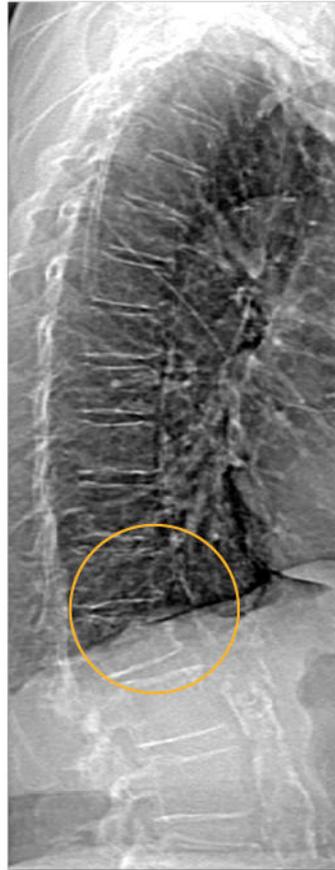


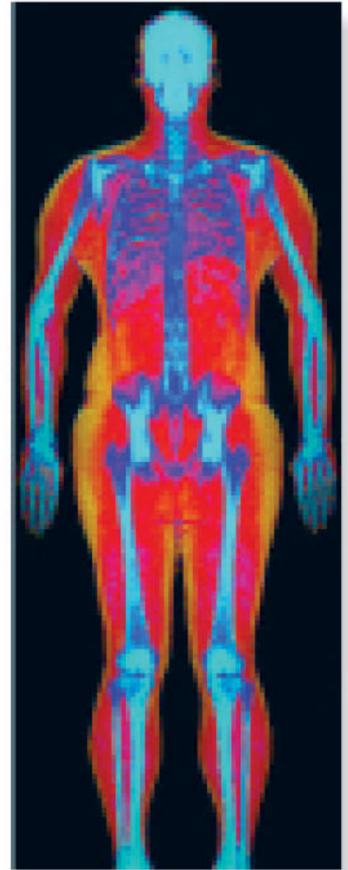
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Effect of Teriparatide or Risedronate in Elderly Patients With a Recent Pertrochanteric Hip Fracture: Final Results of a 78-Week Randomized Clinical Trial

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ABSTRACT

We present final results of a study comparing teriparatide 20 µg every day (QD) with risedronate 35 mg once per week (QW) started within 2 weeks after surgery for a pertrochanteric hip fracture. Patients with BMD *T*-score ≤ -2.0 and 25OHD ≥ 9.2 ng/mL were randomized to receive 26-week double-dummy treatment plus calcium and vitamin D, followed by 52-week open-label treatment with the same assigned active drug. Primary endpoint was change from baseline in lumbar spine (LS) BMD at 78 weeks. Secondary and exploratory endpoints were change in BMD at the proximal femur, function, hip pain (Charnley score and 100 mm Visual Analog Scale [VAS]), quality of life (Short Form-36), radiology outcomes, and safety. Data were analyzed with mixed models for repeated measures (MMRM) and logistic regression. Totally, 224 patients were randomized; 171 (teriparatide: 86) contributed to the efficacy analyses (mean ± SD age: 77 ± 7.7 years, 77% females). Mean baseline LS, femoral neck (FN), and total hip (TH) *T*-scores were -2.16, -2.63, and -2.51, respectively. At 78 weeks, BMD increased significantly more with teriparatide compared to risedronate at the LS (+11.08% versus +6.45%; *p* < 0.001) and FN (+1.96% versus -1.19%; *p* = 0.003), with no significant between-group difference in TH BMD. Timed up-and-go (TUG) test was significantly faster with teriparatide at 6, 12, 18, and 26 weeks (differences: -3.2 to -5.9 s; *p* = 0.045 for overall difference). Hip pain during TUG test by 100 mm VAS was significantly lower with teriparatide at 18 weeks (adjusted difference: -11.3 mm, *p* = 0.033; -10.0 and -9.3 mm at 12 and 26 weeks, respectively; *p* = 0.079 for overall difference). Other secondary and exploratory outcomes were not different. Teriparatide group showed two new hip fractures versus seven with risedronate (*p* = 0.171) and more frequent hypercalcemia and hyperuricemia. In conclusion, 78-week treatment with teriparatide showed significantly greater increases in LS and FN BMD, less pain, and a faster TUG test versus risedronate. © 2016 American Society for Bone and Mineral Research.

KEY WORDS: TERIPARATIDE; BONE MINERAL DENSITY; PERTROCHANTERIC HIP FRACTURE; FRACTURE RECOVERY; BISPHOSPHONATES

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Public clinical trial registration: <http://clinicaltrials.gov/show/NCT00887354>. Comparison of the Effects of Teriparatide With Those of Risedronate on Lumbar Spine BMD (Bone Mineral Density) in Men and Postmenopausal Women With Low Bone Mass and a Recent Pertrochanteric Hip Fracture.

Additional Supporting Information may be found in the online version of this article.

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Introduction

Hip fracture is the most devastating outcome associated with osteoporosis. This fracture causes pain, disability, diminished quality of life, and premature mortality. It is also a growing health problem, as it has been estimated that, worldwide, the number of hip fractures will approximately double to 2.6 million by the year 2025, and 4.5 million by the year 2050.⁽¹⁾ Moreover, patients with a hip fracture have a fourfold to eightfold increased risk of further fracturing at another site.⁽²⁾ The risk of mortality is increased approximately twofold during the first postfracture year, after which it decreases⁽³⁾; however, there remains an excess risk of mortality 5 to 10 years after the hip fracture.⁽⁴⁾ This excess mortality is more pronounced among individuals having lower BMD values⁽⁵⁾ and some data suggest that osteoporosis is a risk factor for long-term mortality in hip fracture.⁽⁶⁾

In spite of the new technical improvements in internal fixation, patients with hip and lower limb fractures have reduced physical activity and variable periods of limited mobility during the weeks or months after the fracture. The consequent absence of weight bearing leads to bone loss at several sites,^(7–12) more notably at the contralateral, unfractured hip, where it can decrease approximately by 5% during the first year after the fracture.^(13–16) Bone loss starts immediately after fracture but can be detected several years later.^(9,17) This additional and rapid bone loss after fracture of a weight-bearing bone substantially increases the risk for subsequent fragility fractures.^(18–20)

Thus, to preserve the bone density and for other reasons, elderly patients with hip fractures need to be mobilized as quickly as possible. Interventions to prevent bone loss associated with reduced mobilization after a hip fracture are needed, especially in patients who have reduced bone mass before the fracture occurs.

Previous investigations demonstrated an effect of bisphosphonates in the prevention of lower limb immobilization-related BMD loss.^(11,21,22) Teriparatide, administered by daily s.c. injection, activates osteoblasts and stimulates the formation of new bone and, thereby, increases bone mass and bone strength,⁽²³⁾ effectively reducing vertebral and nonvertebral fractures in postmenopausal women with severe osteoporosis.⁽²⁴⁾ However, there are no controlled studies in humans analyzing the effects of teriparatide on BMD in patients who are exposed to a certain degree of immobilization. Pivotal teriparatide clinical trials excluded patients who were not ambulatory. Furthermore, there are some conflicting results in studies regarding PTH treatment during conditions of disuse. Some studies suggest that PTH is able to reduce bone loss resulting from disuse,^(25–28) whereas other studies show that the bone anabolic effect of PTH is attenuated if mechanical loading is absent.^(29–31) Moreover, some authors have raised concerns that the increase in intracortical remodeling induced by teriparatide may reduce the hip strength, predisposing patients to second fractures.⁽³²⁾

We performed an active controlled study to evaluate whether teriparatide was superior to risedronate in the change in lumbar spine BMD from baseline to 78 weeks after a recent pertrochanteric fracture of the hip (primary objective), the hypothesis being that a bone anabolic drug will show better effects than an anti-remodeling drug. Results from a preplanned analysis of secondary non-BMD-related, fracture recovery-related outcomes at 26 weeks were reported earlier, and showed that teriparatide was associated with less hip pain and a shorter time to complete the timed up-and-go (TUG) test.⁽³³⁾

Here, we present final results of the efficacy and safety analyses after patients completed the full 78 weeks of treatment.

Patients and Methods

Study design

This multinational, multicenter, prospective, randomized, active-controlled study was conducted from April 2009 to August 2015 across 17 countries in North America, Mexico, and Europe. It included three study periods: (1) a screening phase of up to 14 days from the day of surgery to the day of randomization; (2) a double-blind, double-dummy treatment phase from the time of randomization to the 26-week visit; and (3) an open-label treatment phase where patients continued treatment up to 78 weeks with the same study drug to which they were randomized.

The study included men and postmenopausal women with low bone mass who had sustained a recent unilateral pertrochanteric fracture (Arbeitsgemeinschaft für Osteosynthesefragen [AO]/Orthopaedic Trauma Association [OTA] types 31-A1 and 31-A2) and were treated with osteosynthesis with a sliding compression hip screw or a trochanteric intramedullary nail. Low bone mass was defined by a BMD *T*-score ≤ -2.0 SDs at the total hip, femoral neck, or lumbar spine. Hospital-based physicians with experience in treating hip fractures screened over 2400 patients and enrolled 389 patients who met the eligibility criteria. The key eligibility criteria and reasons for exclusion during screening are summarized in Aspenberg and colleagues.⁽³³⁾

During the screening period, all patients were started on oral supplements with elemental calcium (500 to 1000 mg/day) and vitamin D (approximately 800 IU/day). Those with serum 25OHD level between 9.2 and 16 ng/mL received an oral loading dose of 100,000 IU of vitamin D2 or D3.

Eligible patients were randomly assigned, within 2 weeks of osteosynthesis, in a 1:1 ratio to teriparatide 20 μ g subcutaneous injection once daily plus oral placebo once weekly or placebo subcutaneous injection once daily plus oral risedronate 35 mg once weekly for 26 weeks. Treatment assignment was blinded to patients, investigators, and relevant staff; stratified by type of fracture; and determined by a computer-generated random sequence. At the 26-week visit, the treatment was unblinded and patients continued for an additional 52 weeks with the same treatment to which they were randomized for a total of 78 weeks continuous treatment. Patients were not permitted to take any other antiosteoporosis medication during the study period.

Treatment compliance was assessed by direct questioning and quantifying the study materials returned at scheduled visits. A patient who missed more than 25% of the injectable or oral study drug in two consecutive visits was considered noncompliant.

Outcomes

Primary and secondary BMD-related outcomes

The primary efficacy outcome was the change in lumbar spine BMD from baseline to 78 weeks. Changes in lumbar spine BMD from baseline to 26 and 52 weeks, and changes in femoral neck and total hip BMD from baseline to 26, 52, and 78 weeks were secondary efficacy outcomes. BMD was assessed by dual-energy X-ray absorptiometry (DXA) using either Hologic or Lunar equipment; systematic differences between the equipment were reconciled with a cross-calibration adjustment method.

There were no changes in the DXA scanners during the study at any of the participant study sites. All bone density scans were evaluated centrally by two independent readers blinded to treatment assignment (Synarc Inc., Hamburg, Germany).

Functional and patient-reported outcomes

Functional outcomes included: (1) functional mobility, evaluated with the TUG test^(34,35); (2) self-reported hip pain, assessed with a 100-mm linear Visual Analog Scale (VAS)⁽³⁶⁾ and a modified Charnley pain score⁽³⁷⁾; and (3) patient-reported health status, estimated with the self-administered Short Form-36 (SF-36) survey.^(37–40) For a detailed description of the fracture recovery outcomes, see Aspenberg and colleagues.⁽³³⁾ Functional outcomes were assessed as secondary endpoints up to the 26-week visit, and as exploratory endpoints at 52 and 78 weeks.

Recovery of the ability to walk and use of walking aids were assessed as exploratory endpoints at all postbaseline visits. Ability to walk was evaluated with a classification based on the standard definitions of community and household ambulation.⁽⁴¹⁾ Detailed information on the categories of walking aids used was also collected.⁽³³⁾

Functional and patient-reported outcomes were assessed in the following order at each postbaseline visit: (1) SF-36 survey; (2) TUG test; (3) hip pain assessment by 100 mm VAS; (4) modified Charnley hip pain score; and (5) ability to walk.

Radiological outcomes

These were exploratory outcomes and included radiological evidence of fracture healing, frequency of nonunion, and mechanical failure of the implant. The criteria for defining these outcomes have been described.⁽³³⁾ Radiological healing was evaluated at 6, 12, and 26 weeks by assessing the features of cortical bridging, disappearance of the fracture line, and progressive sclerosis of the fracture line on conventional anteroposterior and lateral radiographs. In addition, the presence of fracture nonunion and potential mechanical failure of the implant was analyzed at 26 weeks and at the final or early discontinuation visit. X-ray images of the hip were centrally adjudicated by two independent radiologists who were blinded to treatment assignment (Synarc Inc.).

Safety

Safety was analyzed in all patients who received at least one dose of study medication. Analyses included treatment-emergent adverse events (TEAEs); incident clinical fractures; analgesic use for hip pain; serum levels of 25OHD, calcium and uric acid; clinical chemistry and hematology; and vital signs.

Statistical methods

Sample size estimation was based on the primary outcome; ie, change in lumbar spine BMD after 78 weeks of treatment. A difference of 0.023 g/cm² and a common SD of 0.047 in each group were expected after treatment for 78 weeks. To detect a difference between treatments with 85% power and a two-sided statistical significance of 0.05, it was planned to enroll 76 patients in each group. Allowing for a 30% dropout, this number was increased to 109 for each group.

Efficacy analyses were conducted on the full analysis set (FAS), which follows the intent-to-treat principle. The FAS included all

randomized patients receiving at least one dose of the study drug and with at least one follow-up efficacy measure. Safety analyses were conducted on all patients who received at least one dose of study drug.

Descriptive statistics were used to summarize baseline patient characteristics in the treatment groups and overall population. The primary efficacy analysis was a mixed models for repeated measures (MMRM) analysis, which included treatment, visit, treatment-by-visit interaction, fracture type, and baseline BMD as fixed effects. MMRM accounts for data missing at random by using the correlation of observations within each patient and without the need of any explicit imputations.⁽⁴²⁾ In addition, a “full model” was constructed by individually adding predefined fixed effects (age, gender, duration of prior bisphosphonates, and use of glucocorticoids at baseline) to the primary model. Charnley hip pain score and radiological outcomes were analyzed with logistic regression with repeated measures to model the probability of a positive outcome. At each follow-up visit, covariate-adjusted (least squares [LS]) mean changes from baseline with SEs were derived from MMRM and logistic regression for the two treatments, and *p* values and 95% CIs were reported for their differences. Frequencies of patients experiencing TEAEs, new clinical fractures, and abnormal laboratory parameters were compared between treatments using Fisher’s exact test. Level of significance for tests was set to *p* < 0.05 (without multiplicity adjustments). All data were analyzed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Due to the statistical analysis method of MMRM applied to the efficacy data and the additional time points at 52 and 78 weeks for functional and patient-reported outcomes, 26-week analysis results as reported in Aspenberg and colleagues⁽³³⁾ vary slightly compared with the results after completing 78 weeks of treatment presented in this manuscript. The 26-week analysis should be considered the primary one for the functional outcomes based on MMRM because it included more cases and was restricted to the double-dummy phase.

The study was approved by institutional review boards at each center, and conducted in accordance with the ethical principles of the Declaration of Helsinki, good clinical practices, and applicable laws and regulations. All patients provided written informed consent before undergoing any screening procedures. The study was funded by Eli Lilly and Company (ClinicalTrials.gov Identifier: NCT00887354). The sponsor designed the protocol with advice from external advisors (PA, JRC), and was responsible for the quality control of data collected and the statistical analyses.

Results

Of the 389 screen patients, 224 patients were randomized, and 171 were included in the FAS (Fig. 1). The most frequent reason for screen failures (47.3% of the non-eligible patients) was BMD above -2.0 SD at all measured sites, followed by secondary hyperparathyroidism (26.7%) and severe vitamin D deficiency (14.5%). A total of 118 patients (52.7%) completed the full 78-week study duration (Fig. 1).

Baseline characteristics of the study patients were balanced between treatment groups and were described in detail by Aspenberg and colleagues.⁽³³⁾ In summary, the mean \pm SD age was 76.8 ± 7.7 years and 77.2% of the patients were females (Table 1). There were no differences in the frequencies of

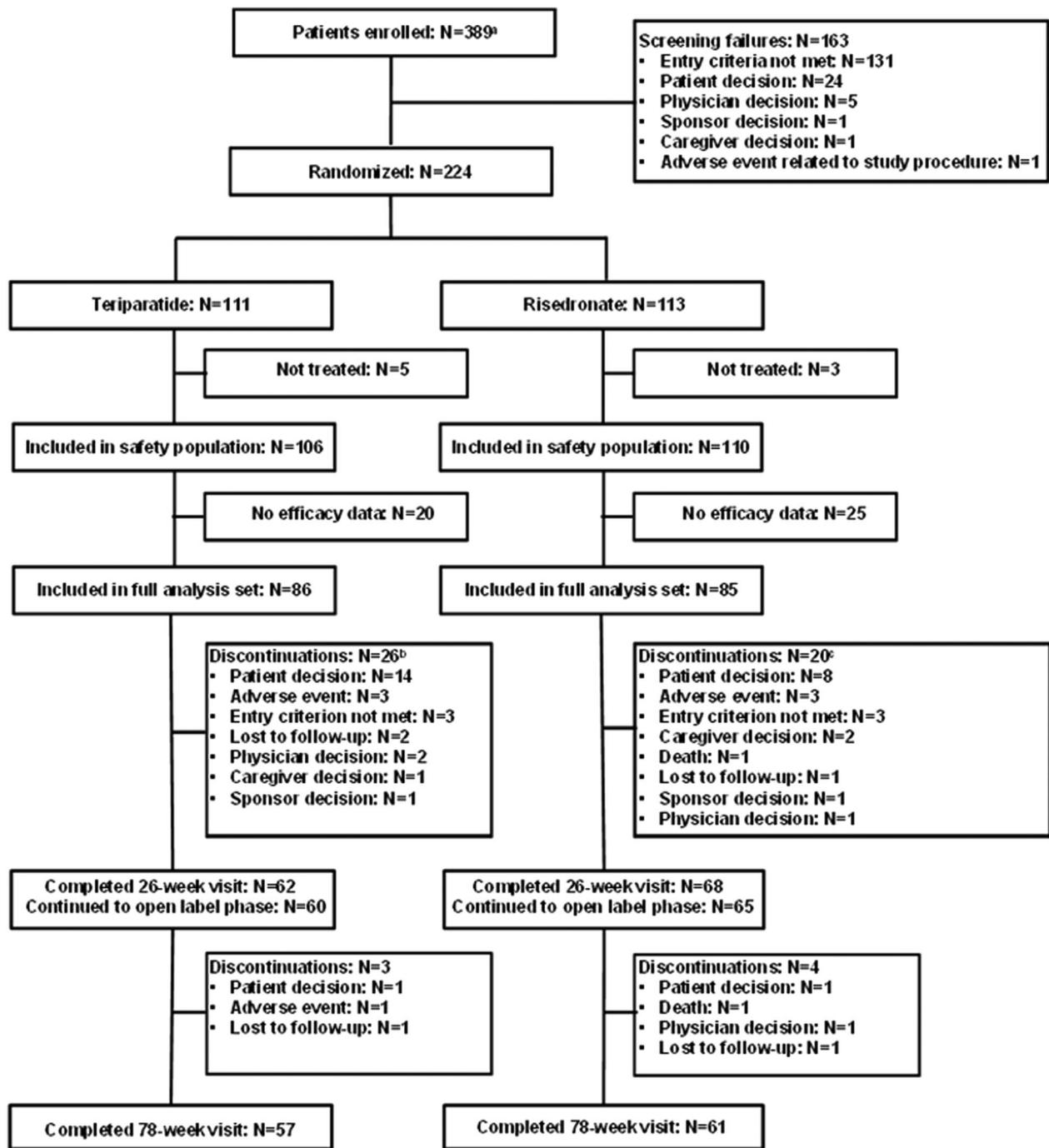


Fig. 1. Flowchart of enrolled patients. Note: One patient who discontinued due to patient decision and another who discontinued due to death (both of the risedronate group) were double-counted in the summary of discontinuations by reason between Week 26 and Week 78. ^aTwo enrolled patients were not screen failures but were not randomized. ^bIncluding two patients who discontinued after completing Week 26 visit. ^cIncluding three patients who discontinued after completing Week 26 visit. N = total number of patients.

common comorbidities between groups (Supporting Table 1). At baseline, the mean \pm SD BMD measured at the lumbar spine, total hip and femoral neck ranged from 0.602 ± 0.107 to 0.862 ± 0.170 g/cm² in the overall population (Table 1). Only 13.5% of the patients reported any previous pharmacological treatment for osteoporosis, and 25.7% reported a previous history of low-trauma fracture after the age of 50 years. Median

(interquartile range [IQR]) time from hip fracture to administration of the first treatment dose was 15 days (IQR, 12 to 18 days). The median durations of teriparatide and risedronate treatment were 545 and 548 days, respectively. The overall median (IQR) daily supplemental doses of calcium and vitamin D were 800 mg (IQR, 500 to 1000 mg), and 800 IU (IQR, 800 to 850 IU), respectively.

Table 1. Baseline Characteristics

	Teriparatide (n = 86)	Risedronate (n = 85)	Total (n = 171)
Age (years), mean ± SD	77.2 ± 8.0	76.4 ± 7.5	76.8 ± 7.7
Gender, n (%)			
Female	66 (76.7)	66 (77.6)	132 (77.2)
Male	20 (23.3)	19 (22.4)	39 (22.8)
Prior osteoporosis drug use, n (%)			
≥1 osteoporosis drug	12 (14.0)	11 (12.9)	23 (13.5)
≥1 bisphosphonate ^a	7 (8.1)	9 (10.6)	16 (9.4)
Other osteoporosis drugs ^b	6 (7.0)	3 (3.5)	9 (5.3)
Duration of prior bisphosphonate use (months), median (IQR)	65.6 (38.0–78.8)	24.4 (5.1–42.8)	40.4 (10.4–74.8)
Glucocorticoid use during the study, n (%)	13 (12.3)	7 (6.4)	20 (9.3)
Vitamin D megadose before randomization, n (%) ^c	12 (14.0)	21 (24.7)	33 (19.3)
Patients with >1 fractures occurring between age 50 years and study entry, n (%)			
All fractures	37 (43.0)	30 (35.3)	67 (39.2)
Low-trauma fractures	27 (31.4)	17 (20.0)	44 (25.7)
Type of fracture, n (%) ^d			
31-A1	39 (45.3)	46 (54.1)	85 (49.7)
31-A2	47 (54.7)	38 (44.7)	85 (49.7)
Other (intracapsular)	0	1 (1.2)	1 (0.6)
Areal density (g/cm ²), mean ± SD			
Lumbar spine BMD	0.873 ± 0.176	0.850 ± 0.163	0.862 ± 0.170
Femoral neck BMD	0.603 ± 0.098	0.602 ± 0.116	0.602 ± 0.107
Total hip BMD	0.670 ± 0.098	0.672 ± 0.113	0.671 ± 0.106
T-score, mean ± SD			
Lumbar spine BMD	-2.03 ± 1.470	-2.28 ± 1.239	-2.16 ± 1.360
Femoral neck BMD	-2.63 ± 0.519	-2.63 ± 0.657	-2.63 ± 0.591
Total hip BMD	-2.52 ± 0.692	-2.49 ± 0.790	-2.51 ± 0.741

Percentages are based on number of patients with nonmissing values. Patients in the full analysis set are included.

IQR = interquartile range.

^aAlendronate, risedronate, or ibandronate.

^bOther osteoporosis drugs included calcium and/or vitamin D, calcitonin, selective estrogen receptor modulators, and vitamin D active metabolites.

^cA vitamin D megadose was administered in patients with 25OHD levels between 9.2 and 16 ng/mL at baseline.

^dAs determined by the central reader.

Primary and secondary BMD-related outcomes

Treatment with teriparatide was superior to risedronate in the change of lumbar spine BMD from baseline to Week 78 (LS mean difference, 0.040 g/cm²; 95% CI, 0.025 to 0.055 g/cm²; $p < 0.0001$; Fig. 2). Thus, the primary objective of the study was achieved. Furthermore, the LS mean change in BMD was significantly greater in the teriparatide group at Week 26 (LS mean difference, 0.020 g/cm²; 95% CI, 0.006 to 0.035 g/cm²; $p = 0.007$; Fig. 2) and Week 52 (0.034 g/cm²; 95% CI, 0.019 to 0.049 g/cm²; $p < 0.0001$; Fig. 2).

At Week 78, femoral neck BMD increased significantly versus baseline with teriparatide, while it decreased with risedronate, leading to a significant LS mean difference in BMD between treatments of 0.019 g/cm² (95% CI, 0.006 to 0.031 g/cm²; $p = 0.003$) (Fig. 3). The treatment difference was not statistically significant at earlier time points (Fig. 3).

There was no significant difference between treatments for the change in total hip BMD from baseline to any of the time points (Fig. 4).

Functional and patient-reported outcomes

As previously reported in the analysis of the double-dummy phase of the trial,⁽³³⁾ the time required to complete the TUG test was significantly shorter with teriparatide versus risedronate at Week 6 (LS mean time, 26.5 versus 32.4 s, $p = 0.016$), Week 12 (20.1 versus 24.5 s, $p = 0.021$), Week 18 (17.8 versus

21.1 s, $p = 0.042$), and Week 26 (16.7 versus 19.9 s, $p = 0.040$). There was no significant difference between treatments at Week 52 or Week 78 (Fig. 5; Supporting Table 2).

Hip pain during the TUG test assessed by VAS was lower with teriparatide versus risedronate at Week 18 (significant adjusted absolute difference: -11.3 mm; 95% CI, -21.65 to -0.94; $p = 0.033$), and 12 and 26 weeks (-10.0 mm, $p = 0.056$; and -9.3 mm, $p = 0.079$). There was no significant difference between treatments at Week 52 or Week 78 (Fig. 6; Supporting Table 3).

There were no significant differences between treatments for patient-reported health status assessed by SF-36 (Supporting Table 4) or self-reported hip pain by the Charnley pain score at any of the time points (data not shown).

There were no significant differences between treatments for the ability to walk (ambulatory category) or the use of different walking aids at any of the follow-up visits (data not shown).

By the 78-week visit, patients were predominantly in the ambulatory category, with only two of 57 patients in the teriparatide group and one of 59 in the risedronate group in a nonfunctional ambulatory status ($p = 0.589$).

Radiological outcomes

Radiological healing (ie, stable fracture alignment and radiographic union) was achieved by all study patients by Week 26,⁽³³⁾

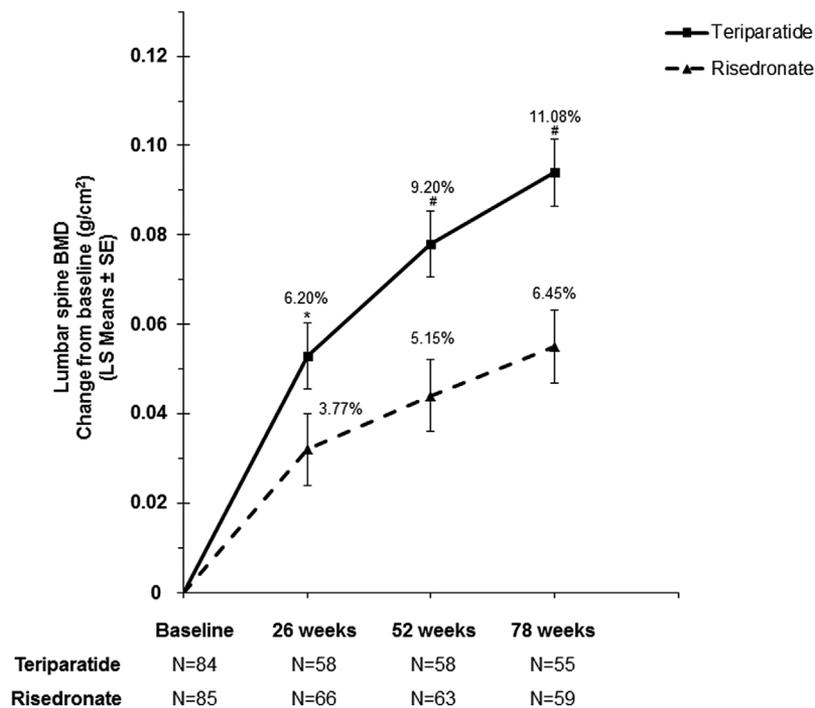


Fig. 2. Change from baseline in lumbar spine BMD (FAS^a). ^aMMRM analysis; predefined variables in the full model included treatment, visit, treatment-by-visit interaction, type of fracture (31-A1, 31-A2), baseline lumbar spine BMD, and glucocorticoid use at baseline. **p* = 0.007 and #*p* < 0.0001 versus risedronate; *p* < 0.0001 versus baseline for both groups at all time points. FAS = full analysis set; LS = least squares.

except one patient in the risedronate group who achieved it by Week 78. At Week 26, there was no significant difference between treatments for the frequency of loss of reduction or mechanical failure of the implant.⁽³³⁾ At Week 78, mechanical

failure of the implant was observed in one additional patient in the risedronate group (teriparatide: 7 [13.0%]; risedronate: 9 [15.5%]; *p* = 0.386). The predominant cause of implant failure was excessive progression of offset in both treatment groups,

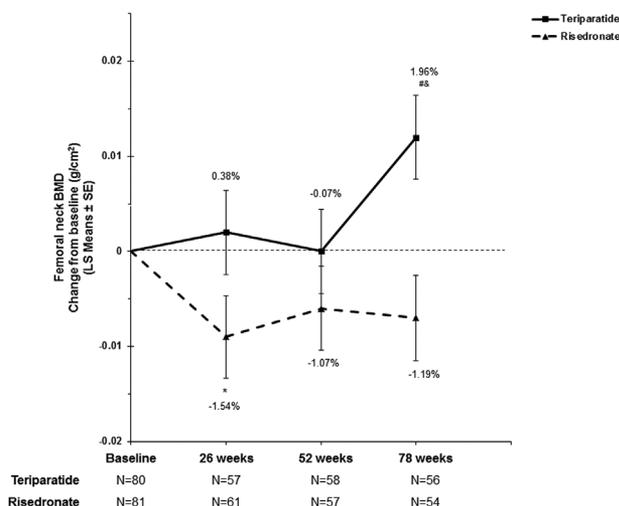


Fig. 3. Change from baseline in femoral neck BMD (FAS^a). ^aMMRM analysis; predefined variables in the full model included treatment, visit, treatment-by-visit interaction, type of fracture (31-A1, 31-A2), and baseline femoral neck BMD. **p* = 0.035 compared to baseline; #*p* = 0.0098 compared to baseline; &*p* = 0.003 versus risedronate. FAS = full analysis set; LS = least squares.

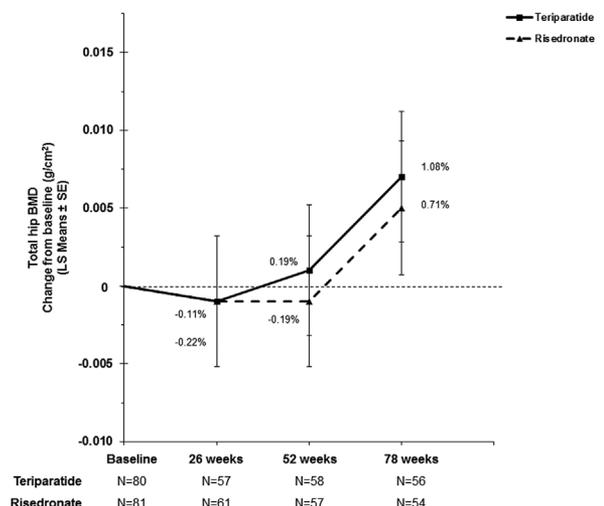


Fig. 4. Change from baseline in total hip BMD (FAS^a). ^aMMRM analysis; predefined variables in the full model included treatment, baseline total hip BMD, visit, type of fracture (31-A1, 31-A2), treatment-by-visit interaction, and duration of prior bisphosphonate therapy. No significant changes between groups or compared to baseline for any of the treatment groups at any time point. FAS = full analysis set; LS = least squares.

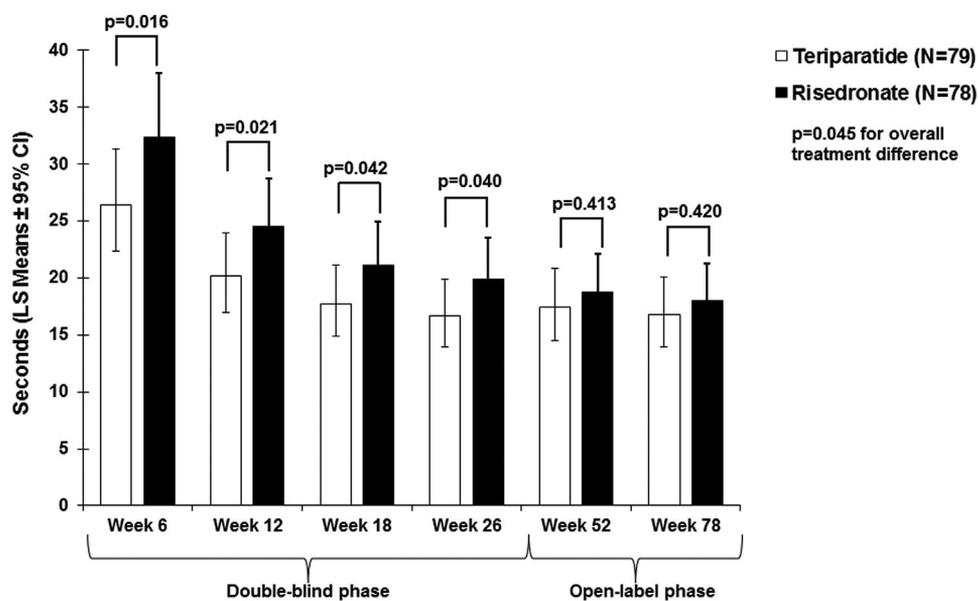


Fig. 5. Assessment of functional mobility: time to complete the TUG test (FAS^a). ^aMMRM analysis (with log-transformation); predefined variables in the full model included treatment, visit, treatment-by-visit interaction, age, type of fracture (31-A1, 31-A2), type of reduction, type of walking aid, recall SF-36 physical component score, and baseline Charnley hip pain score. FAS = full analysis set; LS = least squares; SF-36 = Short Form-36; TUG = timed up-and-go.

with only one patient in each treatment group showing lag screw cutout. Loss of reduction was observed in two (3.2%) and four (6.5%) patients in the teriparatide and risedronate groups, respectively ($p = 0.440$); all cases occurred during the first 26 weeks of follow-up. There were no cases of nonunion in the study cohort.

Safety

Treatment compliance was similar in the two treatment groups (98.6% in the teriparatide group and 98.4% in the risedronate group). The frequencies of deaths, serious adverse events leading to hospitalization, and clinical fractures were higher with risedronate than with teriparatide, but the difference was not statistically significant (Table 2). There were five new fractures in the teriparatide group and 12 in the risedronate group ($p = 0.099$), including two and seven new hip fractures, respectively ($p = 0.171$). The overall analgesic use at 78 weeks was 19.4%, with no significant difference between treatment groups ($p = 0.848$). Patients receiving teriparatide showed significantly higher serum alkaline phosphatase levels versus risedronate at Week 26 ($p = 0.010$) and Week 78 ($p = 0.002$). Hyperuricemia and hypercalcemia were more frequent with teriparatide than risedronate at 6-week and 26-week follow-up visits, respectively (Table 2). Hypercalcemia associated with teriparatide was generally mild with eight of the 15 patients having a maximum albumin-corrected, postbaseline serum calcium level ≤ 2.70 mmol/L (Supporting Table 5). Mean serum levels of 25OHD were approximately 10 pmol/mL (4 ng/mL) significantly lower in the teriparatide group at Week 26 and Week 78, but remained above 50 pmol/mL (20 ng/mL) in the study cohort (Table 2).

Other laboratory parameters and vital signs were not significantly different between the two treatment groups at any time points.

Discussion

Patients with hip fracture represent an important population to target for the prevention of secondary fractures because they are at an increased risk of recurrent fragility fractures. For instance, the reported incidence of a second hip fracture was between 4% and 9% after 1 year of the first hip fracture.⁽⁴³⁻⁴⁶⁾ Furthermore, these patients have two to three times higher risk of fracture at other (non-hip) sites compared with the expected fracture rate in the general population.^(2,47) However, the care of patients after hip fracture has been suboptimal. Less than one-third of patients suffering a hip fracture receive subsequent osteoporosis treatment,^(48,49) and with no trend toward improvement over time in several countries.⁽⁵⁰⁾ Although evidence from randomized clinical trials does not show adverse effects on fracture healing in patients treated with bisphosphonates shortly after surgical repair of a hip fracture,^(51,52) physicians hesitate to initiate osteoporosis treatment upon discharge after a surgery for hip fracture.

In our study, treatment with 78 weeks of teriparatide showed significantly greater increases in lumbar spine and femoral neck BMD of the contralateral unfractured hip compared with risedronate. The increase in lumbar spine BMD was also significantly greater versus risedronate after 26 and 58 weeks of treatment with teriparatide. Change in total hip BMD did not show a statistically significant difference between groups. Our results support previous findings by Kobayashi and colleagues⁽⁵³⁾ who described a greater increase in lumbar spine BMD with teriparatide at 48 weeks postsurgery compared with alendronate, in non-osteoporotic patients from Japan who were partially immobilized after total hip arthroplasty.

Although the current study was not powered to demonstrate a reduction in the rates of new fracture and mortality, the higher increase in BMD observed in the teriparatide-treated group might have clinical relevance because it has been demonstrated

Table 2. Safety Analyses

	Teriparatide (n = 106)	Risedronate (n = 110)	Total (n = 216)	Fischer's p value
Treatment emergent adverse events, n (%)				
Any	59 (55.7)	58 (52.7)	117 (54.2)	0.684
Leading to discontinuation	5 (4.7)	6 (5.5)	11 (5.1)	1.000
Serious	21 (19.8)	27 (24.5)	48 (22.2)	0.418
Leading to hospitalization	19 (17.9)	20 (18.2)	39 (18.1)	1.000
Death	2 (1.9)	7 (6.4)	9 (4.2)	0.171
Clinical fractures				
Patients with ≥1 clinical vertebral fracture, n (%)	0	1 (0.9)	1 (0.5)	1.000
Patients with ≥1 clinical nonvertebral fracture, n (%)	5 (4.7)	10 (9.1)	15 (6.9)	0.286
Number of fractures, n	5	12	17	0.099 ^a
Hip	2	7	9	
Humerus	1	1	2	
Pelvis	0	2	2	
Laboratory parameters				
Serum 25OHD, pmol/mL				
Week 26	n = 62	n = 66		
Mean ± SD	62.16 ± 16.4	71.29 ± 20.3		0.006
Week 78	n = 55	n = 57		
Mean ± SD	59.47 ± 18.6	68.35 ± 24.4		0.032
Serum alkaline phosphatase, IU/L				
Week 26	n = 62	n = 64		
Mean ± SD	95.74 ± 29.3	83.61 ± 21.9		0.010
Week 78	n = 55	n = 56		
Mean ± SD	88.91 ± 26.0	74.52 ± 20.7		0.002
Hypercalcemia ^b				
Week 6	n = 81	n = 78		
n (%)	7 (7.4)	5 (5.1)		0.766
Week 26	n = 62	n = 62		
n (%)	8 (12.9)	1 (1.5)		0.032
Week 78	n = 55	n = 55		
n (%)	3 (5.3)	0 (0)		0.243
Hyperuricemia ^c				
Week 6	n = 82	n = 79		
n (%)	13 (15.9)	4 (5.1)		0.038
Week 26	n = 62	n = 64		
n (%)	9 (14.5)	6 (9.4)		0.420
Week 78	n = 55	n = 56		
n (%)	8 (14.5)	7 (12.5)		0.788

Percentages are based on number of patients with nonmissing values. Safety analyses included all patients receiving at least 1 dose of study medication (active or placebo dummy).

^aPoisson regression.

^bAlbumin corrected serum calcium >10.6 mg/dL

^cSerum uric acid >8.3 mg/dL in men and >7.5 mg/dL in women.

that after an initial fragility fracture, the rate of subsequent mortality increases with declining BMD.⁽⁵⁾

The BMD increases we observed were similar to those reported in non-immobilized patients with severe osteoporosis in the pivotal Phase 3 trials of risedronate^(54,55) and teriparatide.⁽²⁴⁾ The exception was the effect of risedronate on femoral neck BMD at 78 weeks in our study (−1.19%) compared with the +1.5% to +2% increase observed at 18 months of treatment in the pivotal phase 3 trials.^(54,55) The reason for this discrepancy is unclear, but it should be considered that patients with a recent hip fracture show a decline in the contralateral unfractured femoral neck BMD of approximately 5% compared to baseline after 12 months of follow-up.^(13,14,16) Therefore, risedronate was

likely able to stop this quick and profound decline in BMD, although less effectively than teriparatide. Interestingly, previous results in 239 patients with a recent hip fracture treated with weekly alendronate for 12 months also showed a lower than expected increase in femoral neck BMD compared with that in the phase 3 pivotal trials in women with postmenopausal osteoporosis.⁽⁵⁶⁾ The authors hypothesize on the potential impact of changes in bone volume and/or a negative effect of the relative lack of weight-bearing exercise.⁽⁵⁶⁾ This hypothesis was also suggested by Lee and colleagues⁽⁵⁷⁾ who observed that 53.7% of the patients treated with alendronate showed a decline in lumbar spine volumetric BMD, 1 year after a total knee arthroplasty. In another series of patients with lower leg

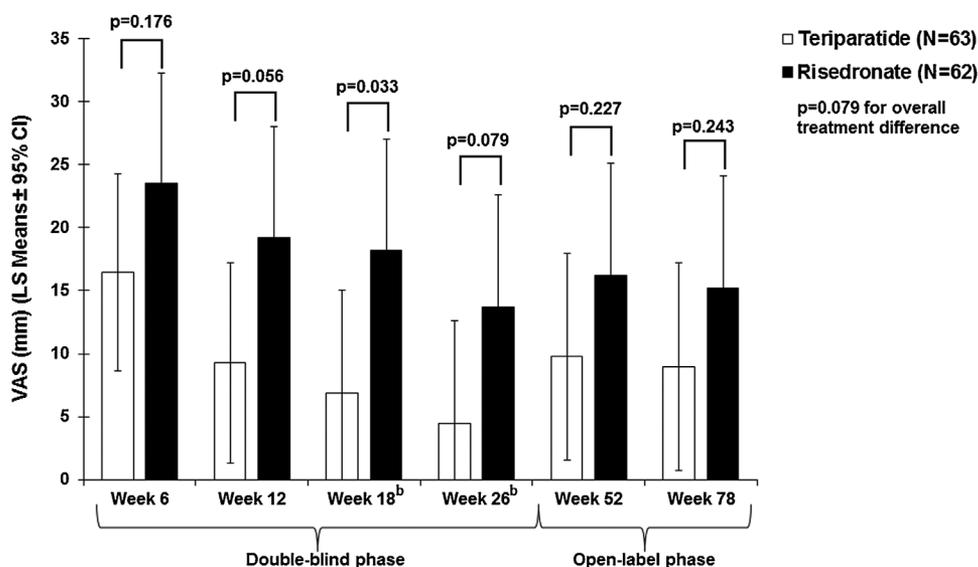


Fig. 6. Evaluation of self-reported hip pain during the TUG test: 100 mm VAS (FAS^a). ^aMMRM analysis; predefined variables in the full model included treatment, visit, treatment-by-visit interaction, type of fracture, type of reduction, adequacy of reduction, use of opioids, and use of nonsteroidal anti-inflammatory drugs. ^bLower confidence interval crosses zero for teriparatide. FAS = full analysis set; LS = least squares; TUG = timed up-and-go test; VAS = Visual Analog Scale.

fractures who received daily alendronate, femoral neck BMD was almost unchanged compared to baseline after 12 months of follow-up, although this bisphosphonate mitigated the 5% reduction in femoral neck BMD observed in the placebo-treated group.⁽¹¹⁾ Finally, in the HORIZON Recurrent Fracture Trial, BMD at the femoral neck increased by +0.8% and +2.2% at 12 and 24 months of treatment with zoledronic acid, respectively.⁽²¹⁾ However, these increases are lower than those described in the pivotal trial in women with postmenopausal osteoporosis (+2.5% and +3.5% at 12 and 24 months, respectively).⁽⁵⁸⁾

The safety profiles of teriparatide and risedronate observed in our study were according to the prescribing information, with no new safety signals identified, and with no change in the benefit-risk assessments of these treatments in this elderly population of patients with low bone mass and a recent hip fracture. Patients in the teriparatide group showed a statistically significant increase in hyperuricemia at 6 weeks (15.9%) and hypercalcemia at 26 weeks (12.9%) of treatment versus risedronate, but these were relatively mild and without clinical complications. Both treatments showed similar frequencies of loss of reduction (2 cases [3.2%] with teriparatide and 4 cases [6.5%] with risedronate) and mechanical failure of the implant with only one case of screw cutout per treatment group, and no case of non-union. Our results support previous work by Kim and colleagues⁽⁵⁹⁾ who showed that the early administration of risedronate does not appear to affect the rate of healing of an intertrochanteric, osteoporotic fracture or the incidence of complications. Our findings are also similar to those in the study by Kim and colleagues⁽⁵⁹⁾ in patients who started oral weekly risedronate 1 week after surgery, where all fractures were radiologically healed by 20 weeks after surgery.

The overall incidence of clinical fracture rates remained relatively low, with a numerically, nonstatistically significant lower risk of nonvertebral fractures in the teriparatide group.

In this study, we also analyzed the effects of the two study drugs on several aspects of fracture recovery, either as secondary or exploratory objectives. Because healing and recovery of a hip fracture are normally completed in approximately 6 months, the study was designed as double-dummy, placebo-controlled during the first 26 weeks after randomization, with the aim of avoiding potential, subjective patient-related outcomes bias. The results of the primary analysis of these endpoints were previously published.⁽³³⁾ In the current report, we extended the analysis of these recovery endpoints to the full 78 weeks of treatment. During the last 52 weeks of treatment, the time required to complete the TUG test and VAS-assessed hip pain during the TUG test—which showed a reduction in the early recovery phase—were no longer significantly different between the two groups, probably reflecting the successful completion of the fracture healing process in the patients remaining in the study. The slight expected differences in the TUG test and hip pain results between the 26-week analyses reported by Aspenberg and colleagues⁽³³⁾ and this work may be attributed to the statistical methodology (MMRM) and the additional time points at 52 and 78 weeks included in the MMRM models. The analysis of data from the full treatment period confirmed the lack of statistically significant difference between treatments for the patient-rated health status by the SF-36 survey, ability to walk, or the Charnley hip pain score.

Although preclinical studies using PTH in animal models are promising^(60–65) and proof-of-concept clinical trials^(66,67) and sporadic case reports in humans^(68,69) showed an anecdotal benefit of teriparatide in various fractures, to date there are no well-controlled clinical trials to support the hypothesis that teriparatide improves fracture healing. Huang and colleagues⁽⁷⁰⁾ have recently reported that 6 months of teriparatide was associated with faster fracture healing, better quality of life, and lower frequency of lag screw cutout and mortality

rates in 189 patients with intertrochanteric fractures. Our findings did not support the results of that retrospective study, but it should be stressed that our study was not powered for any fracture recovery or healing outcomes. A recent report of the effects of teriparatide versus placebo on fracture healing after internal fixation of a femoral neck fracture failed to detect any significant differences between treatment groups due to the small sample size ($n=78$ in the teriparatide group and $n=81$ in the placebo group). This clinical program had to be stopped early because accrual in both studies was much slower than expected given the difficulty in enrolling patients for this kind of study.⁽⁷¹⁾

Our study had some limitations. We had strict eligibility criteria and relied on the willingness of patients and their caregivers for participation in the study. Consequently, only 10% of the patients admitted with pertrochanteric hip fractures in the study centers were enrolled. This may have created a selection bias toward a younger and healthier population, thereby limiting the external validity of the study results in more deteriorated patients with comorbidities such as dementia or a history of malignancy. However, we believe patients in our study were not that healthy, given the long average time required by them to complete the TUG test even at Week 78; a TUG score >13.5 s is used to identify individuals with a high risk of falling in the community setting.^(72,73) Low enrolment rates of 6.3% and 4.0% were also observed in other randomized studies evaluating the effect of anti-osteoporotic medications for hip fracture healing,^(74,75) thus underscoring the challenges of recruiting and retaining elderly patients in such studies. We had a high dropout rate and relative low compliance with visit dates and study procedures. This is not unexpected in frail, elderly patients with a severe fracture, and stresses the difficulties of performing randomized clinical trials involving frequent, cumbersome postoperative assessments in elderly patients with fractures who have substantial transportation issues. The attempted clinical trial by Kanakaris and colleagues⁽⁷⁴⁾ clearly showed that it is very difficult to complete a prospective randomized study aiming to identify and compare the effect of different anti-osteoporotic drugs administered at the time of healing of fragility hip fractures, with the desired sample size and stringent recruitment criteria. The sample size of this study was not large enough to detect a difference in fracture rates between treatments. Rates of incident clinical fractures were prospectively collected as safety-related endpoints. Furthermore, it is likely that we underestimated the incidence of new vertebral fractures because we did not evaluate spinal radiographs unless patients developed symptoms of a possible vertebral fracture.

This study has several strengths. To the best of our knowledge, this is the first well-controlled study of imaging and clinical outcomes with a systemically active biologic drug in patients with a hip fracture, using an active comparator in a double-dummy design during the first 26 weeks of follow-up. The study was performed with a rigorous methodological design, a predefined statistical analysis plan, and using validated instruments to measure functional outcomes and pain. Hip X-rays and BMD scans were evaluated by central, blinded reviewers using prespecified adjudication criteria, widely accepted in the literature. Biases arising from subjective patient-reported outcomes were avoided through a double-dummy design and complete blinding during the 26-week fracture recovery phase. Patients were eligible for participation regardless of prior anti-osteoporotic drug use. Finally,

treatment compliance with both drugs was very high, probably reflecting the experimental framework of a clinical trial.

In conclusion, teriparatide treatment during a 78-week period was associated with a significantly greater increase in BMD at the lumbar spine and femoral neck, and a significantly shorter time to complete the TUG test compared with risedronate, in elderly patients with a recent pertrochanteric hip fracture. We did not observe any signs suggesting that these drugs were unsafe when used immediately after fracture repair. Further studies are warranted to investigate whether these observations in the early recovery phase translate into reduction of subsequent fragility fractures and premature mortality rates.

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