Osteoporos Int
DOI 10.1007/s00198-011-1856-y

ORIGINAL ARTICLE

The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures

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Received: 1 August 2011 / Accepted: 4 November 2011

Abstract
Summary The effect of teriparatide and risedronate on back pain was tested, and there was no difference in the proportion of patients experiencing a reduction in back pain between groups after 6 or 18 months. Patients receiving teriparatide had greater increases in bone mineral density and had fewer vertebral fractures.
Introduction This study aimed to understand the effect of teriparatide in reducing back pain in patients with prevalent back pain and vertebral fracture compared to risedronate.
Methods In an 18-month randomized, double-blind, double-dummy trial, we investigated the effects of teriparatide (20 μg/day) vs. risedronate (35 mg/week) in postmenopausal women with back pain likely due to vertebral fracture. The primary objective was to compare the proportion of subjects reporting ≥30% reduction in worst back pain severity from baseline to 6 months as assessed by a numeric rating scale in each treatment group. Pre-specified secondary and exploratory outcomes included assessments of average and worst back pain at additional time points, disability and

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Published online: 13 December 2011

quality of life, bone mineral density, incidence of fractures, and safety.

Results At 6 months, 59% of teriparatide and 57% of risedronate patients reported ≥30% reduction in worst back pain and there were no differences between groups in the proportion of patients experiencing reduction in worst or average back pain at any time point, disability, or quality of life. There was a greater increase from baseline in bone mineral density at the lumbar spine (p=0.001) and femoral neck (p=0.02) with teriparatide compared to risedronate and a lower incidence of vertebral fractures at 18 months (4% teriparatide and 9% risedronate; p=0.01). Vertebral fractures were less severe (p=0.04) in the teriparatide group. There was no difference in the overall incidence of adverse events.

Conclusions Although there were no differences in back pain-related endpoints, patients receiving teriparatide had greater skeletal benefit than those receiving risedronate.

Keywords Back pain · Bisphosphonate · Osteoporosis · Teriparatide · Vertebral fracture

Introduction

Osteoporosis is a worldwide disease associated with decreased bone strength and quality and an increased risk for fracture. Vertebral fracture, the most common type of osteoporotic fracture, may result in acute back pain, which often resolves, or chronic back pain [1–6]. The disability and chronic back pain associated with vertebral fractures ultimately contribute to functional limitations and a decreased quality of life in these patients. Treatments for back pain include analgesics and invasive surgeries, but these do not treat the underlying condition. Osteoporosis medications improve bone strength and prevent new fractures, but whether these treatments may also be effective for treating chronic back pain caused by vertebral fractures is not clear.

Teriparatide is an anabolic therapy for osteoporosis which increases bone formation, improves bone quality, and reduces the risk of vertebral and nonvertebral fractures [7]. In two separate prospective non-controlled clinical trials [6, 8], patients treated with teriparatide with prevalent vertebral fractures and preexisting back pain at baseline had significant reductions in back pain after 6 months of teriparatide treatment and this effect was sustained through 24 months of treatment [8] or 18 months of treatment and 18 months of follow-up [9]. In this active-controlled phase 3 trial, we tested the hypothesis that in postmenopausal women with back pain thought to be due to vertebral fracture, teriparatide treatment will result in a greater reduction of back pain than treatment with the bisphosphonate risedronate.

Methods

Study design and patients

This was an 18-month, randomized, parallel, double-blind, double-dummy, active-controlled trial comparing the effects of teriparatide (Forteo®, Eli Lilly and Co.) to risedronate (Actonel®, Warner Chilcott and Sanofi-aventis) in women with chronic back pain associated with osteoporotic vertebral fractures. The primary objective was to compare the efficacy of these two drugs based on the proportion of women who reported ≥30% reduction in the severity of back pain as assessed by an 11-point numeric rating scale (0=no pain; 10=severe pain) from baseline to 6 months of therapy [10].

Women ≥45 years of age and at least 2 years postmenopausal were eligible if they had a history of back pain for ≥2 months before screening that was likely, in the opinion of the investigator, to be caused by osteoporotic vertebral fracture, despite conservative analgesic treatment; a baseline mean pain score of at least 4.0 on the numeric rating scale during the week before randomization; lumbar spine, femoral neck, or total hip bone mineral density (BMD) T-score of ≤−2; and a minimum of one moderate vertebral fracture. Exclusion criteria included diseases affecting bone metabolism other than osteoporosis; elevated serum calcium values, abnormal serum thyroid-stimulating hormone, parathyroid hormone, or 25-hydroxyvitamin D levels; imminent need for kyphoplasty or vertebroplasty; and evidence of significant pathology related to back pain which would make the interpretation of the back pain related to an osteoporotic vertebral fracture difficult, based on investigator assessment. Investigators were trained by two of the coauthors (FEM and JHK) prior to participation in the study on the characteristics of vertebral fracture pain and how to distinguish such pain from other sources based on onset, location, intensity, change with position, and physical findings. Prior osteoporosis therapy other than parathyroid hormone (PTH), teriparatide, other PTH analogues, strontium, or fluoride was allowed and was stopped after written consent was obtained.

Subjects were randomly assigned to receive daily teriparatide 20 μg subcutaneous (SQ) injections plus placebo tablet orally once weekly or daily placebo SQ injections plus risedronate 35 mg orally once weekly. A placebo control arm was considered unethical in a population at high risk for fracture. Risedronate is an approved treatment for osteoporosis, and there is no conclusive evidence it has an effect on back pain. Women received approximately 1,000 mg/day elemental calcium and 800 IU/day vitamin D supplements at screening and throughout the study. Conservative concomitant analgesics were allowed.

The study protocol was approved by the investigational review board at each study center. All patients provided written informed consent. The study was designed jointly by representatives of the sponsor and the investigators. Data were collected and analyzed by the sponsor. The primary data were reviewed by the investigators. All authors contributed to the interpretation and vouch for the accuracy and completeness of the data. Authors from the sponsor and the principal investigator wrote the first draft of the manuscript with medical writing support paid for by the sponsor. The manuscript was reviewed and approved by all authors.

Endpoints

Back pain severity was assessed using the numeric rating scale to rate the *worst* and *average* back pain experienced in the preceding 24 h, completed daily in a diary by subjects during the week prior to each scheduled study visit at baseline, 1, 2, 3, 4, 5, 6, 9, 12, 15, and 18 months. The primary endpoint was the proportion of patients experiencing ≥30% reduction in worst back pain at 6 months. A 30% reduction in pain is considered a clinically meaningful change [10–12]. Pre-specified secondary objectives included comparisons between treatment groups on the proportion of patients experiencing ≥30% reduction in average back pain at 6 months and ≥30% reduction of worst and average back pain at 12 and 18 months and mean change in disability as assessed by the Roland Disability Questionnaire and mean change in quality of life as assessed by Quality of Life Questionaire of the European Foundation for Osteoporosis [13, 14]. Exploratory endpoints included incidence and severity of new and new or worsening vertebral fractures from baseline to 6 and 18 months with spine radiographs assessed by a central reader (BioClinica; Newton, PA) blinded to treatment assignment using semiquantitative analysis [15]; osteoporotic nonvertebral fractures assessed by the investigator; and change in BMD measured from locally read dual X-ray absorptiometry (DXA) during the 6 months prior to enrollment to 18 months. Investigators were trained prior to participation in the study on X-ray and DXA techniques. A minimum of two evaluable vertebrae were required for lateral spine DXA measurements. Measurements made on Hologic (Hologic Inc., Bedford, MA) or GE Lunar (GE Medical Systems, Waukesha, WI) equipment were standardized based on accepted conversion formulas [15, 16]. Additional exploratory endpoints included subgroup analyses for the primary 6-month endpoint; assessments of the severity of reported back pain after this primary endpoint; Timed Loaded Standing Test, a measure of combined trunk and arm endurance [17]; days of disability and bed rest due to back pain [1]; and concomitant analgesic use measured using both a four-point scale and the Medication Quantification Scale (MQS) [18].

Data on adverse events (AEs) occurring or worsening after administration of the first dose of a study drug were collected throughout the study. AEs were coded with the use of the Medical Dictionary for Regulatory Activities, version 9.1. Chemistries were monitored and all serum calcium measurements were drawn at least 12 h after administration of study drug. Height was measured without shoes and no specific measuring device was required.

Statistical analysis

The study had a power of approximately 90% to detect a statistically significant difference between groups in the primary endpoint with a significance level of 0.05, assuming a 39% response rate in the teriparatide group based on data from an uncontrolled observational study [8, 19], 25% reduction in the risedronate group due to placebo effect or unknown effects of risedronate, 10% discontinuation rate at 2 months and 15% at 6 months, and 5% of patients without a baseline vertebral fracture. Analyses were conducted on data from patients who received at least one dose of study drug. All tests were conducted at a two-sided alpha level of 0.05. Baseline measurements were observations made at or before the randomization visit. Subjects who discontinued before 18 months and had a minimum of one post-randomization observation had their last-observation-carried-forward added to the 6-month or 18-month endpoint analyses. Visit-wise analyses were performed using mixed-effect model repeated measure model.

Treatment group comparisons for the proportion of subjects with pain reduction were analyzed using Pearson's chi-squared test. Kaplan–Meier survival curves for the time-to-first occurrence of a ≥30% back pain reduction between baseline and 18 months were compared using the log-rank test and Wilcoxon test.

The treatment group comparison for mean change from baseline to the 18-month endpoint in BMD, total score for disability and quality of life, time of the Timed Loaded Standing Test, and days of disability and days of bed rest due to back pain were analyzed using an analysis of covariance model including only patients with baseline and endpoint measurements. Comparison of concomitant analgesic use was analyzed using Fisher's exact test including only patients with baseline and endpoint measurements. Comparisons for AEs and fracture endpoints were analyzed using Fisher's exact test including all patients receiving at least one dose of study drug.

The study had a data lock at 12 months for analysis of the 6-month primary endpoint and a final data lock at 18 months.

After the 12-month data lock, the investigators were only given high-level conclusions without specifics, and the study remained blinded until completion.

Results

Study participants

Figure 1 summarizes the patient flow through the study. A total of 1,611 women were screened, 712 underwent randomization and 710 began treatment (360 received teriparatide; 350 received risedronate) at 78 clinical sites in 12 countries. At 18 months, 182 (25.6%) subjects had discontinued and 54 (7.6%) of these subjects discontinued due to an AE, with no significant differences between treatment groups. Baseline characteristics were similar between the treatment groups, with the exception of a small but statistically significant difference in height and femoral neck BMD (Table 1). Bisphosphonates were the most commonly used prior to osteoporosis therapy. At baseline, the median duration of back pain was 242 and 208 days for the risedronate and teriparatide groups, respectively. Subjects rated their worst and average back pain as 6.9±1.6 and 5.4±1.9, respectively, on the 11-point scale. Approximately two thirds of the subjects had two or more vertebral fractures, and approximately 85% of these fractures had a severity rating of moderate to severe.

Back pain and related endpoints

There were no significant differences between treatment groups at 6, 12, or 18 months in the proportion of subjects with a ≥30% reduction in worst or average back pain severity response rates (Table 2). There were no treatment group differences in the Kaplan–Meier survival curves for time-to-first ≥30% reduction in back pain (worst, $p=0.45$; average, $p=0.35$). There were also no differences in disability score, quality of life, analgesic use (both four-point and MQS scales), Timed Loaded Standing Test, days of disability due to back pain, and days of bed rest due to back pain. There were 182 patients who had back pain of ≤6 months duration, and in these patients, there was no difference in the reduction of worst back pain at 6 months ($p=0.97$).

Between 6 and 12 months, significantly more patients in the risedronate group compared with the teriparatide group reported a worsening (increase ≥1 unit on the numeric rating scale) of worst back pain ($p=0.04$). Between 6 and 18 months, significantly more patients in the risedronate group compared to the teriparatide group reported a worsening of average back pain ($p=0.04$; Table 2).

Bone density and fractures

At 18 months, patients in the teriparatide group had a greater mean ± SE increase in BMD at the lumbar spine (7.8±0.5% vs. 2.63±0.5%, $p<0.001$) and at the femoral neck (2.11±0.4% vs. 0.77±0.4%, $p=0.02$). Increases at the total hip in the teriparitide and risedronate groups, respectively, were 2.05±0.4% vs. 0.83±0.5%, $p=0.054$ (Fig. 2).

In the teriparatide group, there were significantly fewer subjects with ≥1 new radiographic vertebral fractures ($p=0.01$) or ≥1 new or worsening vertebral fractures ($p<0.05$; Table 3) at 18 months. Among patients with new vertebral fractures, subjects treated with teriparatide had overall less severe new fractures compared to risedronate ($p=0.04$, Table 3). Subjects in the teriparatide group had significantly less height loss compared to the risedronate group (0.44 cm vs. 0.70 cm, $p<0.05$) at 18 months. There was no difference between groups in the incidence of non-vertebral fractures (Table 3). There were 16 subjects with at least one new vertebral fracture after 6 months documented by spinal radiograph at 18 months: one subject in the teriparatide group for whom worst and average back pain did not worsen and 15 subjects in the risedronate group for whom worst back pain worsened in eight and the average back pain worsened in ten at 18 months.

Safety

There were no statistically significant differences between groups in the overall incidence of serious AEs (SAEs), treatment emergent AEs (TEAEs), or AEs leading to discontinuation (Table 4). The only individual SAEs with an incidence significantly different were cardiac, respiratory, thoracic, and mediastinal disorders, all more frequent in the risedronate group. There were nine deaths in the study (four in the teriparatide group and five in the risedronate group, Table 4), and none of the deaths were considered to be related to the study drug, the device, or the protocol procedures.

For non-serious AEs, subjects in the teriparatide group had significantly greater numbers of TEAEs for skin injuries not elsewhere classified (NEC), hypokalemia, muscle-related signs and symptoms NEC, and muscle spasms. All events of hypokalemia were not serious, and no subjects discontinued because of these events. Scheduled laboratory results for potassium were comparable between the two treatment arms. Subjects in the risedronate group had significantly greater numbers of TEAEs compared to teriparatide for dental and periodontal infections and inflammations, vomiting, spinal fractures and dislocations, respiratory, thoracic, and mediastinal disorders, and muscular weakness.

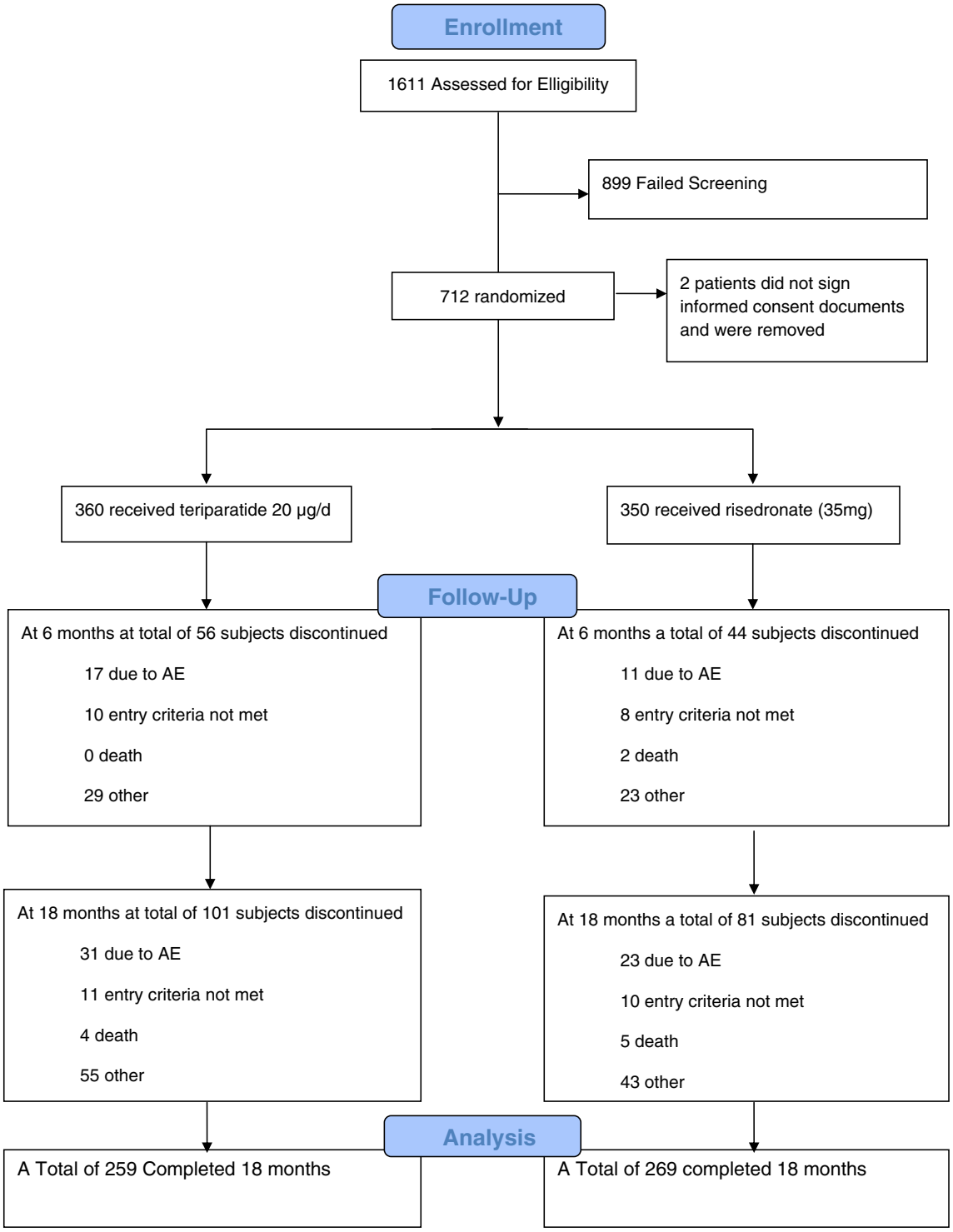

Fig. 1 Patient flow through the study

The number of subjects with hypercalcemia [any post-baseline serum calcium >11.0 mg/dL (2.76 mmol/L)] was significantly greater in the teriparatide group (3.6% vs. 0.6%, p=0.007). There was a small decrease in mean serum magnesium levels from baseline to endpoint in the teriparatide group compared to the risedronate group. There was no significant increase in the TEAE of hypomagnesemia (teriparatide 2, risedronate 0).

Table 1 Baseline demographics and characteristics

	Risedronate 35 mg/week (*N*=350)	Teriparatide 20 μg/day (*N*=360)
Age, years (mean ± SD)	71.6±8.1	70.5±8.8
Origin, no. (%)		
Caucasian	286 (81.7)	285 (79.2)
East Asian	0 (0.0)	3 (0.8)
Hispanic	61 (17.4)	67 (18.6)
Native American	0 (0.0)	3 (0.8)
African descent	3 (0.9)	2 (0.6)
Height, cm (mean ± SD)	153.6±7.9	154.8±7.4*
Body mass index (mean ± SD)[a]	26.4±4.9	26.3±5.0
Worst back pain score (mean ± SD)	6.9±1.5	6.8±1.6
Average back pain score (mean ± SD)	5.4±1.9	5.3±1.9
Duration of back pain[b], days [median, (Q1, Q3[c])]	242 (127, 565)	208 (117, 584)
Prior osteoporosis therapy, no. (%)	258 (73.7)	267 (74.2)
Duration of prior osteoporosis therapy, years (mean ± SD)[d]	3.2±3.5	2.9±3.3
Analgesic use, no. (%)		
No. of patients	325	336
Narcotic	61 (18.8)	63 (18.8)
Anti-inflammatory	204 (62.8)	219 (65.2)
Other	24 (7.4)	11 (3.3)
No analgesic	36 (11.1)	43 (12.8)
Vertebral fractures, radiographically confirmed, no. (%)[e, f]		
0	35 (10.0)	37 (10.3)
1	104 (29.7)	126 (35.0)
≥2	211 (60.3)	197 (54.7)
Severity of vertebral fractures[e, f]		
No. of patients	343	352
Zero or mild	46 (13.4)	50 (14.2)
Moderate	166 (48.4)	160 (45.5)
Severe	131 (38.2)	142 (40.3)
Spinal deformity index, no. (%)[e, f, g]		
No. of patients	343	352
0	28 (8.2)	29 (8.2)
1	16 (4.7)	11 (3.1)
2	67 (19.5)	76 (21.6)
≥3	232 (67.6)	236 (67.0)
Bone mineral density T-Score		
No. of patients	346	359
Lumbar spine (mean ± SD)	−2.67±1.20	−2.64±1.11
No. of patients	338	351
Femoral neck (mean ± SD)	−2.44±0.67	−2.32±0.75*
No. of patients	327	342
Total hip (mean ± SD)	−2.15±0.87	−2.11±0.89

No. of patients = number of intent to treat (ITT) subjects in each treatment group for whom data were available; origin was self-reported

*p value of <0.05 between treatment groups

[a]Body mass index is the weight in kilograms divided by the square of the height in meters

[b]Duration is calculated from the onset date to the date of randomization

[c]Q1 is the first quartile and Q3 is the third quartile

[d]Data available from 257 patients in the risedronate and 266 patients in the teriparatide group

[e]Fractures were assessed using semiquantitative analysis. In the risedronate and teriparatide groups, acceptable radiographs of the spine were obtained for 343 and 352 patients at baseline

[f]Although ≥1 moderate vertebral fracture was an inclusion criterion, the original protocol allowed local reading of spine films and some vertebral fracture assessments were not confirmed by the central reader. Thirty-five patients in the risedronate group and 37 patients in the teriparatide group did not have confirmed vertebral fractures at baseline. A protocol amendment was then instituted which required central reading confirmation of vertebral fracture status before randomization. A per protocol analysis excluding patients with such major protocol violations demonstrated similar results as the primary analysis

[g]Spinal deformity index is an integrated measure of the number and severity of the spine fracture burden calculated by summing the semiquantitative scores of T4–L4

Discussion

In both the teriparatide and risedronate groups, the proportion of patients with a reduction in prevalent back pain was high, and there was no difference between treatment groups in the primary endpoint, the proportion of patients experiencing ≥30% reduction in worst back pain after 6 months. In addition, no significant treatment group differences were

Table 2 Worst and average back pain reduction

	Risedronate 35 mg/week (N=350) no. (%)			Teriparatide 20 μg/day (N=360) no. (%)		
Time point (months)	6	12	18	6	12	18
No. of patients	336	336	349	348	348	360
Patients with ≥30% reduction in worst back pain	193 (57.4)	220 (65.5)	234 (67.0)	206 (59.2), p=0.64	233 (67.0), p=0.68	248 (68.9), p=0.60
No. of patients	336	336	349	347	347	360
Patients with ≥30% reduction in average back pain	211 (62.8)	238 (70.8)	242 (69.3)	221 (63.7), p=0.81	246 (70.9), p=0.99	260 (72.2), p=0.40
No. of patients		340	340		352	352
Patients with worsening of worst back pain from 6 months to 12 and 18 months		110 (32.4)	91 (26.8)		89 (25.3), p=0.04	74 (21.0), p=0.08
Patients with worsening of average back pain from 6 months to 12 and 18 months		108 (31.8)	104 (30.6)		93 (26.4), p=0.12	83 (23.6), p=0.04

P values are for treatment comparison. No. of patients = number of intent to treat (ITT) subjects in each treatment group who had a baseline and at least one post-baseline measurement. At each time point, missing data were imputed by using the last-observation-carried-forward method

seen for other secondary objectives related to back pain, function, disability, or quality of life.

In the design of this trial, the expected response rate for back pain reduction for teriparatide was derived from a previous teriparatide trial with no control group in which approximately 39% of a subset of patients with prevalent vertebral fractures and moderate–severe back pain reported at least a 30% reduction in back pain over 6 months [8, 19] (data on file Eli Lilly and Company). Risedronate was the selected comparator because it is an approved treatment for osteoporosis and was assumed to be neutral with regard to effects on chronic back pain. Because of a possible placebo effect and unknown effects of risedronate on back pain, it was assumed that 25% of the subjects in the risedronate group would demonstrate ≥30% reduction in back pain. The actual response rates turned out to be higher for both study drugs (~60% at 6 months, Table 2). In a recent trial on the effects of vertebroplasty on back pain [20], the clinically meaningful response rate (≥30% reduction in pain) in the control arm (receiving a sham surgery) was approximately 50% only 1 month after surgery.

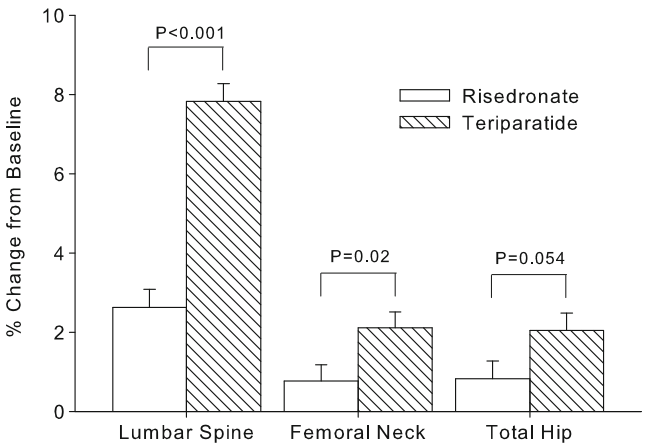

Fig. 2 LS Mean (SE) percent changes from baseline in bone mineral density (BMD) at 18 months

To increase the likelihood that subjects were enrolled with back pain due to vertebral fracture, patients with at least one moderate or severe vertebral fracture (confirmed by a central reader) thought to be the cause of back pain by the investigator were included and those having other significant pathology related to back pain were excluded. However, the reported median duration of prevalent back pain at baseline was approximately 8 months in the risedronate group and 7 months in the teriparatide group, suggesting that patients with chronic back pain due to causes other than vertebral fracture may have been included. This may reflect the challenges clinicians have in distinguishing back pain associated with vertebral fractures from back pain of other etiologies such as post-fracture postural fatiguing. However, in a subgroup analysis, patients with prevalent back pain of less than 6 months duration responded similarly to those with longer duration of pain. Analgesic use may have also confounded the assessment of back pain. Although no differences in analgesic usage were observed, the detriment and relative dosing scoring for the MQS includes subjective assessments, and between group differences may not be captured [18].

Consistent with previous studies comparing the effects of teriparatide with alendronate in postmenopausal women with osteoporosis [21] and in men and women with glucocorticoid-induced osteoporosis [22, 23], treatment

Table 3 Fracture endpoints

	Risedronate 35 mg/week (*N*=350) no. (%)	Teriparatide 20 μg/day (*N*=360) no. (%)	*p* value
Vertebral Fractures, radiographicallly confirmed[a]			
Patients with ≥1 new vertebral fractures at 6 months	18 (5.1)	15 (4.2)	0.6
Patients with ≥1 new or worsening vertebral fractures at 6 months	22 (6.3)	23 (6.4)	1
Patients with ≥1 new vertebral fractures at 18 months	33 (9.4)	16 (4.4)	0.01
Mild	6 (18.2)	8 (50)	0.04[b]
Moderate	17 (51.5)	7 (44)*	
Severe	10 (30.3)	1 (6)*	
Patients with ≥1 new or worsening vertebral fractures at 18 months	39 (11.1)	24 (6.7)	<0.05
Nonverterbral fractures			
Patients with ≥1 new nonvertebral fracture at 18 months	29 (8.3)	28 (7.8)	0.89
Wrist	2 (0.6)	4 (1.1)	0.69
Rib	8 (2.3)	8 (2.2)	1
Hip	2 (0.6)	5 (1.4)	0.45
Ankle/foot	1 (0.3)	3 (0.8)	0.62
Humerus	5 (1.4)	4 (1.1)	0.75
Pelvis	3 (0.9)	2 (0.6)	0.68
Other	13 (3.7)	5 (1.4)	0.06

*$p<0.01$ Fisher's Exact test for between treatment differences calculated separately for incidence of mild, moderate, and severe vertebral fracture incidence (post hoc analysis)

[a] In the risedronate and teriparatide groups, there were 305 and 310 patients through 6 months and 309 and 317 patients through 18 months who had an acceptable baseline and at least one post-baseline radiograph, respectively. Among these patients, missing data for new vertebral fractures were inputed using the last-observation-carried-forward method

[b] *p* value from two-sided Fisher's exact test for overall comparison between groups. For patients experiencing multiple fractures, only the most severe fracture is reported

Table 4 Adverse events at 18 months

	Risedronate 35 mg/week (*N*=350) no. (%)	Teriparatide 20 μg/day (*N*=360) no. (%)	*p* value
Serious adverse events (SAEs)	65 (18.6)	55 (15.3)	0.27
Deaths	5 (1.4)	4 (1.1)	0.75
Treatment emergent adverse events (TEAEs)	285 (81.4)	285 (79.2)	0.45
Discontinuation due to adverse event	28 (8.0)	35 (9.7)	0.43
SAEs significantly different between groups			
Cardiac disorders (HLT)	9 (2.6)	2 (0.6)	0.04
Respiratory, thoracic, and mediastinal disorders (SOC)	9 (2.6)	2 (0.6)	0.04
TEAEs significantly different between groups			
Metabolism and nutrition disorders (SOC)	21 (6.0)	38 (10.6)	0.03
Hypokalemia (PT)	1 (0.3)	8 (2.2)	0.04
Skin injury NEC (HLT)	7 (2.0)	19 (5.3)	0.03
Muscle spasm (PT)	15 (4.3)	32 (8.9)	0.02
Muscle weakness (PT)	5 (1.4)	0	0.03
Respiratory, thoracic, and mediastinal disorders (SOC)	56 (16)	27 (7.5)	<0.001
Asthma (PT)	10 (2.9)	2 (0.6)	0.02
Spinal fractures and dislocation (HLT)	17 (4.9)	5 (1.4)	0.01
Vomiting (PT)	21 (6.0)	9(2.5)	0.03
Dental and periodontal infections and inflammations (HLT)	7 (2.0)	1 (0.3)	0.04

Medical Dictionary for Regulatory Activities version 13.0

SOC System Organ Class, *HLT* high level term, *PT* preferred term

with teriparatide resulted in significant increases in BMD at the lumbar spine and femoral neck as well as a reduced risk for vertebral fractures vs. risedronate (Fig. 1). There were no significant differences in the incidence of nonvertebral fractures, although a longer treatment period with teriparatide may have resulted in greater risk reduction [24].

Among subjects with new vertebral fractures, those treated with teriparatide were less likely to have a moderate or severe fracture compared to those treated with risedronate. This is similar to observations made in placebo-controlled trials in which subjects treated with teriparatide had less severe new fractures and a smaller increase in spinal deformity index [7, 25, 26]. This is clinically meaningful because moderate or severe fractures are often associated with outcomes such as height loss and pain [7, 27, 28]. Less height loss was observed in the teriparatide group. After the 6-month primary endpoint, patients in the teriparatide group were less likely to have a worsening in their back pain than patients in the risedronate group. Consistent with AE reporting from previous studies comparing teriparatide to placebo or antiresorptive comparator drugs, teriparatide may have efficacy in preventing new or worsening of back pain, likely due to a reduction in the severity and number of new vertebral fractures [7, 21, 29–32].

There was an increased incidence of muscle spasms and hypercalcemia with teriparatide. These are expected events and are included in the teriparatide label. In the risedronate group, there were a greater number of TEAEs of spine fractures and dislocations which likely represent clinical vertebral fractures and are reflected in the increased incidence of radiographically confirmed vertebral fractures. The lower number of dental and periodontal infections and inflammations in the teriparatide group may reflect its potential clinical benefits in the oral cavity [33].

In conclusion, there were no differences between risedronate and teriparatide in reduction of back pain due to vertebral fractures in postmenopausal women with osteoporosis. Consistent with previous head-to-head studies with alendronate, teriparatide treatment resulted in greater improvements in BMD and a reduced risk for new vertebral fractures compared to risedronate.

Acknowledgments This study was funded by Eli Lilly and Company. We thank Deborah Gold, Li Xie (Lilly employee and stockholder), Fernando Marin (Lilly employee and stockholder), and Donato Agnusdei (Lilly employee and stockholder) for their contributions to the study design; Sandra Walker (Lilly employee and stockholder), Erin Strouse (Lilly employee and stockholder), Valerie Ruff (Lilly employee and stockholder), Ewa Rogos (Lilly employee and stockholder), Beatriz Sans (Lilly employee and stockholder), Nadine Baker (Lilly employee and stockholder), and Joanne Lorraine (Lilly employee and stockholder) for their efforts in study management; and Mark Rohe (Lilly employee and stockholder), Hassan Jamal (Lilly employee and stockholder), David Shrom (Lilly employee and stockholder), and Gail Dalsky (Lilly employee and stockholder) for their technical assistance and writing support.

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Conflicts of interest P. Hadji was a recipient of a grant/research support from Eli Lilly and Company, Procter & Gamble; speakers bureau with Eli Lilly and Company (Lilly) and Procter & Gamble; advisory board membership of Lilly and Procter & Gamble; consulting fees from Lilly and Procter & Gamble; lecture fees from Lilly and Procter & Gamble; and speaker fees from Lilly and Procter & Gamble.

J. Zanchetta received an advisory board membership of Lilly, Amgen, GlaxoSmithKline, Merck, Pfizer, and Servier and consulting fees from Lilly, Amgen, GlaxoSmithKline, Merck, Pfizer, and Servier.

C. Recknor received an advisory board membership of Lilly, Zelos, Takeda, and Novartis; consulting fees from Lilly, Zelos, Takeda, and Novartis; and lecture fees from Amgen and Novartis.

K. Saag was a recipient of a grant/research support from Lilly, Novartis, GlaxoSmithKline, Sanofi Aventis, and Procter & Gamble; speakers bureau with Novartis; and consulting fees from Lilly, Novartis, Merck, Procter & Gamble, Aventis, and Amgen.

F. McKiernan received consulting fees from Lilly and Amgen.

S. Silverman was a recipient of a grant/research support from Alliance for Better Bone Health, Lilly, Pfizer; speakers bureau with Amgen, Lilly, Pfizer, and Roche Pharmaceuticals; consulting fees from Amgen, Lilly, Novartis, Pfizer, Roche Pharmaceuticals, Roche Diagnostics, and Warner Chilcott.

J. Alam, R. Burge, J. Krege, M. Lakshmanan, D. Masica, B. Mitlak, and J. Stock were shareholders and employees of Lilly.

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