Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial

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Summary

Background No clinical trials have compared osteoporosis drugs with incident fractures as the primary outcome. We compared the anti-fracture efficacy of teriparatide with risedronate in patients with severe osteoporosis.

Methods In this double-blind, double-dummy trial, we enrolled post-menopausal women with at least two moderate or one severe vertebral fracture and a bone mineral density T score of less than or equal to –1·50. Participants were randomly assigned to receive 20 µg of teriparatide once daily plus oral weekly placebo or 35 mg of oral risedronate once weekly plus daily injections of placebo for 24 months. The primary outcome was new radiographic vertebral fractures. Secondary, gated outcomes included new and worsened radiographic vertebral fractures, clinical fractures (a composite of non-vertebral and symptomatic vertebral), and non-vertebral fractures. This study is registered with ClinicalTrials.gov (NCT01709110) and EudraCT (2012-000123-41).

Findings We enrolled 680 patients in each group. At 24 months, new vertebral fractures occurred in 28 (5·4%) of 680 patients in the teriparatide group and 64 (12·0%) of 680 patients in the risedronate group (risk ratio 0·44, 95% CI 0·29–0·68; p<0·0001). Clinical fractures occurred in 30 (4·8%) of 680 patients in the teriparatide group compared with 61 (9·8%) of 680 in the risedronate group (hazard ratio 0·48, 95% CI 0·32–0·74; p=0·0009). Non-vertebral fragility fractures occurred in 25 (4·0%) patients in the teriparatide group and 38 (6·1%) in the risedronate group (hazard ratio 0·66; 95% CI 0·39–1·10; p=0·10).

Interpretation Among post-menopausal women with severe osteoporosis, the risk of new vertebral and clinical fractures is significantly lower in patients receiving teriparatide than in those receiving risedronate.

Funding Lilly.

Introduction

Approved treatments for post-menopausal osteoporosis include anti-resorptive and bone-forming drugs. Anti-resorptive therapies target osteoclast-mediated bone resorption, thereby reducing bone loss, increasing bone mineral density (BMD), and reducing the risk of vertebral fractures.[1] Nitrogen-containing bisphosphonates and denosumab can also reduce the risk of non-vertebral and hip fractures in post-menopausal women who have a high risk of fractures.[2,3] Teriparatide (recombinant human parathyroid hormone) is a bone-forming medication that preferentially stimulates osteoblasts to produce new bone tissue, thereby increasing bone mass and strength.[4] Teriparatide reduces vertebral and non-vertebral fractures in post-menopausal women with established osteoporosis.[5]

Although several studies[6–11] have compared the effects of these two classes of drugs on surrogate markers of bone strength and quality (such as areal and volumetric bone mineral density, biochemical markers of bone turnover, static and dynamic histomorphometry, and finite element analysis estimates of bone strength), no adequately powered head-to-head studies have compared the effects of anti-resorptives and bone-forming drugs on reducing the risk of fractures as the primary outcome. Two clinical trials[12,13] have reported fracture outcomes in a head-to-head comparison of teriparatide and bisphosphonates, showing a greater reduction in the risk of new vertebral fractures with teriparatide than with oral bisphosphonates. However, fractures were secondary or exploratory outcomes in these studies.

We studied the effects of 24 months of treatment with teriparatide compared with risedronate on the incidence of new fractures in post-menopausal women with pre-existing vertebral fractures, regardless of previous osteoporosis treatment.

Methods

Study design

The VERtebral fracture treatment comparisons in Osteoporotic women (VERO) study was a randomised, double-blind, active-controlled, parallel-group trial done at 123 centres with experience in the management of

Research in context

Evidence before the study

Treatments for osteoporosis reduce the risk of incident vertebral fracture compared with calcium and vitamin D supplemented placebo. However, no active-controlled head-to-head studies have compared directly the effect of these therapies on osteoporotic fractures as the primary endpoint. Results of double-blind studies suggest that teriparatide might reduce the risk of new vertebral fractures compared with oral bisphosphonates; however, incident fracture rates were not the primary endpoint in these studies.

Added value of this study

The VERO study is the first double-dummy, active-controlled, head-to-head study designed to compare the effects of two osteoporosis drugs (teriparatide *vs* risedronate) with fracture risk (defined as incidence of new vertebral fractures) as the primary outcome. Because most patients in the study had been treated previously with osteoporosis drugs, this 24-month study provides long-term fracture data in a large study population that closely mimics the targeted patient population in clinical practice. The results show that patients treated with teriparatide have a lower risk of vertebral fractures and clinical fragility fractures than do patients treated with risedronate, and therefore provide relevant data for the treatment of patients with established osteoporosis.

Implications of all the evidence

Bone turnover markers, bone mineral density, bone biopsy, and estimates of bone strength are all intermediate endpoints shown to differ in prior head-to-head trials of bisphosphonate and teriparatide. Our study demonstrates, for the first time to our knowledge, superior clinical and vertebral anti-fracture efficacy of teriparatide (*vs* risedronate) in post-menopausal women with existing vertebral fractures, showing the added value of teriparatide for the prevention of fragility fractures. Clinicians should consider teriparatide for optimal management for patients with osteoporosis who have prevalent vertebral fractures.

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patients with osteoporosis in 14 countries in Europe, South America, and North America. The first patient entered the study in October, 2012, and the last patient completed the study in July, 2016.

Written informed consent was obtained from all patients. The trial was approved by the institutional review board at each trial centre.

Participants

We enrolled ambulatory post-menopausal women older than 45 years of age with a bone mineral density T score less than or equal to –1·50 SDs at the femoral neck, total hip, or lumbar spine. Participants had to have radiographic evidence of at least two moderate (ie, a reduction in vertebral body height of 26–40%) or one severe (more than 40% reduction) prevalent vertebral fragility fracture according to the classification of Genant and colleagues.[14] We excluded patients with unresolved skeletal diseases other than osteoporosis, malignant tumours in the 5 years before screening, osteonecrosis of the jaw, previous atypical subtrochanteric femoral fractures, risk factors for osteosarcoma, gastrointestinal disorders contraindicating risedronate, significantly impaired hepatic function, or a calculated creatinine clearance less than 30 mL/min using the Cockcroft–Gault equation. We also excluded patients who had undergone kyphoplasty or vertebroplasty at three or more levels before randomisation or within the 6 months before randomisation. Participants had to have normal baseline serum albumin-corrected calcium, parathyroid hormone, and free thyroxine concentrations, and 25-hydroxy-vitamin D concentration greater than 23 nmol/L.

Previous treatment with osteoporosis medications was allowed if discontinued at the screening visit, with the following exceptions: (1) intravenous zoledronic acid if the last dose was administered less than 12 months before screening, (2) intravenous ibandronate or pamidronate if the last dose was administered less than 3 months before screening, (3) subcutaneous denosumab if the last dose was administered less than 6 months before screening, (4) any treatment with parathyroid hormone, teriparatide, or other parathyroid hormone analogues, and (5) fluoride at therapeutic doses (for full eligibility criteria see appendix pp 35–39).

See Online for appendix

Randomisation and masking

We randomly assigned patients (1:1) to receive either injectable subcutaneous teriparatide (20 µg daily; Forteo®, Lilly) plus an oral weekly placebo, or oral risedronate (35 mg weekly; Actonel®, Warner-Chilcott) plus injectable subcutaneous daily placebo. Assignment to treatment groups was determined by an interactive voice-response system, based on a computer-generated random sequence prepared by Lilly. Randomisation was stratified by history of clinical vertebral fragility fracture (<12 months *vs* >12 months before screening), and by recent use of bisphosphonates. Recent bisphosphonate use was defined as: (1) a total of 6 months or more of treatment with any oral bisphosphonate—either intermittently or continuously—in the 3 years before screening, (2) intravenous zoledronic acid at any dose within 2 years of screening, or (3) intravenous ibandronate or pamidronate at any dose within 12 months before screening. Patients, investigators, central imaging radiologists, and sponsor representatives were blinded to treatment assignment. Placebos were matched for colour, shape, and size.

Procedures

The study had a screening phase of up to 4 weeks, followed by a treatment phase of 24 months. Patients had

study visits scheduled at 3, 6, 12, 18, and 24 months after randomisation. Teriparatide or its placebo was administered by subcutaneous injection with a prefilled pen device. Patients received daily supplements of 500–1000 mg of elemental calcium and roughly 400–800 IU of vitamin D3 or D2. In patients with 25-hydroxy-vitamin D concentrations of 23–50 nmol/L at screening, the supplemental dose of vitamin D was 2000 IU per day. Study data were collected by investigators and transmitted to the sponsor according to the study protocol (appendix p 54), and analyses were done by the sponsor according to the prespecified analysis plan (appendix p 91).

Lateral spine radiographs were repeated at 12 and 24 months or early termination for new vertebral fractures. Additional unscheduled radiographs were done at any interim visit to detect new clinical vertebral fractures if the patient reported back pain clinically suggestive of a vertebral fracture. A central radiologist (at BioClinica, San Francisco, CA, USA) assessed the incidence of new vertebral fractures by quantitative vertebral morphometry, confirmed with qualitative visual semiquantitative grading, according to the scale by Genant and colleagues.[14,15]

A new vertebral fracture was defined as a vertebral body height loss of at least 20% (and 4 mm) of a vertebra that was unfractured at baseline, based on a 6-point placement of the vertebral bodies from T4 to L4, and confirmed by an increase by one or more severity grades. Worsening of a pre-existing fracture identified at baseline was diagnosed if the decrease in vertebral height was at least one severity grade in the semiquantitative assessment. A clinical vertebral fracture was defined as an episode associated with signs and symptoms highly suggestive of a vertebral fracture, such as acute onset severe back pain, pain with little or no exertion, pain localised to specific vertebra and associated with limited back mobility, pain relieved by bed rest, pain worsened when upright, coughing, or sneezing, limited back flexion, or paravertebral muscle tenderness secondary to spasms,[16] confirmed as new or worsened radiographic vertebral fracture by the central x-ray image readers. Non-vertebral fractures were confirmed by site investigators by radiology or surgical reports. Pathological fractures, fractures of skull, face, fingers, metacarpals, or toes were excluded.

Body height was measured at baseline, 12 months, and 24 months using a stadiometer. Worst back pain during the 24 h before the baseline visit and each subsequent visit was scored with an 11-point numerical back pain rating scale (from 0=no back pain, to 10=worst possible back pain). Health-related quality-of-life was assessed at each visit using the EQ-5D-5L questionnaire. The EQ visual analogue scale measures the respondent's self-rated health on a visual scale rated from 0 (the worst health you can imagine) to 100 (the best health you can imagine).[17]

Safety evaluations included physical examinations, laboratory tests analysed centrally (by Covance, Indianapolis, IN, USA), and reporting of adverse events. Serum albumin-adjusted calcium concentration was assessed at baseline, 6 months, and 24 months at least 16 h after the administration of injectable study drug. Serum concentrations of 25-hydroxy-vitamin D were assessed at baseline, 3 months, and 6 months for adjustment of vitamin D supplement dose.

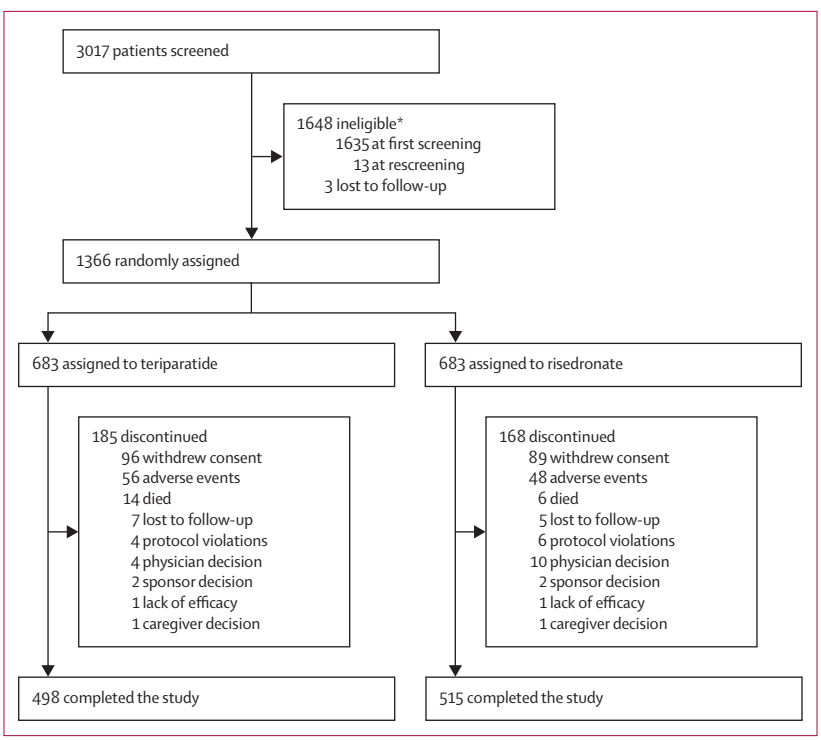

Figure 1: **Trial profile**
Three patients in each group were randomly assigned but did not begin treatment (two in each group discontinued at their decision and one in each group discontinued because of protocol violations). *1397 did not meet entry criteria, 188 patient decision, 39 sponsor decision, 16 physician decision, seven because of adverse events, one caregiver decision.

Outcomes

The primary endpoint was the percentage of patients with at least one new vertebral fracture during the 24-month study period. Key secondary outcomes were the incidence of pooled new and worsened vertebral fractures, the incidence of clinical fractures (a composite of clinical vertebral and non-vertebral fragility fractures), non-vertebral fragility fractures, and major non-vertebral fragility fractures (hip, radius, humerus, ribs, pelvis, tibia, or femur). Additional secondary outcomes were the incidence of new moderate or severe and multiple vertebral fractures, pooled fragility and high trauma non-vertebral fractures, and the change from baseline in body height, back pain, and health-related quality of life.

Prespecified exploratory outcomes were the time to first clinical fracture, non-vertebral fracture and clinical vertebral fracture events, and the incidence of new

	Teriparatide group (n=680)	Risedronate group (n=680)
Age (years)		
<50	7 (1%)	2 (<1%)
50 to <65	144 (21%)	162 (24%)
65 to <80	382 (56%)	405 (60%)
≥80	147 (22%)	111 (16%)
Mean (SD)	72·6 (8·77)	71·6 (8·58)
Race		
White	670 (99%)	653 (96%)
Black or African American	5 (1%)	15 (2%)
Asian	4 (1%)	8 (1%)
Other	1 (<1%)	4 (1%)
Mean height (cm; SD)	154·7 (7·2)	155·0 (7·4)
Mean body mass index (kg/m²; SD)	26·9 (4·61)	27·1 (4·64)
Geographical region*		
North America	91 (13%)	100 (15%)
South America	142 (21%)	159 (23%)
Europe	447 (66%)	421 (62%)
Mean bone mineral density (SD)		
Lumbar spine (g/cm²)	0·86 (0·15)	0·86 (0·15)
T score†	−2·27 (1·24)	−2·29 (1·22)
Femoral neck (g/cm²)	0·66 (0·11)	0·67 (0·11)
T score†	−2·27 (0·76)	−2·24 (0·74)
Total hip (g/cm²)	0·74 (0·11)	0·74 (0·12)
T score†	−1·95 (0·87)	−1·95 (0·82)
Prevalent fractures		
Vertebral fractures‡		
≥1	679 (100%)	679 (100%)
1	231 (34%)	240 (35%)
2	178 (26%)	174 (26%)
3	104 (15%)	101 (15%)
4	60 (9%)	62 (9%)
≥5	106 (16%)	102 (15%)
Grade of the most severe vertebral fracture§		
SQ2	73 (11%)	67 (10%)
SQ3	606 (89%)	612 (90%)
Non-vertebral fractures		
Patients older than 40 years with ≥1 fracture	298 (44%)	284 (42%)
1	166 (24%)	164 (24%)
2	80 (12%)	81 (12%)
3	40 (6%)	21 (3%)
4	6 (1%)	11 (2%)
≥5	6 (1%)	7 (1%)
(Continued from previous column)		
Previous osteoporosis medication use		
Patients with ≥1 previous osteoporosis therapy¶	496 (73%)	485 (71%)
Antiresorptives	418 (61%)	410 (60%)
Bisphosphonates	402 (59%)	386 (57%)
Calcium or vitamin D only	64 (9%)	69 (10%)
Selective oestrogen receptor modulators	21 (3%)	26 (4%)
Hormone or oestrogen replacement therapy	9 (1%)	3 (<1%)
Other osteoporosis therapy‖	78 (11%)	80 (12%)
Median duration of previous osteoporosis therapy (years; IQR)	3·2 (1·0–6·8)	3·3 (1·0–6·3)
Any antiresorptive	3·8 (1·2–7·0)	3·7 (1·2–6·3)
Bisphosphonates	3·6 (1·1–7·0)	3·6 (1·3–6·1)
Calcium or vitamin D only	0·3 (0·1–3·1)	0·3 (0·1–2·2)
Selective oestrogen receptor modulators	4·2 (1·2–6·2)	2·5 (1·0–7·4)
Hormone or oestrogen replacement therapy	3·2 (2·8–4·0)	14·9 (7·0–22·7)
Other osteoporosis therapy‖	1·0 (0·5–2·1)	0·7 (0·1–2·3)
Median duration of previous osteoporosis therapy in recent bisphosphonate users (years; IQR)**		
Bisphosphonates (oral)	3·7 (1·8–6·7)	3·9 (2·0–5·9)
Zoledronic acid (intravenous)	1·1 (0·0–3·0)	2·0 (1·0–2·2)
Ibandronate–pamidronate (intravenous)	0·5 (0·0–2·2)	3·6 (2·9–4·2)
Patients taking glucocorticoid therapy††	71 (10%)	56 (8%)
Mean 25-hydroxy-vitamin D concentration (nmol/L, SD)	79·7 (65·8)	78·5 (47·7)

Percentages might not sum to 100 because of rounding. SQ=qualitative visual semiquantitative grading. *North America=Canada and USA; South America=Argentina and Brazil; Europe=Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, Poland, and Spain. †Number of SDs below the respective mean bone mineral density in young adults. ‡Assessed by central, blinded reading. §Assessed with the grading scale of Genant and colleagues.[14] Per protocol, none of the patients had vertebral fractures of SQ1 as worst severity at baseline. ¶See appendix page 1 for details of the specific drugs and the treatment duration. ‖Other therapies included strontium ranelate (n=76), denosumab (n=49), calcitonin (n=34), 1αhydroxyvitamin D (n=9), fluoride (n=4), and 1,25-di-hydroxy-vitamin D (n=1). **Oral bisphosphonates: teriparatide (n=240), risedronate (n=242); intravenous zoledronic acid: teriparatide (n=23), risedronate (n=25); intravenous ibandronate–pamidronate: teriparatide (n=3), risedronate (n=2). ††Prednisone-equivalent doses of >5 mg per day at baseline or any visit after baseline.

Table 1: **Baseline characteristics (full-analysis set)**

vertebral fractures during the first 12 months (appendix p 104). Fractures were considered fragility fractures if the associated trauma would not have resulted in the fracture of a normal bone, as determined at the investigative site. This definition included low-energy trauma fractures, such as those resulting from a fall from standing height, a fall from the sitting position, or a fall from laying down on a bed or a reclining chair from less than 1 m height, a fall after having missed one to three steps in a staircase, or after a movement outside of the typical plane of motion.

Statistical analysis

Assuming a 24-month new vertebral fracture incidence of 4·5% in the teriparatide group and 10% in the risedronate group, 466 patients per group would provide 90% power

	Teriparatide group	Risedronate group	Effect size (95% CI)*	p value
Primary endpoint				
New vertebral fracture†	28 (5%)	64 (12%)	0·44 (0·29–0·68)	<0·0001
Secondary gated endpoints				
New and worsened vertebral fracture†	31 (6%)	69 (13%)	0·46 (0·31–0·68)	<0·0001
Pooled clinical fracture‡§	30 (5%)	61 (10%)	0·48 (0·32–0·74)	0·0009
Non-vertebral fragility fracture§	25 (4%)	38 (6%)	0·66 (0·39–1·10)	0·10
Major non-vertebral fragility fracture§	18 (3%)	31 (5%)	0·58 (0·32–1·05)	0·06
Secondary non-gated endpoints				
New moderate (SQ2) or severe (SQ3) vertebral fracture†	26 (5%)	63 (12%)	0·42 (0·27–0·65)	<0·001
New multiple vertebral fracture†	2 (<1%)	12 (2%)	0·16 (0·04–0·74)	0·007
Pooled fragility and traumatic non-vertebral fracture§	40 (7%)	57 (9%)	0·70 (0·46–1·05)	0·08

SQ=qualitative visual semiquantitative grading. *For morphometric vertebral fractures analyses (new, new and worsened, new moderate and severe, and new multiple fractures) the relative risk is presented; for all other endpoints, the hazard ratio is presented. Estimates for teriparatide versus risedronate (ie, risedronate in the denominator). †Spine radiographs after randomisation were available for assessing spine fracture outcomes in 516 participants (75·5%) in the teriparatide group and 533 (78·0%) in the risedronate group (modified full analysis set—ie, patients with ≥x-ray assessment after baseline). Treatment comparison based on Cochran-Mantel-Haenszel χ^2 test at a two-sided significance level of 0·05 adjusted for antecedent of recent clinical vertebral fracture and recent bisphosphonate use. ‡Pooled clinical vertebral and non-vertebral fragility fractures. §Based on the full analysis set (680 patients in each treatment group); proportion of patients and treatment comparison calculated by Kaplan-Meier method and stratified log-rank test adjusted for antecedent of recent clinical vertebral fracture and recent bisphosphonate use. Patients who were lost to follow-up, died, or completed the study without having had the event of interest were censored at the last date of contact.

Table 2: **Fracture efficacy outcomes during 24 months**

to detect a difference between groups in the incidence of new vertebral fractures using a Pearson χ^2 test (two-sided α of 0·05). Assuming a dropout rate of 30%, we aimed to enrol 670 patients per group.

We analysed efficacy following a modified intention-to-treat principle and included randomly assigned patients who received at least one dose of investigational product (full analysis set). For analysis of the primary outcome, we included only patients with at least one evaluable spinal radiograph at baseline and at least one after baseline (modified full analysis set). Sensitivity analyses were done for the per-protocol population, which included all patients without major protocol deviations as predefined in the analysis plan. No imputation was made for fracture data. Patients with missing x-ray data at 24 months and no evidence of vertebral fracture during the 24-month study period did not contribute to the analyses.

We used a fixed-sequence gatekeeping testing procedure for the primary and four key secondary fracture analyses (pooled new and worsened vertebral fractures, clinical fractures, non-vertebral fragility fractures, major non-vertebral fragility fractures) to maintain the overall study type I error rate at 5%. For the primary efficacy analysis (and other endpoints that included non-clinical vertebral fractures), we did a two-sided Cochran-Mantel-Haenszel test at a significance level of 0·05, adjusted for the two stratification factors. For clinical fractures (vertebral and non-vertebral), we estimated the cumulative incidence of fractures by the Kaplan-Meier method; the comparison was based on the stratified log-rank test adjusted for the stratification factors. We calculated stratified hazard ratios (HRs) and their corresponding 95% CIs from the number of observed and expected events as part of the stratified log-rank test calculations. Patients who were lost to follow-up, died, or completed the study without experiencing the event of interest were censored at the last date of contact. We did additional Cochran-Mantel-Haenszel and log-rank tests adjusted for geographical region (North America, South America, and Europe). We fitted mixed models for repeated measures,[18] adjusted for the two stratification factors and the baseline covariate corresponding to the dependent variable to estimate the difference between treatments in the change from baseline to 24 months for body height, back pain, health-related quality of life, and safety laboratory parameters.

We did a longitudinal analysis of repeated fractures with a logistic regression model for repeated measures using a population-averaged generalised estimating equation approach. Two binary measures were available per patient, one each indicating whether or not the patient had a fracture during the first or the second 12-month study period. The model included treatment, time period, treatment-by-time-period interaction, and the two stratification variables. An unstructured covariance matrix was specified to account for the correlation between observations of the same patient. We used Poisson regression models, adjusted for the two stratification factors, to analyse fracture count data. An offset variable, defined as the follow-up time for each patient in months, was included in the Poisson models to account for the potential differences in individual follow-up times. As a consequence, Poisson model estimates are given as rate ratios. We calculated the number needed to treat as the inverse of the absolute risk reduction multiplied by 100.

The compliance rate was computed as the percentage of study drug actually taken versus planned between the dates of first and last dose of study drug. A patient was considered treatment-compliant, if she took at least 75% of the injectable or oral study medication on at least one of any two consecutive post-baseline study visits, or in case of only one post-baseline visit, took at least 75% of the injectable or oral study medication. We tested differences between groups in the proportion of adverse events with a Pearson χ^2 or Fisher's exact test. All statistical analyses were conducted with SAS (version 9.4). Kaplan-Meier curves were obtained with R (version 3.3.0). Predefined subgroup analyses to assess the homogeneity of the treatment effect on fracture outcomes across ten different subgroups will be reported elsewhere.

Role of the funding source

The funder designed the study, analysed the data, and had a role in interpreting the data and writing the paper.

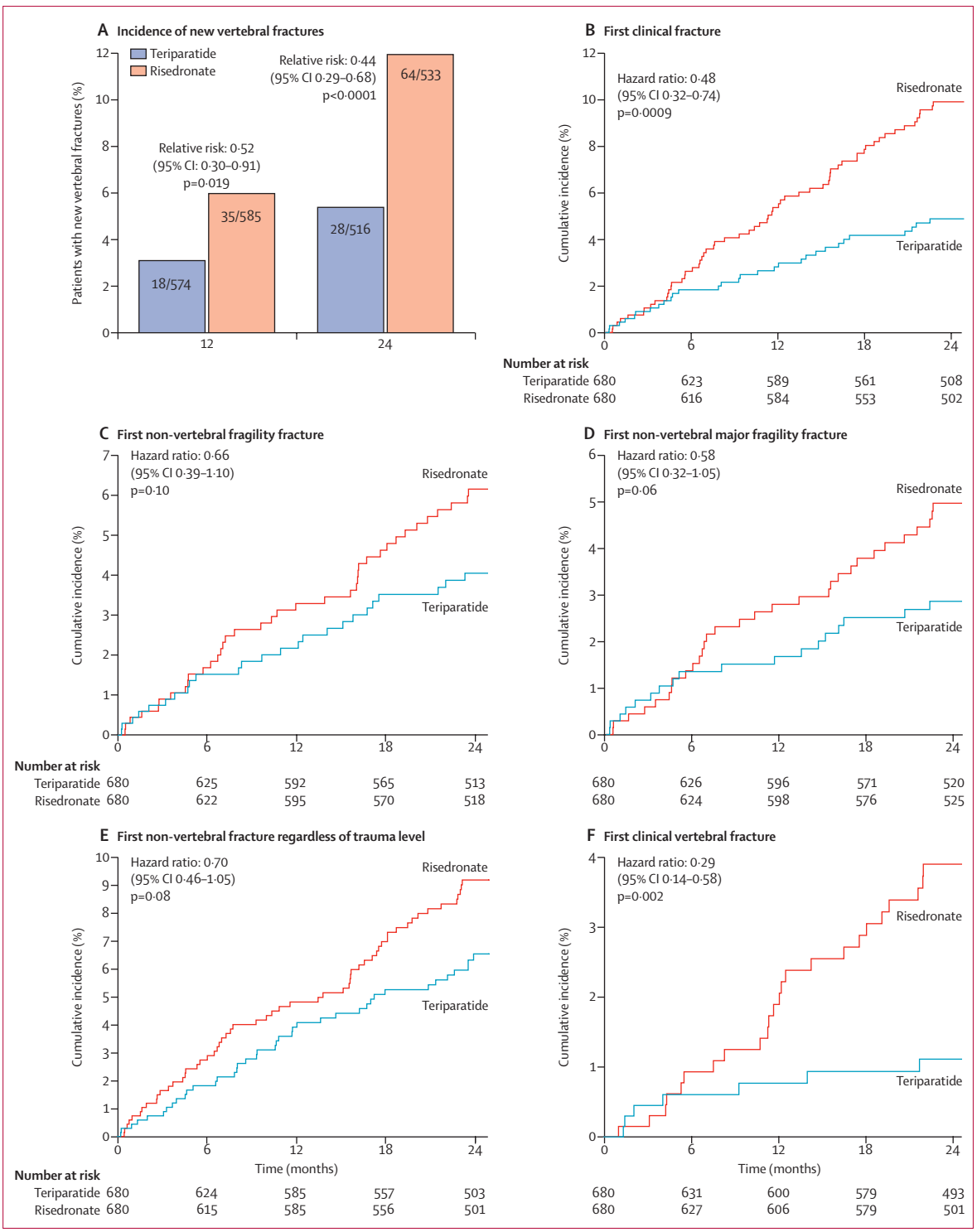

Figure 2: **Incidence of fractures over 24 months**
(A) Incidence of new vertebral fractures after 24 months (primary endpoint) and 12 months. Kaplan-Meier estimates of the cumulative incidence of the first clinical fracture (B), first non-vertebral fragility fracture (C), first non-vertebral major fragility fracture (D), first non-vertebral fracture regardless of trauma level (E), and first clinical vertebral fracture (F); p-value from the stratified log-rank test adjusted for antecedent of recent clinical vertebral fractures and recent bisphosphonate use.

	Non-vertebral fragility fractures		Pooled non-vertebral fragility and traumatic fractures	
	Teriparatide group (n=680)	Risedronate group (n=680)	Teriparatide group (n=680)	Risedronate group (n=680)
Patients with ≥1 fracture	25 (4%)	38 (6%)	40 (6%)	57 (8%)
Patients with ≥1 major fracture	18 (3%)	31 (5%)	..	..
Location*				
Radius†	6 (1%)	10 (1%)	12 (2%)	12 (2%)
Rib†	4 (1%)	4 (1%)	7 (1%)	7 (1%)
Humerus†	4 (1%)	2 (<1%)	5 (1%)	6 (1%)
Femur†	2 (<1%)	5 (1%)	5 (1%)	5 (1%)
Hip†	2 (<1%)	5 (1%)	2 (<1%)	6 (1%)
Tibia†	1 (<1%)	2 (<1%)	2 (<1%)	3 (<1%)
Pelvis†	0	4 (1%)	1 (<1%)	5 (1%)
Carpal bones	2 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
Fibula	1 (<1%)	4 (1%)	2 (<1%)	4 (1%)
Ulna	0	5 (1%)	1 (<1%)	7 (1%)
Sternum	0	1 (<1%)	2 (<1%)	1 (<1%)
Sacrum	0	1 (<1%)	1 (<1%)	1 (<1%)
Calcaneus	0	1 (<1%)	0	1 (<1%)
Clavicle	0	0	1 (<1%)	2 (<1%)
Patella	0	0	0	2 (<1%)
Scapula	0	0	0	1 (<1%)
Other‡	5 (1%)	3 (<1%)	11 (2%)	6 (1%)

*Patients with more than one fracture per location were only counted once. †Prespecified major non-vertebral fracture locations. ‡Talus bone, midfoot, or metatarsal bones.

Table 3: **Incidence of non-vertebral fractures by location (full-analysis set)**

The funder had no role in data collection. All authors had unrestricted access to the data, and agreed to submit the Article for publication.

Results

683 patients were enrolled in each treatment group, 680 of whom in each group started treatment. 1031 (75%) of 1366 enrolled patients completed the trial (figure 1). Six patients (three in each treatment group) did not receive any study drug and were excluded from the analysis. Baseline demographics and clinical characteristics were similar between groups (table 1, appendix p 3). The overall mean age was 72·1 years (SD 8·7). Most patients were white. The mean number of prevalent vertebral fractures was 2·7 (SD 2·1). 496 (36%) of 1366 patients had a clinical vertebral fracture within the 12 months before entering the study. Overall, 72% of patients had received at least one previous osteoporosis medication, most commonly a bisphosphonate (58% of patients; table 1, appendix pp 3–5). The median duration of previous bisphosphonate use was 3·5 years (IQR 1·1–7·0) in the teriparatide group and 3·6 years (1·3–6·1) in the risedronate group. 534 patients (39%) had been treated recently with bisphosphonates. Few patients (≤4% per group) had previously been treated with denosumab.

The median duration of treatment was 23·9 months (IQR 18·8–24·1) in the teriparatide group and 23·7 months (IQR 22·8–24·0) in the risedronate group. A similar proportion of patients in each group were considered treatment-compliant (490 [72%] of 680 in the teriparatide group and 487 [72%] of 680 in the risedronate group). Mean compliance was 96·1% (SD 16·9%) in the teriparatide group and 97·2% (SD 16·0%) in the risedronate group.

The 24-month incidence of new radiographic vertebral fractures was 5·4% (28 of 516 patients) in the teriparatide group, and 12·0% (64 of 533) in the risedronate group, an absolute risk reduction of 6·6% (risk ratio 0·44, 95% CI 0·29–0·68; p<0·0001; table 2, figure 2A). 31 patients (6·0%) In the teriparatide group had at least one new or worsened vertebral fracture compared with 69 patients (12·9%) in the risedronate group, corresponding to a 54% relative risk reduction (table 2). The estimated cumulative incidence of clinical fractures at 24 months was 4·8% in the teriparatide group, compared with 9·8% in the risedronate group (HR 0·48; 95% CI 0·32–0·74; p=0·0009; table 2). The estimated number of patients needed to treat with teriparatide compared with risedronate to avoid new vertebral fractures was 15, and with regard to new clinical fractures it was 20. The cumulative incidence of a first non-vertebral fragility fracture was 25 (4·0%) in the teriparatide group and 38 (6·1%) in the risedronate group (HR 0·66; 95% CI 0·39–1·10; p=0·10; figure 2). There was no significant difference in the incidence of major non-vertebral fragility fractures (3% *vs* 5%; HR 0·58, 0·32–1·05; p=0·06). Two patients in the teriparatide group and ten patients in the risedronate group had two new non-vertebral fragility fractures during the 24 months. The rate ratio of all non-vertebral fragility fractures between teriparatide (27 fractures in 25 patients) and risedronate (48 fractures in 38 patients) estimated with a Poisson regression model was significant in favour of teriparatide (rate ratio 0·56; 95% CI 0·35–0·90; p=0·017).

The incidence of new moderate (SQ2) and severe (SQ3) vertebral fractures, multiple vertebral fractures, and all non-vertebral fractures regardless the level of trauma were consistent with the other fracture results (table 2). 18 patients (3·1%) in the teriparatide group compared with 35 patients (6·0%) in the risedronate group had at least one new vertebral fracture by 12 months (relative risk 0·52, 95% CI 0·30–0·91; p=0·019; figure 2). The percentage of patients having at least one fracture during the first and second 12-month intervals and during the entire 24 months was consistently lower with teriparatide than with risedronate (appendix p 6), with significant differences across all time intervals for new vertebral fractures, pooled new and worsened vertebral fractures, pooled clinical fractures, and moderate (SQ2) or severe (SQ3) vertebral fractures. Between-treatment differences in the reductions of non-vertebral fragility fractures or new pooled fragility and high trauma non-vertebral fractures were not statistically significant (appendix p 6).

Results for the primary and key secondary efficacy endpoints were also consistent in the per-protocol population (data not shown). The analyses of the primary and all secondary fracture endpoints adjusted for geographical region also yielded similar results (data not shown).

There were six and ten new fragility fractures of the radius, the most commonly reported non-vertebral fracture site, and two and five hip fractures in the teriparatide and risedronate groups, respectively (table 3).

There were no significant differences between treatment groups in the change from baseline in body height, back pain, and health-related quality of life. At 24 months, the mean change in height was a 0·6 cm loss in the teriparatide group and a 0·5 cm loss in the risedronate group. However, significant and clinically relevant improvements from baseline were seen within both treatment groups for back pain and health-related quality-of-life measures, with improvements of approximately one point in the 11-point back pain scale (figure 3) and approximately 5 mm in the 100 mm EQ VAS (figure 4). EQ-5D-5L health index scores yielded similar results (data not shown).

There were no significant differences between the two groups in the proportions of patients with one or more treatment-emergent adverse events (table 4). Pain in the extremities (5·4% *vs* 2·6%), dizziness (4·4% *vs* 1·8%), and hypercalcaemia (2·2% *vs* 0·1%) were more frequently reported in the teriparatide group (table 4). The most common serious adverse event was fall (15 patients [2·2%] in the teriparatide group *vs* 19 [2·8%] in the risedronate group; p=0·60). The most common adverse event leading to discontinuation was nausea (four patients [0·6%] in each group). There were 22 deaths during the study (table 4), all of which were considered unrelated to study drug. Cardiovascular accident, myocardial infarction, and pneumonia were the only adverse events with fatal outcome in more than one patient overall (two patients each). Blood pressure, heart rate, bodyweight, and body-mass index were similar in the two groups with no relevant differences in changes over time (data not shown).

During the study, the mean daily calcium dosages were 809 mg (SD 311) in the teriparatide group and 794 mg (SD 283) in the risedronate group, and mean daily vitamin D doses were 1408 IU (SD 710) and 1206 IU (SD 699), respectively. Hypercalcaemia occurred in 61 (10%) of 630 patients in the teriparatide group and 3 (1%) of 637 patients in the risedronate group (p<0·001). Most of these hypercalcaemia cases were mild (≤2·75 mmol/L; table 4). Serum 25-hydroxy-vitamin D concentrations of less than 50 nmol/L were more common at 3 months in patients who received teriparatide than in those who received risedronate (182 [30%] of 604 *vs* 42 [7%] of 613; p<0·001) and at 6 months (153 [27%] of 572 *vs* 33 [6%] of 591; p<0·001). The mean serum 25-hydroxy-vitamin D concentrations at 6 months were 61·2 nmol/L (SD 19·7) in the teriparatide group and 80·3 nmol/L (SD 25·9) in the risedronate group. Asymptomatic hyperuricaemia and hypomagnesaemia were also more common in the teriparatide group (table 4). Significantly more patients in the teriparatide group had an estimated creatinine clearance of less than 30 mL/min at 6 months (13 patients [2·2%] *vs* four [0·7%]; p=0·029), but not at 24 months (eight patients [1·6%] *vs* four [0·8%]; p=0·26). This difference may be explained by the imbalance in the number of patients with a creatinine clearance equal to 30 mL/min at baseline (six patients in the teriparatide group *vs* one patient in the risedronate group). The

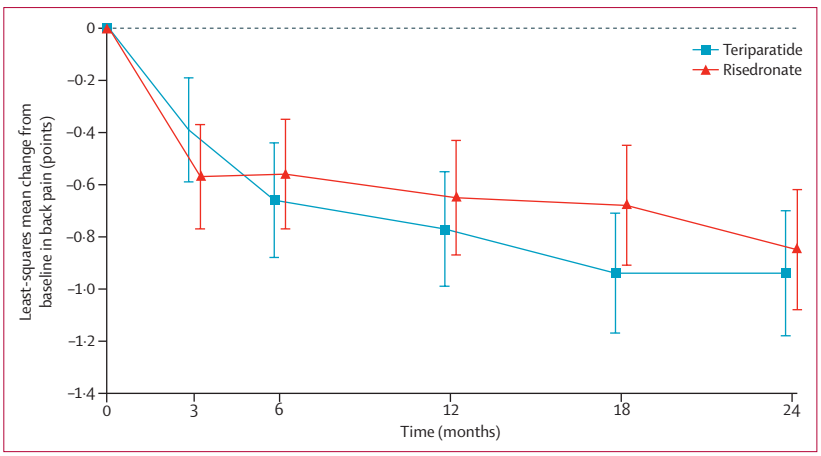

Figure 3: **Change from baseline in back pain over 24 months (full analysis set)**
Error bars indicate 95% CIs. Back pain was assessed using an 11-point rating scale ranging from 0 (no back pain) to 10 (worst possible back pain). At baseline, the mean back pain was 4·5 points (SD 2·9) in both treatment groups. Differences between treatment groups at each point were not significant, but the changes from baseline within each treatment group were significant (p<0·001 each), based on a mixed model for repeated measures including the following fixed effects: treatment, visit, treatment-by-visit interaction, antecedent of recent clinical vertebral fractures (yes or no), recent use of bisphosphonate (yes or no), age (years), and baseline back pain.

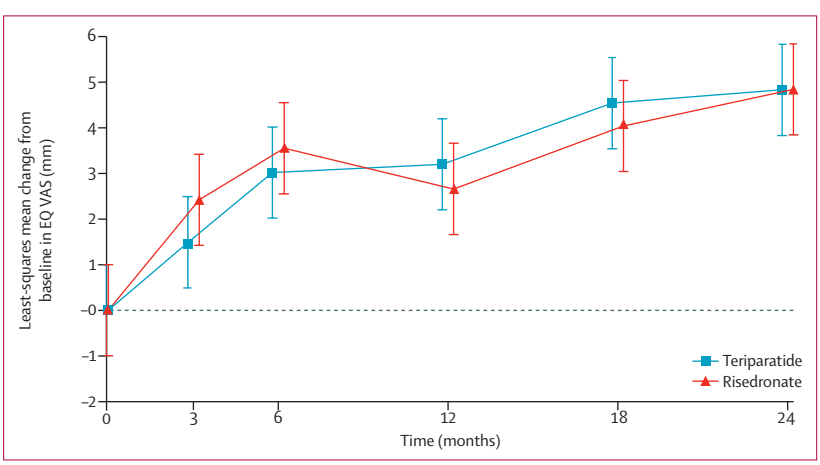

Figure 4: **Change from baseline in EQ VAS over 24 months (full analysis set)**
Error bars indicate 95% CIs. The EQ VAS recorded the respondent's self-rated health on a visual scale ranging from 0 (the worst health you can imagine) to 100 (the best health you can imagine). At baseline, mean EQ VAS value was 64·2 mm (SD 20·0) in the teriparatide group and 65·0 mm (SD 20·9) in the risedronate group. Differences between treatment groups at each time were not significant, but the changes from baseline within each treatment group were significant (p<0·001 each), based on a mixed model for repeated measures including the following fixed effects: treatment, visit, treatment-by-visit interaction, antecedent of recent clinical vertebral fractures (yes or no), recent use of bisphosphonate (yes or no), age (years), and baseline EQ VAS. VAS=visual analogue scale.

	Teriparatide group (n=680)	Risedronate group (n=680)	p value
≥1 adverse event	495 (72·8%)	500 (73·5%)	0·76
Serious	137 (20·1%)	115 (16·9%)	0·13
Related to study drug	87 (12·8%)	66 (9·7%)	0·07
Related to study procedure	4 (0·6%)	4 (0·6%)	1·000
Leading to treatment discontinuation	67 (9·9%)	48 (7·1%)	0·06
Leading to death*	15 (2·2%)	7 (1·0%)	0·13
Adverse events†			
Back pain	76 (11·2%)	83 (12·2%)	0·61
Fall	46 (6·8%)	49 (7·2%)	0·83
Arthralgia	44 (6·5%)	51 (7·5%)	0·52
Pain in hands or feet	37 (5·4%)	18 (2·6%)	0·013
Nausea	31 (4·6%)	26 (3·8%)	0·59
Nasopharyngitis	31 (4·6%)	33 (4·9%)	0·90
Dizziness	30 (4·4%)	12 (1·8%)	0·007
Osteoarthritis	29 (4·3%)	21 (3·1%)	0·31
Bronchitis	27 (4·0%)	29 (4·3%)	0·89
Hypertension	23 (3·4%)	29 (4·3%)	0·48
Hypercalcaemia	15 (2·2%)	1 (0·1%)	<0·001
Pain	10 (1·5%)	2 (0·3%)	0·038
Vitamin D concentration decreased	9 (1·3%)	1 (0·1%)	0·021
Dental caries	6 (0·9%)	0	0·031
Bone contusion	0	6 (0·9%)	0·031
Key laboratory events‡			
Hypercalcaemia§	61/630 (9·7%)	3/637 (0·5%)	<0·001
>2·65 to ≤2·75 mmol/L	39/630 (6·2%)	3/637 (0·5%)	<0·001
>2·75 to ≤3·125 mmol/L	18/630 (2·9%)	0	<0·001
>3·125 mmol/L	4/630 (0·6%)	0	0·06
Hyperuricaemia			
At 6 months	63/594 (10·6%)	13/605 (2·1%)	<0·001
At 24 months	65/500 (13·0%)	17/511 (3·3%)	<0·001
Hypomagnesaemia			
At 6 months	31/594 (5·2%)	4/604 (0·7%)	<0·001
At 24 months	24/500 (4·8%)	4/511 (0·8%)	<0·001

The safety analysis set included all the randomly assigned patients who received at least one dose of study drug. Adverse events were coded according to the Medical Dictionary for Regulatory Activities. p values are from χ^2 test or Fisher's exact test (if fewer than ten evaluable patients in either treatment group). *All deaths were considered unrelated to study drug. †Treatment-emergent adverse events that occurred in at least 4% of the patients in either group, or those with a significant difference between the two groups. ‡Based on central laboratory data and not on reports of clinical adverse events. Hypercalcaemia was predefined as albumin-corrected serum calcium concentration of 2·65 mmol/L or more at any time, hyperuricaemia as serum urate concentration of 7·5 mg/dL or more at any time, and hypomagnesaemia as a serum magnesium concentration of less than 1·5 mg/dL at any time. To convert the laboratory values for calcium to mg/dL multiply by 4·0. §Based on the maximum albumin-corrected serum calcium value after baseline.

Table 4: **Safety and adverse events (all treated patients)**

adjusted mean change from baseline to 24 months in creatinine clearance was –3·0 mL/min (to a mean of 64·8 mL/min) in the teriparatide group and –0·9 mL/min (to 66·8 mL/min) in the risedronate group, with an adjusted treatment difference of –2·0 mL/min (p=0·002).

Discussion

In this study, involving post-menopausal women with severe osteoporosis at high risk of fracture, teriparatide was associated with a lower risk of new vertebral fractures than risedronate at 12 months and 24 months. A smaller percentage of patients in the teriparatide group had at least one non-vertebral fracture, in all of the predefined non-vertebral fracture categories, during 24 months, but there were no significant differences between groups. However, the total number of clinical fractures and of non-vertebral fractures during the 24-month follow-up were significantly lower in the teriparatide group.

This study is the first double-dummy, active-controlled, head-to-head trial comparing two osteoporosis medications with fracture risk reduction as the primary outcome in an adequately powered study. Active-controlled trials are needed for studies of patients with osteoporosis with fractures because a placebo control group would be ethically unacceptable.[19,20] A few studies have reported fracture outcomes in a head-to-head design comparing two osteoporosis drugs; however, incident fractures were defined either as secondary or exploratory outcomes[12,13,21] or as safety outcomes.[8,22,23] Moreover, some of these studies were open-label, lacked a placebo-matched group,[8,21] or were stopped early because of slow patient accrual.[24] Our findings accord with previous hypothesis-generating results indicating that patients treated with teriparatide have a lower risk of new vertebral fractures than do patients treated with alendronate or risedronate in double-blind studies in glucocorticoid-induced osteoporosis[12] and in post-menopausal osteoporosis.[13] In the VERT study, risedronate reduced vertebral and non-vertebral fractures compared with placebo in post-menopausal women with osteoporosis and spine fractures,[25] including patients with baseline characteristics and risk factors similar to our study, as well as being associated with a 60% relative reduction in the risk of hip fractures in elderly patients with osteoporosis and prevalent spine fractures.[26]

Our study is the largest trial of 24-month duration with the approved dose of teriparatide in post-menopausal women with osteoporosis; the pivotal phase 3 trial was terminated early after a mean duration of 18 months because the finding of osteosarcoma in rat toxicology studies.[5] The effects of teriparatide compared with risedronate on morphometric vertebral fractures in the VERO trial, with a relative risk reduction of 56% and an absolute risk reduction of 6·6%, are similar to those comparing teriparatide with placebo in the study by Neer and colleagues,[5] with a relative risk reduction of 65% and absolute risk reduction of 9·0%.

Teriparatide treatment after long-term exposure to potent anti-resorptive drugs is associated with a transient decrease in bone mineral density at cortical-rich skeletal sites, such as the distal radius and the hip.[9,27] Some investigators have raised concerns that this process might reduce bone strength, predisposing patients to fractures.[28] Our results for non-vertebral fractures do not support that hypothesis, given the comparable efficacy of risedronate, which has shown a 59% relative risk reduction compared with placebo for non-vertebral

fractures and 60% reduction for hip fractures in post-menopausal women with established osteoporosis after 3 years of treatment.[26,29] Based on the predefined Poisson regression analysis of fracture counts, we noted a significant reduction in the total number of non-vertebral fractures in teriparatide-treated patients. A detailed analysis of the results by previous treatments will be presented elsewhere.

Patient reported outcomes were similar between the treatment groups at all study visits, with an improvement in back pain and health-related quality of life in both treatment groups. These improvements accord with findings from a double-blind, active-controlled study in patients with vertebral fractures and back pain.[13]

This study has limitations. In contrast to the pivotal phase 3 studies of both study drugs, it did not include the prospective assessment of bone mineral density or biochemical markers of bone turnover. However, these surrogate endpoints have been extensively analysed and reported in previous studies,[5,6,12,25] including head-to-head studies of the two drugs,[13] and were therefore deemed not crucial in a phase 4 trial focused on fracture outcomes. Furthermore, given the patient characteristics, our results might not be applicable to women at low risk of fracture.

Adverse events were balanced in the two groups and both drugs were well tolerated. No cases of osteonecrosis of the jaw or atypical femur fractures were reported. The significantly higher incidences of dizziness and limb pain in the teriparatide group are consistent with the pivotal study by Neer and colleagues.[5] The higher incidence of pain in the teriparatide group could be related to extremity pain, which is associated with teriparatide. Similarly, the incidences of hypercalcaemia, hyperuricaemia, and hypomagnesaemia were higher with teriparatide than with risedronate, consistent with previous studies.[5,12,13] These biochemical abnormalities were relatively mild and were not associated with clinical symptoms or sequelae. As expected, serum 25-hydroxy-vitamin D concentrations were lower in the teriparatide group despite a higher mean dose of vitamin D supplements. This finding probably does not have negative clinical consequences because teriparatide, like endogenous PTH, induces renal 1-α-hydroxylase, thereby increasing the conversion of 25-hydroxy-vitamin D to 1,25-di-hydroxy-vitamin D.[30] Moreover, most of the patients had normal concentrations of serum 25-hydroxy-vitamin D. Monitoring of serum 25-hydroxy-vitamin D might be advisable in patients treated with teriparatide who have low baseline concentrations, low sun exposure, or obesity.

In conclusion, in post-menopausal women with established osteoporosis who are at high risk of fracture, treatment with teriparatide was associated with a significant reduction in the incidence of vertebral and clinical fractures compared with risedronate. Differences between groups in the incidence of non-vertebral fractures were not statistically significant. Adverse events and safety laboratory findings accorded with the safety profile of either drug. These data show that teriparatide is better at preventing fractures in patients with severe osteoporosis, and confirm previous data from clinical trials of teriparatide versus bisphosphonates with fracture as a secondary endpoint.

Contributors

FM had the idea for the study. FM and PL-R designed the study. DLK, CAFZ, LAR, SLG, VZ, AB, JM-S, PL, AF-P, EL, SM, JJB, PG, and RM recruited patients and collected the data. PRL did the statistical analysis. DLK, FM, CAFZ, LAR, SLG, VZ, AB, JM-S, PL, AF-P, EL, SM, JJB, PG, RM, and PL-R analysed and interpreted the data. DLK and FM wrote the first draft of the Article. CAFZ, LAR, SLG, VZ, AB, JM-S, PL, AF-P, EL, SM, JJB, PG, RM, and PL-R revised the report. All authors had unrestricted access to the data and participated in data interpretation. All the authors contributed to subsequent drafts and agreed to submit the Article for publication.

Collaborators

The following investigators enrolled at least one patient in the VERO trial. Argentina: A Alvarisqueta, A Bagur, C Gómez, L Maffei, F Massari; Austria: E Boschitz, A Fahrleitner-Pammer, G Höfle, H Koller, C Muschitz, E Preisinger; Belgium: I Beyer, J J Body, K de Vlam, V Gangji, P Geusens, E Gielen, S Goemare, M Leon, J-Y Reginster, M van den Berghe, R Witvrouw; Brazil: J Borges, M Castro, L A Russo, C A Zerbini; Canada: J Adachi, J P Brown, A Cheung, S Kaiser, A Karaplis, D L Kendler, F Morin, W Olszynski, S Seigel; Czech Republic: E Dokoupilova, M Ladova, R Pikner, J Stepan, V Zikan; France: R Chapurlat, J Fulpin, C Marcelli, M Laroche, E Lespessailles, T Thomas; Germany: G Dahmen, J Fakler, I Frieling, P Hadji, R Möricke, F Thomasius, L Unger, V Ziller; Greece: M Daniilidis, E Foufoulas, G Ioannidis, M Kita, I Kyrkos, I Panagiotopoulos, S Pnevmaticos; Hungary: E Kanakaridu, K Kudlak, P Lakatos, K Nagy, P Somogyi, P Suranyi, Z Valkusz; Italy: G Bianchi, M L Brandi, S Giannini, G Isaia, S Minisola, G Osella, M Rossini; Poland: T Blicharski, J Brzezicki, P Leszczynski, M Mazurek, M Rell-Bakalarska, J Supronik; Spain: M J Amerigo, M Bernad, E Casado, N Chozas, M Díaz-Curiel, J Malouf-Serra, J A Román, F J Tarazona; USA and Puerto Rico: N Binkley, M Bolognese, P Bressler, M Carroll, A Chang, D Cox, A de la Llana, A Dulgeroff, H El-Kadi, M Goldberg, S Greenspan, H Kenney, A Kivitz, M E Lewiecki, M Lillestol, P Miller, A Myers, P Norwood, M Perini, S Rao, R R Recker, C P Recknor, H Rodríguez, K G Saag, R Sachson, C Shuhart, O Soto-Raíces, M Spiegel.

Declaration of interests

DLK has received grant and research support from Amgen, Eli Lilly, Astellas, and AstraZeneca; has consulted for Amgen, Eli Lilly, and Pfizer; and is a member of the speakers' bureau for Amgen, Eli Lilly, and GlaxoSmithKline. FM is an employee of Lilly. CAFZ and SLG have received research support from Lilly. JM-S has received speaker and consultant fees from Amgen, Lilly, Gruenenthal, Mundipharma, Esteve, and FAES Pharma. AF-P has received speaker fees from Amgen, Alexion, Bristol-Myers Squibb, Lilly, and Fresenius. EL has received speaker and consultant fees from Amgen, Expanscience, Lilly, and MSD; and research grants from Abbvie, Amgen, Lilly, MSD, and UCB. SM has received speaker fees from Abiogen, Amgen, Diasorin, Lilly, Fujii, MSD, and Takeda; and consulting fees from Italfarmaco. JJB has received speaker fees from Amgen and research support from Lilly. PG has received research support and consultant and speaker fees from Pfizer, Abbott, Lilly, Amgen, MSD, Roche, UCB, Bristol-Myers Squibb, and Novartis. PL-R is an employee of Lilly. The other authors declare no competing interests.

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