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ORIGINAL ARTICLE

Zoledronic acid results in better health-related quality of life following hip fracture: the HORIZON–Recurrent Fracture Trial

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Abstract
Summary This study evaluated the benefits of ZOL versus placebo on health-related quality of life (HRQoL) among patients from HORIZON–RFT. At month 24 and end of the study visit, ZOL significantly improved patients' overall health state compared to placebo as assessed by the EQ-5D VAS.
Introduction To evaluate the benefits of zoledronic acid (ZOL) versus placebo on health-related quality of life (HRQoL) among patients from The Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Recurrent Fracture Trial (HORIZON–RFT).
Methods In this randomized, double-blind, placebo-controlled trial, 2,127 patients were randomized to receive annual infusion of ZOL 5 mg (n=1,065) or placebo (n=1,062) within 90 days after surgical repair of low-trauma hip fracture. HRQoL was measured using EQ-5D Visual Analogue Scale (VAS) and utility scores (EuroQol instrument) at months 6, 12, 24, 36, and end of the study visit. Analysis of covariance model included baseline EQ-5D value, region, and treatment as explanatory variables.
Results At baseline, patients (mean age 75 years; 24% men and 76% women) were well matched between treatment groups with mean EQ-5D VAS of 65.82 in ZOL and 65.70 in placebo group. At the end of the study, mean change from baseline in EQ-5D VAS was greater for ZOL vs. placebo in all patients (7.67±0.56 vs. 5.42±0.56), and in subgroups of patients experiencing clinical vertebral frac-

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tures (8.86±4.91 vs. −1.69±3.42), non-vertebral fractures (5.03±2.48 vs. −1.07±2.16), and clinical fractures (5.19±2.25 vs. −0.72±1.82) with treatment difference significantly in favor of ZOL. EQ-5D utility scores were comparable for ZOL and placebo groups, but more patients on placebo consistently had extreme difficulty in mobility (1.74% for ZOL vs. 2.13% for placebo; $p=0.6238$), self-care (4.92% vs. 6.69%; $p=0.1013$), and usual activities (10.28% vs. 12.91%; $p=0.0775$).

Conclusion ZOL significantly improves HRQoL in patients with low-trauma hip fracture.

Keywords EQ-5D · Health-related QoL · Low-trauma hip fracture · Zoledronic acid

Introduction

Osteoporosis-related fractures are associated with significant morbidity [1–5] and mortality [6]. Fractures of the vertebrae (spine), proximal femur (hip), and distal forearm are the commonest osteoporotic fractures. Hip fractures are the most serious consequence of osteoporosis and are associated with significant functional disability, and increase in mortality and morbidity including costly hospitalization and lengthy rehabilitation. Moreover, most patients with hip fractures fail to regain their pre-fracture level of activities and functioning [7–11]. The burden these osteoporotic fractures impose in terms of costs, hospitalization, and impaired quality of life (QoL) are a major public health concern for men and women 50 years of age and older, and make osteoporosis one of the most significant chronic diseases in older adults [2, 12].

The societal burden of osteoporosis-related fractures has largely been assessed by the impact on health-related quality-of-life (HRQoL) and healthcare costs. HRQoL is an important indicator of functional status, well-being, and disease experience of patients with osteoporosis-related fractures. It refers to a patient's perceived physical and mental health over time and may be used by clinicians to better understand how a chronic illness interferes with a person's day-to-day life [1, 13–15].

The EuroQol instrument is a standardized, non-disease-specific, preference-based instrument, which provides a comprehensive framework for measuring HRQoL and determining health status. The EuroQol instrument is intended to complement other forms of quality of life measures and to generate a cardinal index of health that can be used in economic evaluations. It has four components, but only one component, namely the EQ-5D, is commonly used for collecting data on HRQoL [16, 17]. Unlike disease-targeted instruments, preference measures determined by the EQ-5D can be used as a quality adjustment factor in evaluating quality-adjusted life years (QALY) in cost–utility analyses [16–18]. Furthermore, EQ-5D measurements may be compared to others without osteoporosis [3] or to those with various diseases [19].

Lyles et al. [20] demonstrated that intravenous (i.v.) zoledronic acid (ZOL) 5 mg infusion, administered annually to men and women after surgical repair of low-trauma hip fracture, significantly reduced the time-adjusted clinical fracture and mortality rate compared with placebo. As a secondary pre-defined exploratory objective of the same study, this analysis compared the benefits of ZOL versus placebo on quality of life measures using EQ-5D health questionnaire in selected countries.

Patients and methods

Men and women 50 years of age or older were eligible for inclusion within 90 days after surgical repair of a hip fracture sustained with minimal trauma (i.e., a fall from standing height or a lower height). Additional enrollment criteria included being ambulatory before the hip fracture and having both legs. Patients were enrolled from 24 countries in North America, South America, and Europe including a variety of cultural, ethnic, and racial groups. Exclusion criteria were previous hypersensitivity to a bisphosphonate, a potential for pregnancy, a calculated creatinine clearance of less than 30 ml per minute, a corrected serum calcium level of more than 11.0 mg/dL (2.8 mmol/L) or less than 8 mg/dL (2 mmol/L), active cancer, metabolic bone disease other than osteoporosis, and a life expectancy of less than 6 months in the investigator's judgment [20, 21].

Eligible patients received a loading dose of 50,000–125,000 U of vitamin D2 or 50,000–75,000 U of vitamin D3 administered intramuscularly or orally to help correct vitamin D deficiency. Different formulations of vitamin D were allowed based on the approved therapy in the study country. Patients then began daily oral doses of vitamin D (800–1,200 IU) and elemental calcium (1,000–1,500 mg daily in a divided dose). Patients took these supplements for at least 14 days prior to receiving the study drug in order to mitigate the small risk of transient hypocalcemia resulting from ZOL administration in vitamin D-deficient patients [22]. If a patient was randomized in less than 14 days, a 25-hydroxyvitamin D (25-OHD) level ≥15 ng/mL was ascertained before administering study drugs. Patients received their first dose of study drug at any time between 14 days after vitamin D2 or D3 administration and 90 days after surgical repair of their low-trauma hip fracture. Serum creatinine and calcium were measured by a central laboratory prior to each study drug infusion [20, 21].

The maximum study participation of each patient was to be 36 months with a maximum of three doses of study drug. The study was considered completed when 211 patients had reached the adjudicated primary endpoint. Therefore, the final visit for each patient was either at 36 months or earlier if 211 patients had reached the adjudicated primary endpoint. Once the adjudicated primary endpoint number had been achieved, all the active patients came in for a final visit. The final visit was not to be within 30 days from the patient's last dose of study medication or more than 90 days after the 211 patients have reached the adjudicated primary endpoint.

EQ-5D, a validated quality of life tool available [23] in the USA, Canada, Argentina, Austria, Belgium, Brazil, Colombia, Czech Republic, Denmark, Finland, France, UK, Guatemala, Norway, Peru, Poland, Russian Federation, Slovakia, Sweden, Switzerland, Turkey, Fiji, and Spain, was included at screening, randomization, 6 months, 12 months, and annually thereafter, and an end of the study visit to collect patient-reported data on HRQoL.

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki (1989) and local applicable laws and regulations. Approval was obtained from an Institutional Review Board or Independent Ethics Committee for each participating study center. All patients provided written informed consent prior to participating in the study. Clinical Trial Registration Number NCT00046254.

HRQoL: EQ-5D

The EQ-5D consists of two parts, a self-reported description using a five-dimensional classification (health profile—EQ-5D profile) and a self-rated global evaluation of perceived health using a visual analogue scale (VAS) or thermometer (perceived health—EQ-5D VAS) (worst possible health=0; perfect health=100). The EQ-5D profile describes health status in terms of five dimensions—mobility, self-care, performance of usual activities, pain or discomfort, and anxiety or depression. Each of the five dimensions of the EQ-5D profile are divided into three levels of difficulty: "no problem", "some problem", or "extreme problem". Based on these five-dimensional scores, a health utility score, that is EQ-5D utility, is derived. EQ-5D utility ranges from −0.594 (corresponding to the worst health state) to 1 (corresponding to the perfect health state) [24].

Statistical analysis

For this analysis, HRQoL was measured using the EuroQol instrument (EQ-5D VAS and EQ-5D utility scores). Descriptive statistics (mean, median, and standard error) of change from baseline in EQ-5D VAS and EQ-5D utility at each visit were presented by treatment group. Between-treatment differences for EQ-5D VAS and EQ-5D utility at each visit were evaluated using the analysis of covariance model with baseline EQ-5D value, region, and treatment in the model. The number and percentage of patients who had (a) problem (including some and extreme problem) and (b) extreme problem for each of the five dimensions of the EQ-5D profile was presented at each visit by treatment group. The number and percentage of patients who had (a) improvement from baseline, (b) no change from baseline, and (c) worsening from baseline for each of the five dimensions of the EQ-5D profile was presented at each visit by treatment group. In addition, the frequency of each category for a general question to assess the general state of health over the past 6 months was summarized.

Additional analyses of EQ-5D by treatment group comparisons were made for patients classified by the type of fracture they had over the study follow up period as described previously [20, 21].

Results

The study population consisted of 508 men and 1,619 women aged 50 years and older who had experienced a recent low-trauma hip fracture and were ambulatory prior to the fracture (Table 1). The mean age, range of ages, and proportions of patients within the different age groups were similar between treatment groups as were the mean height, weight, and BMI. The mean baseline EQ-5D VAS was 65.82 in ZOL group and 65.70 in the placebo group. The total duration of the study was 60 months, and 231 patients had confirmed clinical fractures during follow-up.

Change from baseline in EQ-5D VAS measurements by visit was consistently greater for those in the ZOL group (Fig. 1), regardless of whether or not a fracture occurred.

Between-treatment comparison of change from baseline in EQ-5D VAS measurements (mean±SE) at month 24 revealed significant treatment difference (Δ) in the ZOL group for all patients (ZOL=9.26±0.76; placebo=6.17±0.77; Δ=+3.08; 95% CI=1.09, 5.08; p=0.0024), in the subgroups of patients who experienced clinical fractures (ZOL=10.55±2.80; placebo=3.54±2.18; Δ=7.01; 95% CI=0.92, 13.09; p=0.0244) and clinical vertebral fractures (ZOL=10.92±3.74; placebo=−1.89±2.48; Δ=+12.81; 95% CI=4.34, 21.27; p=0.0042) (Table 2 and Fig. 2a), and patients who experienced no clinical fractures (ZOL=9.02±0.79; placebo=6.80±0.83; Δ=+2.23; 95% CI=0.11, 4.34; p=0.0395). The treatment differences in EQ-5D VAS measurements for ZOL compared to placebo at month 12 and month 36 did not reach statistical significance (Table 2). EQ-5D VAS measurements for hip fracture did not reach

Table 1 Demographic and baseline characteristics in ITT population

Variable	Zoledronic acid (*N*=1,065)	Placebo (*N*=1,062)
Sex, *n* (%)		
Male	248 (23.3)	260 (24.5)
Female	817 (76.7)	802 (75.5)
Race, *n* (%)		
Caucasians	973 (91.4)	965 (90.9)
Blacks	6 (0.6)	12 (1.1)
Hispanics	70 (6.6)	70 (6.6)
Orientals	2 (0.2)	1 (0.1)
Others	14 (1.3)	14 (1.3)
Age (years), mean (SD)	74.41 (9.49)	74.59 (9.86)
min–max	50–95	50–98
Age group (years), *n* (%)		
<65	172 (16.2)	192 (18.1)
65–74	307 (28.8)	269 (25.3)
75–84	446 (41.9)	449 (42.3)
≥85	140 (13.2)	152 (14.3)
Weight (kg)	*n*=1,055	*n*=1,056
Mean (SD)	65.08 (13.7)	65.53 (14.0)
Min–max	34.4–133.8	30.5–145.5
Height (cm)	*n*=1,027	*n*=1,031
Mean (SD)	162.14 (9.7)	162.06 (10.0)
Min–max	128.0–193.0	127.0–203.0
BMI (kg/m^2)	*n*=1,027	*n*=1,031
Mean (SD)	24.7 (4.4)	24.8 (4.5)
Min–max	13.7–46.8	12.4–44.7
EQ-5D VAS	*n*=996	*n*=1,002
Mean (SE)	65.82 (0.56)	65.70 (0.58)
EQ-5D utility score	*n*=1,005	*n*=1,005
Mean (SE)	0.58 (0.01)	0.57 (0.01)

N number of patients in the analysis population, *n* number of patients meeting the criterion (for categorical variables) or the number of patients with a measurement (for continuous variable)

statistical significance in ZOL-treated group compared to placebo at month 24 (Δ=+7.05; 95% CI=−7.15, 21.25; p=0.3151) and the end of the study visit (Δ=+10.91; 95% CI=−2.95, 24.77; p=0.1197) (Table 2).

At the end of the study, the EQ-5D VAS measurements (mean±SE) in all patients were significantly greater for ZOL group when compared with placebo (ZOL=7.67±0.56; placebo=5.42±0.56 for placebo; Δ=+2.25; 95% CI=

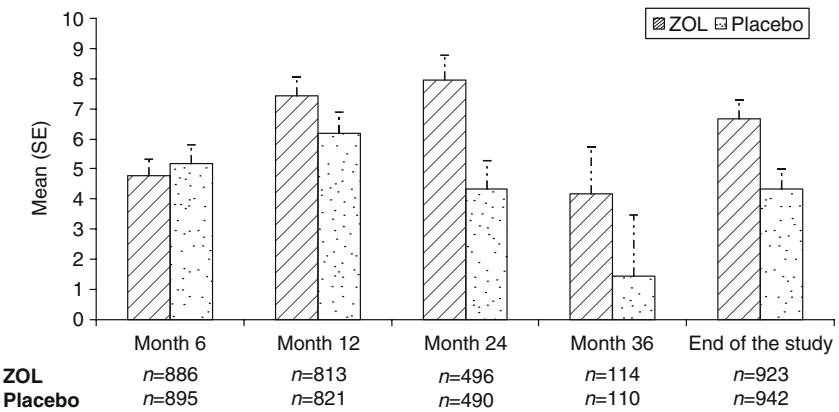

Fig. 1 Change from baseline in EQ-5D VAS by visit in ITT population

Table 2 Change from baseline in EQ-5D VAS between treatment groups by visit in ITT population

	Zoledronic acid LSM (SE)	Placebo LSM (SE)	Treatment difference	95% CI	*p* value
All patients					
Month 6	5.43 (0.51) *n*=886	5.73 (0.51) *n*=895	−0.31	−1.68, 1.06	0.6573
Month 12	7.96 (0.57) *n*=813	7.03 (0.56) *n*=821	0.93	−0.58, 2.44	0.2285
Month 24	9.26 (0.76) *n*=496	6.17 (0.77) *n*=490	3.08	1.09, 5.08	0.0024
Month 36	7.12 (2.05) *n*=114	4.06 (2.04) *n*=110	3.05	−1.07, 7.17	0.1457
End of study	7.67 (0.56) *n*=923	5.42 (0.56) *n*=942	2.25	0.74, 3.75	0.0034
Patients with clinical fractures					
Month 6	2.01 (1.99) *n*=78	3.43 (1.59) *n*=120	−1.42	−5.99, 3.15	0.5404
Month 12	5.38 (2.27) *n*=75	3.29 (1.85) *n*=110	2.09	−3.04, 7.23	0.4222
Month 24	10.55 (2.80) *n*=46	3.54 (2.18) *n*=77	7.01	0.92, 13.09	0.0244
Month 36	13.80 (6.04) *n*=13	1.64 (4.63) *n*=27	12.16	−0.46, 24.78	0.0585
End of study	5.19 (2.25) *n*=84	−0.72 (1.82) *n*=124	5.91	0.77, 11.04	0.0243
Patients with non-vertebral fractures					
Month 6	1.88 (2.18) *n*=66	2.44 (1.88) *n*=90	−0.56	−5.70, 4.58	0.8302
Month 12	5.00 (2.53) *n*=63	3.86 (2.23) *n*=82	1.14	−4.66, 6.94	0.6987
Month 24	9.21 (3.36) *n*=37	5.97 (2.66) *n*=59	3.24	−3.88, 10.35	0.3683
Month 36	15.59 (8.72) *n*=9	9.53 (8.53) *n*=19	6.06	−11.81, 23.92	0.4901
End of study	5.03 (2.48) *n*=72	−1.07 (2.16) *n*=94	6.1	0.30, 11.89	0.0393
Patients with clinical vertebral fractures					
Month 6	−0.01 (4.28) *n*=18	6.97 (2.89) *n*=36	−6.98	−16.08, 2.11	0.1292
Month 12	4.64 (4.68) *n*=20	1.31 (3.30) *n*=34	3.34	−6.71, 13.38	0.5072
Month 24	10.92 (3.74) *n*=15	−1.89 (2.84) *n*=23	12.81	4.34, 21.27	0.0042
Month 36	7.56 (12.50) *n*=5	−3.16 (6.76) *n*=9	10.72	−18.92, 40.37	0.4343
End of study	8.86 (4.91) *n*=20	−1.69 (3.42) *n*=37	10.55	0.21, 20.89	0.0456
Patients with hip fractures					
Month 6	2.31 (4.08) *n*=17	5.34 (3.45) *n*=26	−3.03	−13.83, 7.76	0.5725
Month 12	10.77 (5.35) *n*=18	7.91 (4.53) *n*=24	2.86	−10.65, 16.37	0.6704
Month 24	16.23 (5.88) *n*=11	9.18 (4.33) *n*=18	7.05	−7.15, 21.25	0.3151
Month 36	7.98 (24.43) *n*=2	−11.18 (13.52) *n*=5	19.16	−63.14, 101.46	0.5125

Table 2 (continued)

	Zoledronic acid LSM (SE)	Placebo LSM (SE)	Treatment difference	95% CI	*p* value
End of study	10.61 (5.25) *n*=20	−0.29 (4.56) *n*=27	10.91	−2.95, 24.77	0.1197
Patients with no clinical fractures					
Month 6	5.66 (0.53) *n*=808	6.10 (0.54) *n*=775	−0.44	−1.87, 0.99	0.5483
Month 12	8.13 (0.58) *n*=738	7.61 (0.59) *n*=711	0.52	−1.05, 2.10	0.5138
Month 24	9.02 (0.79) *n*=450	6.80 (0.83) *n*=413	2.23	0.11, 4.34	0.0395
Month 36	5.82 (2.03) *n*=101	5.00 (2.08) *n*=83	0.81	−3.57, 5.20	0.7149
End of study	7.77 (0.58) *n*=839	6.29 (0.59) *n*=818	1.48	−0.09, 3.04	0.0642

Scale 0 corresponds to worst possible health and scale 100 corresponds to perfect health. The *p* value is obtained from an analysis of covariance model with baseline scale, region, and treatment as explanatory variables

n number of patients with measurements at both baseline and post-baseline visit, *LSM* least squares mean, *SE* standard error of LSM, *CI* confidence interval, *Treatment difference* LSM difference of zoledronic acid vs. placebo on the change from baseline

0.74, 3.75; $p=0.0034$). Greater EQ-5D VAS with ZOL was also seen in the subgroups of patients who experienced clinical fractures (ZOL=5.19±2.25; placebo=−0.72±1.82; Δ=+5.91; 95% CI=0.77, 11.04; $p=0.0243$), non-vertebral fractures (ZOL=5.03±2.48; placebo=−1.07±2.16; Δ=+6.10; 95% CI=0.30, 11.89; $p=0.0393$), and clinical vertebral fractures (ZOL=8.86±4.91; placebo=−1.69±3.42; Δ=+10.55; 95% CI=0.21, 20.89; $p=0.0456$) (Table 2 and Fig. 2b). However, in patients who experienced no clinical fractures, the EQ-5D VAS measurements at the end of the study visit, though clinically greater for ZOL group versus placebo group (Δ=+1.48; 95% CI=−0.09, 3.04; $p=0.0642$), did not reach statistical significance (Table 2).

Although the treatment difference in EQ-5D utility scores was not statistically significant at the end of the study (Table 3), more patients in the placebo group consistently had extreme difficulty with mobility [17 (1.74%) for ZOL vs. 21 (2.13%) for placebo; $p=0.6238$], self-care [48 (4.92%) for ZOL vs. 66 (6.69%) for placebo; $p=0.1013$], and usual activities [100 (10.28%) for ZOL vs. 127 (12.91%) for placebo; $p=0.0775$].

Using a Cox regression model stratified by treatment group, the effect of baseline EQ-5D utility scores on clinical fracture was not statistically significant [$p=0.0635$, hazard ratio (HR)=0.660; 95% CI=0.426, 1.024 for a unit increase]; however, the effect of baseline EQ-5D VAS on clinical fracture was statistically significant ($p=0.0047$, HR=0.989; 95% CI=0.982, 0.997 for a unit increase).

Change in HRQoL by treatment after incident fracture by fracture type is represented in Table 4. The treatment difference in EQ-5D VAS and utility scores was not statistically significant, which may be due to small number of patients with incident fractures by fracture type in each treatment group.

Discussion

In this study, clinically relevant and statistically significant differences were seen between the ZOL and placebo groups using the EQ-5D VAS. The difference was noticed between the treatment groups in all patients as well as in the fracture subsets. These findings were not seen until 24 months of follow-up and may reflect the time needed to see a benefit. The end of study time point for the most part had the power to show a treatment benefit, while the 36-month time point in most instances did not. In the subset of patients with hip fractures, the difference in the EQ-5D VAS was statistically insignificant between the treatment groups, probably due to insufficient number of patients to compare in this subset. EQ-5D utility scores, though not statistically significant, showed extreme difficulty with mobility, self-care, and usual activities in the placebo group compared with ZOL group. The lack of statistically significant difference between treatment groups may reflect the generic nature of the questionnaire and the lack of power. The differences in statistical significance seen between the EQ-5D VAS and EQ-5D utility scores likely reflect the fact that the VAS score is a measure of pain while the summary utility score is a composite of several domains, some of which may not be impacted by ZOL.

Fractures are associated with significant morbidity and mortality [1, 6]. Moreover, hip fractures have a profound effect on HRQoL, particularly for the mobility, ambulation, and self-care attributes in both men and women and additionally pain for women [2, 10].

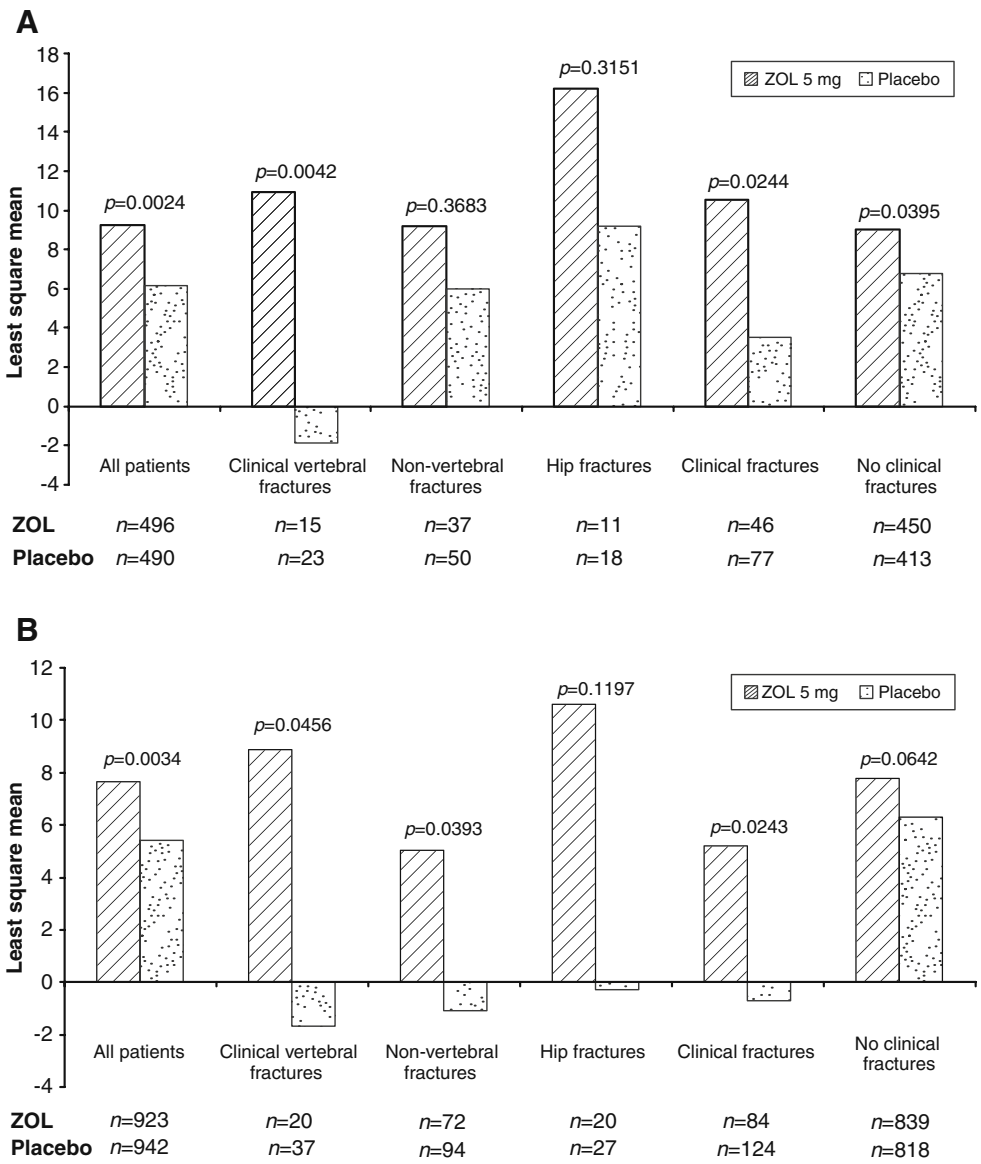

Fig. 2 Between-treatment comparison of change from baseline in EQ-5D VAS **A** at month 24 and **B** at the end of the study visit in ITT population

Multiple prior studies have documented declines in HRQoL with incident and prevalent fractures. Oleksik et al. [25] demonstrated in a cross-sectional study that those with prevalent fractures had worse HRQoL and that the greater the number of vertebral fractures the greater the reduction in quality of life. This was particularly noticeable in fractures of the lumbar spine.

Papaioannou et al. [2] reported that men and women with incident hip fractures, compared to those without, had lower HRQoL and greater declines in HRQoL along with increased mortality, which was noticed following both hip and clinical spine fractures. The results from this Canadian Multicenter Osteoporosis study confirmed that the hip fractures have a profound effect on HRQoL, and patients with hip fracture never regain previous levels of functioning.

Magaziner et al. [11] in the report on the sequelae of hip fracture in eight areas of functioning using data obtained from community-dwelling hip fracture patients entering eight Baltimore area hospitals, 1990–1991, and followed prospectively for up to 2 years concluded that functional disability following hip fracture is significant and patterns of recovery differ by area of function.

Similarly, Boonen et al. [8] in a prospective controlled study evaluating the functional outcome and quality of life following hip fracture in elderly women reported that women who sustain a hip fracture continue to suffer from substantial functional impairment and loss in HRQoL at 1 year, despite a significant recovery during this 12-month period. Also, assessing HRQoL in hip fracture women through self-administered questionnaires is subject to

Table 3 Change from baseline in EQ-5D utility scores in treatment groups by visit in ITT population

	Zoledronic acid LSM (SE)	Placebo LSM (SE)	Treatment difference	95% CI	*p* value
All patients					
Month 6	0.12 (0.01) *n*=891	0.11 (0.01) *n*=902	0	−0.02, 0.03	0.7397
Month 12	0.15 (0.01) *n*=814	0.13 (0.01) *n*=828	0.02	−0.00, 0.04	0.0935
Month 24	0.14 (0.01) *n*=503	0.13 (0.01) *n*=505	0.01	−0.02, 0.04	0.4452
Month 36	0.10 (0.03) *n*=113	0.08 (0.03) *n*=112	0.02	−0.05, 0.09	0.5649
End of study	0.12 (0.01) *n*=936	0.11 (0.01) *n*=951	0.01	−0.02, 0.03	0.6605
Patients with clinical fractures					
Month 6	0.02 (0.03) *n*=77	0.05 (0.03) *n*=121	−0.03	−0.11, 0.05	0.4339
Month 12	0.09 (0.04) *n*=72	0.06 (0.03) *n*=113	0.04	−0.05, 0.12	0.4016
Month 24	0.02 (0.04) *n*=46	0.00 (0.04) *n*=78	0.02	−0.08, 0.11	0.7527
Month 36	0.15 (0.09) *n*=13	−0.08 (0.07) *n*=29	0.23	0.03, 0.42	0.0226
End of study	0.00 (0.04) *n*=83	−0.04 (0.03) *n*=129	0.05	−0.04, 0.13	0.2976
Patients with non-vertebral fractures					
Month 6	0.03 (0.04) *n*=65	0.05 (0.03) *n*=89	−0.02	−0.11, 0.06	0.5716
Month 12	0.10 (0.04) *n*=60	0.08 (0.03) *n*=84	0.02	−0.07, 0.11	0.6610
Month 24	0.02 (0.05) *n*=36	0.02 (0.04) *n*=57	0.00	−0.11, 0.11	0.9896
Month 36	0.18 (0.13) *n*=9	0.01 (0.13) *n*=21	0.17	−0.10, 0.44	0.2106
End of study	−0.01 (0.04) *n*=70	−0.04 (0.04) *n*=97	0.03	−0.06, 0.13	0.5091
Patients with clinical vertebral fractures					
Month 6	0.02 (0.07) *n*=18	0.05 (0.05) *n*=39	−0.03	−0.19, 0.13	0.7019
Month 12	0.05 (0.09) *n*=19	0.00 (0.06) *n*=36	0.05	−0.13, 0.23	0.5643
Month 24	−0.09 (0.08) *n*=15	−0.04 (0.06) *n*=26	−0.05	−0.24, 0.13	0.5750
Month 36	0.21 (0.15) *n*=5	−0.18 (0.09) *n*=10	0.39	0.04, 0.75	0.0326
End of study	0.02 (0.09) *n*=20	−0.05 (0.06) *n*=39	0.07	−0.12, 0.26	0.4862
Patients with hip fractures					
Month 6	0.00 (0.07) *n*=18	0.03 (0.06) *n*=25	−0.02	−0.21, 0.16	0.7839
Month 12	0.08 (0.07) *n*=18	0.07 (0.06) *n*=23	0.01	−0.17, 0.19	0.8906
Month 24	0.03 (0.07) *n*=12	0.12 (0.06) *n*=16	−0.09	−0.26, 0.08	0.2987
Month 36	0.49 (0.55) *n*=2	0.05 (0.33) *n*=4	0.44	−1.61, 2.49	0.4548

Table 3 (continued)

	Zoledronic acid LSM (SE)	Placebo LSM (SE)	Treatment difference	95% CI	*p* value
End of study	−0.01 (0.07) *n*=21	−0.07 (0.06) *n*=27	0.06	−0.13, 0.25	0.5121
Patients with no clinical fractures					
Month 6	0.12 (0.01) *n*=814	0.12 (0.01) *n*=781	0.00	−0.02, 0.03	0.7913
Month 12	0.16 (0.01) *n*=742	0.14 (0.01) *n*=715	0.01	−0.01, 0.04	0.2871
Month 24	0.15 (0.01) *n*=457	0.15 (0.01) *n*=427	0.00	−0.03, 0.03	0.9700
Month 36	0.08 (0.03) *n*=100	0.12 (0.03) *n*=83	−0.04	−0.11, 0.03	0.2756
End of study	0.13 (0.01) *n*=853	0.14 (0.01) *n*=822	−0.01	−0.03, 0.02	0.5046

Score −0.594 corresponds to worst possible health and score 1.00 corresponds to perfect health. The *p* value is obtained from an analysis of covariance model with baseline score, region, and treatment as explanatory variables

n number of patients with measurements at both baseline and post-baseline visit, *LSM* least squares mean, *SE* standard error of LSM, *CI* confidence interval, *Treatment difference* LSM difference of zoledronic acid vs. placebo on the change from baseline

considerable bias due to non-response. While it is intuitive that the medications and interventions leading to reductions in fractures should also result in better outcomes in HRQoL, no study to date has explored or defined the magnitude of HRQoL difference between subjects who receive effective fracture prevention therapies and those who do not.

Several randomized controlled trials have explored whether osteoporosis therapies have an impact on HRQoL. In a randomized, double-blind trial, Oleksik et al. [3] found that in patients with previous vertebral fractures, incident vertebral fractures (clinical and subclinical) were associated with a significant decline in HRQoL in terms of an increase in back pain, deterioration of physical function, and worsening general health perception. The score changes for patients with subclinical vertebral fractures were intermediate between those for patients with clinical vertebral fractures and patients without incident vertebral fracture. They both showed that the clinical and subclinical incident vertebral fractures both have an adverse impact on HRQoL. However, the effect of treatment with active ingredient (raloxifene) versus placebo on HRQoL was not significant in this study.

Table 4 Change from baseline in EQ-5D VAS and EQ-5D utility scores measured after the incident fracture by fracture type (ITT population)

Fracture type	Zoledronic acid LS mean (SE)	Placebo LS mean (SE)	Treatment difference (95% CI)	*p* value
EQ-5D visual analogue scale				
Clinical	4.55 (2.08) *n*=75	1.83 (1.70) *n*=109	2.72 (−2.02, 7.46)	0.2585
Non-vertebral	5.20 (2.28) *n*=63	2.10 (2.02) *n*=80	3.10 (−2.21, 8.42)	0.2505
Clinical vertebral	2.16 (4.58) *n*=19	−0.36 (3.19) *n*=34	2.52 (−7.35, 12.38)	0.6103
Hip	10.26 (4.69) *n*=18	−0.09 (4.19) *n*=22	10.34 (−2.19, 22.87)	0.1027
EQ-5D utility scores				
Clinical	−0.02 (0.04) *n*=75	−0.04 (0.03) *n*=114	0.02 (−0.07, 0.11)	0.6536
Non-vertebral	−0.03 (0.04) *n*=62	−0.06 (0.04) *n*=83	0.03 (−0.07, 0.13)	0.5235
Clinical vertebral	−0.03 (0.08) *n*=20	−0.05 (0.06) *n*=36	0.02 (−0.15, 0.20)	0.7941
Hip	−0.14 (0.08) *n*=19	−0.08 (0.08) *n*=22	−0.06 (−0.28, 0.16)	0.5971

Silverman et al. [26] in the Fracture Prevention Trial examined the relationship of back pain and HRQoL using the Osteoporosis Assessment Questionnaire in postmenopausal women with osteoporosis receiving teriparatide or placebo. They demonstrated that both prevalent back pain and new or worsening back pain affected HRQoL negatively. Osteoporosis therapies that prevent the development of back pain in postmenopausal women may also prevent decreases in HRQoL. However, no significant difference was seen between treatment groups and placebo in any HRQoL domain.

To our knowledge, this is the first study that has demonstrated significant differences in HRQoL between treatment groups with an osteoporosis therapy using the generic EQ-5D VAS instrument, suggesting that treatment may make a difference. Meunier et al. [27] also recently demonstrated an improvement in HRQoL with strontium ranelate therapy for 4 years in patients with postmenopausal osteoporosis using the disease-specific QUALIOST® [28] instrument. The significant findings in our study, compared to prior osteoporosis therapy studies, may be related to the population studied; hip fracture patients tend to be older, more frail, and at risk for functional decline. Preventing additional fracture events may therefore have a greater impact on them than on a healthier postmenopausal population.

Limitations of our analysis include the small number of patients in the treatment groups at later time points, including the patients with hip fractures. This is expected, given the fact that this was an event-driven trial and all the patients may not have all the time points. Indeed the insignificant 36-month QoL changes are a reflection of the small numbers to that time point. Moreover, the study was not powered to demonstrate the changes in HRQoL and multiple measures were made at different time points noting this as a limitation. Despite this, the results consistently showed benefit.

In conclusion, infusions of ZOL 5 mg in patients with a recent hip fracture leads to improved HRQoL, as measured by the EQ-5D VAS, when compared with placebo. This was true for all patients and in the subset of patients with clinical fractures, non-vertebral fractures, and clinical vertebral fractures. Summary utility scores, however, did not show differences between treatment and placebo and, while not statistically significant, the mobility, self-care, and usual activities domains showed extreme difficulty in the placebo group compared with ZOL group.

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Conflicts of interest Dr. Adachi reports receiving consulting fees from Amgen, AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis, and Servier and grant support from Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Procter & Gamble, and Roche.

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Dr. Eriksen (now an employee of Oslo University, Oslo, Norway), being an employee of Novartis during the design and initiation of the study, and receiving advisory board fees from Novartis, Eli Lilly and Amgen.

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