

## Combination Teriparatide and Raloxifene Therapy for Postmenopausal Osteoporosis: Results From a 6-Month Double-Blind Placebo-Controlled Trial\*

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**ABSTRACT:** We compared combination treatment with teriparatide plus raloxifene with teriparatide alone in women with postmenopausal osteoporosis in a 6-month double-blind, placebo-controlled trial that measured biochemical markers of bone turnover and BMD. Markers of bone formation and spine BMD increased similarly with teriparatide alone and combination therapy. However, combination therapy induced a significantly smaller increase in bone resorption versus teriparatide alone and significantly increased total hip BMD versus baseline.

**Introduction:** The effects of combining two approved treatments for osteoporosis with different modes of action were examined by comparing teriparatide [rhPTH(1-34)] monotherapy with combination teriparatide and raloxifene therapy.

**Materials and Methods:** A 6-month randomized, double-blind trial comparing teriparatide plus raloxifene ( $n = 69$ ) versus teriparatide plus placebo ( $n = 68$ ) was conducted in postmenopausal women with osteoporosis.

**Results:** Bone formation (N-terminal propeptide of type 1 collagen [PINP]) increased similarly in both treatment groups. However, the increase in bone resorption (serum C-terminal telopeptide of type I collagen [CTX]) in the combination group was significantly smaller than in the teriparatide-alone group ( $p = 0.015$ ). Lumbar spine BMD significantly increased  $5.19 \pm 0.67\%$  from baseline in the teriparatide-alone group. In the combination group, lumbar spine ( $6.19 \pm 0.65\%$ ), femoral neck ( $2.23 \pm 0.64\%$ ), and total hip ( $2.31 \pm 0.56\%$ ) BMD significantly increased from baseline to study endpoint, and the increase in total hip BMD was significantly greater than in the teriparatide-alone group ( $p = 0.04$ ). In the teriparatide-alone group, mean serum calcium levels increased from baseline to endpoint ( $0.30 \pm 0.06$  mg/dl,  $p < 0.001$ ), whereas mean serum phosphate remained unchanged. In the combination group, mean serum calcium was unchanged, and mean serum phosphate decreased ( $-0.20 \pm 0.06$  mg/dl,  $p < 0.001$ ) from baseline to endpoint. Changes in serum calcium ( $p < 0.001$ ) and phosphate ( $p < 0.004$ ) were significantly different between treatment groups. The safety profile of combination therapy was similar to teriparatide alone.

**Conclusions:** Combination therapy increased bone formation to a similar degree as teriparatide alone. However, the increase in bone resorption was significantly less and total hip BMD significantly increased for combination therapy compared with teriparatide alone. Combination treatment with raloxifene may thus enhance the bone forming effects of teriparatide. Further studies over longer treatment duration that include fracture endpoints are necessary to fully ascertain the clinical significance of combination raloxifene plus teriparatide therapy in postmenopausal osteoporosis.

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**Key words:** osteoporosis treatment, teriparatide, PTH, raloxifene

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### INTRODUCTION

ANTIRESORPTIVE AGENTS TREAT osteoporosis by inhibiting osteoclast activity to decrease bone turnover and decrease the depth of bone resorption cavities. These ef-

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fects have been shown to improve the mechanical competence of bone and increase bone mineralization. Furthermore, significant reduction of osteoporotic fractures has been shown with several antiresorptive therapies, including raloxifene, a selective estrogen receptor modulator (SERM) approved for the prevention and treatment of osteoporosis in postmenopausal women.<sup>(1-3)</sup> The risk of osteoporotic fractures is also significantly reduced by daily subcutaneous injections of the first 34 amino acids of recombinant human PTH [rhPTH(1-34), teriparatide], which stimulates osteoblast activity, bone formation, and increases bone mass and biochemical markers of bone turnover.<sup>(4-6)</sup> Teriparatide is approved in the United States for the treatment of low BMD in men with osteoporosis and for the treatment of postmenopausal osteoporosis in women who are at high risk for fracture.

An appealing hypothesis has been that the combined use of an antiresorptive with a bone-forming drug might result in superior effects on the skeleton. Studies in ovariectomized rats support the hypothesis of combining a SERM with teriparatide for the treatment of osteoporosis.<sup>(7,8)</sup> In postmenopausal women, the addition of hPTH(1-34) to ongoing estrogen therapy increased bone turnover and BMD versus continued estrogen monotherapy,<sup>(5,9,10)</sup> but these studies did not evaluate monotherapy with hPTH(1-34). Other studies have shown that concomitant alendronate impaired the increase in bone formation induced by PTH(1-84) and hPTH(1-34) therapy.<sup>(11,12)</sup> The authors of these studies concluded that there was no evidence of synergy between PTH(1-84) and alendronate in women<sup>(11)</sup> and that alendronate impairs the ability of hPTH(1-34) to increase the BMD at the lumbar spine and the femoral neck in men.<sup>(12)</sup>

We hypothesized that raloxifene given in combination with teriparatide would reduce the increase in bone resorption observed with teriparatide alone. Bone resorption markers decrease within 3 months of initiating raloxifene therapy<sup>(13)</sup> and are relatively unchanged between 6- and 12-month treatment with raloxifene as well as teriparatide monotherapy.<sup>(13,14)</sup> We conducted a 6-month, randomized, double-blind, oral placebo-controlled trial comparing combination teriparatide and raloxifene versus teriparatide alone in postmenopausal women with osteoporosis.

## MATERIALS AND METHODS

### *Study design and participants*

The study was a multicenter, randomized, double-blind, oral placebo-controlled, 6-month trial examining the treatment effects of teriparatide alone with combination teriparatide and raloxifene. The study was conducted by 12 investigators at 13 study sites in the United States. Participants were postmenopausal women between the ages of 45 and 85 with a prior lumbar spine, femoral neck, or total hip BMD T score <2.5 SD below the average of healthy premenopausal women and at high risk for fracture in the opinion of the investigator. Women were required to be ambulatory and free of severe chronically disabling conditions other than osteoporosis and to have normal labora-

tory values for serum calcium (reference range, 8.3–10.6 mg/dl), alkaline phosphatase, and PTH(1-84). Serum 25 hydroxyvitamin D was required to be  $\geq 20$  nM and at most three times the upper limit of normal. Women were excluded if they were ever treated with >1 month of oral bisphosphonate therapy or two doses within 6 months of study randomization, more than one dose of intravenous bisphosphonate therapy during the last 2 years or any doses within 6 months of study randomization, and any other osteoporosis therapy or drugs known to affect bone metabolism within 3–6 months before randomization. Additional exclusion criteria included severe postmenopausal symptoms likely to require hormonal therapy, other diseases affecting bone metabolism or causing secondary osteoporosis, radiation therapy involving the skeleton, skeletal tumors or metastases, history of venous thromboembolism, nephrolithiasis or urolithiasis within the past 2 years, carcinoma of the breast ever or with other malignancies in the past 5 years, and abnormal thyroid, liver, or renal function. The protocol was approved by institutional review boards, and written informed consent was obtained from all participants. All study methods and procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki.

### *Treatments and blinding*

Patients self-administered either daily teriparatide 20  $\mu$ g subcutaneous injections plus oral placebo or a daily combination of teriparatide 20  $\mu$ g subcutaneous injections plus oral raloxifene 60 mg at 12 study sites in the United States. Eligible women began a 6-month treatment phase with a baseline enrollment visit and visits after 1, 3, and 6 months of study drug. Patient compliance was assessed by direct questioning of the patients and by quantifying the amount of study materials returned. Patients, investigative site staff, and personnel involved with study monitoring, data cleaning, and authorship were blinded to group assignment throughout the study. Calcium carbonate (500 mg) and vitamin D (400 IU) tablets were provided to participants at the screening visit. Patients were instructed to take open-label supplements providing at least 1000 mg/day of elemental calcium and 400–800 IU/day of vitamin D on a daily basis for the duration of the study. Calcium supplementation was quantified at the study randomization visit.

### *Baseline and follow-up assessments*

Patient demographics, health history, and medication use data were obtained at baseline. Biochemical markers of bone resorption (serum C-terminal telopeptide of type I collagen [CTx]; ELISA, Crosslap; Osteometer Biotech, Herlev, Denmark; intra-assay CV, 4.7%; interassay CV, 13.5%) and bone formation (N-terminal propeptide of type 1 collagen [PINP]; RIA, Orion Diagnostica, Espoo, Finland; intra-assay CV, 4.8–13.7%; interassay CV, 3.1–8.2%) were measured in serum collected after an overnight fast at baseline and after 1, 3, and 6 months of treatment.

BMD was assessed by DXA at the posterior-anterior lumbar spine, total hip, and femoral neck at baseline and month 6 using either Hologic (Bedford, MA, USA) or Lu-

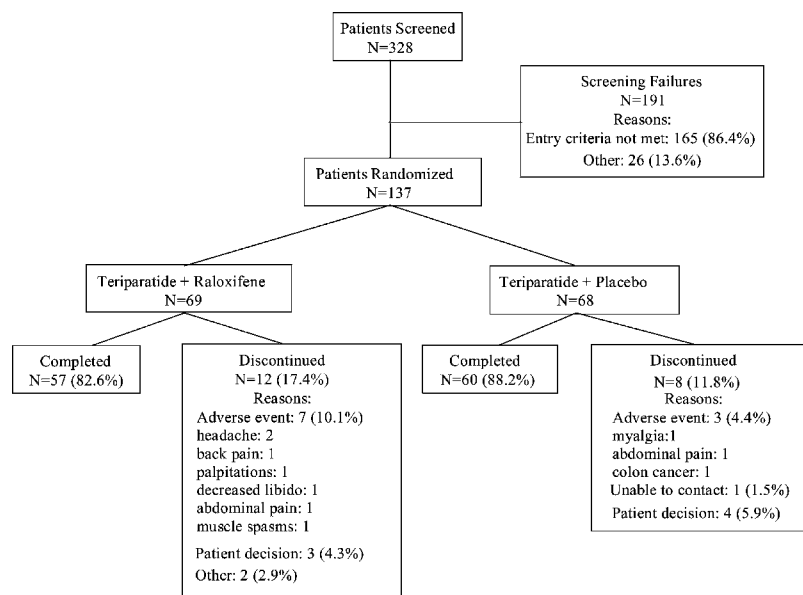


FIG. 1. Patient recruitment and follow-up.

nar equipment (GE Lunar, Madison, WI, USA). For lumbar spine BMD measurements, at least two evaluable vertebrae in the lumbar region ( $L_1$ – $L_4$ ) were required. Quality control of densitometric equipment was performed at each laboratory by validating scanners with a standard anthropomorphic spine phantom.

Standard laboratory tests were performed and included fasting clinical chemistry, hematology, and urinalysis. Twenty-four hour urine chemistry was assessed at baseline and month 6. The safety profile and the effects on mineral and urate metabolism were assessed for each treatment group.

### Statistical analysis

The primary efficacy comparison in the study was CTx change from baseline between treatment groups. The study was designed to enroll 60 patients per treatment group. Using a two-sample *t*-test with a significance level of 0.05 and an estimated 3000 pM within group SD for change from baseline in CTx, the study design provided at least 80% power to detect a between-group difference in CTx of 1580 pM.

Efficacy analyses were conducted on a modified intent-to-treat (ITT) basis and included all data from patients receiving at least one dose of study medication who had at least one baseline and one postbaseline efficacy variable measurement. Safety analyses were conducted using all ITT patients. For baseline to endpoint analyses, the endpoint was the last postbaseline observation carried forward (LOCF). For analyses at specific time-points, previous observations were not carried forward if data were missing.

Tests for treatment effects were conducted using a two-sided significance level of 0.05. An analysis of covariance (ANCOVA) model was used to analyze changes in both CTx (primary efficacy variable) and PINP (secondary efficacy variable) with therapy and study center (pooled) as main effects with baseline values as a covariate. An

ANCOVA model was used to analyze the changes from baseline to endpoint in BMD (lumbar spine, total hip, femoral neck) and mineral and urate metabolism. Comparisons between treatment groups were made using Fisher's exact test for categorical data and ANOVA with treatment and pooled center/investigator(s) as the independent effects for quantitative data.

## RESULTS

During patient recruitment and follow-up, 328 patients were screened, and 191 patients were ineligible for study participation (Fig. 1). A total of 137 women met eligibility requirements, 68 patients were randomly assigned to teriparatide plus oral placebo, and 69 patients were randomly assigned to teriparatide plus raloxifene. The mean duration of treatment was  $162.6 \pm 4.4$  days in the teriparatide-alone group versus  $159.8 \pm 5.1$  days in the combination group.

In general, treatment groups were similar at baseline (Table 1). However, alkaline phosphatase ( $p = 0.03$ ) and PINP ( $p = 0.03$ ) were both significantly higher in the combination group compared with teriparatide alone. Importantly, the baseline biochemical marker value was included in the ANCOVA model used to analyze both PINP and CTx; thus, the imbalance in PINP was not expected to have any important effect on data interpretation. To confirm that the baseline imbalance in PINP did not affect the results of the between-group comparisons, additional analyses were conducted that excluded patients with the highest baseline PINP values in the teriparatide plus raloxifene group. These analyses continued to show no between-group differences ( $p > 0.05$  for all comparisons, data not shown).

### Biochemical markers of bone turnover

No statistically significant increase from baseline in CTx was observed in either treatment group after 1 month of treatment (Fig. 2A). At 3 months, CTx had significantly

TABLE 1. BASELINE DEMOGRAPHICS\*

Characteristic	TPTD20 (N = 68)	TPTD + RLX (N = 69)	p*
Age (years)	66.1 ± 7.8	66.6 ± 7.5	.73
BMI (kg/m <sup>2</sup> )	25.7 ± 5.9	25.3 ± 4.2	.79
White (%)	92.6	91.3	1.0
Postmenopausal (years)	21.2 ± 9.5	20.4 ± 10.1	.70
Calcium supplement (mg)	1066 ± 271	1040 ± 295	.71
Smokers (%)	11.8	17.4	.47
Serum calcium (mg/dl)	9.76 ± 0.48	9.8 ± 0.44	.54
25-dihydroxyvitamin D (nM)	62.7 ± 22.6	65.6 ± 29.1	.49
PTH(1-84) (ppm/L)	3.52 ± 1.3	3.34 ± 1.4	.45
Alkaline phosphatase (U/liter)	78.5 ± 22.3	88.3 ± 27.4	.03
CTx (ppM/L)	4926 ± 3981	6030 ± 9407	.39
PINP (μg/liter)	49.30 ± 18.3	58.86 ± 27.8	.03
LS BMD T score	-2.92 ± 0.84	-2.67 ± 1.14	.18
FN BMD T score	-2.42 ± 0.81	-2.47 ± 0.82	.68
Total hip BMD T score	-2.12 ± 0.90	-2.04 ± 0.95	.62

\* Values are means ± SD.

TPTD20, teriparatide 20 μg/day; TPTD + RLX, combination teriparatide 20 μg/day plus raloxifene 60 mg/day.

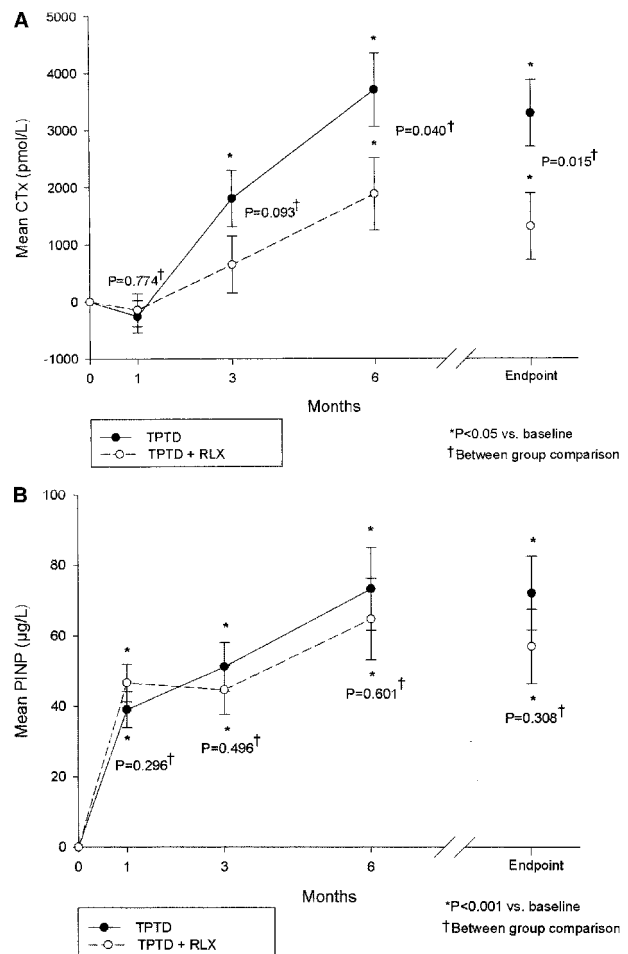
increased from baseline in the teriparatide-alone group ( $p < 0.001$ ) but not in the teriparatide plus raloxifene group ( $p = 0.197$ ); there was a trend toward a lesser increase in the teriparatide plus raloxifene group compared with the teriparatide-alone group at this time ( $p = 0.093$ ). At 6 months, CTx had significantly increased in both treatment groups ( $p < 0.005$  for both comparisons), with a significantly smaller increase in the teriparatide plus raloxifene group ( $p = 0.040$ ). CTx change from baseline to endpoint was significantly smaller ( $p = 0.015$ ) in the teriparatide plus raloxifene group ( $1312 \pm 582$  [SE] pM) versus the teriparatide-alone group ( $3294 \pm 579$  pM). PINP was significantly increased from baseline at all time-points measured (1, 3, and 6 months and endpoint;  $p < 0.001$  for all comparisons; Fig. 2B). Increases in PINP were not significant between groups at any time-point.

### BMD

Six months of treatment with teriparatide alone significantly increased BMD only at the lumbar spine (Fig. 3). Lumbar spine ( $6.19 \pm 0.65\%$ ), femoral neck ( $2.23 \pm 0.64\%$ ), and total hip ( $2.31 \pm 0.56\%$ ) BMD increased significantly from baseline to study endpoint in the combination group, and the increase in total hip BMD was significantly greater than in the teriparatide-alone group ( $p = 0.04$ ). Increases in lumbar spine ( $p = 0.28$ ) and femoral neck ( $p = 0.19$ ) BMD were not statistically different between treatment groups.

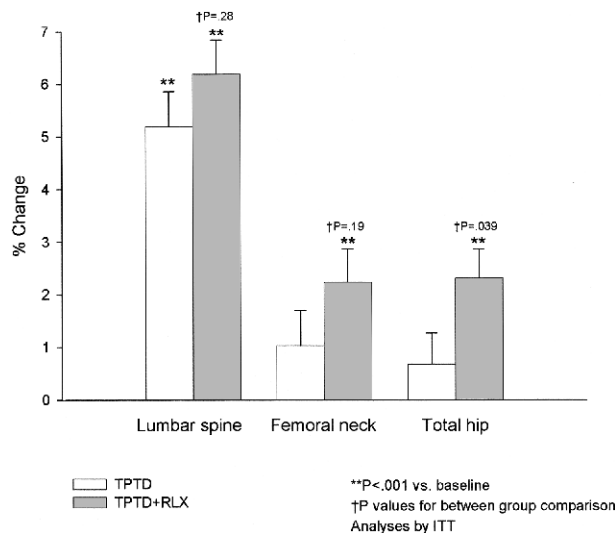
### Mineral and urate metabolism

Serum calcium was significantly increased in the teriparatide-alone group from baseline to endpoint ( $p < 0.001$ ) and at all time-points ( $p < 0.05$  for all comparisons) but not in the combination group ( $p = 0.91$ , Fig. 4). The increase in serum calcium was significantly greater in the teriparatide-

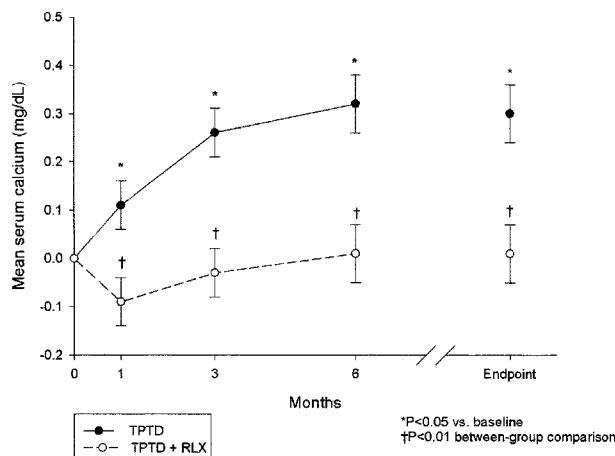


**FIG. 2.** Treatment comparisons over time in (A) serum CTx and (B) serum PINP. The baseline-to-endpoint analysis was conducted using ITT and LOCF techniques. All analyses were conducted using ITT techniques. For the baseline-to-endpoint analysis, last observation was carried forward for patients without data at the final visit. Errors bars indicate ±SE.

alone group compared with the combination group at all time-points ( $p = 0.004$  at 1 month and  $p < 0.001$  for all other comparisons). Mean calcium supplementation at randomization was  $1066 \pm 271$  mg/day in the teriparatide-alone group and  $1040 \pm 295$  mg/day in the combination group ( $p = 0.71$ ; Table 1). Mean change from baseline to endpoint in 24-h urinary calcium excretion was not significantly different between treatment groups ( $p = 0.63$ ). Serum calcium values  $>11$  mg/dL were considered possibly clinically significant and according to protocol patients were excluded if levels were above normal (reference range, 8.3–10.6 mg/dl) at screening. Although the inclusion criteria included a requirement that serum calcium be normal, one patient in the combination group was enrolled with serum calcium values of 10.7 mg/dl at screening and 11.2 mg/dl at randomization and on two occasions after initiating study drug. Excluding that patient, two patients in the combination group and five patients in the teriparatide-alone group had one or more postrandomization serum calcium values  $>11$  mg/dl and sustained hypercalcemia was confirmed ( $>11$



**FIG. 3.** Mean percent change in BMD from baseline to 6 months for lumbar spine, femoral neck, and total hip. Errors bars indicate  $\pm$ SE.



**FIG. 4.** Mean change over time in serum calcium by treatment group. Errors bars indicate  $\pm$ SE.

mg/dl on at least two occasions) in two teriparatide-alone group patients compared with no combination group patients. Importantly, no patients were reported to have symptoms of hypercalcemia or discontinued the trial because of hypercalcemia.

In the combination group, there was a significant decrease in serum phosphorus from baseline to endpoint (baseline, 3.78 mM; mean decrease,  $-0.20$  mM;  $p = 0.001$ ), but not in the teriparatide-alone group (baseline, 3.83 mM; mean increase,  $0.05$  mM;  $p = 0.43$ ). The baseline-to-endpoint change was significantly different between groups ( $p = 0.003$ ). Twenty-four-hour urinary phosphorus excretion was not different between treatment groups ( $p = 0.23$ ).

Serum uric acid was significantly increased at endpoint in both treatment groups ( $p < 0.001$  for both comparisons), and this increase was significantly smaller ( $p = 0.031$ ) in the combination group (baseline,  $4.64$  mg/dl; mean increase,

$0.94$  mg/dl) compared with the teriparatide-alone group (baseline,  $4.96$  mg/dl; mean increase,  $1.28$  mg/dl). Urinary uric acid excretion trended toward an increase in the combination group (baseline,  $433.8$  mg/dl; mean increase,  $37.82$  mg/dl;  $p = 0.072$ ), but not in the teriparatide-alone group (baseline,  $443.9$  mg/dl; mean increase,  $12.83$  mg/dl;  $p = 0.55$ ). However, the between-group comparison was not significant ( $p = 0.39$ ).

### Renal function

Creatinine clearance was significantly increased from baseline to endpoint in the combination group (baseline,  $94.85$  ml/min; mean increase,  $18.23$  ml/min;  $p = 0.007$ ). This increase was significantly different ( $p = 0.029$ ) from the nonsignificant decrease in the teriparatide-alone group (baseline,  $102.5$  ml/min; mean decrease,  $2.52$  ml/min).

### Adverse events

A total of eight patients (5.8%) experienced at least one serious adverse event: four patients in the combination group (5.8%) and four patients in the teriparatide-alone group (5.9%). In total, 10 patients (7.3%) discontinued the study because of an adverse event: 7 patients in the combination group (10.1%) and 3 patients in the teriparatide-alone group (4.4%;  $p = 0.33$ , between-group comparison). Muscle spasm was the only serious adverse event considered by the investigator to be possibly related to study drug. Reasons for study discontinuation are listed in Fig. 1. Two treatment-emergent adverse events were reported in  $\geq 2\%$  of patients. Hot flushes were reported in 3 patients (4.4%) in the teriparatide-alone group and in 12 patients (17.4%) in the combination group ( $p = 0.026$ , between-group comparison), and vomiting was reported in 5 patients (7.4%) in the teriparatide-alone group and in no patients in the combination group ( $p = 0.028$ , between-group comparison).

## DISCUSSION

Raloxifene administered in combination with teriparatide in postmenopausal women was well tolerated and significantly increased total hip BMD compared with teriparatide alone. Our findings suggest an effect of raloxifene to reduce the increase in bone resorption induced by teriparatide. However, the increases in PINP were not significantly smaller in the combination group compared with the teriparatide alone group, indicating a similar increase in markers of bone formation in both groups. The initial effect of teriparatide to increase bone formation markers without increasing resorption markers may result from the direct stimulation of bone formation without prior resorption; this initial effect of teriparatide has been termed an "anabolic window."

BMD results are consistent with the bone marker data and show that 6 months of treatment with teriparatide alone significantly increased BMD only at the lumbar spine, whereas 6 months of treatment with teriparatide plus raloxifene significantly increased BMD from baseline at the lumbar spine, femoral neck, and total hip. Teriparatide therapy is known to increase both porosity of cortical bone

and cortical thickness,<sup>(15)</sup> whereas raloxifene therapy is known to significantly increase femoral neck BMD.<sup>(1)</sup> In this study, femoral neck and total hip BMD significantly increased at 6 months and suggested that combination raloxifene treatment may mitigate the teriparatide-induced increase in cortical porosity.

Our results are consistent with findings from preclinical studies of raloxifene and other SERMS plus PTH(1-34).<sup>(7,8,16)</sup> However, our results differ from those observed with combination PTH(1-84) plus alendronate, where markers of bone formation did not increase.<sup>(11)</sup> In the parathyroid and alendronate (PaTH) trial, PINP increased at 1 month, but by 3 months had fallen below baseline and was 15.7% below baseline at 12 months in the combination group.<sup>(11)</sup> Here we report that combination teriparatide and raloxifene treatment increased PINP at 1 month and was >150% higher than baseline at 6 months. In PaTH, CTx was 50% below baseline at 1 month and remained at this level for 12 months after PTH(1-84) plus alendronate treatment.<sup>(11)</sup> This result is contrary to our findings of no change in CTx at month 1 with teriparatide plus raloxifene and a 50% lower increase at 3 and 6 months compared with the teriparatide-alone group.

The reasons for differences in bone turnover markers are unknown but could be caused by differences in study population, PTH preparations, or the antiresorptive agents. Bone turnover marker differences when raloxifene or alendronate are added to PTH could be a result of either differences in the effect of these agents on bone biology or because of differences in the relative potency of these antiresorptive agents. The actions of raloxifene are mediated through binding to estrogen receptors, whereas those of alendronate are mediated through binding to hydroxyapatite. The potency of raloxifene 60 mg/day is less than that of alendronate 10 mg/day. Thus, the differences in effects of these two antiresorptive drugs when used in combination with PTH could be caused by differences in the pathways used to reduce bone turnover or by differences in potency. If the latter hypothesis is correct, doses of alendronate <10 mg might have more favorable effects in combination with PTH. The differences observed in this study with combination teriparatide plus raloxifene versus those observed with combination PTH(1-84) plus alendronate highlight the importance of systematic investigation of specific antiresorptive drugs in combination with PTH.<sup>(17)</sup>

Serum calcium values significantly increased in the teriparatide-alone group but did not increase in the combination group. Conversely, serum phosphorous was unchanged in the teriparatide-alone group but significantly decreased in the combination group. Calcium supplementation initiated at screening and quantified at randomization was not significantly different between treatment groups, and measured 24-h calcium and phosphorous excretions in the two groups were also not significantly different. We hypothesize that the addition of raloxifene to teriparatide therapy increases incorporation of calcium and phosphorous into new bone. This hypothesis is supported by the combination group having similar bone formation, but significantly reduced bone resorption with increased BMD relative to teriparatide alone. Further studies are nec-

essary to confirm or reject this hypothesis. The clinical significance of the lesser increase in serum uric acid is uncertain. Uric acid significantly increased in the teriparatide group versus placebo in the Fracture Prevention Trial, but the teriparatide group did not have an associated increased incidence of gout or nephrolithiasis.<sup>(4)</sup>

The study was designed to evaluate surrogate endpoints and was not designed to assess fracture outcomes. A 6-month treatment period was selected for the study because of the pharmacodynamics of biochemical markers of bone formation and resorption in patients treated with teriparatide or raloxifene. Markers of bone formation increase rapidly in the first month of treatment with teriparatide, followed by secondary increases in markers of bone resorption.<sup>(5,18-20)</sup> The initial increase in bone formation markers without an immediate increase in bone resorption is believed to reflect the initial direct stimulation of osteoblasts without direct stimulation of osteoclasts. In postmenopausal women who begin treatment with raloxifene, markers of bone resorption are decreased within 2-3 months and remain suppressed.<sup>(13)</sup> For both raloxifene and teriparatide, markers of bone resorption are relatively unchanged between 6 and 12 months of treatment.<sup>(13,14)</sup> However, bone marker responses after 6 months of combination treatment were not assessed in this study.

In conclusion, raloxifene blunted the increase in bone resorption observed with teriparatide therapy without decreasing bone formation. Combination therapy resulted in significantly increased BMD from baseline at the lumbar spine, femoral neck, and total hip, with a significantly greater effect at the total hip compared with teriparatide alone. Confirmation that combination therapy provides advantages over monotherapy will require a longer study sufficiently powered to include fracture endpoints.

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## APPENDIX

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