (0.2)	3 (0.5)	0.3 (0.0, 3.3)
Clinical nonvertebral fractures, n (%)	5 (0.9)	8 (1.3)	0.6 (0.2, 2.0)

(C) Bayesian analyses of any clinical and nonvertebral fractures using the HORIZON-PFT[1] and -RFT[2] as historical data (ITT population)

Between-trial variation	Posterior hazard ratio (95% credible interval)	Posterior probability for hazard ratio<1
Clinical fractures		
Mild	0.66 (0.50, 0.85)	0.999
Moderate	0.66 (0.40, 1.00)	0.975
Substantial	0.64 (0.29, 1.21)	0.922
Large	0.63 (0.20, 1.40)	0.890
Nonvertebral fractures		
Mild	0.74 (0.56, 0.97)	0.986
Moderate	0.74 (0.45, 1.15)	0.915
Substantial	0.74 (0.32, 1.45)	0.832
Large	0.74 (0.21, 1.78)	0.799

*p<0.05, **p<0.01

For Table A, results are based on data from patients included in the mITT population, which consisted of 553 patients in the zoledronic acid group and 574 patients in the placebo group; the relative risk was calculated based on a 2x2 table and the normal approximation was used to calculate its 95% CI. P-values were from logistic regression models, which included adjustments for prevalent vertebral fracture and region.

For Table B, the hazard ratio and 95% CI were computed from a Cox proportional hazard regression model with treatment as a factor. The p-value was calculated from a log-rank test.

For Table C, log hazard ratios from the HORIZON-PFT and -RFT were combined using the inverse variance meta-analysis method. The meta-analysis mean was used as the prior mean. The prior variance was the meta-analysis mean variance plus a between-trial variance that was used to discount these data. The 95% credible interval was calculated based on the equal-tail method. The analysis was performed based on 4 assumptions (mild to large) of the between trial standard deviation: 0.125 for mild, 0.25 for moderate, 0.5 for substantial, and 1 for large.

CI, confidence interval; HORIZON, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly; ITT, intent-to-treat; mITT, modified ITT; PFT, Pivotal Fracture Trial; RFT, Recurrent Fracture Trial.

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