Sustained Vertebral Fracture Risk Reduction After Withdrawal of Teriparatide in Postmenopausal Women With Osteoporosis

Robert Lindsay, MBChB, PhD; Wim H. Scheele, MD; Robert Neer, MD; Gerhardt Pohl, PhD; Silvano Adami, MD; Carlos Mautalen, MD; Jean-Yves Reginster, MD, PhD; Jan J. Stepan, MD, DSc; Stephen L. Myers, MD; Bruce H. Mitlak, MD

Background: Teriparatide (recombinant human parathyroid hormone [1-34]) reduces fracture risk in postmenopausal women with osteoporosis. We assessed the safety and incidence of new vertebral fractures after withdrawal of teriparatide.

Methods: This study is a follow-up to the Fracture Prevention Trial (FPT), a randomized, placebo-controlled study of postmenopausal women with osteoporosis treated with teriparatide (20 or 40 µg) once daily for a mean of 18 months. More than 90% of the women remaining at the end of the FPT continued into the follow-up study (n=1262). Patients and investigators were unblinded to original treatment group assignment. Women were treated according to standard clinical practice, including elective use of osteoporosis drugs. New vertebral fractures were determined by semiquantitative scoring of lateral thoracic lumbar spine radiographs 18 months after the end of the FPT.

Results: During the follow-up study, the reduction in fracture risk associated with previous treatment with teriparatide, 20 and 40 µg, was 41% (P=.004) and 45% (P=.001), respectively, vs placebo. The absolute reduction from the FPT baseline to the 18-month follow-up visit was 13% for both doses. Osteoporosis drugs were used by 47% of women during follow-up, with greater use in the former placebo group (P=.04); nevertheless, persistent fracture protection of previous teriparatide therapy was evident. Post hoc analysis also suggests that teriparatide treatment substantially reduced the increased risk of subsequent fracture in women who sustained a fracture during the FPT (P=.05).

Conclusion: Vertebral fracture risk reduction by teriparatide administration persists for at least 18 months after discontinuation of therapy.
METHODS

THE FPT

All of the women in this follow-up study had participated in the FPT, a randomized, placebo-controlled trial of teriparatide that took place at 99 medical centers in 17 countries. Briefly, patients were randomly assigned to receive placebo or 20 or 40 µg of teriparatide by daily self-injection (Eli Lilly and Co). Patients also received supplemental calcium carbonate (1000 mg) and cholecalciferol (400-1200 IU) daily. Women were eligible for enrollment in the FPT if they were ambulatory, were at least 5 years postmenopausal, and had at least 1 moderate or 2 mild atraumatic vertebral fractures on radiographs of the thoracic or lumbar spine. The primary end point of the FPT was the incidence of new vertebral fractures. Eligibility criteria and further baseline clinical and demographic information are included in the primary report of that trial.  

FOLLOW-UP TO THE FPT

This study was initiated after early termination of the FPT. All women from the FPT were eligible for enrollment in the follow-up study, which was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983. Ethical review boards at each medical center approved the study; patients gave written informed consent for participation. Participants in the FPT were invited to return for a first follow-up study visit that occurred a median of 6 months (interquartile range, 5-7 months) after the closeout visit of the original trial and for a second visit 12 months later, a median of 18 months (interquartile range, 17-19 months) after the end of the trial. Shortly after the 6-month visit, patients and investigators were no longer masked to the treatment previously received during the FPT. During the follow-up study, patients were treated by their personal physicians according to standard clinical practice, including the elective use of any available osteoporosis drug. Calcium and cholecalciferol supplements were used at the discretion of the patient and the physician.

The primary objective of this ongoing study is safety surveillance. At each visit, patients are asked to report adverse events and concomitant medication use. Lateral thoracic lumbar spine radiographs were obtained for the last time at the 18-month visit. The period from the end of the treatment study to the 18-month visit is the basis of the present study. A new vertebral fracture during the follow-up study was one that occurred after the radiograph taken at the closeout visit of the FPT and before the 18-month follow-up visit. Experienced radiologists at a central location (Synarc Inc, San Francisco, Calif), masked to original treatment assignment, graded all vertebrae from T4 through L4 using a semiquantitative method, as described previously. A new vertebral fracture was defined as a deterioration of a normal vertebra from grade 0 to grade 1, 2, or 3; deteriorations to grades 2 and 3 were defined as moderate and severe, respectively. Fractures that occurred during the follow-up study in women who experienced a fracture during the original clinical trial were defined as subsequent fractures if they involved a normal vertebra, not worsening of an existing fracture.

Bone mineral density was measured at the 6- and 18-month follow-up study visits by dual-energy x-ray absorptiometry using various densitometers (DXA; Hologic, Bedford, Mass; GE Lunar, Madison, Wis; and Norland; CooperSurgical Inc, Trumbull, Conn). Data from the different densitometers were converted to standardized units, expressed in grams per square centimeter, and pooled for the analysis. All scans were centrally reviewed and analyzed (Osteoporosis and Arthritis Research Center, University of California San Francisco, and Osteoporosediagnostik, Universitätsklinik CAU Kiel, Kiel, Germany). Vertebrae with fractures or artifacts were excluded from the analysis.

STATISTICAL ANALYSIS

All analyses were conducted according to the original randomized group assignment. Vertebral fracture incidence was analyzed using the Pearson χ² test. Number needed to treat is expressed as the number of patients who must be treated to prevent 1 woman from sustaining 1 or more new vertebral fractures. Odds ratios (ORs) for subsequent fracture in patients who had or had not sustained a fracture during the FPT were compared within treatment groups using a χ² test. Because of the small number of patients who sustained fractures in the teriparatide groups during the FPT, these groups were combined in the analysis of subsequent fractures. For comparisons of ORs between treatments, the Breslow-Day homogeneity test was used. Bone mineral density was analyzed using analysis of variance, including terms for treatment and country. End point BMD data from patients who discontinued before the last visit of the FPT but entered the follow-up study were included by using the last-observation-carried-forward data imputation method. Bone mineral density data during the follow-up study are summarized by observed cases at each visit. In each treatment group, within-patient changes in BMD were tested via paired t tests. The frequency of adverse event reports of new or worsened back pain reported at visits during the follow-up study was compared among groups using the Pearson χ² test.

In post hoc sensitivity analyses, we constructed logistic regression models to adjust factors that might affect the incidence of vertebral fracture during the observational study. The data used to construct the models were from women with either 12 months or more of bisphosphonate use or no use of osteoporosis drugs during the follow-up study. Other osteoporosis drugs were used too infrequently for analysis. The effect of teriparatide treatment was modeled for the combined teriparatide groups vs placebo. All tests were 2-sided, with a significance level of P<.05. The data were analyzed using a statistical software program (MVS SAS V6.09; SAS Institute Inc, Cary, NC). Data are given as mean±SD.

RESULTS

THE FOLLOW-UP STUDY POPULATION

Of 1637 women randomly assigned to receive either teriparatide or placebo in the FPT, 1262 (77%) volunteered for the follow-up study, including more than 90% of all women still participating at the end of the FPT (Figure 1). Participation was more frequent among patients who were participating in the FPT at the time of its termination than among patients who had withdrawn earlier. This resulted in a slightly longer duration of therapy, 19 months, among patients who entered the follow-up study than was seen in the overall FPT population. There were no statistically significant differences in previous exposure to the study drug among the 3 original treatment groups. Women in each of the original treatment groups who entered the follow-up study also had similar baseline clinical and demographic characteristics (Table 1). Compared with women who did not enroll, women who entered were younger (69.2±6.7 vs
70.4 ± 7.7 years; P = .003), were taller (157.4 ± 6.6 vs 156.7 ± 6.3 cm; P = .009), and had a higher body mass index (calculated as weight in kilograms divided by the square of height in meters) (26.8 ± 4.3 vs 26.0 ± 4.7; P = .005). The former teriparatide groups were observed for a slightly longer period during the follow-up study than the former placebo group.

SAFETY

There were no safety concerns during the follow-up study that would suggest latent adverse effects of previous teriparatide treatment or adverse effects related to withdrawal of therapy. There was no increased incidence of carcinoma. In particular, no occurrence of osteosarcoma or primary bone malignancy has been reported in any patient known to have been exposed to teriparatide.

NEW VERTEBRAL FRACTURES

Of the 1262 women who participated in the follow-up study, 1071 had radiographs adequate for evaluation at the end of the FPT and at the 18-month visit of the follow-up study. The proportions of missing radiographs did not differ among the randomized treatment groups. Patients with and without paired radiographs differed only in years past menopause (21 ± 8 vs 23 ± 10 years) and daily dietary calcium intake (783 ± 453 vs 634 ± 385 mg/d) (P < .001 for both). The reason for missing data was either that the radiograph was not performed or that the central quality assurance center deemed the radiograph to be of insufficient quality. Radiographs at the end of participation in the FPT were not available for 48 of the patients who withdrew from the FPT but reenrolled in the follow-up. For the period covering baseline of the FPT to the 18-month visit of the follow-up study, 1098 women had paired radiographs adequate for evaluation.

Despite greater use of osteoporosis drugs during the follow-up study in the original placebo group (P = .04), the antifracture efficacy of teriparatide persisted for 18 months (Figure 2). The relative risk of 1 or more new vertebral fractures during the follow-up study was reduced by 41% in the 20-µg teriparatide group (P = .004) and by 45% in the 40-µg teriparatide group (P = .001). In the placebo group, 19.0% of women had 1 or more new vertebral fractures compared with 11.3% of women in the 20-µg teriparatide group and 10.4% in the 40-µg teriparatide group, resulting in absolute risk reductions of 7.7% and 8.6%, respectively. For the entire period (FPT baseline to the 18-month follow-up study visit), the absolute risk reduction was 12.9% in the 20-µg teriparatide group and 13.5% in the 40-µg teriparatide group, yielding a number needed to treat of 8 patients for both doses.

Efficacy for prevention of moderate- or severe-grade vertebral fractures also persisted for 18 months. The relative risk of 1 or more new moderate or severe vertebral fractures during the follow-up study was reduced by 57% in the 20-µg teriparatide group (P = .003) and by 71% in the 40-µg teriparatide group (P < .001). In the placebo group, 9.9% of women sustained 1 or more new moderate or severe vertebral fractures compared with 4.3% in the 20-µg teriparatide group and 2.9% in the 40-µg teriparatide group, resulting in absolute risk reductions of 5.6% and 7.0%, respectively. For the entire period (FPT baseline to the 18-month follow-up study visit), the absolute risk reduction was 11.0% in the 20-µg teriparatide group and 11.2% in the 40-µg teriparatide group, yielding a number needed to treat of 9 to prevent 1 patient from sustaining 1 or more new moderate or severe vertebral fractures.

The reduction in back pain in the teriparatide groups persisted at the 18-month follow-up visit. New or worsened back pain during this study in excess of that reported at baseline was seen in 82 patients (19.8%) in the placebo group, 61 (14.0%) in the 20-µg teriparatide group, and 53 (12.9%) in the 40-µg teriparatide group (P = .01).

EFFECT OF ADDITIONAL OSTEOPOROSIS DRUG USE DURING THE FOLLOW-UP STUDY

Use of osteoporosis drugs confounded the interpretation of results during the follow-up study. At the 6-month visit, 28% of women reported use of an osteoporosis drug, by the 18-month visit, the proportion had increased to 47% (Table 2). Although more women in the placebo group reported osteoporosis drug use than in the teriparatide groups at the 6- and 18-month visits (P = .048 and P = .04, respectively), the increase in BMD from baseline...
in the teriparatide groups remained statistically significantly greater than the change in the placebo group (Figure 3A). In the subgroup of 549 women who had paired radiographs and who did not report the use of any osteoporosis drugs during the follow-up study, 27 (16.4%) of 165 in the placebo group, 21 (10.3%) of 204 in the 20-µg teriparatide group, and 17 (9.4%) of 180 in the 40-µg teriparatide group experienced 1 or more new vertebral fractures during the follow-up study. This represents a reduction in relative risk of 37% in the 20-µg teriparatide group and 42% in the 40-µg teriparatide group (P=.08) and 42% in the 40-µg teriparatide group (P=.054).

To determine whether the introduction of other osteoporosis drugs during the follow-up study affected vertebral fracture incidence, we conducted a logistic regression analysis that focused on bisphosphonates, the most frequently used osteoporosis drug class during the follow-up study. We further limited our analysis to patients who reported using bisphosphonates for 12 months or longer. Preliminary analyses indicated that this subgroup reflected the effect of bisphosphonates more strongly than subgroups with use for shorter periods (data not shown). The analysis included data from 710 women for whom all radiographs and values for explanatory variables were available. Ninety of the 710 women experienced 1 new vertebral fracture during the follow-up study: 40 (17.6%) of 227 in the placebo group and 50 (10.4%) of 483 in the combined teriparatide group. Bisphosphonates were used for 12 months or longer by 190 of the 710 women. Use was more frequent in women who had previously been treated with placebo vs teriparatide (30.8% vs 24.8%). Demographic factors at baseline of the FPT suggest that women who chose to use bisphosphonates for 12 months or longer during follow-up were potentially at greater risk of vertebral fracture than those who did not use osteoporosis drugs (baseline vertebral T-score: -2.5±1.6 vs -2.3±1.5; P<.001; body mass index: 26.0±4.1 vs 27.3±4.4; P<.001; >1 prevalent vertebral fracture: 65% vs 52%; P=.01; and age: 70.7±6.3 vs 68.8±6.7 years; P=.02). These factors were included in the logistic regression model, as was duration of the follow-up period between radiographs. Overall, women who used bisphosphonates for 12 months or longer maintained BMD gains achieved during treatment to a greater extent than women who used no osteoporosis drugs (Figure 3B and C). However, the logistic regression analysis did not show that bisphosphonate use enhanced the ability of previous teriparatide therapy to prevent vertebral fractures after withdrawal of teriparatide therapy (OR, 0.97; 95% CI, 0.58-1.61; P=.91). Significant predictors

Table 1. Characteristics of Women Enrolled in the Observational Study by Previous Randomized Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (n = 414)</th>
<th>20-µg Teriparatide Group (n = 436)</th>
<th>40-µg Teriparatide Group (n = 412)</th>
<th>P</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline of the Fracture Prevention Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69.0 ± 6.8</td>
<td>69.1 ± 6.7</td>
<td>69.5 ± 6.8</td>
<td>.58</td>
<td></td>
</tr>
<tr>
<td>Years postmenopausal</td>
<td>21 ± 9</td>
<td>21 ± 8</td>
<td>21 ± 8</td>
<td>.81</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>157.5 ± 6.5</td>
<td>157.0 ± 6.7</td>
<td>157.6 ± 6.7</td>
<td>.37</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.3 ± 11.9</td>
<td>66.5 ± 11.2</td>
<td>66.2 ± 11.6</td>
<td>.94</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.8 ± 4.5</td>
<td>27.0 ± 4.2</td>
<td>26.6 ± 4.2</td>
<td>.46</td>
<td></td>
</tr>
<tr>
<td>Baseline lumbar spine BMD, g/cm²</td>
<td>0.82 ± 0.17</td>
<td>0.83 ± 0.17</td>
<td>0.81 ± 0.17</td>
<td>.64</td>
<td></td>
</tr>
<tr>
<td>Baseline vertebral fracture (&gt;1), No. of readable radiographs (%)</td>
<td>395 (61)</td>
<td>420 (58)</td>
<td>400 (58)</td>
<td>.67</td>
<td></td>
</tr>
<tr>
<td>Smoker, %</td>
<td>17</td>
<td>15</td>
<td>16</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Previous osteoporosis drug use, %</td>
<td>14</td>
<td>16</td>
<td>13</td>
<td>.32</td>
<td></td>
</tr>
<tr>
<td>Dietary calcium intake, mg/d</td>
<td>744 ± 431</td>
<td>781 ± 451</td>
<td>782 ± 457</td>
<td>.52</td>
<td></td>
</tr>
<tr>
<td>End Point of the Fracture Prevention Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of therapy, mo</td>
<td>19.1 ± 3.1</td>
<td>18.8 ± 3.5</td>
<td>18.6 ± 3.9</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>157.0 ± 6.6 (n = 413)</td>
<td>156.8 ± 6.7 (n = 435)</td>
<td>157.2 ± 6.6 (n = 409)</td>
<td>.62</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.4 ± 12.0 (n = 414)</td>
<td>66.6 ± 11.5 (n = 436)</td>
<td>66.2 ± 11.6 (n = 411)</td>
<td>.91</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.9 ± 4.7 (n = 413)</td>
<td>27.1 ± 4.4 (n = 435)</td>
<td>26.8 ± 4.4 (n = 408)</td>
<td>.71</td>
<td></td>
</tr>
<tr>
<td>Change in lumbar spine BMD, %</td>
<td>1.1 ± 5.2 (n = 403)</td>
<td>9.4 ± 6.8 (n = 421)</td>
<td>13.4 ± 8.5 (n = 397)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>New vertebral fracture (&gt;1), %</td>
<td>13.8 (52/378)</td>
<td>4.5 (18/400)</td>
<td>4.3 (16/374)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>End of trial to 18-mo visit of observational study, mo</td>
<td>18.4 ± 3.0</td>
<td>18.6 ± 3.6</td>
<td>19.0 ± 4.1</td>
<td>.04</td>
<td></td>
</tr>
</tbody>
</table>
of vertebral fracture during the observational period were randomization to receive teriparatide rather than placebo (OR, 0.52; 95% CI, 0.33-0.83; \(P = .005\)) and baseline vertebral T-score (0.78 per unit increase, 95% CI, 0.66-0.92; \(P = .004\)).

Additional statistical modeling was performed that considered the status of patients at the beginning of the follow-up period. The added factors—new vertebral fracture during the FPT and change in vertebral T-score—were outcomes of treatment during the FPT. New vertebral fractures that occurred during the FPT had been more common among patients who later chose to use bisphosphonates for 12 months or longer: 11.6% of patients vs 4.0% who did not use osteoporosis drugs (\(P = .005\)). Development of 1 or more new vertebral fractures during the FPT was significantly associated with an increased risk of a new vertebral fracture during follow-up (OR, 3.50; 95% CI, 1.71-7.17; \(P < .001\)). An increase in the vertebral T-score by 1 SD during the FPT also tended to reduce risk of fracture during the follow-up study (OR, 0.83; 95% CI, 0.67-1.03; \(P = .10\)). Despite inclusion of these competing factors that were significantly affected by treatment with teriparatide, there remained a trend toward decreased risk of fracture during the follow-up study associated with previous teriparatide therapy (OR, 0.67; 95% CI, 0.41-1.09; \(P = .10\)).

**RISK OF NEW VERTEBRAL FRACTURE IN WOMEN WHO SUSTAINED A FRACTURE DURING THE FPT**

In the original placebo group, additional vertebral fractures occurred during the follow-up study in 44% of women who had fractured a vertebra during the FPT compared with 15% of women who had not (OR, 4.29; \(P = .001\)) (Figure 4). Treatment with teriparatide substantially reduced the increased risk of a subsequent fracture. In women treated with teriparatide, the risk of additional fractures during the follow-up study in women who had fractured a vertebra during the FPT was not significantly different from the risk in women who had not (OR, 1.25; \(P = .69\)). The comparison of the ORs between treatments was significant (\(P = .05\)) (Figure 4).

**COMMENT**

The follow-up study to the FPT allowed us to observe the residual effect of teriparatide after withdrawal of therapy under conditions that approximate a “real-world” setting. We found that the reduction in vertebral fracture risk in patients treated with teriparatide for a mean...
of 19 months persisted for at least an additional 18 months after daily treatment was discontinued. The effect on non-vertebral fracture incidence at the end of the follow-up period will be the subject of a subsequent study.

Women in the 20- and 40-µg teriparatide groups experienced 41% and 45% reductions in relative risk of new vertebral fracture during the follow-up study, respectively, in addition to the 67% and 69% reductions experienced during the FPT. Therefore, the absolute risk reduction continued to improve during the follow-up period. Twenty micrograms of teriparatide daily was as effective as 40 µg in reducing vertebral fracture risk. Statistical analyses found that protection against new vertebral fractures during follow-up was related to previous teriparatide therapy and to the fewer number of vertebral fractures that occurred during the FPT in women treated with teriparatide. The lower risk of new vertebral fractures in the follow-up period may, in part, result from a substantial reduction in the risk of more severe vertebral fractures that could cause greater stresses on adjacent vertebrae (90% relative risk reduction in fractures of moderate or severe grade vs 65% for all vertebral fractures during the FPT). Consistent with the reductions in the incidence and severity of vertebral fractures during the observational study, the reduction in back pain during the FPT in the teriparatide-treated patients was maintained during follow-up.

Although the conduct of the study was observational, the primary comparisons of previous teriparatide treatment with placebo use are based on randomized allocation at the start of the FPT. This is in contrast to typical observational designs, in which the decision to initiate the therapy of interest may be confounded with clinical factors associated with the outcome under study. Most patients remaining in the trial continued into the observational study, preserving the balance in the randomized groups. This balance is evident in the original demographic and clinical characteristics of the patients in the study. Therefore, the primary conclusions of this study have validity as the continuation of a randomized clinical trial rather than a nonrandomized retrospective observational trial.

Use of osteoporosis drugs in the follow-up study was partially confounded with treatment group. Greater use of osteoporosis drugs in the placebo group may have caused us to slightly underestimate the residual effects of teriparatide treatment. Patients remained responsive to antiresorptive therapy after teriparatide use, as demonstrated by the finding that women who used bisphosphonates for 12 months or longer maintained bone density gains achieved during treatment to a greater extent than women who reported no use of osteoporosis drugs. We attempted to control for use of osteoporosis drugs in the logistic regression modeling. The model confirmed the residual effect of teriparatide therapy and demonstrated the relative effect size of several prognostic factors, including BMD and disease severity.

In the logistic regression model, bisphosphonate use for 12 months or longer during the follow-up study added little or nothing to the effect of previous teriparatide treatment on risk of a new vertebral fracture. The model indicated that previous treatment with teriparatide was a statistically significant predictor of reduced vertebral frac-

![Figure 4. Risk of new vertebral fracture during the follow-up study for women who did and did not sustain a fracture during the Fracture Prevention Trial (FPT). Asterisk indicates Breslow-Day test for homogeneity of odds ratios. Teriparatide is a recombinant human parathyroid hormone 1-34.](https://archinte.jamanetwork.com/netcat/doi/10.1001/jamainternmed.2004.357)
sional and 3-dimensional morphometric analyses, Dempster and colleagues described improvements in bone microarchitecture in paired biopsy samples from postmenopausal women and men with osteoporosis treated with human parathyroid hormone (1-34) for 36 and 18 months, respectively. Parathyroid hormone (1-34) treatment increased trabecular connectivity and cortical thickness and eliminated defects in microarchitecture associated with increased skeletal fragility. These improvements might affect fracture risk after withdrawal of parathyroid hormone (1-34) therapy and might partially account for the consistent effects of teriparatide therapy despite varying rates of BMD change during follow-up associated with the use of additional osteoporosis drugs.

To our knowledge, this is the first large osteoporosis study to provide data on vertebral fracture incidence after withdrawal of osteoporosis drug therapy. Despite the limitation of being observational, the results provide information in the setting in which patients may elect to receive additional osteoporosis treatment after discontinuation of teriparatide treatment, based on individual risk factors. A strength of the study is that nearly all of the FPT population remaining at the end of the trial participated in the follow-up assessments, which preserved the original randomization. The large database allowed for exploratory analysis of factors that affected vertebral fracture incidence during the observational study.

The results of this study show that the effect of treatment with teriparatide persists for at least 18 months beyond the end of therapy. Additional randomized controlled trials are needed to verify the extent to which sequential therapy with other agents might further reduce vertebral fracture risk.

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From the Regional Bone Center, Helen Hayes Hospital, West Haverstraw, NY (Dr Lindsay); Lilly Research Laboratories, Eli Lilly and Co, Indianapolis, Ind (Drs Scheele, Pohl, Myers, and Mitlak); Endocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston (Dr Neer); Rheumatologic Unit, University of Verona, Valeggio sul Mincio, Italy (Dr Adami); the División Osteopatías Médicas, Hospital de Clínicas, Universidad de Buenos Aires, Buenos Aires, Argentina (Dr Mautalen); Department of Public Health, University of Liège, Liège, Belgium (Dr Reginster); and Department of Internal Medicine, Charles University, Prague, Czech Republic (Dr Stepan). Dr Scheele is now with the Women's Health and Bone Department, Wyeth Research, Cambridge, Mass.

Dr Lindsay is a consultant for Procter & Gamble, Eli Lilly and Co, Merck & Co Inc, and Wyeth; is a speaker for Aventis Pharmaceuticals Inc, Procter & Gamble, Eli Lilly and Co, and Wyeth; and has received research support from Wyeth and ILEX Oncology Inc. Drs Scheele and Mitlak own stock in Eli Lilly and Co. Dr Neer is a consultant to Eli Lilly and Co and Merck & Co Inc. Dr Reginster is a consultant for or on a paid advisory board for Servier, Novartis, Negma-Lerads, Eli Lilly and Co, Wyeth, Amgen Inc, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS Pharmaceuticals, and Theramex; is a speaker for Merck & Co Inc, Eli Lilly and Co, Rottapharm, IBSA Institut Biochimique, Laboratoires GENEVERIER, Novartis, Servier, Roche, Merckle, Teijin, Normalab Analis, Theramex, Nycomed, and Novo Nordisk; and has received research support from Bristol-Myers Squibb, Fondation Leon Frédéricq (Liège), Standard de Liège, Merck & Co Inc, Novartis, Roche, and GlaxoSmithKline.

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Correspondence: Robert Lindsay, MBChB, PhD, Regional Bone Center, Helen Hayes Hospital, 51-53 North Route 9W, West Haverstraw, NY 10993 (lindsay@helenhayeshosp.org).

Reprints: Bruce Mitlak, MD, Lilly Research Laboratories DC 6134, Eli Lilly and Co, Indianapolis, IN 46285.

REFERENCES