

CLINICAL STUDY

Effects of teriparatide in postmenopausal women with osteoporosis pre-treated with bisphosphonates: 36-month results from the European Forsteo Observational Study

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Abstract

Objectives: To describe fracture rates, back pain, and health-related quality of life (HRQoL) in postmenopausal women with osteoporosis and prior bisphosphonate therapy, treated with teriparatide for up to 18 months and followed up for a further 18 months.

Design: Prospective, multinational, and observational study.

Methods: Data on prior bisphosphonate use, clinical fractures, back pain visual analog scale (VAS), and HRQoL (EQ-5D) were collected over 36 months. Fracture data were summarized in 6-month intervals and analyzed using logistic regression with repeated measures. Changes from baseline in back pain VAS and EQ-VAS were analyzed using a repeated measures model.

Results: Of the 1581 enrolled patients with follow-up data, 1161 (73.4%) had a history of prior bisphosphonate use (median duration: 36 months). Of them, 169 (14.6%) sustained ≥ 1 fracture during 36-month follow-up. Adjusted odds of fracture were significantly decreased at each 6-month interval compared with the first 6 months of teriparatide treatment: 37% decrease in the 12 to <18 months period during teriparatide treatment ($P=0.03$) and a 76% decrease in the 12- to 18-month period after teriparatide was discontinued ($P<0.001$). Significant reductions in back pain and improvement in HRQoL were observed.

Conclusions: Postmenopausal women with severe osteoporosis previously treated with bisphosphonates had a significant reduction in the incidence of fractures compared with the first 6 months of therapy, a reduction in back pain and an improvement in HRQoL during up to 18 months of teriparatide treatment. These outcomes were still evident for at least 18 months after teriparatide was discontinued. The results should be interpreted in the context of an uncontrolled, observational study in a routine clinical setting.

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Introduction

Postmenopausal women with osteoporosis have increased risk of fractures and associated complications, such as chronic back pain, eventually leading to reduced health-related quality of life (HRQoL) (1–3). Osteoporosis treatment aims to reduce fracture risk and its associated burden. Antiresorptives, especially bisphosphonates, are routinely used as first-line treatment for postmenopausal osteoporosis (4–6).

Teriparatide recombinant DNA origin human parathyroid hormone (1–34), PTH 1-34 is a bone anabolic agent that reduces the risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis (7). It also reduces the risk of

vertebral fractures in men with primary osteoporosis (8), and in women and men with glucocorticoid-induced osteoporosis (9). Teriparatide is typically used as a second-line treatment for patients with severe osteoporosis who are at high risk of fracture. It is also an alternative treatment for patients who have contraindications or are intolerant of other osteoporosis agents, or who sustained new fractures while on other osteoporosis medications. Thus, in clinical practice, the majority of patients receiving teriparatide have previously received at least one of different types of bisphosphonates. However, published data on the effect of sequential treatment regimens are scarce.

Some clinical trials have shown that previous exposure to bisphosphonates can delay the increase in

areal bone mineral density (BMD) induced by teriparatide treatment (10–13). However, no previous clinical trials or observational studies involving postmenopausal women with osteoporosis have specifically examined the effectiveness of teriparatide treatment on the fracture risk of patients previously treated with bisphosphonates.

The European Forsteo Observational Study (EFOS) was a 36 month, prospective, observational study initiated soon after the European approval of teriparatide for the treatment of postmenopausal women with established osteoporosis at high risk for fracture. EFOS was designed to collect data from an outpatient setting and to evaluate fracture outcomes, back pain, and HRQoL in postmenopausal women with severe osteoporosis treated with teriparatide for up to 18 months, followed by a post-teriparatide treatment period of a further 18 months (14). The women who participated in EFOS were at very high risk of fracture as indicated by their age, low BMD values, number of prior osteoporotic fractures, numerous comorbidities, and risk factors for low bone mass and falls (14).

Although randomized clinical trials (RCTs) are considered the gold standard for investigating drug effects, their design, in general, limits the capacity to provide answers to questions about unselected 'real-life' patient populations and issues found only in clinical practice (15). RCTs have rigorous entry criteria and a fairly homogenous patient population, which may differ from patients in real-life practice who often have comorbidities and use concomitant medications that commonly exclude them from controlled clinical trials (16). Moreover, in real-life clinical practice, most patients receiving teriparatide have been pre-treated with other osteoporosis therapies.

There is no published information about fracture risk and QoL after anabolic teriparatide treatment in patients pre-treated with bisphosphonates. Hence, the aim of this pre-defined analysis is to describe clinical fracture outcomes, back pain, and HRQoL in the EFOS subgroup of postmenopausal women with osteoporosis previously treated with bisphosphonates. Another important feature of this study is that we evaluated outcomes in the context of patients receiving sequential therapy (as is usual in clinical practice). We describe these outcomes both during treatment with teriparatide for up to 18 months and in the subsequent 18-month follow-up period after teriparatide was discontinued when most patients were receiving other osteoporosis medications to investigate a potential sustained effect after teriparatide treatment was stopped. The changes in clinical vertebral and non-vertebral fracture risk, back pain, and HRQoL during the up to 18-month teriparatide treatment period and the 18-month follow-up period for the total study cohort have been reported previously (17, 18).

Materials and methods

Study design and patients

EFOS was a multicenter, prospective, observational study conducted in eight European countries (Austria, Denmark, France, Germany, Greece, Ireland, The Netherlands, and Sweden). The study design and characteristics of the patient population have been described in detail elsewhere (14). Briefly, the study enrolled 1649 postmenopausal women with a diagnosis of established osteoporosis who, at the discretion of their physician, were about to initiate teriparatide treatment. Patients were followed for the duration of their teriparatide treatment (20 µg once daily by s.c. injection), which could be discontinued at any time, and were asked to return for two additional visits after discontinuing teriparatide, irrespective of when they stopped teriparatide administration. Patients were not included in the study if they were currently being treated with an investigational drug or procedure, or had any contraindications as described in the teriparatide label (19). The observational design meant there were no further restrictions for the selection of patients and all patient care provided was according to the clinical judgment and usual practice of the participating physicians.

Women provided written informed consent before enrollment and were able to withdraw without consequence at any time. The study was approved by local ethics committees or review boards, depending on local requirements, and was conducted in accordance with the ethics standards of the Declaration of Helsinki. The study was conducted from April 2004 (first patient enrolled) until February 2009 (last patient completed).

Data collection and outcomes

Patient demographic characteristics, risk factors for osteoporosis and falls, disease status as well as the number and type of prior and current medications for the treatment of osteoporosis was recorded (14). Information on compliance with previous treatments, including prior bisphosphonate therapy, was not collected. Participants attended visits at baseline (when teriparatide was initiated) and then at ~3, 6, 12, and 18 months after teriparatide initiation, and at 6 and 18 months after discontinuing teriparatide treatment.

Diagnosis of osteoporosis was documented by medical history and, where appropriate, confirmed by dual X-ray absorptiometry. Incident clinical vertebral and non-vertebral fragility fractures during the observational period were diagnosed and confirmed by review of the original X-rays and/or the radiology or surgical reports at the investigational site. Different from typical clinical trial procedures, there was no scheduled vertebral radiograph to capture potential asymptomatic

new or worsened morphometric vertebral fractures. Therefore, vertebral fractures were only diagnosed if these were clinical fractures, i.e. after a patient became symptomatic with signs and/or symptoms suggestive of a new vertebral fracture (20), which was then confirmed by radiography.

Back pain was self-assessed by patients at each study visit using two different tools: i) a 100 mm visual analog scale (VAS), ranging from 0=no back pain to 100=worst possible back pain and ii) a back pain questionnaire that captured the frequency and severity of back pain as well as its impact on patient activity in the previous month (17).

HRQoL was measured at each visit using the European Quality of Life Questionnaire (EQ-5D; formerly EuroQol) (21). Patients classified their own health status according to five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which was scored on a three-point scale (no problems, some problems, or extreme problems). Patients also completed another VAS (EQ-VAS), which assessed their perceived overall health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). The health state value (HSV) was calculated from the five EQ-5D dimensions using the UK scoring algorithm, to allow for comparisons across countries (22).

Statistical analysis

For data analyses, the total study cohort included all patients with a baseline visit and at least one follow-up visit. In addition, the post-teriparatide cohort included those patients who discontinued teriparatide treatment at any time between baseline and 18 months and had at least one post-teriparatide follow-up visit. Patients were categorized as either prior bisphosphonate users or no prior bisphosphonate users. Prior bisphosphonate users were defined as those taking bisphosphonates any time before the baseline visit, or currently taking bisphosphonates at the baseline visit. Patients in the no prior bisphosphonate use group could have prior use of any other type of antiresorptive medications or be treatment-naïve.

Descriptive statistics, such as frequencies, percentages, means, median, s.d., and ranges, were used to describe the characteristics of the groups with and without prior bisphosphonate use. These were compared by χ^2 or Fisher's exact tests for categorical variables and the Kruskal-Wallis or *t*-test for continuous variables.

The number of fractures occurring in prior bisphosphonate users was summarized in 6-month intervals. A logistic regression with repeated measures was used to assess the change in number of patients with one or more fractures over time (23, 24), giving an analysis of the odds of one or more fractures. Patients were included in the model at all observed intervals,

regardless of whether or not they had fractured during a previous interval. The repeated observations of each patient were assumed to be related but no further assumptions were made about the relationship. Unadjusted and adjusted analyses (including age and fracture in the last 12 months before starting teriparatide) were performed. The risk of fracture, calculated as the ratio of fractured vs non-fractured patients (odds), was reported for the first 6 months of treatment (0 to <6 months) and for each subsequent 6-month interval. Odds ratio (ORs) and 95% confidence intervals (CIs) were derived to compare the risk at each of the subsequent 6-month intervals with the first 6 months of treatment (0 to <6 months). Fracture modeling was repeated for all vertebral, all non-vertebral, and main non-vertebral (forearm/wrist, hip, humerus, leg, and sternum/ribs) fractures.

Back pain and HRQoL were summarized over the teriparatide treatment period and after teriparatide discontinuation. The Cochran-Mantel-Haenszel test was used for between-group comparisons of categorical variables and the Kruskal-Wallis or *t*-test for between-group comparisons of continuous variables.

Changes in back pain VAS from baseline were analyzed by a mixed model of repeated measures (MMRM), using prior bisphosphonate use subgroup, months and their interaction as fixed effects and adjusting for back pain VAS at baseline, number of previous fractures, age, diagnosis of rheumatoid arthritis, duration of prior bisphosphonate therapy, and a history of fracture in the 12 months before entering the study. The percentage of patients reporting an improvement or worsening in the severity of back pain, frequency of back pain, limitation of activities, and number of days in bed due to back pain was analyzed by the sign test.

A similar MMRM was used to assess the change from baseline in EQ-VAS, including its baseline value. The percentage of patients reporting an improvement or worsening from baseline in each of the five EQ-5D domains was analyzed by the sign test. Changes from baseline in EQ-5D HSV were assessed by the Wilcoxon sign-rank test because this parameter has a nonparametric distribution.

Results

Patients and baseline characteristics

Of the 1649 postmenopausal women with osteoporosis enrolled in EFOS, 1581 had a baseline visit and at least one post-baseline visit comprising the total study cohort (Fig. 1). Of these patients, 1161 (73.4%) had a history of prior or current bisphosphonate use at the baseline visit. Patient disposition throughout the observation for the subgroups with and without prior bisphosphonate use is shown in Fig. 1.

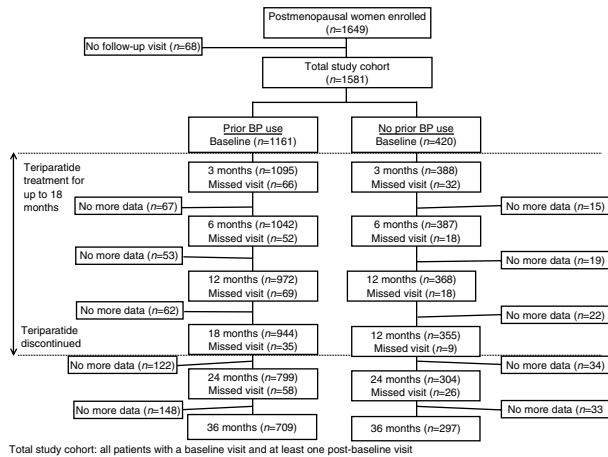


Figure 1 Study flow and disposition of patients in the prior bisphosphonate (BP) use and no prior BP use groups in the total study cohort.

The main demographic and baseline characteristics of the patients are summarized in Table 1. The type and duration of prior bisphosphonate treatment are given in Table 2. In the subgroup with prior bisphosphonate use, 91 (10.3%) were still taking a bisphosphonate at the baseline visit, and 19 (1.7%), 21 (2.0%), and 24 (2.5%) patients reported taking a bisphosphonate at the 3-, 6-, and 12-month visits respectively. Prior bisphosphonate user patients were significantly older and had a lower BMI than the group of patients who were bisphosphonate-naïve. The prior bisphosphonate users had a higher mean lumbar spine BMD *T*-score at baseline, but more frequently reported a history of previous fracture, surgical menopause, sight problems, glucocorticoid, anticonvulsant, and benzodiazepine use than the bisphosphonate-naïve group. Prior bisphosphonate users also reported a larger number of prevalent fractures (Table 1).

Teriparatide treatment and osteoporosis medication taken during and after teriparatide

The median duration of teriparatide treatment was similar in the two groups: 541 days (Q1, Q3: 451, 553) for the prior bisphosphonate group and 541 days (Q1, Q3: 375, 551) for the group without prior bisphosphonate use. Persistence with teriparatide treatment was high and similar for the groups with and without prior bisphosphonate use (see Supplementary Figure 1, see section on supplementary data given at the end of this article).

In the subgroup of prior bisphosphonate users, calcium was taken at baseline or any time during the study by 1077 (92.9%) patients and vitamin D was taken by 1067 (92.1%) patients. For the subgroup

without prior bisphosphonate use, calcium and vitamin D were taken by 358 (85.2%) and 355 (84.5%) patients respectively.

Of the prior bisphosphonate users with data on osteoporosis medication taken after teriparatide was discontinued ($n=639$), 454 (71.0%) took an anti-resorptive, mainly a bisphosphonate ($n=427$, 66.8%). Likewise, for the non-prior bisphosphonate users ($n=268$), 187 (69.8%) took an antiresorptive, mainly a bisphosphonate ($n=147$, 54.9%) after discontinuation of teriparatide.

Fracture outcomes

The incidence of clinical fractures in prior bisphosphonate users during the observation period is summarized in Table 3. Of the 1161 women in the prior bisphosphonate group, 169 (14.6%) sustained a total of 212 clinical fractures during the 36-month follow-up. Of the 169 prior bisphosphonate users with incident fractures, 136 sustained a single fracture during the 36-month follow-up period and 33 sustained two or more fractures. Of the total 212 fractures, 70 (33.0%) were clinical vertebral fractures and 142 (67.0%) were non-vertebral fractures; 106 (50.0%) of all fractures were main non-vertebral fractures at the forearm/wrist ($n=34$), hip ($n=22$), humerus ($n=19$), leg ($n=18$), and sternum/ribs ($n=13$). Table 3 shows that there was a significant risk reduction of clinical fractures at each subsequent 6-month interval compared with the first 6 months of teriparatide treatment (0 to <6 months): there was a 37% decrease in the odds of fracture in the 12 to <18 months period during teriparatide treatment, and a 76% decrease in the 12 to <18 months period after teriparatide was discontinued (i.e. from 30 to <36 months follow-up). Prior bisphosphonate users who had a fracture in the 12 months before baseline were more likely to fracture during the study than those without a fracture in the 12 months before baseline (adjusted OR 1.39; 95% CI: 1.06–1.84; $P=0.019$).

Figure 2 presents the risk of fracture (adjusted odds with 95% CIs) by fracture type for each 6-month interval in patients who were treated with bisphosphonates before teriparatide. For vertebral fractures, there was a significant risk reduction at 12 to <18 months of teriparatide treatment and during the post-teriparatide period, compared with the first 6 months of teriparatide treatment. The risk of having a non-vertebral fracture was significantly lower during the 24 to <30 months interval, resulting in an OR of 0.41 (95% CI: 0.21–0.82) and the 30 to <36 months interval (OR 0.37; 95% CI: 0.18–0.76), compared with the first 6 months of teriparatide treatment. Similar results were seen for the main non-vertebral fractures (Fig. 2).

Table 1 Demographics and other patient characteristics at baseline by prior bisphosphonate (BP) use. Data are presented as mean (s.d.) unless stated otherwise.

Characteristic	Prior BP use (n=1161)	No prior BP use ^a (n=420)	P value ^b
Demographics			
Age (years)	71.2 (8.1)	70.2 (9.0)	0.038
Caucasian (%)	99.1	99.5	0.738
BMI (kg/m ²)	25.0 (4.3)	25.5 (4.3)	0.035
Menopausal status			
Early menopause, <40 years of age (%)	8.4	10.4	0.253
Surgical menopause (%)	20.4	13.9	0.005
Risk factors			
Nulliparous (%)	13.5	11.9	0.401
Current smoker (%)	13.2	12.4	0.675
Osteoporotic hip fracture in mother (%)	20.3	22.4	0.445
Lumbar spine BMD T-score	-3.22 (1.22)	-3.41 (0.96)	0.018
Total hip BMD T-score	-2.59 (1.06)	-2.71 (0.99)	0.087
Uses arms when standing up from chair (%)	60.8	70.2	0.001
Sight problems (%)	47.8	37.4	<0.001
>1 fall in the last year (%)	22.7	23.9	0.821
Concomitant medications			
Antihypertensives (%)	747 (65.0)	253 (60.5)	0.102
Glucocorticoids (%) ^c	36.6	39.0	0.377
Thyroid hormones (%)	16.1	11.2	0.017
Benzodiazepines (%)	13.3	13.4	0.967
Benzodiazepines (%)	13.2	8.6	0.013
Antidepressants (%)	10.9	8.4	0.147
Anticonvulsants (%)	2.3	0	<0.001
Comorbidities			
Rheumatoid arthritis (%)	12.4	10.5	0.296
Chronic obstructive pulmonary disease (%)	9.2	7.4	0.254
Diabetes mellitus (%)	4.7	7.9	0.014
Parkinson disease and other movement disorders (%)	1.2	2.9	0.023
Prior fractures			
Patients with prior fractures (%)	91.6	78.3	<0.001
Time since most recent fracture (years) ^d	0.9 (0.2:2.6)	0.4 (0.1:1.7)	<0.001
Number of previous fractures after age 40	3.2 (2.0)	2.1 (1.7)	<0.001
At least one fracture in 12 months before study entry (%)	47.2	51.7	0.117
Baseline back pain and HRQoL			
Back pain VAS	57.1 (26.4)	59.4 (27.3)	0.135
EQ-VAS	52.2 (20.8)	51.6 (25.1)	0.653

^aOf these 420 patients, 292 (69.5%) reported having prior osteoporosis medication use, mostly antiresorptives (n=217, 51.7%); 121 (28.8%) reported being treatment naive; data on other osteoporosis medication was missing/unknown for seven patients.

^bP values for age and BMI are calculated by pooled t-test; other continuous variables are calculated by the Kruskal–Wallis test. P values for discrete variables are calculated by χ^2 test, with the exception of Caucasian, which uses Fisher's exact test.

^cIn addition, glucocorticoid use during the study was higher in prior BP group than in the no prior BP group: 20.0 vs 14.8%, respectively; P=0.018.

^dMedian time from baseline (Q1:Q3).

Data from the post-teriparatide cohort showed no evidence of further change in fracture risk during the 18 months after stopping teriparatide (see [Supplementary Table 1](#), see section on [supplementary data](#) given at the end of this article).

In the group without prior bisphosphonate therapy (n=420), 39 (9.3%) patients sustained a total of 46 fractures. Of the 46 fractures, 17 (37%) were vertebral and 29 (63%) were non-vertebral fractures, including forearm/wrist (n=7), sternum/ribs (n=6), hip (n=5), leg (n=3), and humerus (n=2). The adjusted regression model found no statistically significant reduction in the risk of clinical fractures during each 6-month interval compared with the first 6 months of teriparatide treatment (data not shown) probably because of the low number of cases.

Back pain

There were statistically significant reductions in the adjusted mean change in back pain VAS from baseline at each post-baseline visit in the groups with and without prior bisphosphonate use ([Fig. 3](#)). The between-group analyses revealed that the reduction in back pain VAS score was significantly higher in the group with no prior bisphosphonate use at all post-baseline time points ([Fig. 3](#)), although the absolute difference was <11 mm. Results from the back pain questionnaire in prior bisphosphonate users (see [Supplementary Table 2](#), see section on [supplementary data](#) given at the end of this article) showed reductions in both the frequency and severity of back pain and in the limitations of activities because of back pain during teriparatide treatment.

Table 2 Number (%) of patients with prior bisphosphonate (BP) use at the baseline visit and duration of prior use.

	Number of patients ^a (% of total study cohort, n=1581)	Duration of prior therapy (months; median (Q1:Q3))
Any prior BP use	1157 (73.6)	36 (16:66)
Alendronate	739 (47.0)	23 (8:44)
Risedronate	479 (30.5)	18 (8:34)
Etidronate	293 (18.6)	36 (18:57)
Other BP	155 (9.9)	26 (12:52)

^aFour patients had incomplete BP data.

These changes were maintained after teriparatide treatment was discontinued. At every post-baseline visit, the change from baseline (i.e. percentage of patients reporting an improvement) in frequency of back pain, severity of back pain, limitations of activities, and days in bed due to back pain was significant (sign test, $P < 0.001$; [Supplementary Table 2](#), see section on [supplementary data](#) given at the end of this article).

Health-related quality of life

There were significant increases in EQ-VAS (i.e. improvement in HRQoL) from baseline in both the prior and no prior bisphosphonate user groups at all post-baseline visits ([Fig. 4](#)). The increase in EQ-VAS was statistically significantly higher in the no prior bisphosphonate user group from the 6-month visit onwards ([Fig. 4](#)). Furthermore, there was less improvement in HRQoL with each additional 5 mm in baseline EQ-VAS (-2.94 mm; 95% CI: -3.11 to -2.77 ; $P < 0.001$), every additional 5 years of age (-1.05 mm; 95% CI: -1.51 to -0.60 ; $P < 0.001$), each additional fracture (-0.68 mm; 95% CI: -1.08 to -0.27 ; $P = 0.001$), and a diagnosis of rheumatoid arthritis (-4.15 mm; 95% CI: -1.83 to -6.47 ; $P < 0.001$).

The percentage of prior bisphosphonate users reporting some/extreme problems for each of the five EQ-5D

domains (see [Supplementary Table 3](#), see section on [supplementary data](#) given at the end of this article) shows significant improvements from baseline ($P < 0.001$, sign test) in all five EQ-5D domains during teriparatide treatment that were maintained after teriparatide was discontinued. In the prior bisphosphonate user group, median (Q1, Q3) HSV increased from 0.587 (0.088, 0.691) at baseline to 0.691 (0.587, 0.796) at 18 months and increased further to 0.725 (0.587, 0.848) at 36 months. The change in HSV from baseline was significant at each visit (Wilcoxon signed-rank test; $P < 0.001$).

Discussion

The EFOS is the first observational study to report effectiveness results in clinical fractures risk reduction, back pain, and HRQoL in postmenopausal women with severe osteoporosis in routine clinical practice both during teriparatide treatment for up to 18 months and in the subsequent 18-month post-teriparatide period. The subgroup of patients described in the current pre-defined analysis had received bisphosphonate therapy for a substantial period of time (median 36 months) before starting treatment with teriparatide. These patients represent the majority of patients being treated with teriparatide in Europe, given the reimbursement and treatment guidelines with this drug, and constituted 73.4% of subjects initiating teriparatide. Similar to what we observed in the total study cohort (18), the subgroup of prior bisphosphonate users showed a significant reduction in the odds of clinical fractures during teriparatide treatment, with no evidence of further change after teriparatide was discontinued. Fracture reduction in this observational study could not be compared with a placebo or another osteoporosis medication, but rather was compared with the first 6 months of teriparatide treatment. Applying this approach, there was a 34% decrease in the adjusted odds of fracture in the period from 6 months up to 12 months during teriparatide treatment, and a similar

Table 3 Incident clinical fractures during teriparatide treatment (0 to <18 months) and after teriparatide discontinuation (18 to <36 months) in prior bisphosphonate users (total study cohort).

Time interval (months)	n (data missing/unknown)	No. of fractures/10 000 pt-years	Total no. of fractures	Patients with ≥ 1 fracture n (%) ^a	Odds ratio ^{b,c} (95% CI)	P
0 to <6	1161 (3)	1299	73	65 (5.6)	–	–
6 to <12	1077 (2)	926	48	41 (3.8)	0.66 (0.45, 0.98)	0.04
12 to <18	1000 (1)	783	38	36 (3.6)	0.63 (0.41, 0.96)	0.03
18 to <24	925 (1)	562	24	22 (2.4)	0.41 (0.25, 0.68)	<0.001
24 to <30	786 (4)	467	17	15 (1.9)	0.33 (0.19, 0.59)	<0.001
30 to <36	695 (0)	376	12	10 (1.4)	0.24 (0.13, 0.48)	<0.001
Total	1161 (3)		212	169 (14.6)		

^aAs some patients experienced a fracture in more than one time interval, the total was not the sum of patients with a fracture in each interval.

^bAdjusted model by age and a history of fracture in last 12 months before starting teriparatide.

^cCompared with 0 to <6 months interval.

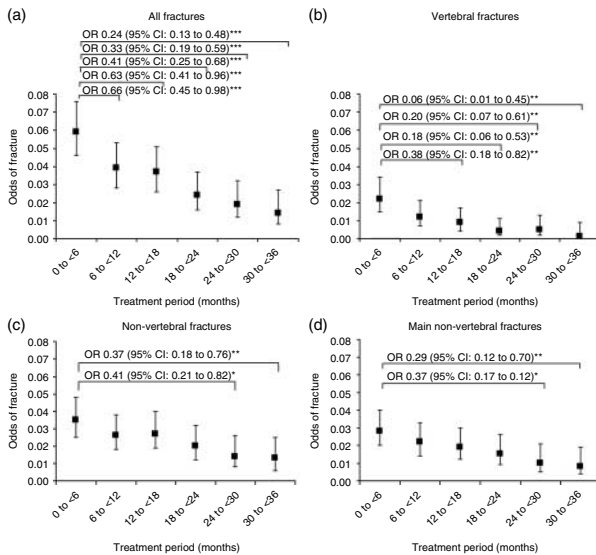


Figure 2 Risk of fracture (adjusted odds with 95% confidence intervals (CIs)) by fracture type: (a) all fractures pooled, (b) clinical vertebral, (c) non-vertebral, and (d) main non-vertebral, in each 6-month interval for the prior bisphosphonate user group. Note: odds ratios (ORs) and 95% CI for the comparison with the first 6 months of treatment are given where significant. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ vs 0 to <6 months interval. Main non-vertebral fracture includes forearm/wrist, hip, humerus, leg, and sternum/ribs.

decrease (37%) in the period from 12 months up to 18 months during teriparatide treatment. Interestingly, after teriparatide was stopped, the reductions of the odds of clinical fractures (range: 59–76%) were still statistically significant compared with the first 6 months of treatment. Our results complement previous follow-up data from the pivotal phase III trial (with patients who had no prior bisphosphonate treatment), where it was observed that those patients who received teriparatide during the randomized, controlled phase showed a 41% reduction in the hazard ratios of vertebral fractures (25) and a 30% reduction in the hazard ratios of non-vertebral fractures (26) at 18 and 30 months after stopping teriparatide, respectively, compared with those patients who were originally assigned to the placebo group. Similar to what was observed during follow-up of the patients included in the registration trials (25, 26), ~70% of the subjects in EFOS received another osteoporosis medication, mainly a bisphosphonate, as part of the standard clinical care after teriparatide was stopped. The results of our study and those of the observational follow-up period of the pivotal trial (25, 26), which found a sustained reduction in fracture incidence after teriparatide was discontinued, would support the use of an antiresorptive drug after a full-course of teriparatide.

Because changes in bone microarchitecture, density and strength take time to occur, it is highly likely that fracture risk reduction does not occur immediately after starting teriparatide therapy. For example, in the

placebo-controlled Fracture Prevention Trial, the reduction in risk of non-vertebral fractures was not seen until 9–12 months after starting teriparatide (7). Hence, in the present observational study, our assumption that the odds of fracture in the first 6 months after starting teriparatide reflects the baseline fracture risk in the patient cohort appears to be justified. Therefore, we compared the odds of fracture during each subsequent 6-month period with those in the initial 6-month period after starting teriparatide therapy. This type of approach has been used previously in an observational study of the longitudinal change in fracture incidence during bisphosphonate therapy (27). Our results are also consistent with a recent analysis of data from the pivotal Fracture Prevention Trial, where a progressive decrease in the rate of non-vertebral fracture with increasing duration of teriparatide therapy was observed (28).

The findings of a sustained clinical fracture risk reduction during and after teriparatide treatment in patients with prior bisphosphonate use are of particular clinical interest since the results of certain clinical studies have created some controversy about whether pre-treatment with potent antiresorptive agents that

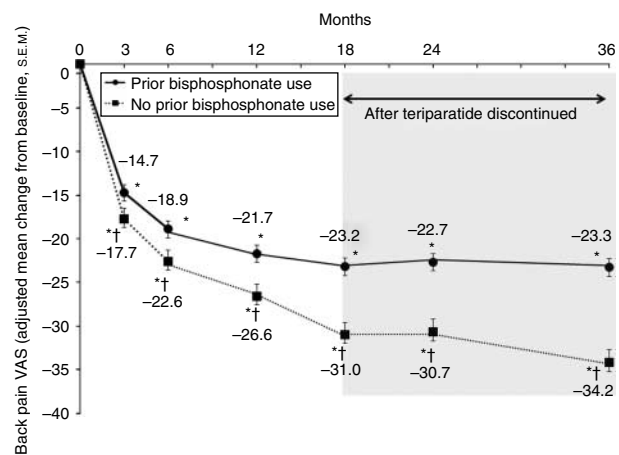


Figure 3 Back pain VAS: adjusted mean change (s.e.m.) from baseline during and after teriparatide treatment in patients with and without prior bisphosphonate (BP) use. Note: * $P < 0.001$ vs baseline and † $P < 0.05$ vs prior BP users. Data presented are from MMRM analysis using prior BP use subgroup, months and their interaction as fixed effects and adjusting for baseline back pain VAS score, number of previous fractures, fracture in 12 months before study entry, age, prior bisphosphonate duration, and diagnosis of rheumatoid arthritis. The unadjusted mean (s.d.) back pain VAS scores at baseline, 3, 6, 12, 18, 24, and 36 months and end of study (L.O.C.F.) for prior BP users were 57.1 (26.4), 43.5 (24.7), 39.5 (25.1), 36.1 (25.4), 34.3 (25.6), 34.4 (26.8), 32.5 (26.8), and 36.1 (27.4) respectively. For patients with no prior BP use, the corresponding unadjusted mean (s.d.) scores were 59.4 (27.3), 41.2 (25.7), 35.1 (25.9), 30.7 (25.9), 25.4 (24.2), 26.3 (25.8), 21.7 (23.5), and 26.7 (26.0) respectively. The between-group difference for the unadjusted scores was significant from the 6-month visit onwards ($P < 0.05$, two-sample t -test). The unadjusted mean changes from baseline to endpoint for the groups with and without prior BP use were -20.9 (s.d. 30.7) and -33.1 (s.d. 33.5) respectively.

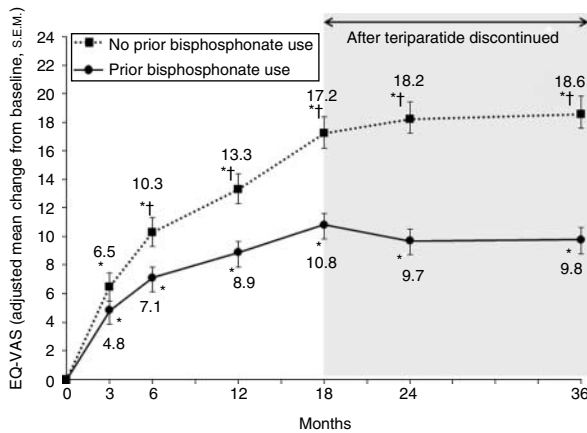


Figure 4 EQ-VAS: adjusted mean change (s.e.m.) from baseline during and after teriparatide treatment in patients with and without prior bisphosphonate (BP) use. Note: * $P < 0.001$ vs baseline and † $P < 0.05$ vs prior BP users. Data presented are from MMRM analysis using prior BP use subgroup, months and their interaction as fixed effects and adjusting for baseline EQ-VAS score, number of previous fractures, fracture in 12 months before study entry, age, prior bisphosphonate duration, and diagnosis of rheumatoid arthritis. For prior BP users, unadjusted mean (s.d.) EQ-VAS values at baseline, 3, 6, 12, 18, 24, and 36 months and end of study (L.O.C.F.), were 52.2 (20.8), 58.4 (19.2), 60.8 (19.5), 62.9 (21.0), 65.3 (20.9), 64.4 (21.9), 65.7 (22.2), and 62.3 (22.9) respectively. The corresponding values for the no prior BP use group were 51.6 (25.1), 60.7 (21.5), 65.0 (21.2), 68.8 (22.1), 73.1 (21.6), 75.0 (22.1), 75.7 (21.6), and 71.5 (23.0) respectively. The between-group difference for the unadjusted scores was significant from the 6-month visit onwards ($P < 0.001$, two-sample *t*-test). The unadjusted mean (s.d.) change from baseline to endpoint was 10.0 (25.9) and 20.0 (27.2) in the prior and no prior BP user groups respectively.

have a long bone retention time (such as bisphosphonates) will inhibit the skeletal anabolic response to PTH. Bisphosphonates selectively bind to the mineral phase of bone matrix, markedly suppress bone activation frequency (29–32), have a (varying) long retention time in bone (33), and suppress bone turnover for many months after discontinuation (34). Therefore, as a result of reduced bone turnover, we may expect a delay in the increase of biochemical markers of bone resorption and formation and of areal BMD after starting teriparatide treatment in patients previously treated with bisphosphonates, compared with either less potent antiresorptives (e.g. raloxifene) or in treatment-naïve patients (11). A slower increase in areal BMD during the initial months of teriparatide treatment has been demonstrated in the EUROFORS trial in those patients pre-treated with antiresorptives (mainly bisphosphonates), compared with treatment-naïve patients (12). In spite of the delayed initial response to teriparatide treatment, there were robust gains in BMD between 18 and 24 months of teriparatide treatment, especially in patients defined as inadequate responders to prior antiresorptive therapy (12). In the same study, bone formation markers (which were reduced at baseline in the antiresorptive pre-treated group

compared with treatment-naïve subjects) quickly caught up after 1 month of teriparatide treatment, and the levels of procollagen type I N-terminal propeptide and bone-specific alkaline phosphatase were no longer different among groups after 6 months of treatment (35).

Several other clinical studies have shown that the suppressive effects of a bisphosphonate pre-treatment can be overcome during continued teriparatide treatment, as assessed by quantitative histomorphometry (36), by high-resolution computed tomography (HRCT)-based structural analyses (37), by HRCT-based finite element analyses (FEA) of vertebral trabecular bone (38), and by CT-based analyses of biomechanical properties of the femoral neck, which showed an improvement in the moment of inertia and buckling ratio after 24 months of teriparatide treatment (39). These findings further support the recommendation that there is no rationale for a washout period after stopping a bisphosphonate therapy before initiating teriparatide treatment (40, 41).

Previous research has indicated that the marked suppression of bone turnover by bisphosphonates may be associated with an increase in bone microcracks in postmenopausal women with osteoporosis (42). While it is unclear whether this microdamage accumulation affects fracture risk, a recent study of iliac crest bone biopsies has shown that teriparatide treatment can reduce the microdamage accumulation in patients previously treated with bisphosphonates and it might be speculated that this may be associated with improved bone structure and strength (43).

In a substudy of the OPTAMISE study using CT-based FEA of the vertebral body, Chevalier *et al.* (44) found that teriparatide treatment for 12 months resulted in a greater increase in vertebral bone strength in patients previously treated with risedronate than in those previously treated with alendronate. However, because these analyses were performed after only 12 months of teriparatide treatment, we cannot draw any conclusions about whether there is a clinically relevant difference between the two bisphosphonates.

We observed rapid and significant improvements in both back pain and HRQoL in the prior and no prior bisphosphonate groups during teriparatide treatment, and these benefits were maintained 18 months after teriparatide was discontinued. The smaller changes from baseline in back pain VAS and EQ-VAS in the prior bisphosphonate users may reflect a greater severity of osteoporosis in this group of patients, as shown by their baseline clinical risk factors. However, the baseline VAS and EQ-VAS values were not different between groups. Hence, another possible explanation for these differences may be that the time since the most recent clinical fracture was shorter in the bisphosphonate-naïve group (0.4 vs 0.9 years in the prior bisphosphonate user group; i.e. ~4.8 vs ~10.8 months), and the larger improvements in back pain and QoL may be

the result of analgesic use and/or a spontaneous resolution of back pain associated with a more recent spine fracture. In any case, the absolute differences between the two groups, albeit statistically significant, were small and in the range of clinically non-relevant values (45). The back pain results observed in EFOS are similar to previously reported values in the EUROFORS trial (46).

Our study has several limitations. First, the information on prior osteoporosis treatments was collected retrospectively and was based on patient self-report. It is, therefore, subject to recall bias. Moreover, although we know that the median duration of prior bisphosphonate use was 36 months and that 10% of the prior bisphosphonate user group were still taking a bisphosphonate at study enrollment, we do not know the lag time between stopping previous therapy and starting teriparatide. Secondly, because previous bisphosphonate therapy was not randomized, we cannot attribute the observed differences to prior use of bisphosphonates. Similarly, as there is no randomized comparison group, the suggestive attribution of the observed changes in endpoints to teriparatide is not controlled. Another limitation is that we did not gather data on the use of analgesics during the study, which may have affected the back pain results. Finally, the maximum treatment duration with teriparatide when the study was conducted was 18 months in Europe, but the currently approved duration is 24 months.

As the safety of teriparatide has already been established and was not an objective of this observational study, adverse events were not collected as a part of the study. Investigators were reminded to report any significant adverse events to the sponsor. All spontaneously reported adverse events for participants of the study have been reported previously (17) and were consistent with current prescribing information.

The strengths of our study include the large sample size and the enrollment of a diverse range of subjects without the strict inclusion and exclusion criteria used in RCTs, reflecting normal clinical practice. Notably, patients taking part in EFOS had comorbidities, including rheumatoid arthritis, and received numerous concomitant medications. Another advantage of EFOS is that it examined patients with severe osteoporosis receiving sequential therapies in the routine care setting. Further work is needed to clarify the influence of different sequential treatments on fracture risk reduction.

In conclusion, we found that postmenopausal women with severe osteoporosis previously treated with bisphosphonates who were prescribed teriparatide in a routine setting had a significant reduction in the incidence of fractures that was accompanied by a reduction in back pain and improvements in HRQoL during 18 months of teriparatide treatment. These changes from baseline were still evident 18 months after discontinuation of teriparatide therapy when the majority of patients were

receiving other osteoporosis therapy. These findings should be interpreted in the context of a non-controlled observational study.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-11-0740>.

Declaration of interest

F Jakob has received honoraria for lectures and advice from Lilly, Amgen, Novartis, Merck Sharp and Dohme (MSD), Nycomed, Servier, and Roche, has received unrestricted research grants from Novartis and is involved in clinical studies related to osteoporosis drugs initiated by Lilly, Amgen, Servier, and Novartis. B Langdahl has participated on advisory boards for Eli Lilly and Company, MSD, Amgen, Nycomed, and Novartis, has received research grants from Eli Lilly and Company, MSD, Amgen, and Novartis, and serves on Speaker's Bureau with Eli Lilly and Company, MSD, and Amgen. W F Lems has received fees for speaking/advisory boards from MSD, Warner Chilcott, Eli Lilly, Amgen, and Servier. A Fahrleitner-Pammer has received research grants from Amgen, Eli Lilly and Company, Nycomed, Roche, and Servier, has contributed to Speaker's Bureau for Amgen, Daiichi Sankyo, Eli Lilly and Company, Genzyme, GSK, MSD, Novartis, Nycomed, Roche, Sanofi-Aventis, and Servier. O Ljunggren has received lecture fees from and participates as a clinical investigator and on advisory boards for Lilly, Amgen, Astra Zeneca, and Nycomed. J B Walsh has received honoraria for lectures from Servier, Eli Lilly and Company, MSD, and Amgen. F Marin and H Oertel are full-time employees and stockholders of Eli Lilly and Company. A Barrett is an employee of Eli Lilly and Company. C Barker is a former employee of Eli Lilly and Company. D Karras and G Rajzbaum have nothing to disclose.

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