JBMR®

The Effect of 6 Versus 9 Years of Zoledronic Acid Treatment in Osteoporosis: A Randomized Second Extension to the HORIZON-Pivotal Fracture Trial (PFT)

Dennis M. Black,[1] Ian R. Reid,[2] Jane A. Cauley,[3] Felicia Cosman,[4] Ping Chung Leung,[5] Peter Lakatos,[6] Kurt Lippuner,[7] Steven R. Cummings,[8] Trisha F. Hue,[1] Amitava Mukhopadhyay,[9] Monique Tan,[10] R. Paul Aftring,[10] and Richard Eastell[11]

[1]University of California, San Francisco, CA, USA
[2]University of Auckland, Auckland, New Zealand
[3]University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA
[4]Helen Hayes Hospital, New York, NY, USA
[5]Chinese University of Hong Kong, Hong Kong, China
[6]Semmelweis University Medical School, Budapest, Hungary
[7]Bern University Hospital, Bern, Switzerland
[8]San Francisco Coordinating Center, San Francisco, CA, USA
[9]Novartis Healthcare Pvt. Ltd., Hyderabad, India
[10]Novartis Pharmaceutical Corporation, East Hanover, NJ, USA
[11]University of Sheffield, Sheffield, UK

ABSTRACT

While bisphosphonates reduce fracture risk over 3 to 5 years, the optimal duration of treatment is uncertain. In a randomized extension study (E1) of the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly−Pivotal Fracture Trial (HORIZON−PFT), zoledronic acid (ZOL) 5 mg annually for 6 years showed maintenance of bone mineral density (BMD), decrease in morphometric vertebral fractures, and a modest reduction in bone turnover markers (BTMs) compared with discontinuation after 3 years. To investigate the longer-term efficacy and safety of ZOL, a second extension (E2) was conducted to 9 years in which women on ZOL for 6 years in E1 were randomized to either ZOL (Z9) or placebo (Z6P3) for 3 additional years. In this multicenter, randomized, double-blind study, 190 women were randomized to Z9 (n = 95) and Z6P3 (n = 95). The primary endpoint was change in total hip BMD at year 9 vs. year 6 in Z9 compared with Z6P3. Other secondary endpoints included fractures, BTMs, and safety. From year 6 to 9, the mean change in total hip BMD was −0.54% in Z9 vs. −1.31% in Z6P3 (difference 0.78%; 95% confidence interval [CI]: −0.37%, 1.93%; p = 0.183). BTMs showed small, non-significant increases in those who discontinued after 6 years compared with those who continued for 9 years. The number of fractures was low and did not significantly differ by treatment. While generally safe, there was a small increase in cardiac arrhythmias (combined serious and non-serious) in the Z9 group but no significant imbalance in other safety parameters. The results suggest almost all patients who have received six annual ZOL infusions can stop medication for up to 3 years with apparent maintenance of benefits. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: RANDOMIZED CLINICAL TRIALS; FRACTURE PREVENTION; OSTEOPOROSIS; ANTIRESORPTIVES; BIOCHEMICAL MARKERS OF BONE TURNOVER

Introduction

Bisphosphonates, the most commonly used treatment for osteoporosis, inhibit osteoclast-mediated bone resorption and increase bone mineral density (BMD). Trials of 3–4 years duration have shown that these reduce the risk of vertebral, hip, and other non-vertebral fractures, particularly in women with established osteoporosis.[1–6] Studies of longer term use of zoledronic acid (ZOL, up to 6 years) and alendronate (up to 10 years) have shown that in women who discontinue after 3–5 years of use, some benefits, including reduced bone loss and reduction in vertebral fractures, are retained.[7] Retention of benefits after the use of risedronate is less apparent compared with alendronate[8] and there are no data available for

ibandronate. Recent concerns about a possible association of bisphosphonates with osteonecrosis of the jaw (ONJ) and atypical femur fractures (AFF), particularly with long-term use, have led patients and clinicians to try to limit the duration of use.[9] Therefore, it is important to provide long-term data about benefits vs. risks which can guide clinical decision-making regarding optimal duration of long-term bisphosphonate use.

In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly – Pivotal Fracture Trial (HORIZON–PFT), a single annual intravenous (IV) infusion of the ZOL 5 mg for 3 years decreased the risk of spine, hip, and other non-vertebral fractures; increased BMD; and decreased the levels of bone re-modeling in women with postmenopausal osteoporosis.[3] The first 3-year extension of HORIZON-PFT (E1) showed that the continuation of ZOL treatment from 3–6 years resulted in maintenance of BMD, a decrease in morphometric vertebral fractures, and a modest reduction in bone turnover markers (BTMs) vs. discontinuation with no evidence of difference in the incidence of non-vertebral fracture.[10] In order to assess the long-term efficacy and safety, and need for continued treatment with ZOL, we conducted a second extension of the HORIZON-PFT (E2), in which women on ZOL for 6 years in the first extension were randomized to either ZOL or placebo for 3 additional years, that is, for a total of up to 9 years of treatment.

Materials and Methods

Study design and participants

This was a 3-year, multicenter, randomized, double-blind, second extension (E2) study of the HORIZON-PFT. In the core study, 3889 women with postmenopausal osteoporosis were randomized to receive annual IV ZOL 5 mg and 3876 to receive placebo for 3 years.[3] Randomization was stratified by center. This was followed by the E1 study, in which 1233 women who had originally received three ZOL infusions were randomized to receive three additional annual infusions of ZOL or placebo.[10] The results from the core and E1 studies have previously been reported.[3,10] In this E2 study, women who had received at least the first and third doses of ZOL in E1 and completed the E1 study (n = 451) were eligible. Patients with major protocol violations during the E1 study, specific bone-active medication use (e.g., use of oral bisphosphonates, strontium, and parathyroid hormone), and those with some other specific conditions were excluded (see online appendix, study protocol). All patients signed the written informed consent. The study was conducted according to the ethical principles of the Declaration of Helsinki (2008) and local applicable laws and regulations. The study is registered with ClinicalTrials.gov with the identifier NCT00718861.

The study was jointly designed by the HORIZON-PFT Steering Committee and sponsor. The sponsor was responsible for data collection and quality control. Analyses for publication were performed by the sponsor according to a pre-specified analysis plan developed by the first author and approved by the HORIZON-PFT Steering Committee.

Randomization and treatment

Eligible women were randomized (1:1) to receive either a 15-minute once-yearly IV infusion of ZOL (Z9 group) or placebo (Z6P3 group) for 3 additional years. The final visit of the patient in the E1 study (at year 6) served as the baseline and screening visit for this E2 study. In addition, all patients received daily oral calcium (1000 to 1500 mg) and vitamin D (400 to 1200 IU) as dietary supplements. All personnel involved in conduct of the study were blinded to treatment assignments including the study investigators, site personnel, the Novartis clinical team, as well as the clinical research organization and the University of California, San Francisco Coordinating Center personnel. To ensure blinding, patients were randomized centrally by an interactive voice response system.

Endpoints

The primary endpoint was percentage change in total hip BMD at year 9 relative to year 6 in Z9 compared with Z6P3. The secondary endpoints included change in hip BMD (total and femoral neck) at years 7 and 8 vs. year 6 and at years 7, 8, and 9 vs. year 0. Other secondary endpoints included the incidence of fractures (morphometric vertebral and clinical fractures) at year 9 relative to year 6 and change in BTMs at years 7, 8, and 9 relative to year 6.

Efficacy measurements

Total hip and femoral neck BMD were measured using dual x-ray absorptiometry (DXA). Quality control and BMD scan analyses were performed centrally (Synarc, Portland, OR, USA).

Serum levels of procollagen type I N-terminal propeptide (PINP) were batch-assayed using archived serum collected at years 7, 8, and 9 in all participants. The numbers of PINP assay results from years 0–6 are limited, reducing the numbers for longer-term comparisons. Other biochemical markers, C-terminal type 1 collagen telopeptide (β-CTx) and bone-specific alkaline phosphatase (BSAP), were measured in a small subset and compared with the E2 baseline (primary analysis) and also to the core study baseline. All assays were performed on the Roche Elecsys ElectroChemiLuminescence (Synarc, Lyon, France) platform.

Fractures were assessed using methods identical to those in the core and E1 studies.[3,10] At each visit and at each quarterly telephone contact, patients were asked whether they had a fracture since the last visit. Clinical fractures were initially identified by self-report and a copy of the radiographic or surgical reports was sent for adjudication to the University of California, San Francisco Coordinating Center. The incidence of morphometric vertebral fractures was assessed by comparison of E2 baseline to the final study radiographs using the standard criteria that required both a quantitative morphometric change (20% or ≥ 4 mm) and a semiquantitative grade change ≥ 1.

Safety assessment

Safety was assessed by recording all self-reported adverse events (AEs) and serious AEs (SAEs); regular monitoring of hematology, blood chemistry, and urinary values; assessment of vital signs; and physical examinations. Renal safety was assessed by measuring serum creatinine and creatinine clearance (CrCl) on days 9 to 11 after each infusion. Potential renal events were pre-defined by any of the following: (1) serum creatinine increase from either pre-infusion or E2 baseline >0.5 mg/dL, (2) CrCl<30 mL/min, (3) CrCl decrease from E2 baseline $\geq 30\%$ when E2 baseline was ≤ 60 mL/min, (4) protein urinary dipstick >2 +, (5) reported AEs associated with a change in renal function. All potential renal events were submitted for adjudication.

AEs were categorized using the Medical Dictionary for Regulatory Activities. An independent Data Safety Monitoring Board met annually. Blinded, independent expert review committees reviewed and adjudicated information related to

several AEs of interest: ocular events, hypocalcemia, maxillofacial complications (i.e. ONJ), skeletal events (e.g. avascular necrosis and delayed/nonunion following fractures), renal and relevant renal laboratory abnormalities, arrhythmia SAEs, and underlying cause of death. ONJ events were adjudicated based on the predefined criteria of "exposed bone of the jaw for more than 6 weeks".[3,11] All fractures of the hip and any region of the femur, except femoral neck, were referred for adjudication as AFF based on the revised criteria from the American Society for Bone and Mineral Research (ASBMR) requiring radiographic confirmation.[12] All other non-serious AEs were based on self-report only. Twelve-lead electrocardiogram (ECG) tests were conducted to assess pro-arrhythmic events following ZOL infusion. A total of 10 ECG tests could have been performed for each participant. ECG tests were performed prior to annual ZOL/placebo infusion at years 6, 7 and 8, and on days 9 – 11 and 76 – 104 post-annual infusions (all contributing to a total of 9 ECG tests). A final ECG test was performed at year 9.

Statistical analyses

The primary efficacy analysis used the modified intent-to-treat population including all patients in the intent-to-treat population who had undergone hip DXA measurements at years 6 and 9. The percentage change in total hip BMD at year 9 relative to year 6 was analyzed using an analysis of variance with treatment and geographic region as covariates. All tests were performed at 5% significance levels without adjustments for multiple comparisons.

BTMs were analyzed using $\log_e$ transformation. Differences between Z9 and Z6P3 were evaluated using analysis of covariance on $\log_e$ (ratio of year 9 and year 6 measurements) with treatment, geographic region, and $\log_e$ (year 6 measurement) as explanatory variables.

Between-treatment comparison of clinical fractures used a Cox regression model, with clinical fracture during the core and E1 studies as explanatory variables. The incidence of clinical fracture was estimated using the Kaplan–Meier method. New morphometric vertebral fractures were compared between the treatments using logistic regression with year 6 vertebral fractures (0, 1, and ≥ 2) as explanatory variables.

AEs that occurred after the first dose during the E2 study were reported. If a patient reported more than one AE with the same preferred term, the patient was counted only once. Safety events were compared using the Fisher's exact test. The categories of safety events were generally chosen to be consistent with the categories used in the core and first extension reports.[3,10] The proportion of patients with AEs were compared using a chi-squared test.

Results

A total of 451 women completed the E1 study with at least two infusions and therefore, met the broad criteria for eligibility. However, many clinics chose not to participate in this second extension study and some women or their physicians did not want to continue in a second randomized study leaving 190 women who were randomized into E2: Z9 (n = 95) and Z6P3 (n = 95; Figure 1). Reasons for non-participation of the other 266 women are summarized in Figure 1. The mean age was 78 years (Table 1). The baseline characteristics were comparable between the treatment groups including hip BMD and proportion with vertebral fractures (Z9 [58%] vs. Z6P3 [55%]). The baseline data

was also found to be similar between treatment groups in patients who completed BMD and BTM assessments. The serum 25-OH-D was not measured at baseline in this study. Discontinuations were similar between the two groups (21 in Z9 vs. 18 in Z6P3, not significant). The most common reason for discontinuation was withdrawal of consent (Figure 1).

Bone mineral density

The mean change from year 6 to 9 in total hip BMD was −0.54% in Z9 compared with −1.31% in Z6P3 producing a mean between-group difference of 0.78% (95% confidence interval [CI]: −0.37%, 1.93%; p = 0.183). Small differences from years 6 to 8 were significant (Z9: −0.14 vs. Z6P3: −1.06%; p = 0.033, Table 2A) whereas differences from years 6 to 7 did not significantly differ by treatment. Compared to the core study baseline (year 0) to year 9, there was no significant difference between the treatments in total hip BMD changes (Z9: 4.6% vs. Z6P3: 3.7%, Figure 2A) or to years 7 or 8. Femoral neck BMD changes from year 6 to 7–9 did not significantly differ by treatment. Over the 9 years, there was about a 4% increase in femoral neck BMD, which did not differ by E2 treatment at any time point (Figure 2B).

Bone turnover markers

The mean serum levels of PINP and the other BTMs remained within the premenopausal reference range in both the groups (Figure 3A). In Z9, the percentage of patients with serum PINP values within the pre-menopausal reference range was 87.9%, 85.2% and 86.5% at years 7, 8 and 9, respectively. Small increases from year 6 in the mean serum levels of PINP and β-CTx were observed in both the Z9 and Z6P3 groups at years 7, 8 and 9 compared with year 6 (Figures 3A and 3B). However, the difference between the groups in PINP was only significant at year 7 (Table 2B). For β-CTX and BSAP, fewer patients had data to assess the change. For β-CTX, there was no evidence of a difference by treatment. The pattern of change was similar for BSAP in Z6P3 (gradual increase over time), whereas almost no change was observed in Z9 from year 6 to years 7, 8 and 9. However, for BSAP, a statistically significant difference was observed between groups at year 9 (p = 0.010, Figure 3C). Within the Z9, the mean BTM values increased from those in the early years of treatment (e.g. year 1): the within-group increase from year 1 was significant for both PINP (p = 0.004) and β-CTX (p = 0.002).

Fractures

Fractures were too few for meaningful comparison. There were three morphometric vertebral fractures in Z9 and five in Z6P3 (3.2% vs. 5.3%, odds ratio = 0.58, 95% CI: 0.13, 2.55; p = 0.461, Figure 4A). Similarly, no significant difference in the risk of all clinical fractures was observed between the treatment groups. A total of 19 women (Z9 group: 10 patients, Z6P3 group: 9 patients) suffered with 26 clinical fractures during the study. The estimated event rate was 12.2% in Z9 group and 9.5% in Z6P3 groups (hazard ratio = 1.11, 95% CI: 0.45, 2.73; p = 0.821 Figure 4B). The Kaplan-Meier curve on time to first clinical fracture is presented in the Supplementary Figure.

Height

There were no significant differences in change in height from baseline between Z9 and Z6P3 at years 7, 8, and 9 relative to year 6. Least square (LS) mean changes from baseline in height in the Z9 and Z6P3 treatment groups, respectively, were −13.31 mm

Fig. 1. Study flow chart.
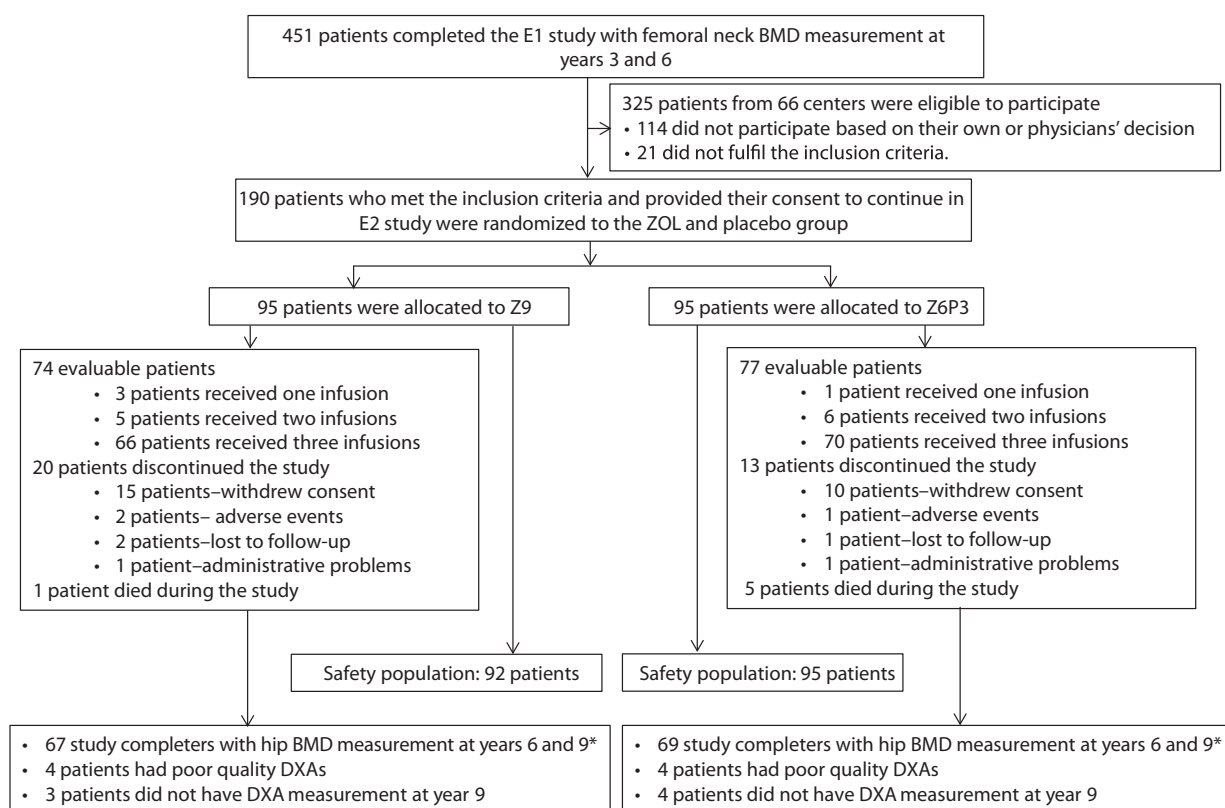
A patient's participation in the study was considered completed when all year 9 study procedures had been done.
*Modified intent-to-treat population, which consisted of all subjects in the ITT population, who had DXA measurements of total hip BMD at years 6 and 9
Safety population consisted of all subjects in the intent-to-treat population who received at least one dose of study drug during the extension 2 study
DXA, dual x-ray absorptiometry; ITT, intent-to-treat; PINP, procollagen type I N-terminal propeptide; ZOL, zoledronic acid; Z9, patients received zoledronic acid for 9 years; Z6P3, patients received zoledronic acid for 6 years and placebo for 3 years.

and −11.65 mm at Year 9 (p = 0.428); −10.16 mm and −9.90 mm at Year 8 (p = 0.896); and −5.29 mm and −4.84 mm at Year 7 (p = 0.724).

Safety

Overall incidences of AEs and SAEs were similar in the two treatment groups (Table 3). One (1.1%) patient died in Z9 and five (5.3%) patients died in Z6P3 (hazard ratio = 0.20, 95% CI: 0.02, 1.74; p = 0.107). Over the 3 year study, at least one protocol-defined renal laboratory abnormality occurred in 11% of patients of Z9 vs. 6.4% of patients in the Z6P3 group (p = 0.304). Only one of the changes was seen at the 9–11 day follow-up assessment; the remainder were observed at one of the later annual follow-up visits. All the changes occurred in participants above 82 years of age. Other than AEs associated with these laboratory abnormalities, a total of eight clinically significant renal AEs were reported which did not differ by treatment (Table 3). Renal events (either laboratory abnormalities or AEs) were sent for adjudication in 11 patients in Z9 vs. 9 in Z6P3 and the total adjudicated as clinically significant was two in Z9 vs. three in Z6P3. Mean increases in serum creatinine from year 6 were slightly higher in Z9 vs. Z6P3 but these differences were small and not statistically significant (e.g. mean increases from years 6 to 9 were 6.1 μmol/L in Z9 vs. 3.3 μmol/L in Z6P3, p = 0.061). Similarly, the mean decreases in CrCl did not differ by

treatment (years 6 to 9, −6.8 mL/min in Z9 vs. −5.6 mL/min in Z6P3, p = 0.257). Cardiac arrhythmia AEs were reported in 14.1% of patients in Z9 vs. 4.2% of patients in the Z6P3 group (p = 0.022). Atrial fibrillation was the most common arrhythmia observed in five patients in Z9 vs. one patient in Z6P3 (p = 0.114). There was one SAE arrhythmia in Z9 (atrial fibrillation) vs. three in Z6P3 (atrial fibrillation, arrhythmia and palpitations). Ischemic stroke was reported in one participant in Z9. None of the patients with atrial fibrillation reported a stroke. The electrocardiography (ECG) results showed no clinically important difference between the treatment groups. Although there were numerically more atrial fibrillation instances defined from ECG in Z9 (four patients) than Z6P3 (one patient), the difference was not significant.

Six maxillofacial events were sent for adjudication (Z9 = 4, Z6P3 = 2) but no adjudicated confirmed ONJ cases were found. Four non-femoral neck femur fracture cases (one with radiograph and three with radiographic reports only) of potential AFF were sent for adjudication but none were found after adjudication. Post-dose symptoms (<3 days after infusion) were rare and did not differ by treatment (Table 3).

Death was reported (∼8.5 months after the first infusion) in one patient due to malignancy (brain neoplasm), in the Z9 group. Five deaths were reported in the Z6P3 group; based on adjudication two deaths were ascribed to cardiac causes (sudden death for both), and for the other three, the underlying

Table 1. Baseline Characteristics of the Study Population of 190 Subjects in the HORIZON-PFT E2 Study

Variables	Z9 (N = 95)	Z6P3 (N = 95)
Age, years (mean ± SD)	78.0 ± 4.71	78.1 ± 4.85
>70–75, n (%)	32 (33.7)	33 (34.7)
>75–80, n (%)	35 (36.8)	37 (38.9)
>80, n (%)	28 (29.5)	25 (26.3)
Mean BMI (± SD), kg/m^2	24.6 ± 4.13	25.0 ± 3.98
Region, n (%)		
Western Europe	39 (41.1)	37 (38.9)
Eastern Europe	21 (22.1)	22 (23.2)
North America/Oceania	19 (20.0)	19 (20.0)
Latin America/Asia	16 (16.8)	17 (17.9)
Mean BMD (± SD), g/cm^2	N = 94	N = 95
Total hip[a]	0.69 ± 0.09	0.71 ± 0.09
Femoral neck	0.58 ± 0.08	0.58 ± 0.07
Mean femoral neck T-score, (± SD)	−2.44 ± 0.72	−2.43 ± 0.6
T-score at femoral neck, n (%)	N = 94	N = 95
≤ −2.5	44 (46.3)	42 (44.2)
>−2.5 to −1.5	43 (45.3)	47 (49.5)
> −1.5	7 (7.4)	6 (6.3)
Bone turnover markers, (ng/mL)		
β-CTx, median (n)	0.19 (59)	0.18 (58)
BSAP, median (n)	8.16 (59)	8.95 (62)
PINP, median (n)	25.9 (88)	25.0 (86)
Prevalent vertebral fracture,[a] n (%)		
0	40 (42.1)	43 (45.3)
1	32 (33.7)	22 (23.2)
≥2	23 (24.2)	30 (31.6)
Number of study drug infusions received during the core and first extension study		
5 infusions	3 (3.2)	2 (2.1)
6 infusions	92 (96.8)	93 (97.9)

± Values are means ± SD. BMD, bone mineral density; BMI, body mass index; BSAP, bone-specific alkaline phosphatase; β-CTx, beta C-terminal type 1 collagen telopeptide; HORIZON-PFT, Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly - Pivotal Fracture Trial; PINP, Serum procollagen type I N-terminal propeptide; SD, standard deviation.
[a]None of the differences between treatment groups are statistically significant at p = 0.05.

Table 2A. Between-Treatment Comparison in Percentage Change in Bone Mineral Density at Years 7, 8, and 9 Relative to Year 6 (ITT)

Location	Year of assessment from core study baseline (mean [SD] time to follow-up)	Treatment	n	Mean change (%)	Mean % difference (95% CI)	p value
Total hip	Year 7 (7.3 [0.26])	Z9	83	−0.28	0.55 (−0.39, 1.49)	0.248
		Z6P3	76	−0.83		
	Year 8 (8.3 [0.28])	Z9	73	−0.14	0.92 (0.07, 1.76)	0.033
		Z6P3	72	−1.06		
	Year 9[a] (9.3 [0.27])	Z9	67	−0.54	0.78 (−0.37, 1.93)	0.183
		Z6P3	69	−1.31		
Femoral neck	Year 7 (7.3 [0.26])	Z9	83	−0.78	0.46 (−0.75, 1.67)	0.454
		Z6P3	76	−1.24		
	Year 8 (8.3 [0.28])	Z9	73	0.00	0.88 (−0.53, 2.30)	0.220
		Z6P3	72	−0.88		
	Year 9 (9.3 [0.27])	Z9	67	−1.11	0.06 (−1.41, 1.53)	0.935
		Z6P3	69	−1.17		

n is the number of patients with values at year 6 and the follow-up visit. 95% CI is calculated based on a t-distribution for BMD. p value is obtained from ANOVA with treatment and region as explanatory variables. ANOVA, analysis of variance; CI, confidence interval; ITT, intent-to-treat; LS, least squares; MITT, modified-intent-to-treat population.
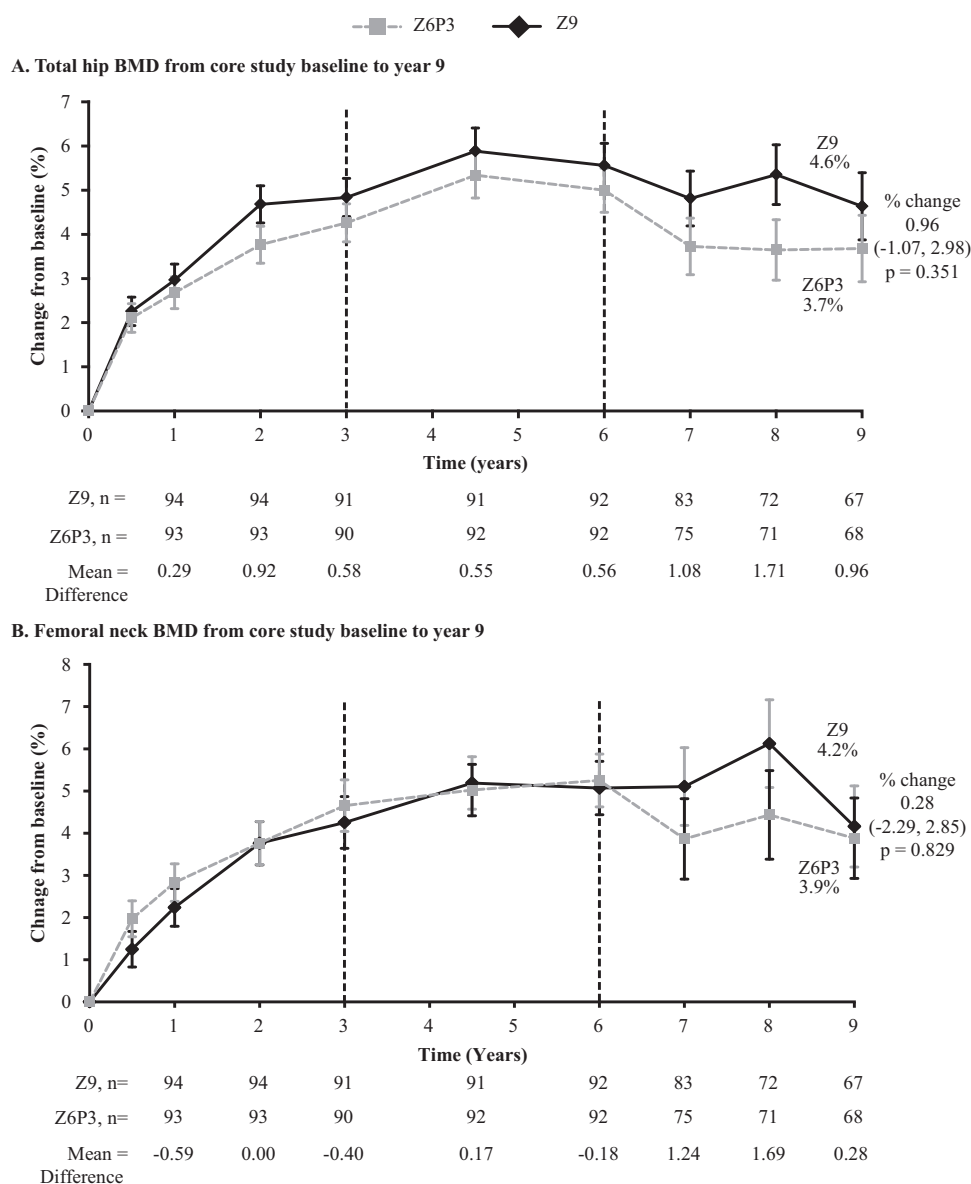[a]MITT population.

A. Total hip BMD from core study baseline to year 9

	Z9, n =							
Z9, n =	94	94	91	91	92	83	72	67
Z6P3, n =	93	93	90	92	92	75	71	68
Mean = Difference	0.29	0.92	0.58	0.55	0.56	1.08	1.71	0.96

B. Femoral neck BMD from core study baseline to year 9

	Z9, n=							
Z9, n=	94	94	91	91	92	83	72	67
Z6P3, n=	93	93	90	92	92	75	71	68
Mean = Difference	-0.59	0.00	-0.40	0.17	-0.18	1.24	1.69	0.28

Fig. 2. Mean changes in bone mineral density (BMD) over 9 years of treatment. (A) Total hip BMD from core study baseline to year 9 (ITT) and (B) femoral neck BMD from core study baseline to year 9 (ITT). Bracketed numbers are 95% confidence interval calculated based on a t-distribution. The numbers at the bottom of the figure panel show the number of available measurements at each time point. The LS mean difference is the percentage change in BMD from baseline. For the core and E1 study periods, only values for those continuing in the E2 study are shown. BMD, bone mineral density; ITT, intention-to-treat; LS, least square.

disease was unknown, although one of these patients was reported by the investigator to have died as a result of myocardial ischemia. On the basis of investigator assessment, the primary cause of death was not suspected to be related to the study medication in any of the cases.

Discussion

This second extension of the HORIZON-PFT allowed us to examine in a randomized, placebo-controlled trial, the effect of 9 years of annual infusions of ZOL vs. 6 years followed by 3 years of placebo. A trend toward better maintenance of BMD in Z9 vs.

Z6P3 was observed, but the difference was small and there were minimal, if any, changes in bone turnover markers in those who continued vs. discontinued. The study did not have sufficient power to compare fracture rates. Taken together, the results show continued efficacy in both the groups and do not provide convincing evidence of a benefit from continuing annual ZOL infusions for more than 6 years.

The BTM results are particularly interesting in reinforcing the bone safety of long-term use of ZOL as well as bisphosphonates in general. Prior to long-term studies of bisphosphonates, there were concerns that with continued use, bone turnover would progressively decrease leading to levels which might increase bone fragility. This study did not show a progressive decrease in
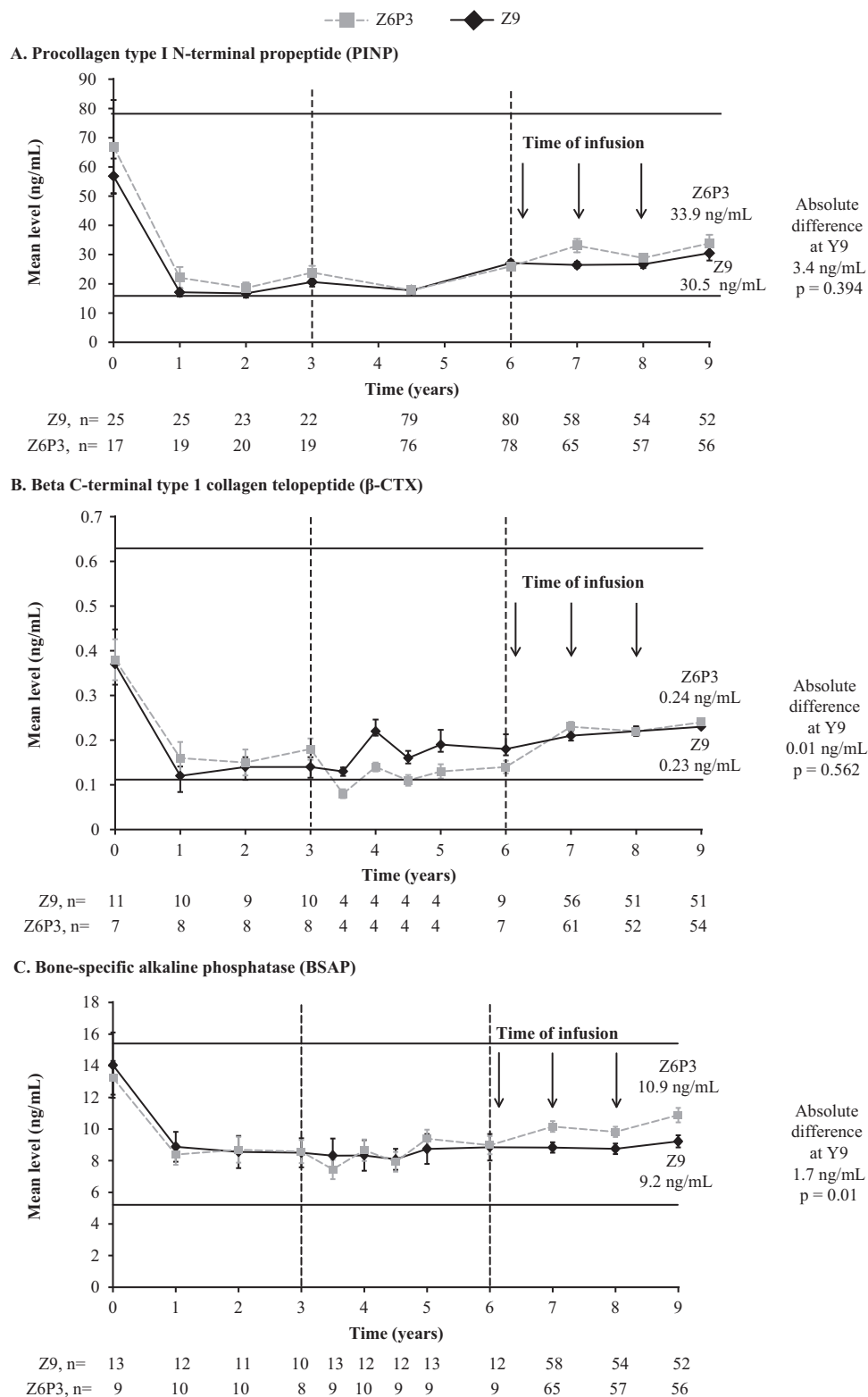
Fig. 3. Mean changes in bone turnover markers over 9 years of treatment. (A) Serum PINP; (B) β-CTX, and (C) BSAP. Horizontal dashed lines represent premenopausal reference range.[9] The numbers at the bottom of the figure panel show the number of available measurements at each time point and the mean is based on this total. For the core and E1 study periods, only values for those continuing in the E2 study are shown. The results represent geometric means. Statistical significance is based on comparison of values at year 9 (not change). β-CTX, beta C-terminal type 1 collagen telopeptide; BSAP, bone-specific alkaline phosphatase; PINP, procollagen type I N-terminal propeptide.

Table 2B. Between-Treatment Comparison in Percentage Change in Procollagen Type I N-terminal Propeptide (PINP) at Years 7, 8, and 9 Relative to Year 6 (ITT)

Parameter	Visit	Treatment	n	g-LSM of ratio[a]	Relative treatment effect[b] (95% CI)[c]	p value
PINP	Year 7	Z9	56	0.97	0.82 (0.73, 0.92)	0.0007
		Z6P3	61	1.19		
	Year 8	Z9	52	0.99	0.91 (0.81, 1.02)	0.094
		Z6P3	53	1.09		
	Year 9	Z9	50	1.09	0.88 (0.76, 1.02)	0.100
		Z6P3	52	1.23		

n is the number of patients with values at year 6 and the follow-up visit. p value is obtained from an analysis of covariance model on $\log_e$ (visit/baseline measurement) with treatment, region, and $\log_e$ (baseline measurement) as explanatory variables. ANOVA, analysis of variance; CI, confidence interval; ITT, intent-to-treat; LSM, least square mean; PINP, procollagen type I N-terminal propeptide.
[a]Geometric LSM (g-LSM) of ratio is the exponential of LSM on the $\log_e$ (visit/baseline measurement).
[b]Relative treatment effect is the exponential of LSM difference on $\log_e$ (visit/baseline measurement).
[c]95% CI is calculated by anti-log inversing the 95% CI for $\log_e$ (visit/baseline measurement).
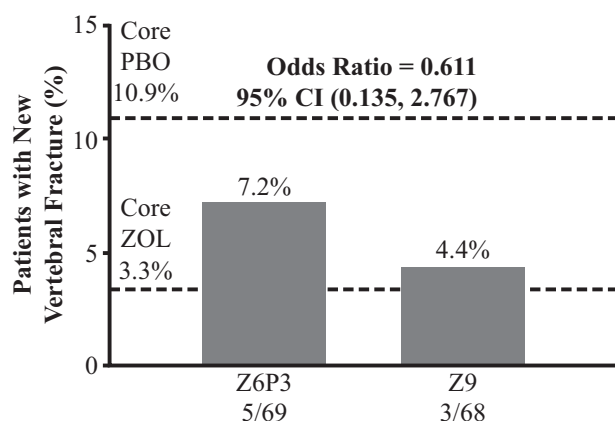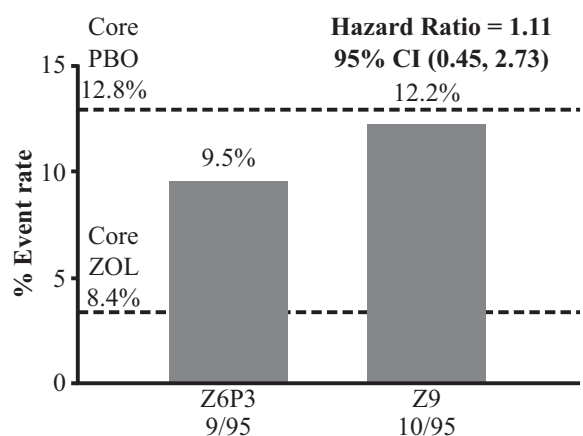

Fig. 4. The incidence of morphometric vertebral fractures and clinical fractures during the E2 study. (A) Morphometric vertebral fractures and (B) all clinical fractures. For clinical fractures, the event rate is estimated from the Kaplan–Meier curve at month 36. The dashed lines indicate the incidence in the core trial by core treatment for the corresponding fracture types. CI, confidence interval; PBO, placebo; ZOL, zoledronic acid.

the average bone turnover as assessed by PINP over 9 years of ZOL administration. In fact, the opposite was observed with a small, but steady, increase in the mean PINP after about 4 years of continued treatment. While the patient numbers with other BTMs were quite small, the data were consistent with this trend in PINP. The fact that the incidence of vertebral fracture remained similar after 6 years to the rate observed in ZOL patients in the core phase of the trial, despite the patients' older age, suggests that long-term continuation of ZOL is associated with maintenance of bone strength similar to that observed with shorter-term therapy. The randomized data from 10 years of alendronate[7,13] and more limited data for risedronate have been similarly reassuring in suggesting that long-term use will continue to maintain bone strength and sustained decreases in bone remodeling are not associated with any increase in overall fracture risk.

It is of interest to compare the results from this second randomized extension from 6 to 9 years with the results seen during the E1 study from 3 to 6 years. In that study, we saw a trend toward a larger decrease in BMD from discontinuing ZOL vs. continuing (about 1.5% for hip BMD), after 6 years (about 0.8% for total hip) although a formal statistical comparison was not performed. While the confidence intervals in second extension study are wide, the results suggest the residual effect of ZOL after discontinuing may be more pronounced after 6 than after 3 years of use. Similarly, a larger difference in BTMs with stopping after 3 years compared to after 6 years supports the view that continued use of ZOL for up to 6 years results in a larger residual effect after it is stopped. In the E1 study, those who continued ZOL experienced a significantly lower risk of morphometric vertebral fracture but similar risk of non-vertebral fracture leading us to recommend that women at high risk of vertebral fracture should be continued beyond 3 years. From this second extension to 9 years, there was a numerical reduction in vertebral fracture in those who continued, but numbers were much too small to draw a meaningful conclusion. As in the E1 study, we did not see evidence of reduction in clinical fractures but very small numbers preclude a definitive conclusion.

The only other comparable data for other bisphosphonates are for alendronate where the FLEX study had a similar design to our extensions but the initial period was longer (5 years) as was the first randomized extension (for another 5 years to a total of 10 years). The results of FLEX BMD were consistent with E1 as

Table 3. Number of Participants With Adverse Events

Adverse events	Z9 (N = 92) n (%)	Z6P3 (N = 95) n (%)	p value
General			
Total subjects with any AE	80 (87.0)	80 (84.2)	0.679
Total subjects with any SAE	24 (26.1)	28 (29.5)	0.628
Total deaths[a]	1 (1.1)	5 (5.3)	0.212
Total discontinuations due to AE	5 (5.4)	8 (8.4)	0.568
Renal abnormalities based on laboratory measurements			
Increase in serum creatinine >0.5 mg/dL[b]	1 (1.1)	1 (1.1)	1.000
Urinary protein dipstick >2+[c]	1 (1.3)	0 (0.0)	1.000
Calculated CrCl<30 mL/min[d]	7 (8.2)	3 (3.5)	0.211
CrCl decrease from baseline ≥30% with E2 baseline value ≤60 mL/min[e]	5 (7.9)	3 (5.3)	0.493
Any of the above in years 7–9	10 (11.0)	6 (6.4)	0.304
Clinically significant renal AEs[f]			
Renal failure	2 (2.2)	1 (1.1)	0.617
Renal impairment	2 (2.2)	1 (1.1)	0.617
Acute prerenal failure	0 (0.0)	1 (1.1)	1.000
Renal failure acute	0 (0.0)	1 (1.1)	1.000
Most commonly occurring post-dose symptoms (<3 days)[g]			
Pyrexia	2 (2.2)	0 (0.0)	0.241
Myalgia	1 (1.1)	2 (2.1)	1.000
Influenza-like illness	1 (1.1)	0 (0.0)	0.492
Headache	1 (1.1)	0 (0.0)	0.492
Any of the above in years 7–9	5 (5.4)	2 (2.1)	0.273
Cardiovascular AEs			
Arrhythmia			
Any AE[h]	13 (14.1)	4 (4.2)	0.022
SAE[i]	1 (1.1)	3 (3.2)	0.621
Atrial fibrillation			
Any AE	5 (5.4)	1 (1.1)	0.114
SAE	1 (1.1)	1 (1.1)	1.000
Myocardial infarction			
Any AE	0 (0.0)	1 (1.1)	1.000
SAE	0 (0.0)	1 (1.1)	1.000
Ischemic stroke			
Any AE	1 (1.1)	0 (0.0)	0.492
SAE	1 (1.1)	0 (0.0)	0.492
Hypertension Any AE	10 (10.9)	8 (8.4)	0.626

AE, adverse event; SAE, serious adverse event; CrCl, creatinine clearance; E2, extension 2.

[a]On the basis of investigator assessment, the primary cause of death was not suspected to be related to the study medication in any of the cases.

[b]Increase in serum creatinine >0.5 mg/dL (Z9: N = 91, Z6P3: N = 94), one patient in the Z6P3 group reported an increase in serum creatinine at the 9–11 day measurement following the Year 8 zoledronic acid infusion.

[c]Urinary protein dipstick >2+ (Z9: N = 80, Z6P3: N = 80), an extension criterion of baseline urinary protein dipstick ≤2+ is required.

[d]CrCl <30 mL/min (Z9: N = 85, Z6P3: N = 86), an extension criterion of baseline creatinine clearance ≥30 mL/min is required.

[e]CrCl decrease from baseline ≥30% with baseline value ≤60 mL/min (Z9: N = 63, Z6P3: N = 57), E2 baseline CrCl ≤60 mL/min is required.

[f]Of the significant renal AEs, two were reported as serious in one patient in the Z6P3 group: acute prerenal failure and renal failure acute. These events were sent for adjudication and the outcome was indeterminate.

[g]The four most common AEs reported within 3 days of infusion in the ZOL group in the core and E1 studies. There were no reported arthralgias during the days following infusions.

[h]Arrhythmia AEs include atrial fibrillation (total = 6; Z9 = 5, Z6P3 = 1), atrioventricular block first degree (total = 2; Z9 = 2, Z6P3 = 0), bundle branch block left (total = 2; Z9 = 2, Z6P3 = 0), bundle branch block right (total = 2; Z9 = 2, Z6P3 = 0), arrhythmia (total = 2; Z9 = 1, Z6P3 = 1), sinus bradycardia (total = 1; Z9 = 1, Z6P3 = 0), supraventricular extrasystoles (total = 1; Z9 = 0, Z6P3 = 1), tachycardia (total = 1; Z9 = 0, Z6P3 = 1), and ventricular extrasystoles (total = 1; Z9 = 0, Z6P3 = 1).

[i]Arrhythmia SAEs include atrial fibrillation (total = 2; Z9 = 1, Z6P3 = 1), arrhythmia (total = 1; Z9 = 0, Z6P3 = 1), and palpitations (total = 1; Z9 = 0, Z6P3 = 1).

were the fracture results (a reduction in vertebral but not non-vertebral fractures). However, the resolution of effect for BTMs stopping after 5 years of alendronate was more pronounced, suggesting that the residual effect of alendronate after 5 years is less than ZOL for 3 years and certainly less than ZOL after 6 years. Limited data for risedronate suggest a much faster resolution of

effect than for alendronate, and there are no data available for ibandronate.

The data from our long-term extension are consistent with the established safety profile of ZOL. For renal safety, we included a number of assessments. The overall number of participants meeting the pre-specified criteria for serum

creatinine or CrCl changes was small and did not differ by treatment. Changes in CrCl did not differ by treatment and increases in serum creatinine were only slightly, but not significantly, larger in Z9 vs Z6P3. Taken together, the renal results did not suggest that concern regarding renal safety should play a role in the clinical decision about the length of ZOL use beyond 6 years.

Increases in arrhythmias in general and atrial fibrillation in particular have been noted in some but not all studies of bisphosphonates. In the core ZOL study, there was a significant increase in serious AE atrial fibrillations but not in non-serious atrial fibrillation events among those on ZOL compared with placebo. In the E1, no significant difference for arrhythmias or either category of atrial fibrillation was observed in those who continued vs. those who stopped although atrial fibrillations were numerically more frequent in those who continued ZOL. In this study, we observed more arrhythmias (combined serious and non-serious) in the group on continued ZOL treatment (13 vs. 4, p = 0.022) but arrhythmias classified as serious did not differ in Z9 vs. Z6P3 (one vs. three, p = 0.621) and arrhythmia assessed from ECG did not significantly differ by the treatment group. Another large randomized trial of ZOL in post-hip fracture patients with a mean age of 74.5 years did not show a difference in arrhythmias or atrial fibrillation between ZOL vs. placebo.[14] For alendronate, a small but non-significant increase was also observed in arrhythmias in the FIT trial among those on alendronate.[15] However, other studies of alendronate and other oral bisphosphonates have not reported any increase. Possible effects of ZOL and other bisphosphonates on atrial fibrillation were added to the prescribing information for ZOL in 2008 as required by both the FDA and other regulatory agencies (MHRA and CHM). (http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085167) (Drug safety update from MHRA and CHM. 2008;1(12):4)

Using the recent ASBMR criteria, we also observed no confirmed cases of AFF, although we did not have the radiographs to review in most cases. However, it should be noted that the incidence of AFF is much too low to be assessed in this study of 190 participants and we only had x-rays (required for recent ASBMR criteria) in one participant of the four that were sent for AFF adjudication. The recent ASBMR review suggests that the risk of AFF may be increased by longer duration of use but also notes the inconsistency in the evidence base with respect to duration of use.[9]

Although this randomized trial is informative about the long-term use of ZOL, it also has some important limitations. As mentioned in statistical analyses, with only 190 patients, the study is underpowered to detect a difference in fracture rates, as well as the difference in some adverse events. Only about 451 patients had completed E1 on study medications in Z6, therefore, a much larger study was not possible. Another limitation is the relatively high rate of discontinuation (about 27%) from the protocol although given the age of the patients and the length of the trial, this is perhaps difficult to avoid.

In summary, in this extension of annual ZOL to 9 years, we showed little difference in efficacy between the patients who continued on active ZOL for 9 years compared with those who continued for 6 years and then discontinued for next 3 years. Overall, the 9-year study suggests sustained benefits on fracture and BMD from ZOL, but a diminishing return from its ongoing administration: a dramatic fracture benefit for 3 years of annual ZOL, more modest benefit for 6 vs. 3 years and inconclusive benefits for 9 vs. 6 years of continued ZOL. Long-term treatment with ZOL for 9 years was found to well tolerated, as shown for other bisphosphonates, although there was a suggestion of a small increase in cardiac arrhythmias (combined serious and non-serious) between groups but no significant imbalance in other safety parameters. On balance, comparing the minimal additional benefit and the rare but possible safety issues, there is little compelling evidence for continuation of annual ZOL administration beyond 6 years. Therefore, almost all patients who receive ZOL for 6 years can probably stop the medication and expect continued benefit for up to 3 subsequent years.

Disclosures

Acknowledgments

Authors' role: study design: DMB, IRR, JAC, FC, SRC, RE, MT; study conduct: All the authors; data collection: DMB, TFH, MT, RPA; data analysis: AM, DMB; Data interpretation: AM, DMB, IRR, JAC, FC, SRC, RPA, MT; drafting manuscript and revising contents: All the authors; approving final version: all the authors; took responsibility for integrity of data analysis: all the authors.

References

1. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet. 1996;348: 1535–1541.

2. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA. 1998;280: 2077–2082.

3. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356: 1809–1822.

4. Chesnut III, Skag CH, Christiansen A, Recker C, Stakkestad R, Hoiseth JA, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res. 2004;19: 1241–1249.

5. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral,nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. 1999;282: 1344–1352.

6. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med. 2001;344: 333–340.

7. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006;296: 2927–2938.

8. Watts NB, Chines A, Olszynski WP, McKeever CD, McClung MR, Zhou X, et al. Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int. 2008;19: 365–372.

9. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD, et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2010;25: 2267–2294.

10. Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res. 2012;27: 243–254.

11. Grbic JT, Landesberg R, Lin SQ, Mesenbrink P, Reid IR, Leung PC, et al. Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. J Am Dent Assoc. 2008;139: 32–40.

12. Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the american society for bone and mineral research. J Bone Miner Res. 2014;29: 1–23.

13. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004;350: 1189–1199.

14. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357: 1799–1809.

15. Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. N Engl J Med. 2007;356: 1895–1896.