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Original Article

Denosumab Significantly Increases DXA BMD at Both Trabecular and Cortical Sites: Results From the FREEDOM Study

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Abstract

Denosumab is an approved therapy for postmenopausal women with osteoporosis at high or increased risk for fracture. In the FREEDOM study, denosumab reduced fracture risk and increased bone mineral density (BMD). We report the spine and hip dual-energy X-ray absorptiometry (DXA) BMD responses from the overall study of 7808 women and from a substudy of 441 participants in which more extensive spine and hip assessments as well as additional skeletal sites were evaluated. Significant BMD improvements were observed as early as 1 mo at the lumbar spine, total hip, and trochanter (all $p < 0.005$ vs placebo and baseline). BMD increased progressively at the lumbar spine, total hip, femoral neck, trochanter, 1/3 radius, and total body from baseline to months 12, 24, and 36 (all $p < 0.005$ vs placebo and baseline). BMD gains above the least significant change of more than 3% at 36 months were observed in 90% of denosumab-treated subjects at the lumbar spine and 74% at the total hip, and gains more than 6% occurred in 77% and 38%, respectively. In conclusion, denosumab treatment resulted in significant, early, and continued BMD increases at both trabecular and cortical sites throughout the skeleton over 36 mo with important gains observed in most subjects.

Key Words: Bone mineral density; denosumab; DXA; osteoporosis.

Introduction

Postmenopausal osteoporosis is a chronic, progressive disease characterized by loss of bone mass and strength leading to increased fracture risk. Inhibition of receptor activator of nuclear factor kappa-B (RANK) ligand, an essential mediator of osteoclast formation, activation, and survival *(1–4)*, by the fully human monoclonal antibody, denosumab, is associated with improvements in bone mineral density (BMD) *(5–8)* and reductions in fracture risk *(9)*. Denosumab was recently approved for the treatment of postmenopausal women with osteoporosis at high or increased risk for fracture *(10,11)*.

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In clinical practice, dual-energy X-ray absorptiometry (DXA) remains widely used to help assess and follow the risk of fracture in individual patients and to monitor therapeutic intervention. Guidelines support repeating DXA measurements at periodic intervals to identify bone loss, monitor for disease progression, and assess response to treatment over time *(12−15)*. In clinical trials, BMD remains an important endpoint to analyze the efficacy of osteoporosis treatments *(5,16,17)*. Therefore, further description of the effect of denosumab on BMD at key skeletal sites is of relevance to all involved in the care of patients with osteoporosis and in the evaluation of treatments for this condition.

In the pivotal, phase 3 FREEDOM study in postmenopausal women with osteoporosis, denosumab increased BMD relative to placebo by a mean 9.2% at the lumbar spine and 6% at the total hip after 36 mo *(9)*. Those BMD gains were associated with a reduced risk of new vertebral fractures by 68% ($p < 0.001$), hip fractures by 40% ($p = 0.04$), and nonvertebral fractures by 20% ($p = 0.01$) relative to placebo *(9)*. Here, we describe the effect of denosumab on BMD at key skeletal sites measured during the FREEDOM study. These data further describe the effects of denosumab at both primarily trabecular and primarily cortical sites, the rapidity of its effect on BMD, and the characterization of individual subject BMD responses.

Materials and Methods

Study Design

FREEDOM was an international, multicenter, randomized, double-blinded, placebo-controlled study in 7808 postmenopausal women with osteoporosis. The details and primary endpoints of the FREEDOM study have been previously reported *(9)*. Subjects were randomized to receive either 60 mg denosumab or placebo subcutaneously every 6 mo for 36 mo. All subjects received daily calcium (≥1000 mg) and vitamin D (≥400 IU) supplements. Institutional review boards and ethics committees approved the protocol and consent process. The study was conducted in 213 centers with DXA capabilities to obtain baseline and follow-up DXA measurements in all subjects at the spine and hip at 36 mo. Additionally in 19 of those centers, more frequent BMD assessment and evaluation of additional skeletal sites were performed in a substudy of 441 subjects (DXA substudy), representing 34% of the total number of subjects enrolled in these sites. Within a site, subjects' interest in participation in the DXA substudy was queried on enrollment and consent was obtained; study participants were allowed to enter the substudy until it was fully enrolled.

Subjects

Eligible subjects were postmenopausal women with a BMD T-score lower than −2.5 at the lumbar spine or total hip and −4.0 or higher at both sites, naïve to osteoporosis treatment or had received prior bisphosphonate treatment for less than 3 yr and not within 12 mo of study entry, and free of other conditions known to impact bone metabolism (i.e., Paget's disease and osteomalacia). A minimum of 2 evaluable lumbar vertebrae in the L1−L4 region and 1 evaluable hip (i.e., either the left or right side) was required for inclusion. Subjects with any severe or more than 2 moderate prevalent vertebral fractures were excluded.

DXA BMD Assessments

For all subjects in the FREEDOM study, BMD assessments were performed at baseline and at 36 mo for the lumbar spine, and at baseline and months 12, 24, and 36 for the proximal femur (total hip, femoral neck, and trochanter). In the DXA substudy, BMD assessments were performed more frequently and at additional sites: both lumbar spine and proximal femur (total hip, femoral neck, and trochanter) were measured at baseline and at months 1, 6, 12, 24, and 36; 1/3 radius and total body were measured at baseline and at months 12, 24, and 36. BMD was measured by General Electric Lunar (n = 4797 in the FREEDOM study; n = 103 in the DXA substudy) (GE Healthcare, Chalfont St. Giles, UK) or Hologic (n = 3009 in the FREEDOM study; n = 338 in the DXA substudy) DXA bone densitometers (Hologic Inc., Bedford, MA) and the same machine was used for all measurements for an individual subject. Lumbar spine scans included L1 to L4 vertebrae; prevalent or incident fractured vertebrae confirmed by x-rays were excluded from the lumbar spine analysis. When possible, the left side was scanned for the proximal femur and 1/3 radius assessments. DXA scans were submitted to a central imaging vendor for analysis (Synarc Inc., San Francisco, CA) who also monitored scanner stability and cross-calibration over the duration of the study as well as the quality and reliability of the individual subject scans. Owing to the inclusion of a placebo arm, proximal femur BMD was measured yearly in all subjects to enable identification of significant bone loss during the study and notification of subjects and investigators.

Statistical Methods

Analyses of BMD changes included all subjects who had a baseline and 1 or more postbaseline BMD values at or before the time point of interest. Missing values were imputed by carrying forward the last nonmissing postbaseline value from the same anatomical site. Subjects were analyzed according to their randomized treatment assignment, regardless of the actual treatment received. The comparisons were based on analysis of covariance adjusting for treatment, baseline BMD, machine type (Lunar vs Hologic), and baseline BMD-by-machine-type interaction. The least-squares means of the treatment difference (denosumab-placebo) and corresponding 95% confidence intervals (CIs) were summarized by time points of interest.

For the overall FREEDOM population, a predefined analysis was conducted to determine the percent of subjects in each treatment group who achieved BMD changes from baseline at the lumbar spine, total hip, and femoral neck of ≤0%, >0−3%, >3−6%, and >6% after 36 mo. Odds ratios were estimated based on a proportional odds model adjusting for age.

Table 1
Baseline Demographics and Disease Characteristics

Parameters	FREEDOM (N = 7808)		DXA substudy (N = 441)	
	Placebo (N = 3906)	Denosumab (N = 3902)	Placebo (N = 209)	Denosumab (N = 232)
Age (yr), mean (SD)	72.3 (5.2)	72.3 (5.2)	73.0 (5.4)	73.0 (4.8)
Years since menopause, mean (SD)	24.2 (7.5)	24.2 (7.4)	25.2 (7.8)	25.1 (7.3)
Body mass index (kg/m^2), mean (SD)	26.0 (4.2)	26.0 (4.1)	25.2 (4.2)	25.4 (4.4)
Lumbar spine BMD T-score DXA, mean (SD)	−2.8 (0.7)	−2.8 (0.7)	−2.8 (0.6)	−2.8 (0.8)
Total hip BMD T-score DXA, mean (SD)	−1.9 (0.8)	−1.9 (0.8)	−1.9 (0.7)	−1.9 (0.8)
Prevalent vertebral fracture, n (%)	915 (23)	929 (24)	49 (23)	49 (21)

Abbr: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; SD, standard deviation.

Results

Subject Characteristics

The baseline characteristics of the 7808 (3906 placebo and 3902 denosumab) women in the overall FREEDOM study have been previously reported *(9)*. The 441 subjects (209 placebo and 232 denosumab) who participated in the DXA substudy had similar baseline demographics and characteristics to the overall population with regard to age, years since menopause, body mass index, BMD T-scores, and prevalent vertebral fracture status at baseline (Table 1). These parameters were balanced between treatment groups within the overall FREEDOM study and DXA substudy. Subjects in the DXA substudy had a mean (standard deviation [SD]) age of 73.0 (5.1) years, and mean (SD) baseline lumbar spine and total hip BMD T-scores of −2.8 (0.8) and −1.9 (0.7), respectively; 22% had any prevalent vertebral fracture at baseline. Similar to the completion rate for the overall FREEDOM study *(9)*, 83% of the substudy participants completed the 36-mo study.

BMD Changes From Baseline Over Time

BMD changes over time for all sites in the DXA substudy are provided in Fig. 1. Denosumab significantly increased BMD from baseline and compared with placebo ($p < 0.005$ to $p < 0.0001$) at the lumbar spine and regions of the proximal femur at all time points except for the 1-mo assessment at the femoral neck. At the 1/3 radius and total body, measured annually, significant improvements were also seen at all measured time points in response to denosumab treatment. The gains in BMD in the denosumab group were progressive over the 36 mo of the study. Accordingly, BMD changes in the denosumab group were significantly greater at 24 mo compared with 12 mo at all measured skeletal sites ($p < 0.0001$); and at 36 mo compared with 24 mo, BMD changes were significantly ($p < 0.0001$) greater at all measured skeletal sites with the exception of the femoral neck and 1/3 radius. Placebo subjects lost BMD over time at all skeletal sites except at the lumbar spine where mean BMD remained largely unchanged from baseline for the group.

At 36 mo, denosumab significantly increased BMD from baseline and compared with placebo at all skeletal site endpoints (all $p < 0.0001$; Fig. 1). The differences (95% CI) in mean percent change from baseline to month 36 between the denosumab and placebo groups were 9.2% (8.2% and 10.1%) at the lumbar spine and 6.0% (5.2% and 6.7%) at the total hip. The mean differences (95% CI) at the other measured skeletal sites were 4.8% (3.9% and 5.6%; $p < 0.0001$) at the femoral neck, 7.9% (7.0% and 8.9%; $p < 0.0001$) at the trochanter, 3.5% (2.7% and 4.2%; $p < 0.0001$) at the 1/3 radius, and 4.1% (3.7% and 4.6%; $p < 0.0001$) at the total body.

Consistent with the results of the DXA substudy, in the overall FREEDOM population, differences (95% CI) in mean percent change from baseline to month 36 between the denosumab and placebo groups were 8.8% (8.6% and 9.1%; $p < 0.0001$) at the lumbar spine, 6.4% (6.2% and 6.6%; $p < 0.0001$) at the total hip, 5.2% (5.0% and 5.4%; $p < 0.0001$) at the femoral neck, and 8.3% (8.0% and 8.6%; $p < 0.0001$) at the trochanter.

Percent of Subjects With BMD Improvements

The BMD change from baseline for individual subjects in the overall FREEDOM study is plotted from lowest to highest in Fig. 2, showing BMD increased (>0%) in 95% of denosumab subjects compared with 53% of placebo subjects at the lumbar spine, and 92% compared with 35%, respectively, at the total hip at month 36. At the femoral neck, BMD increases were observed in 85% of denosumab-treated subjects compared with 40% of placebo-treated subjects at month 36 (data not shown). Of the denosumab-treated subjects who did not show BMD gains (5% [n = 145] at the lumbar spine and 8% [n = 276] at the total hip), the majority of subjects (89/145 [61%] at the lumbar spine and 195/276 [71%] at the total hip) had a loss of 3% or lower (i.e., a negative change within the putative least significant change). A total of 56 (1.7%) denosumab-treated subjects at the lumbar spine and 81 (2.2%) subjects at the total hip had a BMD loss higher than 3%. Of note, the majority of these subjects (42/56 at

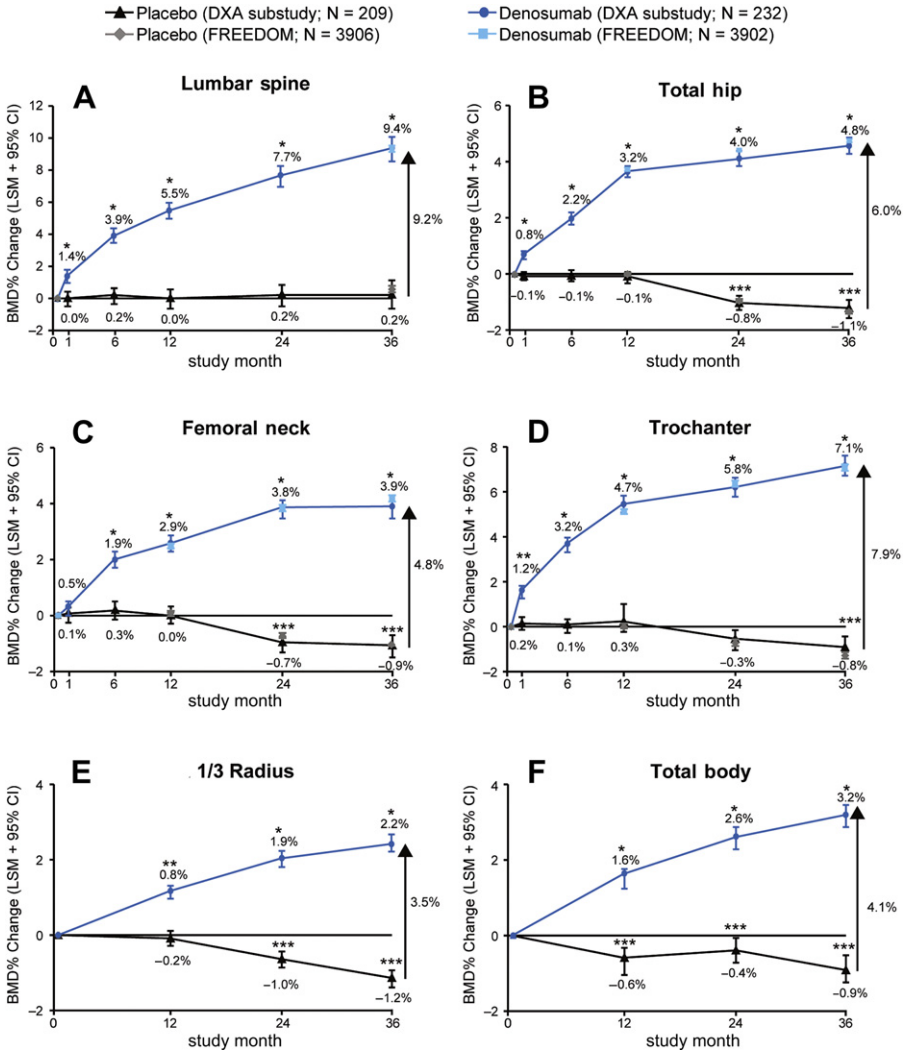

Fig. 1. Data shown are BMD percent change from baseline (LSM and 95% CI) over time for the DXA substudy at the (**A**) lumbar spine, (**B**) total hip, (**C**) femoral neck, (**D**) trochanter, (**E**) 1/3 radius, and (**F**) total body. Values for BMD percent change were overlaid at time points where DXA BMD was measured in the entire FREEDOM study population. The differences between the treatment groups may not add up from the mean percent change reported for each individual treatment group owing to rounding. The *p* values for comparisons relative to baseline or placebo were based on an analysis of covariance model adjusting for treatment, baseline BMD, machine type, and baseline BMD-by-machine-type interaction. $*p < 0.0001$ and $**p < 0.005$ for denosumab compared with baseline and placebo. $***p < 0.05$ for placebo compared with baseline. N's included randomized subjects enrolled in the DXA substudy or the overall FREEDOM study. BMD, bone mineral density; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; LSM, least-squares mean.

the lumbar spine and 54/81 at the total hip) discontinued or missed doses of denosumab during the study. Furthermore, only 0.6% (n = 17) of denosumab-treated subjects who received all 6 doses during the study experienced no change or a decrease in BMD from baseline at both the lumbar spine and total hip at 36 mo. Of the subjects in the placebo group who did not show BMD gains, 695 of 1473 (47%) and 1126 of 2335 (48%) had a BMD loss higher than 3% at the lumbar spine and total hip, respectively.

The percent of subjects who experienced BMD gains (>0%, >3%, or >6%) were examined in the overall FREEDOM study population as a preplanned analysis (Fig. 3). Gains higher than 3% (putative least significant change) were observed in 90% of denosumab-treated subjects compared with 30% of placebo-treated subjects at the lumbar spine, 74% vs 11%, respectively at the total hip, and 64% vs 17%, respectively at the femoral neck at month 36 (data not shown). Large BMD gains higher than 6% occurred in 77% of denosumab-treated subjects vs 13% for placebo at the lumbar spine, 38% vs 3%, respectively, at the total hip, and 33% vs 6%, respectively, at the femoral neck (data not shown) at month 36.

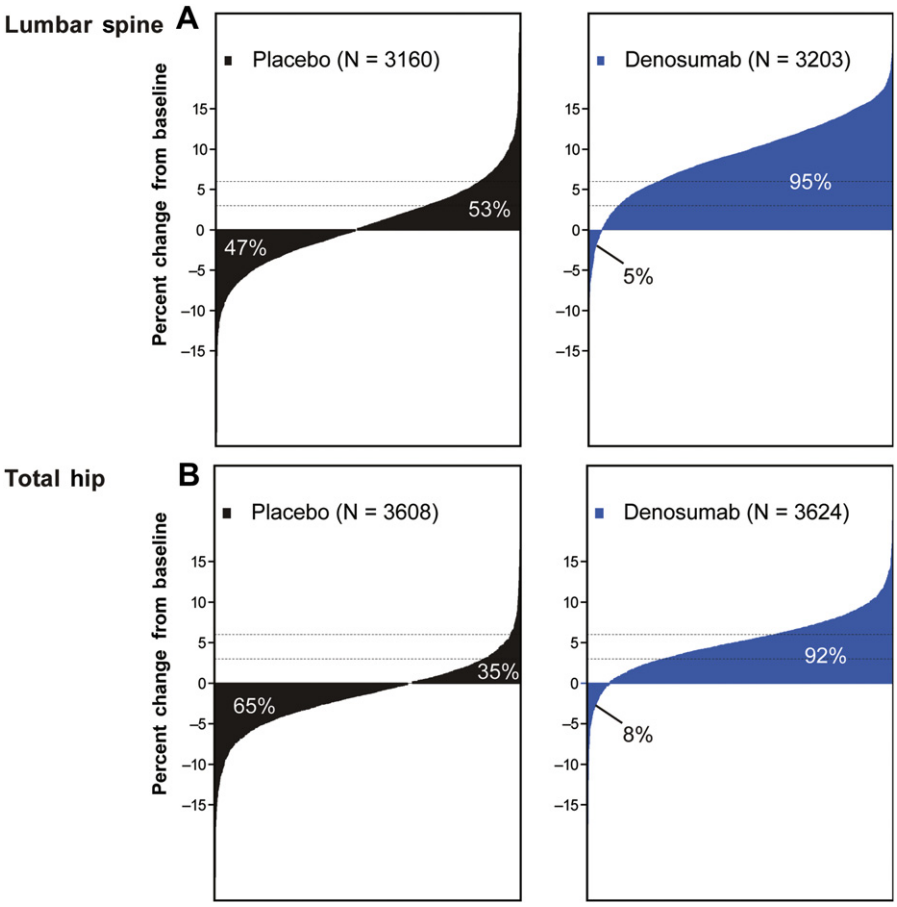

Fig. 2. Data are percent change in BMD from baseline to 36 mo by individual subject at the (**A**) lumbar spine and (**B**) total hip in the FREEDOM study. N's included subjects with baseline and ≥1 postbaseline measurement; missing data were imputed by last observation carried forward. X-axis represents each individual subject. BMD, bone mineral density.

Discussion

BMD as measured by DXA is an important and widely used measure in clinical practice to identify patients at risk for fracture and to monitor the effects of treatment *(12–15)*. In the present report, we characterized the BMD changes in the FREEDOM study, the large placebo-controlled, phase 3 study of denosumab in postmenopausal women with osteoporosis. FREEDOM was the pivotal study that demonstrated significant reductions in new vertebral, nonvertebral, and hip fractures with denosumab, leading to its worldwide approval for the treatment of postmenopausal women with osteoporosis at high or increased risk for fracture.

Denosumab is a fully human monoclonal antibody against RANK ligand, the key mediator for the formation, activation, and survival of osteoclasts. As a circulating antibody, denosumab is distributed to all skeletal regions and bone compartments through the extravascular space as reflected in the rapid decrease in bone resorption in all subjects *(7,18)* and the maximal reduction in markers of bone resorption, such as serum C-telopeptide, following subcutaneous denosumab administration *(18)*. Evaluation of the BMD response to denosumab treatment in this DXA substudy revealed consistent increases in BMD at all skeletal sites over the 36 mo of the study. In the placebo group, BMD decreased in a significant number of subjects, despite calcium and vitamin D supplementation. With denosumab, significant gains in BMD occurred not only at the lumbar spine and hip regions but also at the 1/3 radius and total body, sites that represent either a pure cortical region or reflect the 80% cortical bone preponderance of the skeleton, respectively *(19)*. The significant improvements in 1/3 radius and total body BMD observed in the overall FREEDOM study confirm and extend the previously reported positive impact of denosumab on cortical bone *(5,7,8)*. The positive effect of denosumab on cortical BMD has not been observed with other antiresorptive therapies for osteoporosis, and its effect has also been confirmed and further characterized with quantitative computed tomography (QCT) and high-resolution peripheral QCT imaging techniques *(20,21)*. These QCT techniques demonstrated that the cortical BMD gains observed with DXA were associated

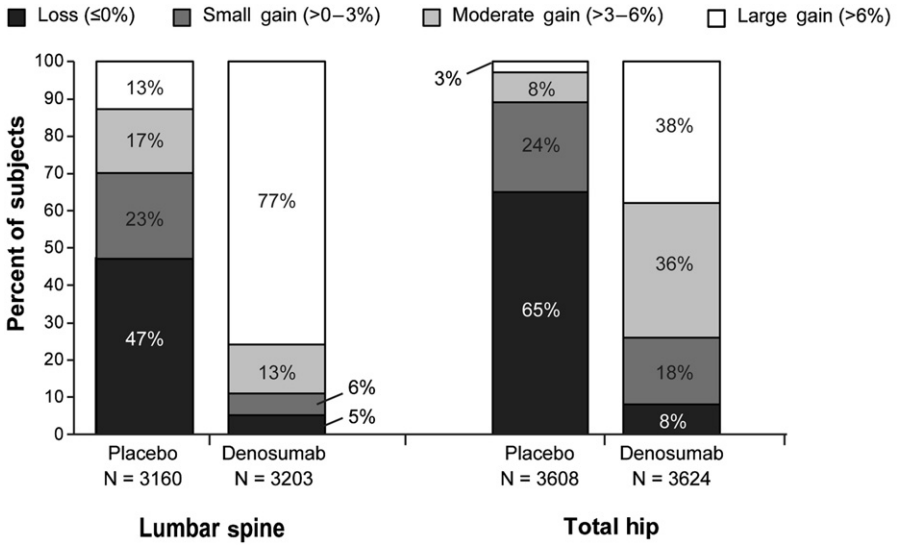

Fig. 3. Percentage of subjects by BMD response category based on the BMD percent change from baseline to month 36 at the lumbar spine and total hip in the FREEDOM study. N's included subjects with baseline and ≥1 postbaseline measurement; missing data were imputed by last observation carried forward. Percentages annotated in the bars were rounded to whole numbers. BMD, bone mineral density.

with increased cortical thickness, increased cortical bone mineral content, decreased cortical porosity, and improved estimated strength in response to denosumab treatment.

The gains in BMD were observed promptly following the administration of denosumab. Statistically significant changes in BMD in subjects treated with denosumab occurred as early as 1 mo when measured in the DXA substudy, consistent with the known rapid pharmacodynamic profile of denosumab on bone resorption markers. BMD progressively increased from baseline over the 36 mo of the study. Statistically significant ($p < 0.0001$) year-over-year increases occurred at all skeletal regions with the exception of the femoral neck and 1/3 radius for the change in BMD between 24 and 36 mo. In fact, it has now been reported from a phase 2 study that BMD continued to significantly increase at both the lumbar spine and total hip with continued denosumab treatment up to 8 yr *(22–24)*. The reason for this distinctive effect of denosumab is not fully understood, but could be the result of 1 or more of the following mechanisms: (1) the dynamic profile of denosumab administration (every 6 mo) on bone turnover markers allows for remodeling to resume at the end of the dosing interval, thus reopening the remodeling space to close it again rapidly with the next injection, (2) a possible indirect action of denosumab to increase the bone balance at the bone remodeling unit level through temporary increases in parathyroid hormone in the context of full inhibition of osteoclastic activity *(25)*, and (3) primary and secondary mineralization of new and existing osteons. Regardless of the mechanism, these progressive increases in BMD observed with long-term denosumab administration remain associated with low fracture rates for up to 6 yr as demonstrated in the ongoing FREEDOM extension study *(26)*.

In addition to the robust BMD improvements, these analyses also demonstrate the individual responses to denosumab treatment at the lumbar spine and proximal femur, which were measured in all subjects during the FREEDOM study. Most subjects responded to treatment with an increase in BMD, and a substantial amount of subjects had large increases in BMD higher than 6%. Losses of BMD were rare with denosumab and very few subjects reached the least significant change level. Furthermore, only 0.6% of denosumab-treated subjects who received all 6 doses of denosumab during the study experienced a decrease in BMD from baseline at both the lumbar spine and total hip at 36 mo. This responder analysis provides important information on the extent of benefit in individual subjects and demonstrates that the significant mean increases in BMD with denosumab reflect positive responses in most subjects.

The clinical relevance of the BMD gains is supported by the reduction in the risk of new vertebral fractures, hip fractures, and nonvertebral fractures observed in the whole FREEDOM study population *(9)* and by the large reductions in new vertebral, hip, and wrist fractures documented in the subgroups at high risk for fracture *(27,28)*. In addition, a recent analysis confirmed that the BMD gains observed with denosumab were of clinical relevance because they explained about half of denosumab's effect on risk reduction of new vertebral fractures and most of the reduction of risk of nonvertebral fractures *(29)*. This important observation supports the concept that gains in BMD assessed with DXA, if occurring in both the trabecular and cortical compartments as observed with denosumab, are relevant to bone strength and fracture protection. These data also suggest that follow-up DXA evaluations in patients receiving

denosumab therapy can be of benefit to assess for improvements in fracture risk.

In conclusion, denosumab treatment in women with postmenopausal osteoporosis in the FREEDOM study led to significant and clinically meaningful increases in BMD throughout the trabecular and cortical skeleton, and these increases were observed early and progressed over 36 mo of treatment.

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