Response to Teriparatide in Patients with Baseline 25-Hydroxyvitamin D Insufficiency or Sufficiency

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Key Words: teriparatide, vitamin D, insufficiency.
Abstract

Context: Serum 25-hydroxyvitamin D (25OHD) concentrations >30 ng/ml have been recommended for lowering fracture risk.

Objectives: To determine if 25OHD sufficiency is a prerequisite for effective response to teriparatide (TPTD).

Design and Patients: Data were from 1620 osteoporotic postmenopausal women in the Fracture Prevention Trial. The response to teriparatide was assessed in women subgrouped by having 25OHD insufficiency (>10 but ≤30 ng/ml) or 25OHD sufficiency (>30 but ≤183 ng/ml) at the baseline (randomization) visit. An abnormal intact PTH was exclusionary.

Interventions: At baseline, after at least 1 month of supplementation with calcium (1000 mg) and vitamin D (400 to 1200 IU) daily, women were randomized to placebo, TPTD 20 µg or TPTD 40 µg by daily subcutaneous injection for a median of 19 months. Observation was for a median of 21 months.

Main Outcome Measures: Vertebral and nonvertebral fractures, change in bone mineral density (BMD) at the lumbar spine and femoral neck, change in bone formation marker amino-terminal extension peptide of procollagen type 1 (PINP), and the proportion of women with serum calcium ≥ 2.76 mmol/L 4 to 6 hours after dosing.

Results: TPTD reduced vertebral and nonvertebral fracture risk, increased lumbar spine and femoral neck BMD, and increased PINP relative to placebo in the two 25OHD subgroups. There were no significant differences in these endpoints between the subgroups (each treatment by-subgroup interaction p >
0.10). However, it should be noted that because of the limited number of fractures, this study does not exclude the possibility of differences in fracture outcome between the subgroups.

**Conclusions:** In postmenopausal women with osteoporosis and normal intact PTH, the responses to TPTD did not differ significantly in women with baseline 25OHD insufficiency or sufficiency.
Introduction

Vitamin D is essential for maintaining calcium homeostasis and optimizing bone health. Low concentrations of vitamin D lead to alterations in calcium and phosphorus homeostasis, secondary hyperparathyroidism, bone loss, osteoporosis, and an increase in fracture risk (1-3). More severe degrees of vitamin D deficiency may lead to impairment of bone mineralization and osteomalacia (4). Additionally, low serum concentrations of 25-hydroxyvitamin D (25OHD), have recently been associated with impaired lower extremity strength and performance (5). Adequate calcium and vitamin D intake is considered an essential component of osteoporosis management (6).

Numerous epidemiological studies have assessed the prevalence of low serum 25OHD (7-10) and found that vitamin D inadequacy is a common problem worldwide. For example, more than half of North American women receiving therapy to treat or prevent osteoporosis have 25OHD inadequacy (10). Worldwide, over one billion people may have vitamin D deficiency or insufficiency (11).

Recently, it has been postulated that having vitamin D insufficiency might impair the therapeutic response to osteoporosis therapy. One study has suggested that without pharmacological vitamin D replacement, etidronate confers smaller increases in bone mineral density (BMD) in patients with vitamin D insufficiency versus sufficiency (12). However, two recent studies showed raloxifene and
alendronate, when co-administered with calcium and vitamin D supplementation, conferred similar increases in BMD in patients with vitamin D insufficiency versus sufficiency (13,14).

Teriparatide [rhPTH(1-34), TPTD] is a bone anabolic drug with an essentially opposite mechanism of action from that of antiresorptive drugs (15). While antiresorptive drugs decrease bone turnover by inhibiting resorption, teriparatide increases bone turnover with a positive balance of bone formation versus resorption. In postmenopausal women with osteoporosis, the clinical effects of teriparatide include increases in lumbar spine and femoral neck BMD and reduced vertebral and nonvertebral fracture risk (16). This analysis was conducted to determine whether it is important to normalize serum 25OHD prior to TPTD initiation or whether the same benefits of therapy can be achieved by initiating supplementation around the time that therapy is initiated. Given that women with osteoporosis commonly have inadequate vitamin D concentrations, the current analysis explores the fracture risk reduction, BMD, and bone turnover marker responses to teriparatide in women with 25OHD sufficiency versus insufficiency at baseline.

**Materials and Methods**

**Study population**

Data from the multicenter Fracture Prevention Trial (FPT) were used in this analysis. The methods and results of the FPT have been previously published
(16). Briefly, this double-blinded, placebo-controlled trial included ambulatory, postmenopausal women with osteoporosis ranging in age from 42 to 86 years. Approximately 1000 mg/d of elemental calcium and approximately 400 to 1200 IU/d of vitamin D were supplied as open-label supplement(s) in which the dose of vitamin D was at the discretion of investigators; these were in the form of a calcium supplement and a vitamin D supplement, a combination calcium and vitamin D supplement, or contained within a multivitamin/multimineral supplement. The patients continued to take their calcium and vitamin D supplements at any time of the day throughout the study. At least a month after initiation of calcium and vitamin D supplementation, women were randomized to receive daily, self-administered, subcutaneous injections of placebo (n = 544), teriparatide 20 µg/d (n = 541), or teriparatide 40 µg/d (n = 552). Inclusion in the study required serum creatinine less than 2 mg/dl and other normal or clinically non-significant abnormal laboratory values, with specific requirements that serum calcium, serum endogenous parathyroid hormone (PTH), and urinary calcium excretion be within normal limits. The number of women excluded because of elevated serum calcium or PTH levels is unknown. By protocol, patients with serum 25OHD <10 ng/ml or >183 ng/ml (three times the upper limit of the reference range) at randomization were excluded. Even so, 6 patients had serum 25OHD less than 10 ng/ml at baseline; these patients were excluded from the current analysis. The median duration of exposure to teriparatide was 19 months and the median duration of observation was 21 months.
Fracture assessment

Thoracic and lumbar spine radiographs were performed at baseline and study endpoint. Radiographs were assessed at a central site (Osteoporosis and Arthritis Research Center, University of California San Francisco, San Francisco, CA, USA) by radiologists who were blinded to treatment, using a visual semi-quantitative (SQ) technique (17). A new vertebral fracture was reported for vertebrae not fractured at baseline with approximately 20% or greater height loss at follow-up. Nonvertebral fractures were documented by a review of the radiographs or radiologic reports and were classified as fragility fractures if the associated trauma would not have resulted in the fracture of a normal bone, in the opinion of the local investigator. Protocol-specified nonvertebral sites included clavicle, scapula, rib, sacrum, humerus, forearm, carpus, pelvis, femur, patella, tibia, fibula, ankle, calcaneus, tarsus, and metatarsal.

BMD assessment

Lumbar spine and femoral neck BMD were assessed by dual-energy X-ray absorptiometry (DXA) using Hologic (Hologic Corp., Bedford, MA, USA), Norland (Norland Corp., Ft. Atkinson, W Corp., Madison, WI, USA), and GE-Lunar (Lunar Corp., Madison, WI, USA) equipment. To eliminate differences attributable to densitometer manufacturer, BMD values were converted to standardized units (expressed as grams per square centimeter). BMD measurements were analyzed centrally by persons blinded to treatment. Vertebrae that could not be analyzed due to prevalent vertebral fractures apparent on the DXA screen,
surgical artifact, excessive osteophytes, or other permanent artifact were excluded from the analysis. Serial measurements of a spine phantom at each center were used to adjust for minor changes in densitometer performance and to assess the consistency of measurements between centers.

**Laboratory analyses**

Bone formation marker amino-terminal propeptide of type I procollagen (PINP) was used for this analysis because this marker had the highest signal-to-noise ratio of those assessed in the FPT (18), and 3-month changes in this biomarker were correlated with lumbar spine BMD response at 18 months (19). Baseline and 3-month PINP assessments were performed on a subset of 771 patients. The baseline demographics of this PINP subset were not significantly different from those of the overall study population (19). Serum samples were stored at –20°C at Covance Central Laboratories, Inc., (Indianapolis, IN, USA) and later shipped to SUPREME SA (Liege, Belgium) for testing using the UniQ assay (Orion Diagnostica, Espoo Finland; intra-assay CV, 4.8% – 13.7%; inter-assay CV, 3.1% - 8.2%) by persons blinded to group assignment.

Samples for serum calcium were collected at baseline and at approximately 4 to 6 hours after the previous injection (post-dose) of study drug at 1, 3, 6, 12, and 18 months, as well as at early discontinuation and study closeout visits from 1161 women. Patients were defined as having post-dose hypercalcemia if they
had serum concentrations ≥2.76 mmol/L. Previously serum calcium levels were found to be maximal at 4 to 6 hours after TPTD injections (post-dose) (16).

Fasting blood samples for assessment of 25OHD were obtained at a screening visit prior to initiation of calcium and vitamin D supplementation, at the baseline randomization visit at least 1 month after initiation of calcium and vitamin D supplements and 12 months after randomization. Samples were centrifuged and serum was frozen until analyzed. Serum 25OHD was measured by RIA (DiaSorin, Stillwater, MN, USA) with an inter-assay coefficient of variation (CV) between 2.7% and 6.0%.

**Statistical analysis**

25OHD concentrations at the baseline (randomization) visit were defined as “insufficient” if they were >10 ng/ml (25 nmol/liter) and ≤30 ng/ml (75 nmol/liter), and were defined as “sufficient” if they were >30 ng/ml (75 nmol/liter). Binary variables (incidence of new vertebral fractures, non-vertebral fractures, and hypercalcemia) were compared using logistic regression models. Effects in the logistic regression model included treatment, subgroup defined by baseline 25OHD level, and treatment-by subgroup interaction. The term “no significant difference” indicates that there is no statistically significant interaction of 25OHD subgroup with treatment difference in an outcome. Additional analyses were also performed when baseline 25OHD level was treated as a continuous variable in the logistic regression model. For the continuous variables including changes in
BMD from baseline, subgroup analyses of baseline 25OHD status were performed using analysis of variance (ANOVA). Effects in the model included treatment, 25OHD subgroup, and treatment-by-subgroup interaction. The distribution of PINP changes was skewed; therefore, ranked ANOVA was used to compare the actual changes in PINP from baseline to 3-months between the treatment groups.

The assessment of primary interest was the classification of vitamin D status at baseline, i.e. the randomization visit at which study drug was initiated; as noted, patients had taken calcium and vitamin D supplements for at least a month at this timepoint. Additionally, vitamin D status assessed at the screening visit approximately a month prior to initiation of study drug and prior to initiation of calcium and vitamin D supplementation, as well as concentrations measured at 12 months after randomization were considered.

**Results**

**Demographics**

Of 1620 women for whom 25OHD was measured at randomization, 767 (47.3%) had 25OHD insufficiency. There were no other significant differences in baseline characteristics between the treatment groups among the women with sufficient or insufficient 25OHD concentrations. Body mass index (BMI) values tended to be higher in women with sufficient 25OHD concentrations compared to those with...
insufficient 25OHD (Table 1), but these differences were not statistically significant.

**Change in vitamin D status**

The vitamin D status of 1409 patients who had assessments at screening, randomization, and 12 months are provided in Table 2. At screening, 4% to 6% of participants were vitamin D deficient and 55% to 60% were insufficient. At randomization, after approximately a month of calcium and vitamin D supplementation, very few were deficient, but approximately 50% remained insufficient. After 12 months of vitamin D supplementation and study drug, there was no significant change in the proportion of patients with 25OHD deficiency and insufficiency versus randomization in the placebo group, while in the TPTD20 and TPTD40 groups, about 67% of women were 25OHD insufficient. The proportions of women with 25OHD insufficiency were significantly greater at 12 months compared to values at baseline (randomization) (Table 2) in each TPTD group.

**Vertebral and nonvertebral fracture risks**

Among women with baseline 25OHD sufficiency, vertebral fractures occurred in 17 of 447 (3.8%) and 37 of 231 (16.0%) women in the combined TPTD- and placebo-treated groups, respectively [odds ratio (OR) 0.21 (95% CI: 0.11 - 0.38)] (Figure 1). Nonvertebral fractures occurred in 11 of 562 (1.9%) women in the
TPTD group and 18 of 285 (6.3%) women in the placebo group [OR 0.30 (95% CI: 0.14- 0.64)].

Among women with baseline 25OHD insufficiency, vertebral fractures occurred in 23 of 420 (5.5%) women in the TPTD group and 27 of 209 (12.9%) women in the placebo group [OR 0.39 (95% CI: 0.22- 0.70)] (Figure 1). Nonvertebral fractures occurred in 17 of 517 (3.3%) and 12 of 250 (4.8%) women in the TPTD- and placebo-treated groups, respectively [OR 0.67 (95% CI: 0.32- 1.43)].

The ratios of odds ratios for vertebral and non-vertebral fractures between the vitamin D sufficiency and insufficiency subgroups were 0.53 (95%CI: 0.23-1.22) and 0.44 (95%CI: 0.15-1.29), respectively. Although the difference between TPTD and placebo was numerically smaller in women with baseline 25OHD insufficiency compared with those with sufficiency, there were no significant differences in the incidence of vertebral and nonvertebral fractures between the subgroups (Figure 1, treatment-by-subgroup interactions for vertebral fracture p = 0.14, and non-vertebral fracture p = 0.13)

Additional analyses of 25OHD treated as a continuous variable did not show any statistically significant effects of baseline 25OHD concentration (treatment-by-baseline 25OHD level interactions for vertebral fracture p = 0.41, and non-vertebral fracture p = 0.14). The results remained similar after adjusting for BMI.

*BMD and bone turnover marker changes*
The mean changes from baseline in lumbar spine BMD at 18 months, and
femoral neck BMD at 12 months, in women with baseline 25OHD sufficiency or
insufficiency, are presented in Figure 2. Compared to placebo, both teriparatide
20 µg/d and teriparatide 40 µg/d significantly increased mean lumbar spine BMD
in women having either baseline 25OHD sufficiency or insufficiency. Both TPTD
20 µg/d and 40 µg/d significantly increased mean femoral neck BMD in women
with either baseline 25OHD sufficiency or insufficiency. There were no
significant differences in the increases in lumbar spine and femoral neck BMD
across vitamin D subgroups. (treatment-by-subgroup interactions for lumbar
spine BMD p = 0.29, and femoral neck BMD p = 0.64). The results remained
similar after adjusting for BMI.

The changes in bone formation, as assessed by the median increases in PINP
from baseline to 3 months, are shown in Figure 3. Compared to placebo, both
the TPTD20 and TPTD40 groups had similarly increased PINP, regardless of
baseline 25OHD status (treatment-by-subgroup interaction p = 0.28).

**Incidence of elevated serum calcium levels**

The effects of baseline 25OHD status on the incidence of at least one occurrence
of elevated serum calcium concentrations ≥2.76 mmol/L at 4 to 6 hour post-dose)
are presented in Figure 4. In women with sufficient or insufficient 25OHD
concentrations, there was a significantly higher incidence of elevated serum
calcium with TPTD40 treatment compared to the placebo- and TPTD20-treated
groups. There was no significant difference in the incidence of elevated serum calcium between the TPTD20 and placebo groups. There was no significant difference in the incidence of elevated serum calcium concentrations between women with baseline 25OHD sufficiency and insufficiency (treatment-by-subgroup interaction p = 0.54).

**Vitamin D status at other timepoints**

All above analyses were repeated defining the same vitamin D subgroups but considering the 25OHD concentration obtained at the screening visit (approximately a month prior to the baseline randomization visit and prior to initiation of sponsor-provided calcium and vitamin D supplementation), and again considering the 25OHD concentration obtained at 12 months after randomization. The results of these analyses (data not shown) were similar to those described above based on baseline vitamin D status.

**Discussion**

Current standard of care for patients with osteoporosis includes provision of vitamin D. An important clinical question is whether 25OHD should be sufficient prior to initiation of osteoporosis therapy. If so, this could significantly delay the initiation of therapy because it takes about 3 months for the serum 25OHD level to come into steady state after increasing vitamin D intake (20). In postmenopausal women with low bone mass, the effects on BMD of alendronate (14) and raloxifene (13) were not impacted by vitamin D insufficiency or even deficiency. Furthermore, in patients with gastrectomy-induced vitamin D
resistance, alendronate was still able to improve bone health (21). However, in a prospective cohort study, changes in lumbar spine BMD in patients treated with alendronate were strongly positively related to baseline serum 25OHD concentrations (r=0.80) but no such relationships existed at the total hip and femoral neck (22). These data suggest that responses to antiresorptive therapy may not depend on the baseline vitamin D status, as long as patients receive concomitant vitamin D and calcium supplementation.

The question addressed in the current analysis is whether the effects of the bone anabolic drug teriparatide differed in patients with vitamin D insufficiency versus sufficiency. There is no common definition of vitamin D sufficiency and levels from 20 to 36 ng/ml have been suggested (23-26). We used a cut point of 30 ng/ml because it is the level below which serum PTH has been found to rise (10,25) and it reflects the opinions of 5/6 members of a recent expert panel (26). The 30 ng/ml cut point is similar to that used in previous analyses (10,13-14).

The baseline characteristics of the subgroups were well matched. Although BMI and serum 25OHD have been found to be inversely related in other studies (27), BMI tended to be higher in the vitamin D sufficient than in the insufficient group in this study. Possible explanations for this might be that per protocol, a disproportionate number of women with high BMI were excluded from participation on the basis of vitamin D deficiency and increased PTH levels (28,29,30).
There was no significant difference in the effect of teriparatide to reduce the incidence of vertebral and nonvertebral fragility fractures, to increase bone formation as assessed by PINP, and to increase BMD at the lumbar spine and femoral neck in patients with baseline 25OHD sufficiency or insufficiency. The incidence of serum calcium concentrations $\geq 2.76$ mmol/L 4 to 6 hours after dosing was consistent across treatment groups in the two 25OHD subgroups. Thus, the response to TPTD together with calcium and vitamin D was similar in women with baseline 25OHD sufficiency versus insufficiency.

There were several limitations of the current analysis. Because of the entry criteria used in this study, the present findings apply only to patients having normal intact PTH concentrations and 25OHD levels above 10 ng/ml. The fracture data does show some numerical differences in the difference between TPTD and placebo in the two subgroups. While the treatment-by-subgroup interaction is not statistically significant, the study may have included too few fractures to identify a real difference if one indeed existed. Examination of the confidence interval for the ratio of the odds ratios reveals the possible magnitude of the difference between the groups given the experimental findings. In this study, if the confidence interval for the ratio of the odds ratios between the subgroups includes 1, then the results would not be statistically significant. For vertebral fracture, the 95% confidence interval for the ratio of the odds ratios was 0.23-1.22, so the results were not statistically significant. Similarly, the 95% confidence interval for the ratio of odds ratios between the subgroups for non-
vertebral fracture was 0.15-1.29, so those results were also not statistically significant. However, the wide breadth of confidence intervals indicates that one need obviously be cautious about interpreting the nonsignificance. For the fracture outcome, this study does not exclude the possibility of clinically meaningful differences in fracture outcome in patients with vitamin D sufficiency versus insufficiency. However, the similarity of the BMD and marker findings between these subgroups are reassuring that there is unlikely to be a large difference in fracture outcome.

In the authors' view, patients with frank vitamin D deficiency (osteomalacia), should have their vitamin D deficiency corrected prior to initiation of other osteoporosis treatments. Normalization of serum 25(OH)D levels in these patients will usually normalize PTH concentrations within a few weeks, although elevated alkaline phosphatase concentrations may take longer to normalize (31). The prudent physician will probably delay initiation of osteoporosis treatments including teriparatide in a patient with vitamin D deficiency until a normalized alkaline phosphatase concentration provides evidence of skeletal healing. In agreement with current labeling recommendations, we support the requirement to not initiate teriparatide in patients with unexplained elevations in alkaline phosphatase or elevations in serum calcium prior to treatment. Also consistent with current labeling, we do not support routine measurement of serum PTH prior to treatment. We are aware of no evidence that measuring serum PTH prior to treatment adds value for patients with normal serum calcium and alkaline
phosphatase levels. However, as always, physicians may sometimes find assessments of serum PTH concentrations useful in the management of specific patients.

The observation that at entry, 58% of the women in this study had 25OHD insufficiency is in agreement with reports that more than half of North American women receiving therapy to treat or prevent osteoporosis have 25OHD inadequacy (11). After a month of calcium and vitamin D supplementation and after 13 months of supplementation with 400 to 1200 IU of vitamin D, 45% of patients in the placebo group remained vitamin D insufficient. Higher doses of vitamin D supplementation appear to be required to achieve vitamin D sufficiency in most older patients. Serum 25OHD has been estimated to change in direct proportion to the dose, with a slope of ~0.70 nmol/L for each additional 1 µg/d cholecalciferol input (32).

Interestingly, during teriparatide therapy, an increased incidence of vitamin D insufficiency was noted after 12 months of study drug. This apparent decrease in 25OHD during teriparatide therapy is accompanied by an increase in 1,25-dihydroxyvitamin D, consistent with an expected effect of teriparatide to increase the conversion of 25OHD to 1,25-dihydroxyvitamin D. These findings will be reported and discussed in detail in a subsequent publication.
Serum 25OHD assays are widely available from commercial laboratories. Results from assays for 25OHD are somewhat variable and dependent on the laboratory performing the analysis (33,34). Most of the commercial assays tested substantially overestimated serum 25OHD when compared with a gold standard HPLC (34,35). Serum 25OHD levels in this study were all measured using the DiaSorin RIA in a single centralized laboratory. This assay has compared well to the gold standard of HPLC (33,36).

In postmenopausal women with osteoporosis and normal intact PTH supplemented with vitamin D, the response to TPTD was similar in patients with baseline 25OHD insufficiency or sufficiency.

**Acknowledgements**

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References


Figure Legends

**Figure 1.** Fracture efficacy as a function of 25OHD insufficiency or sufficiency. OR, odds ratio (95%CI); TPTD20+40, pooled teriparatide 20 and 40 µg/day groups.

**Figure 2.** Bone mineral density (BMD) as a function of 25OHD insufficiency or sufficiency. *p<0.05 for both TPTD groups vs. placebo. TPTD20, teriparatide 20 mcg/day; TPTD40, teriparatide 40 mcg/day.

**Figure 3.** P1NP levels as a function of 25OHD insufficiency or sufficiency. *p<0.05 for both TPTD groups versus placebo (n=260). TPTD20, teriparatide 20 µg/day (n=257); TPTD40, teriparatide 40 µg/day (n=254). IQR = intra-quartile range.

**Figure 4.** Incidence of 4 to 6 hour post-dose serum calcium ≥ 2.76 mmol/L as a function of 25OHD insufficiency or sufficiency. *p<0.05 for TPTD40 group vs. both placebo and TPTD20. TPTD20, teriparatide 20 µg/day; TPTD40, teriparatide 40 µg/day.
Table 1. Comparison of baseline characteristics (mean ± SD) at randomization of 1614 women by vitamin D status subgroup and randomization to placebo, TPTD 20 µg/d, or TPTD 40 µg/d. SD - standard deviation; TPTD20 - teriparatide 20 µg/d; TPTD40 - teriparatide 40 µg/d; BMI - body mass index; LS - lumbar spine; FN - femoral neck; BMD - bone mineral density; 25OHD - 25-hydroxyvitamin D; PTH - parathyroid hormone.

<table>
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<tr>
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<td>Age (years)</td>
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<td>70.3 ± 7.1</td>
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<td>BMI (kg/m²)</td>
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<td>Weight (kg)</td>
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<td>LS BMD (g/cm²)</td>
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<td>FN BMD (g/cm²)</td>
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<td>PTH (pg/ml)</td>
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<td>Calcium (mg/ml)</td>
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<tr>
<td>Phosphorus (mg/ml)</td>
<td>3.79 ± 0.49</td>
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Table 2. Percentage of participants who were vitamin D deficient (serum vitamin D \(\leq 10\) ng/ml, insufficient (serum vitamin D between 10 and 30 ng/ml), or sufficient (serum vitamin D >30 ng/ml) at study enrollment, after 1 month (randomization), and after 12 months of 400 to 1200 IU/d vitamin D supplements.

<table>
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<th>TPTD40 (N=460)</th>
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<td>Vitamin D deficient (%)</td>
<td>Vitamin D insufficient (%)</td>
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<td>Enrollment</td>
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<td>Randomization</td>
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<td>12 months</td>
<td>0.2</td>
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*P<0.05 compared with baseline.
Figure 1

Vertebral Fracture

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<tr>
<th>Baseline 25-Hydroxyvitamin D</th>
<th>Sufficient (&gt;30 ng/mL)</th>
<th>Insufficient (≤ 30 ng/mL and &gt;10 ng/mL)</th>
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<td>Placebo</td>
<td>OR = 0.21 (0.11, 0.38)</td>
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Nonvertebral Fracture

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<td>OR = 0.30 (0.14, 0.64)</td>
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Figure 2

Lumbar Spine BMD (18 months)

Femoral Neck BMD (12 months)

Baseline 25-Hydroxyvitamin D

Mean Percent Change ± SE

Placebo
TPTD20
TPTD40

Sufficient (>30 ng/mL)
Insufficient (<30 ng/mL and >10 ng/mL)

Base25-Hydroxyvitamin D
Figure 3

PINP
(3 months)

Baseline 25-Hydroxyvitamin D

Median Change from Baseline (ng/mL) ± IQR

Placebo
TPTD20
TPTD40

Sufficient
 (>30 ng/mL)

Insufficient
 (≤30 ng/ml and >10 ng/mL)

Median Change from Baseline (ng/mL) ± IQR

-25 0 25 50 75 100 125 150 175 200

Placebo
TPTD20
TPTD40

*
Figure 4

Elevated Serum Calcium Concentrations
(> 2.76 mmol/L at 4 to 6 hour post-dose)

Baseline 25-Hydroxyvitamin D

Women (%) with Elevated Serum Calcium on 1 Occasion

- Placebo
- TPTD20
- TPTD40

* Sufficient (>30 ng/mL)
* Insufficient (≤30 ng/mL and >10 ng/mL)