Calcif Tissue Int (2009) 85:484–493
DOI 10.1007/s00223-009-9299-6

CLINICAL INVESTIGATIONS

Reduction in Fracture Rate and Back Pain and Increased Quality of Life in Postmenopausal Women Treated with Teriparatide: 18-Month Data from the European Forsteo Observational Study (EFOS)

Bente L. Langdahl · Gerald Rajzbaum · Franz Jakob · Dimitrios Karras · Östen Ljunggren · Willem F. Lems · Astrid Fahrleitner-Pammer · J. Bernard Walsh · Clare Barker · Alexey Kutahov · Fernando Marin

Received: 3 May 2009 / Accepted: 9 September 2009 / Published online: 13 October 2009

Abstract The European Forsteo Observational Study was designed to examine the effectiveness of teriparatide in postmenopausal women with osteoporosis treated for up to 18 months in normal clinical practice in eight European countries. The incidence of clinical vertebral and nonvertebral fragility fractures, back pain, and health-related quality of life (HRQoL, EQ-5D) were assessed. Spontaneous reports of adverse events were collected. All 1,648 enrolled women were teriparatide treatment-naive, 91.0% of them had previously received other anti-osteoporosis drugs, and 72.8% completed the 18-month study. A total of 168 incident clinical fractures were sustained by 138 (8.8%) women (821 fractures/10,000 patient-years). A 47% decrease in the odds of fracture in the last 6-month period compared to the first 6-month period was observed ($P < 0.005$). Mean back pain VAS was reduced by 25.8 mm at end point ($P < 0.001$). Mean change from baseline in EQ-VAS was 13 mm by 18 months. The largest improvements were reported in the EQ-5D subdomains of usual activities and pain/discomfort. There were 365 adverse events spontaneously reported, of which 48.0% were considered related to teriparatide; adverse events were the reason for discontinuation for 79 (5.8%) patients. In conclusion, postmenopausal women with severe osteoporosis who were prescribed teriparatide in standard clinical practice had a significant reduction in the incidence of fragility fractures and a reduction in back pain over an 18-month treatment period. This was associated with a clinically significant improvement in HRQoL. Safety was consistent with current prescribing information. These results should be interpreted in the context of the open-label, noncontrolled design of the study.

Keywords Osteoporosis · Teriparatide · Fracture · Back pain · Quality of life

B. L. Langdahl (✉)
Department of Endocrinology, Århus University Hospital, Tage Hansens Gade 2, Arhus 8000, Denmark
e-mail: bente.langdahl@aarhus.rm.dk

G. Rajzbaum
Hôpital St. Joseph, Paris, France

F. Jakob
Julius-Maximilians-Universität, Wuerzburg, Germany

D. Karras
Veterans Administration Hospital, Athens, Greece

Ö. Ljunggren
Uppsala University Hospital, Uppsala, Sweden

W. F. Lems
Slotervaart Hospital, Amsterdam, The Netherlands

A. Fahrleitner-Pammer
Medical University, Graz, Austria

J. Bernard Walsh
Trinity College, Dublin, Ireland

C. Barker · A. Kutahov · F. Marin
Lilly Research Centre, Windlesham, UK

Osteoporosis, a chronic skeletal disorder characterized by reduced bone quantity and quality, increases bone fragility and predisposes patients to fractures, mainly at the spine, hip, wrist, and proximal humerus. In the year 2000, the number of osteoporotic fractures worldwide was estimated to be 9 million, with 61% of these occurring in women [1]. Osteoporotic fractures substantially impair health-related quality of life (HRQoL) [2, 3] and lead to increased

morbidity and, depending on fracture location, increased mortality [4]. A recent estimate put the projected costs of treating osteoporotic fractures in women in Europe at €76.7 billion by 2050 [5].

Recently approved drugs for the treatment of osteoporosis have been shown to reduce the risk of vertebral and nonvertebral fractures [6, 7]. Currently, the most commonly prescribed medications for osteoporosis are antiresorptive agents, primarily bisphosphonates. Teriparatide is a recombinant human N-terminal fragment of parathyroid hormone (rhPTH [1–34]), a bone anabolic agent that has been shown to increase bone mass and strength. In a placebo-controlled clinical trial, teriparatide reduced the relative risk of new vertebral and nonvertebral fragility fractures after 19 months of treatment by 65% and 53%, respectively, in postmenopausal women with severe osteoporosis [8]. Treatment with teriparatide resulted in a greater increase in bone mineral density (BMD) and reduction in vertebral fracture risk than alendronate in men and women with glucocorticoid-induced osteoporosis [9].

Although randomized controlled trials are considered the gold standard for investigating drug efficacy, their design limits the capacity to provide answers to questions about more "typical" patient populations and issues found only in clinical practice. In a recent retrospective chart review of 120 patients, it was estimated that approximately 80% of patients receiving treatment for osteoporosis would not be eligible for inclusion in a randomized controlled trial because of comorbidities, previous treatment with bone-active agents, or the use of other medications [10]. Observational studies can be an important addition to a clinician's resources by complementing randomized controlled trial data with information on the effectiveness and compliance of a treatment used in routine clinical care in larger and more diverse patient populations [11]. It is well known that compliance with osteoporosis treatments is higher in clinical trials than in normal clinical practice [12]. This is important as it may influence not only the expected outcome of the treatment in the individual patient [13] but also the pharmacoeconomic considerations.

In 2006, the prospective European Forsteo Observational Study (EFOS) was set up to observe the effects of teriparatide treatment for up to 18 months, with a post-treatment follow-up period of a further 18 months' duration, in postmenopausal women with osteoporosis. The patients prescribed teriparatide in the EFOS were severely osteoporotic, with a high fracture risk and poor HRQoL, despite previous therapy for osteoporosis; moderate to severe back pain was also very common [14]. Here, we describe the incidence of clinical vertebral and nonvertebral fragility fractures, the occurrence of back pain and changes in HRQoL, and the compliance with teriparatide during 18 months of treatment.

Patients and Methods

Study Design

The study design and characteristics of the patient population have been described [14]. Briefly, 1,648 postmenopausal women with a diagnosis of osteoporosis who were about to initiate teriparatide treatment were enrolled in eight European countries. Patients were excluded from the study if they were currently being treated with an investigational drug or procedure or had any contraindications as described in the teriparatide label. Apart from this, the study was purely observational and there were no further restrictions for the selection of the patients. All patients gave written informed consent prior to 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.

Data Collection

At the baseline visit, patient demographic characteristics, risk factors for osteoporosis and falls, osteoporosis therapies, and disease status were recorded [14]. The women attended visits at baseline and at approximately 3, 6, 12, and 18 months after teriparatide initiation. Patients were observed for the entire duration of treatment, and compliance with treatment was assessed from their reporting of the number of missed doses in the month prior to each visit.

Incident clinical vertebral and nonvertebral fractures, the primary study end point, were diagnosed and confirmed by review of the original X-rays and/or the radiology or surgical reports at the investigational site. A new or worsened vertebral fracture was defined from the presence of a confirmed radiographic vertebral fracture associated with signs and/or symptoms, such as acute or severe back pain, suggestive of a vertebral fracture as described by Ross [15].

A study-specific back pain questionnaire (Appendix 1) was completed at each visit. Perceived severity of back pain was also evaluated on a horizontal 100 mm Visual Analogue Scale (VAS) ranging from 0 mm (no back pain) to 100 mm (worst possible back pain).

HRQoL was measured using the European Quality of Life Questionnaire (EQ-5D, formerly EuroQol) [16]. EQ-5D is a generic HRQoL questionnaire that evaluates five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each scored on a three-point scale (no problems, some problems, extreme problems) plus a visual analogue scale (EQ-VAS), which assesses the patient-perceived overall health status, on a scale from 0 mm (worst imaginable health state) to 100 mm (best imaginable health state). The Health State

Value (HSV) was calculated from the five EQ-5D dimensions using the U.K. scoring algorithm for all countries, to allow for comparisons across countries [17]. Spontaneously reported adverse events were collected throughout the study.

Statistical Analysis

Descriptive statistics such as frequencies, percentages, means, and standard deviations (SD) were used to describe the study population over time. Incident fractures, back pain, and quality of life results were summarized over the teriparatide treatment period and after completion of 18 months of treatment. The number of fractures occurring in patients receiving teriparatide treatment was summarized in 6-month intervals up to 18 months of treatment. A logistic regression analysis was used to assess the change in the number of patients with one or more fractures over time [18, 19]. Patients were included in the model at all observed intervals, regardless of whether or not they 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. Contrasts were made between the odds of fracture in the first 6 months of treatment (0–6 months) and each subsequent 6-month period (6–12 months and 12–18 months). Unadjusted and adjusted models including age, prior bisphosphonate use, and a history of fracture in the last 12 months before starting teriparatide were performed. Fracture modeling was repeated for all vertebral, nonvertebral, and main nonvertebral (forearm/wrist, hip, humerus, leg, and sternum/ribs) fractures.

The number and percent of patients with improvement, no change, or worsening in each domain of the EQ-5D questionnaire were summarized at each visit. The sign test was used to determine whether significantly more patients showed improvement as opposed to worsening.

Back pain changes from baseline in the VAS were analyzed using a mixed model for repeated measures (MMRM), adjusting for baseline back pain VAS, age, diagnosis of rheumatoid arthritis, duration of prior bisphosphonate therapy, and history of fracture in the 12 months prior to entering the study. *P* values represent the unique influence of the corresponding factor after adjustment for all other factors in the model. The number of patients reporting an improvement or worsening in the severity, frequency, limitation of activities, and number of days in bed ($\leq$2 days, no change) was analyzed using the sign test. A similar MMRM was used to assess the change from baseline in EQ-VAS, including its baseline value. The EQ-5D HSV had a continuous, nonparametric, bimodal distribution; therefore, the Wilcoxon sign-rank test was used to assess changes from baseline in this parameter.

Results

Patient Disposition and Osteoporosis Treatment

A total of 1,648 patients entered the study and were analyzed at baseline. Mean (SD) age was 71.5 (8.4) years, body mass index (BMI) was 25.1 (4.4) kg/m^2, and 12.8% of the patients were current smokers. A previous fracture after the age of 40 years was reported for 91.9% of the women, the mean (SD) number of prevalent fractures at baseline was 2.9 (2.0), and 70% had two or more vertebral deformities. Approximately 48% of the women had sustained a fragility fracture within the 12 months prior to starting teriparatide treatment. Rheumatoid arthritis was the most frequently reported comorbidity (11.9% of the patients). Only 7.7% of the patients were osteoporosis treatment–naive, alendronate being the most frequently used previous treatment (43.6% of the subjects; for more details, see [14]). Once teriparatide was started, 5.2% of the patients reported concomitant use of an antiresorptive drug. Calcium and vitamin D supplements were taken by 74–78% of patients during the course of the study. By the 18-month visit, concomitant use of antiresorptives was reported by 6.3% of the patients, calcitonin being the antiresorptive drug most frequently used (2.3% of the patients).

There were 1,577 patients (95.7%) who returned for at least one follow-up visit and 1,356 (82.3%) who completed a final visit either at 18 months or earlier. There were 79 (5.8%) discontinuations from teriparatide due to adverse events; the other main reasons for treatment discontinuation were patient decision ($n = 109$, 8.0%) and physician decision ($n = 26$, 1.9%).

At the time of this analysis data lock, the duration of teriparatide treatment ranged 1–639 days (mean [SD] 461 [166] days). The proportions of patients known to be still taking teriparatide after 12, 17, and 18 months were 77.0%, 61.5%, and 22%, respectively (Fig. 1). During the 18 months of treatment, 11.9% of patients reported one or more interruptions to treatment of 4 or more weeks. The median self-reported number of missing daily injections during the last month of treatment was three.

Fracture Incidence

Table 1 shows the incidence of fractures during the course of the study. During follow-up, 138 (8.8%) women sustained a total of 168 incident fractures, giving an overall fracture rate of 821/10,000 patient-years. Twenty-three patients (1.5%) sustained two or more new fractures. Of the 168 fractures, 38.7% were clinical vertebral fractures and 61.3% were nonvertebral; 50.6% of all fractures occurred at the main nonvertebral sites (forearm/wrist [$n = 26$], hip

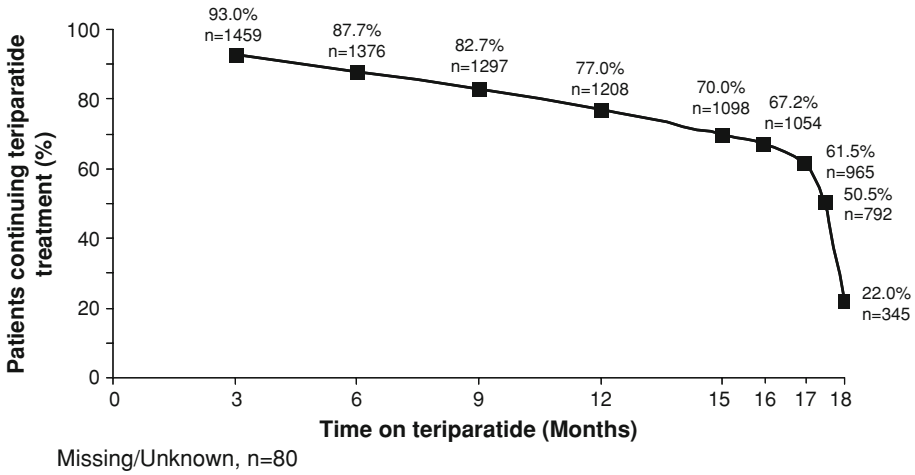

Fig. 1 Percent of patients on teriparatide treatment at each time point in the study. Reimbursement in most participant countries is limited to 18 pen devices (i.e., ≈17 months treatment; see text)

Table 1 Overall risk of incident fractures during treatment with teriparatide

Observation period	Fractures per 10,000 patient-years	Total number of fractures	Patients with ≥1 fracture (*n* [%])	Odds of fracture[a] (95% CI)	OR[a,b] (95% CI)	*P*[a]
0–6 months ($n = 1{,}560$)	1,113	83	72 (4.6)	0.040 (0.030–0.054)		–
6–12 months ($n = 1{,}302$)	768	50	45 (3.5)	0.027 (0.019–0.039)	0.68 (0.47–0.98)	0.038
12–18 months ($n = 1{,}200$)	583	35	33 (2.8)	0.021 (0.014–0.031)	0.53 (0.35–0.82)	0.004
Total ($n = 1{,}577$)	821	168	138 (8.8)[c]			–

n, number of patients who attended observation

[a] Adjusted model by age, prior bisphosphonate use, and history of fracture in the 12 months before starting teriparatide

[b] Compared with 0–6 months

[c] As some patients experienced a fracture in more than one time interval, the total was not the sum of the number of patients with a fracture in each interval

[$n = 21$], leg [$n = 15$], sternum/ribs [$n = 12$], and humerus [$n = 11$]). A history of fracture in the prior 12-month period did not have a statistically significant effect on the risk of first fracture that occurred on teriparatide treatment (hazard ratio [HR] = 1.37, 95% confidence interval [CI] 0.97–1.95, $P = 0.076$).

Overall, the number of patients who had at least one fracture during teriparatide treatment significantly decreased between the first 6-month period ($n = 72$, 4.6%) and the second 6-month period ($n = 45$, 3.5%) (adjusted model odds ratio [OR] = 0.68, 95% CI 0.47–0.98, $P = 0.038$) and between the first 6-month period and the last 6-month period on treatment ($n = 33$, 2.8%) (OR = 0.53, 95% CI 0.35–0.82, $P = 0.004$) (Table 1). The fracture incidence per 10,000 patient-years of 1,113 in the first 6 months decreased to 583 during the 12–18 month period (Table 1). A decline in the incidence of both clinical vertebral and nonvertebral fractures was observed during the study (Fig. 2). The clinical vertebral and main nonvertebral fracture rates were significantly decreased between the first 6-month period and the last 6-month period on treatment (Fig. 2).

Back Pain

The mean (SD) back pain measured by the VAS at baseline was 57.7 (26.6) mm, and this was reduced by 25.8 mm after 18 months of treatment ($P < 0.001$). The greatest reduction in back pain, analyzed using the MMRM, occurred during the first 6 months of treatment (Fig. 3). From the parameters included in the MMRM, only two variables had a potential influence on the changes in back pain VAS ($P < 0.001$); for each additional 5 mm in the baseline VAS value the change after treatment was 2.8 mm less, and for every 5 years of prior bisphosphonate therapy it was 4.4 mm greater.

Table 2 shows the frequency and severity of back pain during the previous month at each assessment. The frequency of back pain decreased over the treatment period; at baseline 65.8% of patients reported experiencing back pain every day or almost every day, and this decreased to 29.9% of patients after completing 18 months of treatment. At every postbaseline visit, there were significantly more patients who reported a decrease in the frequency of back pain compared with baseline than those reporting an increase in frequency of

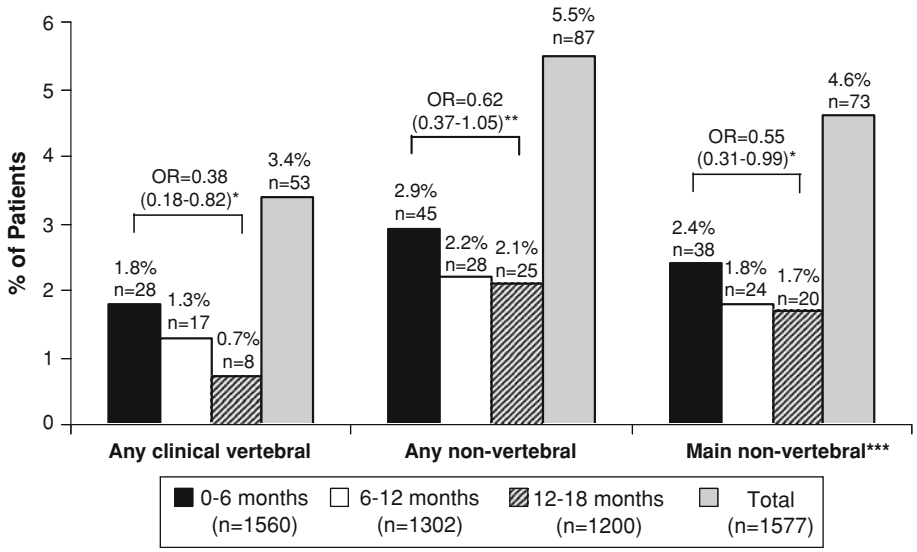

Fig. 2 Number and percent patients with incident fractures in each 6-month period by fracture type. * $P < 0.05$, ** $P < 0.10$. Adjusted models by age, prior bisphosphonate use, and history of fracture in the last 12 months before starting teriparatide. *** Forearm/wrist, hip, humerus, leg, and sternum/ribs

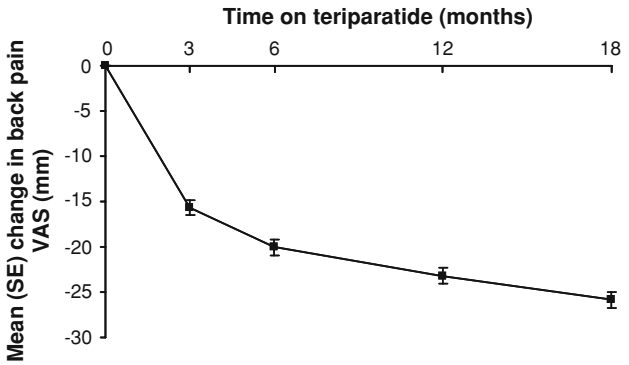

Fig. 3 Adjusted change in back pain from baseline: 100 mm VAS. Model includes back pain VAS baseline value, age, duration of prior bisphosphonate therapy, rheumatoid arthritis, and history of fracture in the 12 months prior to starting teriparatide therapy. All values: $P < 0.001$ compared to baseline. Actual unadjusted values of mean (SD) at 0, 3, 6, 12, and 18 months were 57.7 (26.6), 42.8 (25.1), 38.2 (25.4), 34.6 (25.7), and 31.6 (25.6) mm, respectively

back pain (sign test, $P < 0.001$). The severity of back pain also decreased during the treatment period; at baseline moderate/severe pain was reported by 89.2% of patients, and this was reduced to 57.2% after 18 months. At every post-baseline visit, significantly more patients had a decrease in the severity of back pain than those with an increase (sign test, $P < 0.001$). The limitation on activity and the frequency of days in bed due to back pain also decreased over the course of the study ($P < 0.001$) (Table 2).

After 18 months, fewer patients reported the need to assist themselves with their arms when standing up from a chair (54.6%) compared with baseline (62.9%) ($P < 0.001$).

HRQoL

The mean (SD) EQ-VAS at baseline was 51.7 (22.0) mm. There was a significant increase in adjusted mean EQ-VAS values from baseline at all visits, and the increase was 13 mm at 18 months (Fig. 4). In the MMRM, the baseline EQ-VAS value, duration of prior bisphosphonate therapy, rheumatoid arthritis, and age all had a potential influence on the change in HRQoL. For every 5 years of bisphosphonate therapy the change in EQ-VAS decreased by 2.2 mm ($P < 0.001$), for every 5 years of increased age the change in EQ-VAS decreased by 1.2 mm ($P < 0.001$), and for those with rheumatoid arthritis the change in EQ-VAS was 5.2 mm less than for those without this disorder.

Table 3 shows that, overall, there was a significant improvement in each of the five domains of the EQ-5D ($P < 0.001$). The decrease in the percentage of subjects reporting some/extreme problems was most pronounced in the usual activities and pain/discomfort domains.

Results from the EQ-5D HSV scores are also shown in Table 3. Median (Q1, Q3) HSV scores showed that patients experienced a significant improvement in HRQoL from baseline (0.59, range 0.08–0.73) to 18 months (0.73, range 0.59–0.85) of teriparatide treatment (Wilcoxon rank test $P < 0.001$).

Safety

There was a total of 365 adverse events spontaneously reported by the participant physicians; of these, 135 (37%) were serious and 175 (48.0%) were considered related to use of the drug. The most common adverse events were nausea (5.5%), headache (4.4%), fatigue, and depression (2.7% each). There were four spontaneous reports of hypercalcemia, one of which was considered severe as it resulted in prolonged hospitalization. There were 27 deaths during the study period, representing 1.6% of the EFOS cohort. The treating physicians did not consider any death to be drug-related.

Table 2 Frequency and severity of back pain, limitation of daily activities, and days in bed due to back pain in the last month

	Treatment point				
	Baseline (n = 1,648)	3 months (n = 1,467)	6 months (n = 1,423)	12 months (n = 1,302)	18 months (n = 1,200)
Back pain experienced					
Yes, *n* (%)	1,574 (95.5)	1,360 (92.7)	1,297 (91.1)	1,124 (86.3)	1,003 (83.6)
No, *n* (%)	70 (4.2)	97 (6.6)	112 (7.9)	166 (12.7)	184 (15.3)
Missing/unknown, *n* (%)	4 (0.2)	10 (0.7)	14 (1.0)	12 (0.9)	13 (1.1)
Frequency of back pain					
n	1,574	1,360	1,297	1,124	1,003
Once or twice, *n* (%)	60 (3.8)	154 (11.3)	209 (16.1)	203 (18.1)	223 (22.2)
A few times, *n* (%)	156 (9.9)	391 (28.8)	366 (28.2)	315 (28.0)	251 (25.0)
Fairly often, *n* (%)	288 (18.3)	257 (18.9)	205 (15.8)	171 (15.2)	177 (17.6)
Every day or almost every day, *n* (%)	1,036 (65.8)	507 (37.3)	451 (34.8)	370 (32.9)	300 (29.9)
Missing/unknown, *n* (%)	34 (2.2)	51 (3.8)	66 (5.1)	65 (5.8)	52 (5.2)
Severity of back pain					
n	1574	1360	1297	1124	1003
Minor, *n* (%)	139 (8.8)	315 (23.2)	381 (29.4)	370 (32.9)	375 (37.4)
Moderate/severe, *n* (%)	1,404 (89.2)	997 (73.3)	854 (65.8)	690 (61.4)	574 (57.2)
Missing/unknown, *n* (%)	31 (2.0)	48 (3.5)	62 (4.8)	64 (5.7)	54 (5.4)
Limitation of activities					
n (%)	1,574	1,360	1,297	1,124	1,003
No limitation, *n* (%)	158 (10.0)	259 (19.0)	319 (24.6)	306 (27.2)	318 (31.7)
Minor, *n* (%)	237 (15.1)	355 (26.1)	356 (27.4)	304 (27.0)	244 (24.3)
Moderate/severe, *n* (%)	1,162 (73.8)	718 (52.8)	580 (44.7)	475 (42.3)	413 (41.2)
Missing/unknown, *n* (%)	17 (1.1)	28 (2.1)	42 (3.2)	39 (3.5)	28 (2.8)
Days in bed due to back pain					
None, *n* (%)	1,237 (75.1)	1,247 (85.0)	1,213 (85.2)	1,055 (81.0%)	950 (79.2)
At least one, *n* (%)	324 (19.7)	108 (7.4)	78 (5.5)	62 (4.8%)	49 (4.1)
Median (Q1, Q3)[a]	7 (3, 15)	4 (2, 10)	3 (2, 6)	3.5 (2, 6)	3 (2, 10)
Missing/unknown, *n* (%)	87 (5.3)	112 (7.6)	132 (9.3)	185 (14.2%)	201 (16.8)

[a] For those patients with ≥1 day in bed due to back pain

All changes: $P < 0.001$ compared to baseline (sign test)

Discussion

With the increasingly aging population, osteoporosis is becoming more prevalent and observational studies are essential to determine the effect of treatment in a real-life clinical setting with a broader range of patients. There are differences between patients in clinical practice and subjects in clinical trials, suggesting that most clinical practice patients treated for osteoporosis would not qualify for participation in the clinical trials that provide the data for drug approval [10]. In the community cohort of postmenopausal women with osteoporosis in the EFOS, we found that patients prescribed teriparatide in the eight European participant countries had more severe osteoporosis than those included in the pivotal trial [8]. This observation probably reflects the European guidelines for osteoporosis treatment, which recommend teriparatide as a second-line therapy. Thus, at baseline the mean lumbar spine T-score BMD was lower in the EFOS (–3.3 SD) than in the pivotal trial (–2.6 SD), there were more prevalent fractures (mean 2.9 vs. 2.3), and many more patients had received previous osteoporosis treatment (91.8% vs. 16%), the majority with potent bisphosphonates. Additionally, a high number of patients had chronic comorbidities or took concomitant medications [14] that would have precluded their eligibility for the pivotal trial [8]. In spite of these differences in patient characteristics, we found that patients receiving teriparatide therapy in the EFOS had a significant reduction in the incidence of clinical fractures over time; these results are consistent with those of the placebo-controlled Fracture Prevention Trial, where longer treatment duration with teriparatide was associated with larger reductions in non-vertebral fracture risk [8, 20]. The fracture risk in patients receiving treatment after 12–18 months was reduced by

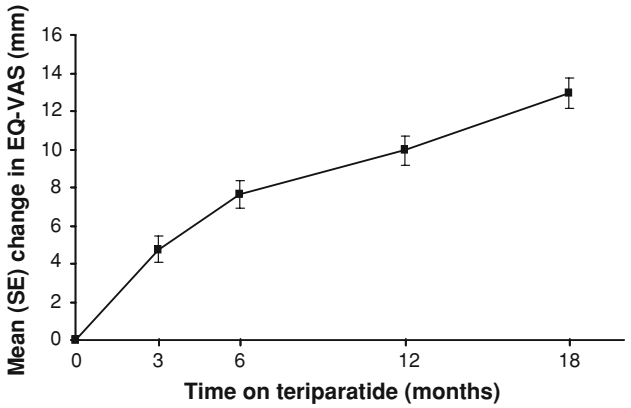

Fig. 4 Change in HRQoL. EQ-VAS model includes EQ-VAS baseline value, age, duration of prior bisphosphonate therapies, rheumatoid arthritis, and history of fracture in the 12 months prior to starting teriparatide therapy. All values: $P < 0.001$ compared to baseline. Actual unadjusted values of mean (SD) at 0, 3, 6, 12, and 18 months were 51.7 (22.0), 58.8 (19.9), 61.8 (20.4), 64.8 (22.0), and 68.1 (21.7) mm, respectively

47% compared with the first 6-month period of treatment. It was of interest that the fracture risk was already significantly reduced by 32% in the second 6-month treatment period (6–12 months) compared with the first 6-month period. A decreased incidence was also observed for clinical vertebral and main nonvertebral fractures.

It is well documented that a prior fracture is a main risk factor for subsequent fractures in postmenopausal women with osteoporosis. From the results of two recent meta-analyses it was concluded that a previous fracture increases the relative risk (RR) for a subsequent fracture by approximately twofold and a prior vertebral fracture increases the RR for a subsequent vertebral fracture by fourfold [21, 22]. It has also been demonstrated that subjects who had experienced a vertebral fracture within the last 12 months had a fivefold risk of sustaining an additional fracture within the next year [23]. In the prospective Observational Study of Severe Osteoporosis (OSSO) study, which included severely osteoporotic patients treated with various osteoporosis medications, women with a fracture within the 12 months prior to baseline were significantly more likely to sustain an incident fracture during the 12-month follow-up than those without a prior fracture (HR = 1.91, $P < 0.001$) [24]. In the EFOS cohort, 48% of the patients had sustained a clinical fragility fracture in the 12 months before starting teriparatide. However, such a trend toward an increased risk of additional fractures in these women with recent prior fractures, compared to those with a prior fracture that occurred more than 12 months before starting treatment, was not seen when they were treated with teriparatide (HR = 1.37, $P = 0.076$), which supports the effectiveness of this drug. This finding is also in agreement with data from the Fracture Prevention Trial, where no increased fracture risk was associated with a larger prior number and increased severity of fractures in women treated with teriparatide [25].

Persistence with treatment is a key factor for the efficacy of any drug in the treatment of osteoporosis [13, 26, 27]. Despite the fact that the administration of teriparatide involves a once-a-day injection, persistence was relatively high, with 77% of patients still on treatment after 12 months and 61.5% after 17 months of treatment. This persistence was similar to that reported in response to teriparatide treatment in other recent European [28, 29] and Canadian [30] studies. The most likely reason for the decline in persistence that we observed between 17 and 18 months (Fig. 1) is that in most participant European countries reimbursement only covers 18 pen devices, which corresponds to 504 days of treatment (16.8 months). Observational studies of various osteoporosis treatments, particularly oral antiresorptive drugs, have reported 1–2 year persistence rates of <50% [12, 13, 31, 32]. The high persistence rate in our study could be explained by several factors. First, postmenopausal women eligible for teriparatide treatment in the EFOS had a mean of approximately three prevalent fragility fractures and a high prevalence and severity of back pain, reflecting severe osteoporosis [14]. Thus, they may well have perceived a greater benefit-to-risk ratio than most patients prescribed oral osteoporosis treatments. Many of these patients had received other osteoporosis treatments prior to teriparatide, during which they had experienced new fractures; therefore, they may have been very interested in getting the most out of this new treatment modality. Second, in contrast with other locations, prescription of teriparatide and treatment follow-up in Europe is largely carried out by specialists and this may have enhanced compliance. Patients are also aware that they will receive a course of teriparatide treatment only once. Finally, most patients were aware that treatment is expensive, which could have influenced adherence to the regimen. In the EFOS, the most common reason for discontinuation of teriparatide was completion of treatment and discontinuations due to adverse events were low.

The decline in the incidence of fragility fractures was accompanied by a significant reduction in the frequency and severity of back pain, as well as a clinically relevant increase in patient-perceived HRQoL. Eighty-nine percent of women enrolled in the present study reported moderate or severe back pain at baseline, which had resulted in a marked deterioration in HRQoL [14]. The reduction in the frequency and severity of back pain following teriparatide treatment in these women is consistent with observations from controlled clinical trials [8, 33]. As expected, the improvements in back pain and HRQoL were greater in those subjects who did not present with a new fracture during the course of the treatment [34, 35]. In meta-

Table 3 HRQoL: EQ-5D domains and EQ-5D HSV

	Baseline (n = 1,648)	3 months (n = 1,467)	6 months (n = 1,423)	12 months (n = 1,302)	18 months (n = 1,200)
Mobility (n [%])					
No problem	502 (30.5)	631 (43.0)	687 (48.3)	684 (52.5)	656 (54.7)
Some problem	1,080 (65.5)	774 (52.8)	684 (48.1)	577 (44.3)	495 (41.3)
Extreme problem	51 (3.1)	12 (0.8)	8 (0.6)	7 (0.5)	6 (0.5)
Missing/unknown	15 (0.9)	50 (3.4)	44 (3.1)	34 (2.6)	43 (3.6)
Self-care (n [%])					
No problem	924 (56.1)	978 (66.7)	1005 (70.6)	958 (73.6)	883 (73.6)
Some problem	619 (37.6)	405 (27.6)	340 (23.9)	276 (21.2)	245 (20.4)
Extreme problem	85 (5.2)	38 (2.6)	32 (2.2)	33 (2.5)	31 (2.6)
Missing/unknown	20 (1.2)	46 (3.1)	46 (3.2)	35 (2.7)	41 (3.4)
Usual activities (n [%])					
No problem	385 (23.4)	496 (33.8)	594 (41.7)	572 (43.9)	583 (48.6)
Some problem	999 (60.6)	822 (56.0)	693 (48.7)	619 (47.5)	506 (42.2)
Extreme problem	245 (14.9)	95 (6.5)	88 (6.2)	74 (5.7)	69 (5.8)
Missing/unknown	19 (1.2)	54 (3.7)	48 (3.4)	37 (2.8)	42 (3.5)
Pain/discomfort (n [%])					
No problem	122 (7.4)	216 (14.7)	286 (20.1)	302 (23.2)	335 (27.9)
Some problem	992 (60.2)	1036 (70.6)	966 (67.9)	857 (65.8)	725 (60.4)
Extreme problem	505 (30.6)	164 (11.2)	115 (8.1)	106 (8.1)	95 (7.9)
Missing/unknown	29 (1.8)	51 (3.5)	56 (3.9)	37 (2.8)	45 (3.8)
Anxiety/depression (n [%])					
No problem	685 (41.6)	722 (49.2)	763 (53.6)	716 (55.0)	682 (56.8)
Some problem	716 (43.4)	603 (41.1)	534 (37.5)	470 (36.1)	425 (35.4)
Extreme problem	228 (13.8)	92 (6.3)	79 (5.6)	81 (6.2)	51 (4.3)
Missing/unknown	19 (1.2)	50 (3.4)	47 (3.3)	35 (2.7)	42 (3.5)
EQ-5D HSV					
n	1599	1401	1357	1259	1151
Median (Q1, Q3)	0.59 (0.08, 0.73)	0.69 (0.52, 0.76)	0.69 (0.52, 0.80)	0.69 (0.59, 0.80)	0.73 (0.59, 0.85)
Missing/unknown (n [%])	49 (3.0)	66 (4.5)	66 (4.6)	43 (3.3%)	49 (4.1)

All changes: $P < 0.001$ compared to baseline (sign test) or Wilcoxon signed rank test for EQ-5D HSV

analyses of other studies evaluating back pain in osteoporosis, teriparatide-treated patients had a reduced incidence of back pain compared with placebo- or active comparator–treated patients [36, 37].

A correlation between the incidence and severity of fractures due to osteoporosis and HRQoL has been demonstrated in various studies [38–40]. Women with an inadequate response to osteoporosis therapy and a consequent high rate of further fracture also had a low HRQoL [24]. In the present study, the reduction in intensity and frequency of back pain was consistent with the reduction in the number of days incapacitated, as revealed in the HRQoL questionnaire. However, it is possible that a placebo effect and/or the spontaneous resolution of back pain associated with a recent vertebral fracture could explain the reduction of 25.8 mm in the VAS observed in the EFOS. In a recent open, randomized, controlled trial of patients eligible for a balloon kyphoplasty procedure due to painful vertebral fractures (baseline VAS > 40 mm), the VAS reduction in the nontreated control group was approximately 30 mm after 12 months of follow-up [41].

The main strength of observational studies is the applicability of the results to a general population. The subjects in the current observational study were drawn from eight European countries and consisted of patients with a mixture of health characteristics, and thus, the results are likely to be relevant to a wide spectrum of women. In contrast to other reported observational studies in this area, the incident fractures were confirmed and validated by the treating physicians. There are limitations to our study. The collection of adherence and persistence data by patients' self-report throughout visits to the clinic did not include refill dates or take the amount of product left in the cartridges into consideration. The study was not

designed to formally analyze safety data or to include centralized evaluation of clinical laboratory abnormal findings. Thus, only spontaneous adverse events were collected and analyzed. The analysis of fracture incidence was based only on the number of patients who fractured in a given time and did not consider multiple fractures in the same time period. Finally, the lack of a randomized control group also limited us from making any definite conclusions regarding the impact of the treatment on the fracture reduction risk and the patient subjective reported outcomes.

In conclusion, it has been shown in the EFOS study that 18 months of treatment with teriparatide is an effective therapeutic option for postmenopausal women with severe osteoporosis in a real-life clinical setting, characterized by highly prevalent comorbidities and concomitant medications. The EFOS results confirm and expand the outcomes reported for the more selective patient populations included in the randomized controlled trials of teriparatide. Nevertheless, these results should be interpreted in the context of the open-label, noncontrolled design of the study.

Compliance with the treatment regimen was high and teriparatide was well tolerated. There was a reduction in the number and severity of clinical fractures, back pain was reduced, and there was an overall beneficial effect on HRQoL. Further studies are necessary to monitor the long-term outcomes of teriparatide treatment and effects on health-related costs.

Acknowledgements The authors thank all physicians participating in the EFOS for help in conducting the study. The authors also thank Christine Jones (Lilly Germany) for the central study coordination and Annabel Barrett (Lilly Europe) for her comments. Influence Medical Communications, UK, helped in the preparation of the manuscript. This study was supported by a research grant from Lilly.

Appendix 1: EFOS Back Pain Questionnaire

Back Pain Evaluation in the Last Month

Not applicable (No back pain within the **last month**)

1. During the **last month**, how often did the patient experience back pain?
   - o Once or twice
   - o A few times
   - o Fairly often
   - o Every day or almost every day
2. During the **last month**, how would you rate the severity of the patient's back pain?
   - o Minor
   - o Moderate
   - o Severe
3. During the **last month**, to what extent has the patient's activities been limited (please tick one response)?
   - o No limitation
   - o Minor extent
   - o Moderate extent
   - o Severe extent
4. During the **last month**, how many days did the patient stay in bed because of back pain? (Please indicate "0" if none).

References

1. Johnell O, Kanis JA (2006) An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 17:1726–1733
2. Cockerill W, Lunt M, Silman AJ, Cooper C, Lips P, Bhalla AK, Cannata JB, Eastell R, Felsenberg D, Gennari C, Johnell O, Kanis JA, Kiss C, Masaryk P, Naves M, Poor G, Raspe H, Reid DM, Reeve J, Stepan J, Todd C, Woolf AD, O'Neill TW (2004) Health-related quality of life and radiographic vertebral fracture. Osteoporos Int 15:113–119
3. Cooper C, Jakob F, Chinn C, Martin-Mola E, Fardellone P, Adami S, Thalassinos NC, Melo-Gomes J, Torgerson D, Gibson A, Marin F (2008) Fracture incidence and changes in quality of life in women with an inadequate clinical outcome from osteoporosis therapy: the Observational Study of Severe Osteoporosis (OSSO). Osteoporos Int 19:493–501
4. Cummings SR, Melton LJ (2002) Epidemiology and outcomes of osteoporotic fractures. Lancet 359:1761–1767
5. Kanis JA, Johnell O (2005) Requirements for DXA for the management of osteoporosis in Europe. Osteoporos Int 16:229–238
6. Delmas PD (2002) Treatment of postmenopausal osteoporosis. Lancet 359:2018–2026
7. Sambrook P, Cooper C (2006) Osteoporosis. Lancet 367:2010–2018
8. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH (2001) Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441
9. Saag KG, Shane E, Boonen S, Marin F, Donley DW, Taylor KA, Dalsky GP, Marcus R (2007) Teriparatide compared with alendronate for the treatment of glucocorticoid-induced osteoporosis. N Engl J Med 357:2028–2039
10. Dowd R, Recker RR, Heaney RP (2000) Study subjects and ordinary patients. Osteoporos Int 11:533–536
11. Silverman SL (2009) From randomized controlled trials to observational studies. Am J Med 122:114–120
12. Cramer JA, Amonkar MM, Hebborn A, Altman R (2005) Compliance and persistence with bisphosphonate dosing regimens

among women with postmenopausal osteoporosis. Curr Med Res Opin 21:1453–1460
13. Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, Silverman S (2006) Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 81:1013–1022
14. Rajzbaum G, Jakob F, Karras D, Ljunggren O, Lems WF, Langdahl BL, Fahrleitner-Pammer A, Walsh JB, Gibson A, Tynan AJ, Marin F (2007) Characterization of patients in the European Forsteo Observational Study (EFOS): postmenopausal women entering teriparatide treatment in a community setting. Curr Med Res Opin 24:377–384
15. Ross PD (1997) Clinical consequences of vertebral fractures. Am J Med 103:30S–42S
16. EuroQol Group (1990) EuroQoL: a new facility for the measurement of health-related quality of life. Health Policy 16:199–208
17. Szende A, Williams A (eds) (2004) Measuring self-reported population health: an international perspective based on EQ-5D. SpringMed, Budapest
18. Laing YY, Zeger SL (1986) Longitudinal data analysis using generalised linear models. Biometrika 73:13–22
19. Hosmer DW Jr, Lemershow S (eds) (2000) Applied logistic regression, 2nd edn. Wiley, New York
20. Lindsay R, Miller P, Pohl G, Glass EV, Chen P, Krege JH (2009) Relationship between duration of teriparatide therapy and clinical outcomes in postmenopausal women with osteoporosis. Osteoporos Int 20:943–948
21. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A (2004) A meta-analysis of previous fracture and subsequent fracture risk. Bone 35:375–382
22. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA III, Berger M (2000) Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 15:721–739
23. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, Licata A, Benhamou L, Geusens P, Flowers K, Stracke H, Seeman E (2001) Risk of new vertebral fracture in the year following a fracture. JAMA 285:320–323
24. Cooper C, Jakob F, Chinn C, Martin-Mola E, Fardellone P, Adami S, Thalassinos NC, Melo-Gomes J, Torgerson D, Gibson A, Marin F (2008) Fracture incidence and changes in quality of life in women with an inadequate clinical outcome from osteoporosis therapy: the Observational Study of Severe Osteoporosis (OSSO). Osteoporos Int 19:493–501
25. Gallagher JC, Genant HK, Crans GG, Vargas SJ, Krege JH (2005) Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures. J Clin Endocrinol Metab 90:1583–1587
26. Weycker D, Macarios D, Edelsberg J, Oster G (2007) Compliance with osteoporosis drug therapy and risk of fracture. Osteoporos Int 18:271–277
27. Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ (2007) Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc 82:1493–1501
28. Arden NK, Earl S, Fisher DJ, Cooper C, Carruthers S, Goater M (2006) Persistence with teriparatide in patients with osteoporosis: the UK experience. Osteoporos Int 17:1626–1629
29. Briot K, Ravaud P, Dargent-Molina P, Zylberman M, Liu-Leage S, Roux C (2009) Persistence with teriparatide in postmenopausal osteoporosis; impact of a patient education and follow-up program: the French experience. Osteoporos Int 20:625–630
30. Adachi JD, Hanley DA, Lorraine JK, Yu M (2007) Assessing compliance, acceptance, and tolerability of teriparatide in patients with osteoporosis who fractured while on antiresorptive treatment or were intolerant to previous antiresorptive treatment: an 18-month, multicenter, open-label, prospective study. Clin Ther 29:2055–2069
31. McCombs J, Thiebaud P, McLaughlin-Miley C, Shi J (2004) Compliance with drug therapies for the treatment and prevention of osteoporosis. Maturitas 48:271–287
32. Weycker D, Macarios D, Edelsberg J, Oster G (2006) Compliance with drug therapy for postmenopausal osteoporosis. Osteoporos Int 17:1645–1652
33. Genant HK, Halse J, Briney WG, Xie L, Glass EV, Krege JH (2005) The effects of teriparatide on the incidence of back pain in postmenopausal women with osteoporosis. Curr Med Res Opin 21:1027–1034
34. Ljunggren Ö, Fahrleitner-Pammer A, Kutahov A, Walsh JB, Langdahl B, Jakob F, Lems W, Rajzbaum G, Barker C, Karras D, Marin F (2008) Back pain is reduced in postmenopausal women with severe osteoporosis treated with rhPTH(1–34) (teriparatide) regardless of incident fractures: 18-month results from the European Forsteo Observational Study (EFOS). J Bone Miner Res 23:S347
35. Langdahl B, Ljunggren Ö, Lems W, Walsh JB, Barker C, Fahrleitner-Pammer A, Karras D, Rajzbaum G, Jakob F, Kutahov A, Marin F (2008) Women with severe osteoporosis treated with rhPTH(1–34) (teriparatide) improve quality of life regardless of incident fractures: 18-month results from the European Forsteo Observational Study (EFOS). J Bone Miner Res 23:S347
36. Nevitt MC, Chen P, Kiel DP, Reginster JY, Dore RK, Zanchetta JR, Glass EV, Krege JH (2006) Reduction in the risk of developing back pain persists at least 30 months after discontinuation of teriparatide treatment: a meta-analysis. Osteoporos Int 17:1630–1637
37. Nevitt MC, Chen P, Dore RK, Reginster JY, Kiel DP, Zanchetta JR, Glass EV, Krege JH (2006) Reduced risk of back pain following teriparatide treatment: a meta-analysis. Osteoporos Int 17:273–280
38. van Schoor NM, Smit JH, Twisk JWR, Lips P (2005) Impact of vertebral deformities, osteoarthritis, and other chronic diseases on quality of life: a population-based study. Osteoporos Int 16:749–756
39. Oglesby AK, Minshall ME, Shen W, Xie S, Silverman SL (2003) The impact of incident vertebral and nonvertebral fragility fractures on health-related quality of life in established postmenopausal osteoporosis: results from the teriparatide randomized, placebo-controlled trial in postmenopausal women. J Rheumatol 30:1579–1583
40. Salaffi F, Cimmino MA, Malavolta N, Carotti M, Di Matteo L, Scendoni P, Grassi W, Italian Multicentre Osteoporotic Fracture Study Group (2007) The burden of prevalent fractures on health-related quality of life in postmenopausal women with osteoporosis: the IMOF study. J Rheumatol 34:1551–1560
41. Wardlaw D, Cummings SR, van Meirhaeghe J, Bastian L, Tillman TB, Ranstam J, Eastell R, Shabe P, Talmadge K, Boonen S (2009) Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet 373:1016–1024