Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Low Bone Mass

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Context: Denosumab treatment for 24 months increased bone mineral density (BMD) and reduced bone turnover markers (BTM) in postmenopausal women.

Objective: The aim was to determine the effects of prior denosumab or placebo injections on BMD, BTM, and safety over 24 months after treatment discontinuation.

Design: We conducted an off-treatment extension of a phase 3, randomized, double-blind, parallel-group study.

Participants: A total of 256 postmenopausal women with a mean age of 59 yr and a mean lumbar spine T-score of −1.61 at randomization participated in the study.

Interventions: Participants received placebo or 60 mg denosumab every 6 months for 24 months, followed by 24 months off treatment.

Main Outcome Measures: We measured the percentage changes in BMD and BTM, and evaluated safety.

Results: Of the 256 participants enrolled in the posttreatment phase, 87% completed the study. During 24 months of denosumab treatment, BMD increased (lumbar spine, 6.4%; total hip, 3.6%; 1/3 radius, 1.4%), and BTM decreased (serum C-terminal telopeptide of type 1 collagen, 63%; and N-terminal propeptide of type 1 procollagen, 47%), compared with placebo. After discontinuation, BMD declined, but the previously treated denosumab group maintained higher BMD than the previously treated placebo group at these sites ($P \leq 0.05$). Final BMD at month 48 strongly correlated with month 0 BMD. After denosumab discontinuation, BTM increased above baseline within 3 months (serum C-terminal telopeptide of type 1 collagen) or 6 months (N-terminal propeptide of type 1 procollagen) and returned to baseline by month 48. Adverse event rates during the off-treatment phase were similar between groups.

Conclusions: In postmenopausal women with low BMD, the effects of 60 mg denosumab treatment for 24 months on BMD and BTM are reversible upon discontinuation, reflecting its biological mechanism of action. Residual BMD measurements remained above those of the group previously treated with placebo. **(*J Clin Endocrinol Metab* 96: 972–980, 2011)**

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Abbreviations: BMD, Bone mineral density; BTM, bone turnover marker; iPTH, intact PTH; PINP, N-terminal propeptide of type 1 procollagen; RANK, receptor activator of nuclear factor-κB; sCTXI, serum C-terminal telopeptide of type 1 collagen.

Osteoporosis is a common skeletal condition that predisposes patients to fracture because of losses in bone mineral density (BMD) and deterioration of bone quality and strength (1–3). Although the individual risk of fracture is generally greater in women whose BMD falls below the diagnostic criterion for osteoporosis, the relationship between low bone density and fragility is maintained across a wide range of BMD. Current therapies intended to reduce fragility do so by modulating bone remodeling and increasing BMD. Most patients are treated with medications that act by decreasing bone resorption. The majority of patients receive aminobisphosphonates, which act by inhibiting farnesyl pyrophosphate synthase in osteoclasts, thereby reducing osteoclast activity (4–6). These drugs are incorporated into bone and have long terminal half-lives. In general, the effects of drugs in this class resolve very gradually after treatment discontinuation (7–11). Estrogens and selective estrogen receptor modulators also modulate bone remodeling by decreasing osteoclast activity, but their effects resolve more promptly after discontinuation (10–22).

Bone remodeling can also be modulated by inhibiting osteoclast activity via the blockade of receptor activator of nuclear factor-κB (RANK) ligand. RANK ligand is a key mediator of osteoclast formation, function, and survival that acts by binding to RANK on the surface of osteoclasts and their precursors. Excessive RANK ligand has been implicated in bone diseases associated with increased bone resorption, such as osteoporosis (23). Denosumab is a fully human monoclonal antibody against RANK ligand. Denosumab treatment decreases bone resorption, increases BMD, and reduces the risk of vertebral, nonvertebral, and hip fractures (24–28).

We previously reported the results from a phase 3, multicenter, randomized, double-blind, placebo-controlled study that investigated the effects of treatment with placebo or 60 mg denosumab every 6 months for 24 months on BMD and bone turnover markers (BTM) in postmenopausal women with low bone mass (24). Compared with placebo, denosumab significantly increased BMD at all measured sites and significantly decreased BTM, regardless of the time since menopause.

Here we report the results from an off-treatment extension of the primary study. The effects of placebo or denosumab discontinuation over 24 months on BMD, BTM, and safety after 24 months of treatment with placebo or denosumab were investigated in these postmenopausal women with low bone mass. This is the first description of the off-treatment effects after treatment with the approved clinical denosumab dose of 60 mg every 6 months.

Participants and Methods

The methods used in this clinical trial for the first 24 months of treatment were published previously and are summarized below (24).

Study design

This trial was a phase 3, multicenter, randomized, double-blind, placebo-controlled study with background calcium and vitamin D supplementation in all participants. The study consisted of two phases [on treatment and off treatment (Fig. 1)]. The on-treatment phase (month 0 to month 24) was conducted at 16 centers in the United States and five centers in Canada. Participants were randomized 1:1 to denosumab (Prolia; Amgen Inc., Thousand Oaks, CA) 60 mg or placebo sc every 6 months for 24 months (last dose at 18 months). Randomization was stratified by the time since onset of menopause (≤5 yr or >5 yr). Participants were instructed to take supplemental calcium (≥1 g) and vitamin D (≥400 IU) daily. The results of the on-treatment phase have been reported (24). All participants who completed the on-treatment phase (including receipt of at least one of the four scheduled doses of blinded placebo or denosumab) were eligible for enrollment in the extension phase of the study (off-treatment phase). All centers except one in the United States enrolled participants in the off-treatment extension (15 in United States, five in Canada). Treatment with investigational product and placebo was discontinued during this phase. Participants were instructed to continue supplemental calcium (≥1 g) and vitamin D (≥400 IU) daily. The participants in the off-treatment phase were not aware of their assignment during the on-treatment phase. During the off-treatment phase, if the study investigator determined that the overall fracture risk of a participant required additional treatment for osteoporosis, they could treat the participant with an approved therapy for osteoporosis.

The study followed country regulations and was conducted in accordance with the

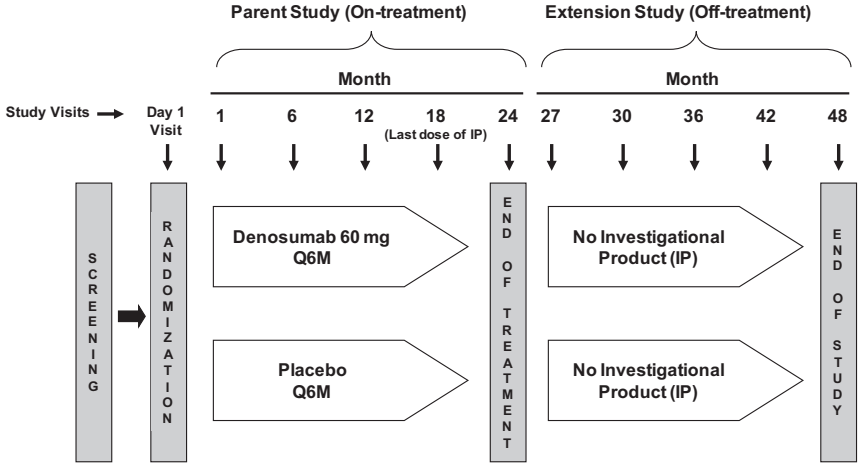

FIG. 1. Study design showing the 24-month parent study (on-treatment) and the 24-month extension study (off-treatment). Q6M, Every 6 months.

Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. The study protocol was approved by an ethics committee or institutional review board for each site. Participants provided written informed consent. Representatives of the sponsor, Amgen Inc., designed the study with investigator consultation and conducted the statistical analysis of the data according to a prespecified plan. All authors had access to the data, made contributions to the manuscript, and vouch for its accuracy and completeness.

Study population

For the on-treatment phase, eligible participants were ambulatory postmenopausal women with a lumbar spine BMD T-score between −1.0 and −2.5 who were not receiving medication that affected bone metabolism (other than calcium and vitamin D), who were free from any underlying condition (other than low BMD) that might have resulted in abnormal bone metabolism, and who had no history of a fracture after 25 yr of age. Key exclusion criteria included receipt of fluoride (apart from dental treatment) or strontium ranelate within 5 yr of enrollment, receipt of PTH or PTH derivatives, steroids, hormone replacement therapy, selective estrogen receptor modulators, tibolone, calcitonin, or calcitriol within 6 wk of enrollment, and receipt of oral bisphosphonates for at least 3 yr cumulatively. If oral bisphosphonates were used for more than 3 months but no more than 3 yr, women were eligible provided the last dose was at least 1 yr before enrollment. If oral bisphosphonates were used for no more than 3 months, women were eligible. Of the participants who enrolled in the extension phase, 96% had received all four doses of study drug during the on-treatment phase. Participants who chose to participate in the extension phase provided written informed consent before transition into the off-treatment phase.

Study procedures

Study visits occurred at months 0, 1, 6, 12, 18, and 24 (on treatment) and months 27, 30, 36, 42, and 48 (off treatment). Denosumab 60 mg or placebo was administered sc at months 0, 6, 12, and 18 (on treatment), and was discontinued during the off-treatment phase. BMD measurements were performed by dual energy x-ray absorptiometry at the lumbar spine and hip (months 0, 1, 6, 12, 24, 30, 36, 42, 48), 1/3 radius (months 0, 12, 24, 30, 36, 42, 48), and total body (months 0, 12, 24, 36, 48) and were read by a central facility (Synarc, Inc., San Francisco, CA). Measurements of the BTM serum C-terminal telopeptide of type 1 collagen (sCTXI) and N-terminal propeptide of type 1 procollagen (PINP) were made using predose, fasting morning samples (months 0, 1, 6, 10, 12, 14, 18, 24, 27, 30, 36, 42, 48). Serum levels of denosumab were measured at all study visits except months 42 and 48. Antidenosumab antibodies were measured at month 0 and at all study visits during the on-treatment phase. Standard safety chemistries were determined using fasting samples at month 0 and at all study visits. Hematology assessments were performed at month 0 and all study visits except month 1. Adverse events, clinical fracture information, and concomitant medications were recorded at all study visits. Safety was monitored by evaluating serum chemistry and hematology values and recording all adverse events. Although all fractures were reported as adverse events, analyses of clinical fractures were limited to those fractures confirmed by the central imaging facility (Synarc, Inc.). Clinical osteoporotic fractures were defined as any fracture excluding skull, facial, mandible, cervical vertebrae, metacarpals, finger and toe phalanges, pathological fractures, and fractures with high-trauma severity.

Statistical analyses

Final analyses of data from the on-treatment phase (months 0 to 24) were reported previously (24) and are presented in this manuscript as appropriate to illustrate the results from the off-treatment phase. However, some results from the on-treatment phase that are reported in this manuscript differ slightly from those reported previously (24) because the results presented in this manuscript only include data from those participants who continued into the off-treatment extension study.

Key exploratory objectives for the off-treatment extension study included changes in BMD of the lumbar spine, total hip, femoral neck, trochanter, and 1/3 radius; changes in BTM; and safety.

Analyses of BMD percentage change from month 0 included participants enrolled in the off-treatment phase with observed values at month 0 and the time points of interest. Analyses of BMD percentage change from month 24 included participants enrolled in the off-treatment phase with observed values at month 24 and the time points of interest. Percentage changes from month 0 or month 24 in lumbar spine, total hip, femoral neck, trochanter, and 1/3 radius BMD were summarized descriptively. Percentage changes from month 0 for the same cohort were also analyzed using a repeated measures mixed model with treatment, visit, month 0 value, treatment-by-visit interaction, densitometer type, and month 0 value-by-densitometer type interaction as fixed effects. Results are presented graphically as least squares means and 95% confidence intervals. Exploratory analyses were performed to investigate correlations between BMD values at month 0 and month 24; month 0 and month 48; and month 24 and month 48. Multivariate regression analyses were also performed to investigate the association between lumbar spine or total hip BMD percentage change from month 24 to month 48 and age, BMI, peaking sCTXI concentration, month 0 BMD T-score, or intact PTH (iPTH).

Analyses of percentage change from month 0 in BTM included participants enrolled in the off-treatment phase with observed values at month 0 and the time points of interest. Percentage changes from month 0 in BTM were summarized descriptively for the combined 48-month study. Exploratory analyses were performed to investigate correlations between values of BTM at month 0 and month 48.

For this report, safety analyses only included adverse events that started during the off-treatment phase. New adverse events occurring during the off-treatment phase were summarized by system organ class and by preferred terms [coded using Medical Dictionary for Regulatory Authorities (MedDRA) version 11.1]. Safety comparisons between the placebo and denosumab groups are considered descriptive and are unadjusted for multiple comparisons.

Results

Study population

Of the 332 participants enrolled in the on-treatment phase (166 placebo, 166 denosumab), 144 participants

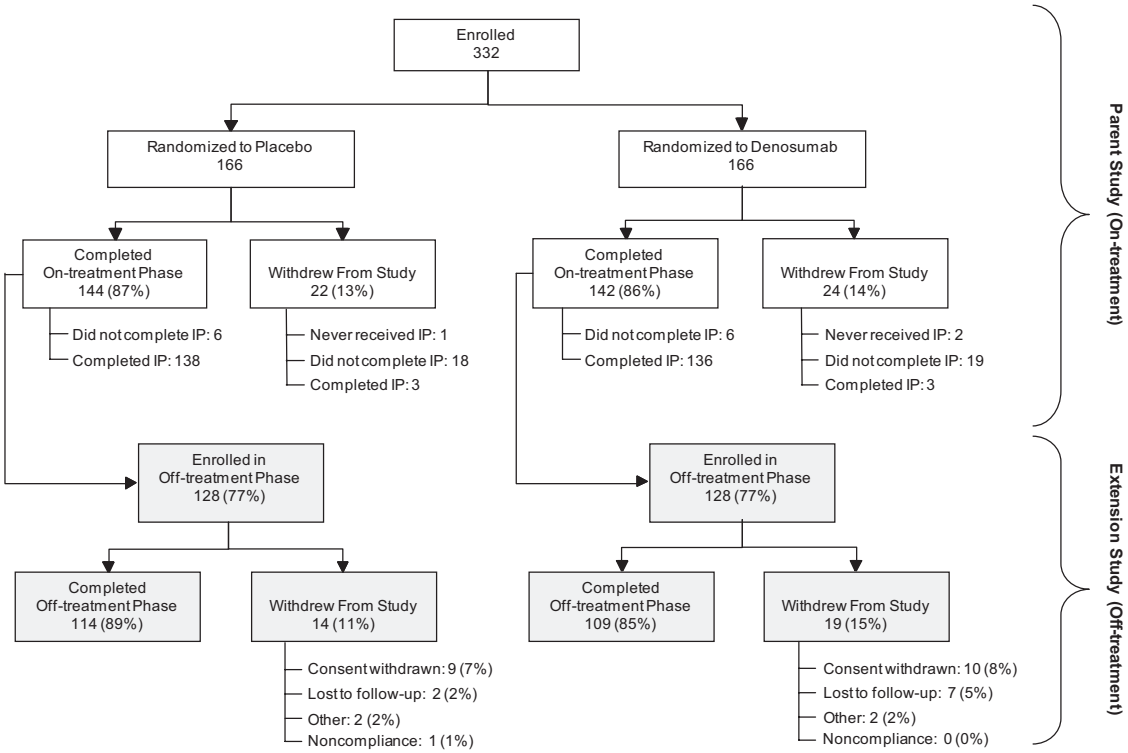

FIG. 2. Disposition of all participants. Participants completed investigational product (IP) if they received all four scheduled doses of blinded placebo or denosumab. Participants could continue on study after withdrawal from IP. All participants who completed the on-treatment phase (including receipt of at least one of the four scheduled doses of blinded placebo or denosumab) were eligible for enrollment in the off-treatment phase. Of the participants who enrolled in the extension phase, 96% had received all four doses of study drug during the on-treatment phase.

(87%) in the placebo group and 142 participants (86%) in the denosumab group completed the on-treatment phase (Fig. 2). Of the 256 participants enrolled in the extension (128 placebo, 128 denosumab), 114 participants (89%) in the placebo group and 109 participants (85%) in the denosumab group completed the off-treatment phase. The most common reason for discontinuing the off-treatment phase was consent withdrawal (n = 19; 7%) followed by loss of the participant to follow-up (n = 9; 4%). A similar percentage of participants in each group used other osteoporosis treatments during the off-treatment phase [seven previous placebo (5.5%), and 10 previous denosumab (7.8%)].

Most participants enrolled in the off-treatment phase were white (82%), mean age was 59 yr, mean years since menopause was 10, and mean month 0 lumbar spine BMD T-score was −1.61 (Table 1). iPTH and vitamin D concentrations were similar between the groups at baseline.

TABLE 1. Demographics and baseline characteristics (at month 0 of 48) of participants enrolled in the off-treatment phase (months 24–48)

Characteristic	Placebo	Denosumab	All
N	128	128	256
Age (yr)	58.9 (7.4)	59.4 (6.8)	59.1 (7.1)
Race/ethnicity, n (%)			
White or Caucasian	106 (83)	105 (82)	211 (82)
Black or African-American	3 (2)	5 (4)	8 (3)
Hispanic or Latino	11 (9)	8 (6)	19 (7)
Asian or Japanese	6 (5)	8 (6)	14 (5)
Other	2 (2)	2 (2)	4 (2)
Years since menopause	9.4 (8.1)	10.3 (8.9)	9.9 (8.5)
Body mass index (kg/m^2)	26.4 (5.0)	27.0 (4.8)	26.7 (4.9)
Lumbar spine BMD T-score	−1.66 (0.44)	−1.56 (0.42)	−1.61 (0.43)
sCTXI (ng/ml)	0.55 (0.25)	0.53 (0.25)	0.54 (0.25)
Serum PINP (μg/liter)	59.9 (30.4)	56.8 (24.7)	58.4 (27.8)
iPTH (pmol/liter)	4.16 (2.04)	4.14 (1.69)	4.15 (1.87)
25 (OH) vitamin D (ng/ml)	25.8 (12.4)	24.4 (10.0)	25.1 (11.3)

Values are expressed as mean (SD) unless otherwise indicated. N, Number of participants who enrolled in the off-treatment phase.

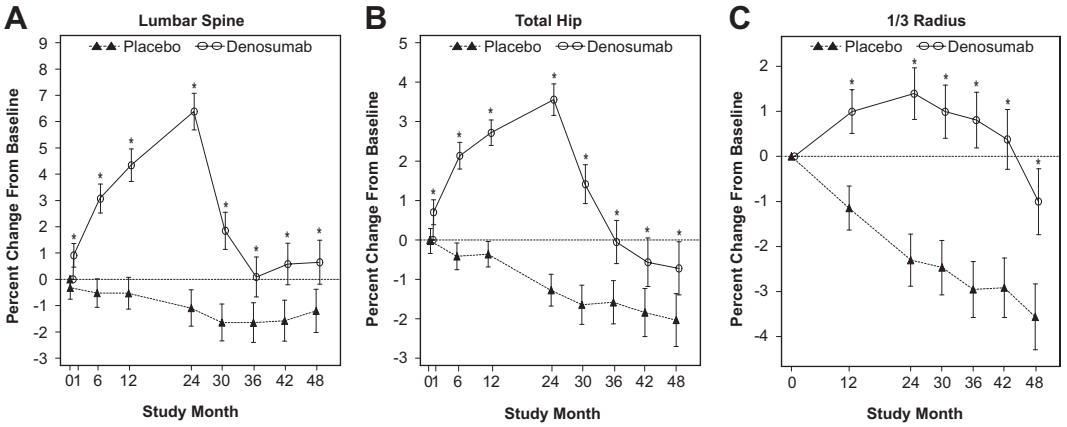

FIG. 3. Percentage change from month 0 in Lumbar Spine (A), Total Hip (B), and 1/3 Radius (C) BMD over 48 months. Percentage change from month 0 in BMD is presented as least squares means and 95% confidence intervals based on a repeated measures model that adjusts for treatment, strata, visit, month 0 value, densitometer type, treatment-by-visit interaction, and month 0 value-by-densitometer type interaction. Includes participants enrolled in the off-treatment phase with observed values at month 0 and the time point of interest [n = 110–128 (placebo) and n = 109–128 (denosumab)]. *, $P \leq 0.0071$.

Mean (SD) iPTH concentrations (picomoles per liter) were similar to baseline (prerandomization) values at month 24 [4.27 (2.24) previous placebo, and 4.57 (2.22) previous denosumab] and month 48 [4.14 (1.90) previous placebo, and 4.15 (1.98) previous denosumab]. Vitamin D concentrations were not measured subsequent to baseline. Overall, demographics and baseline characteristics were balanced among both groups and were similar to those of the participants enrolled in the on-treatment phase (24).

Bone mineral density

As previously reported (24), during the 24-month on-treatment phase, denosumab significantly increased BMD at the lumbar spine (6.4%), total hip (3.6%), 1/3 radius (1.4%) (Fig. 3, A–C), femoral neck (2.9%), and trochanter (5.6%) (data not shown), compared with placebo-treated participants (all $P < 0.0001$). In the off-treatment period from month 24 to month 48, BMD decreased at all sites for both groups (Fig. 3, A–C). Most of the decreases in the former denosumab group occurred between months 24 and 36. From month 36 to month 48, the BMD measurements approximately paralleled those of the former placebo group. The group that previously received denosumab maintained higher BMD than the former placebo group for lumbar spine, total hip, trochanter, femoral neck, and 1/3 radius at all time points (Fig. 3, A–C). At month 48, the BMDs in the former denosumab group did not fall significantly below the baseline values except at the 1/3 radius. These differences met criteria for significance except for the femoral neck at months 1, 42, and 48. As was detailed in the study protocol, these analyses included all participants in the off-treatment phase. Exclusion of participants who took bone medication during the off-treatment phase [seven (5.5%) previous placebo and 10 (7.8%) previous denosumab] demonstrated similar results, except for $P > 0.05$ for the femoral neck at month 36 and the trochanter at month 48. For individual participants previously treated with denosumab, there was a strong relationship between month 0 BMD values and final BMD values at month 48 at the lumbar spine, total hip, and 1/3 radius (r = 0.86, 0.94, and 0.95, respectively; all $P < 0.001$). Similar significant relationships were found between month 0 BMD and month 24 BMD values and between month 24 BMD and month 48 BMD values (data not shown).

Post hoc multivariate regression analyses demonstrated that there was a significant association between the percentage change in lumbar spine BMD after denosumab discontinuation and peaking sCTXI concentration ($P = 0.03$). There were no significant associations demonstrated between the percentage change in lumbar spine BMD after denosumab discontinuation and age, body mass index, or month 24 iPTH concentrations. Additionally, no significant associations were demonstrated between percentage change in total hip BMD after denosumab discontinuation and any of the participant characteristics discussed above.

Bone turnover markers

As previously reported (24), BTM concentrations rapidly declined after initiation of denosumab treatment and remained reduced throughout the 24-month on-treatment phase (Fig. 4, A and B). After denosumab discontinuation, concentrations of BTM increased above month 0 concentrations within 3 months (sCTXI) or 6 months (PINP), peaked at 30 months (sCTXI) or 36 months (PINP), and returned to month 0 concentrations by month 48. The peak median percentage change from month 0 was 63% (sCTXI) and 47% (PINP). BTM concentrations did not change significantly from month 0 in the placebo group throughout the entire 48-month study. As was detailed

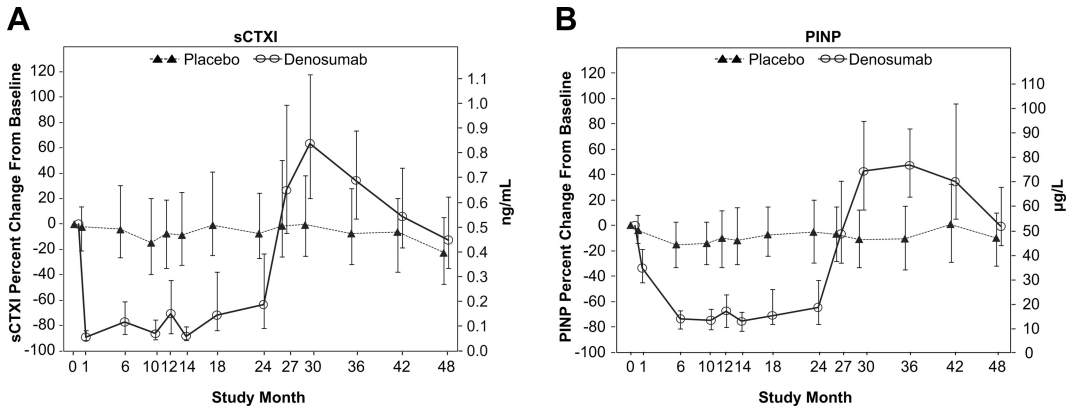

FIG. 4. Percentage change from month 0 in sCTXI (A) and PINP (B) over 48 months. Percentage change from month 0 in BTM are presented as medians and interquartile ranges (*left vertical axes*). Approximate corresponding concentrations are presented for reference (*right vertical axes*). The interquartile ranges shown on the graphs only apply to the percentage change axes. Includes participants enrolled in the off-treatment phase with observed values at the time point of interest [n = 113–128 (placebo) and n = 110–128 (denosumab)].

in the study protocol, these analyses included all participants in the off-treatment phase. Exclusion of participants that took bone medication during the off-treatment phase did not alter these results. For individual participants previously treated with denosumab, the final concentration of sCTXI or PINP at month 48 moderately correlated with the month 0 concentrations of these markers (sCTXI, r = 0.47; PINP, r = 0.46; both $P < 0.001$).

Safety

All participants who enrolled in the off-treatment phase were evaluated for safety. There were no deaths, and no participant withdrew from the study due to an adverse event during the off-treatment phase (Table 2). The proportions of participants reporting adverse events and serious adverse events during the off-treatment phase were similar between the two groups. There were 98 participants (76.6%) in the previously treated placebo group and 108 participants (84.4%) in the previously treated denosumab group who reported at least one adverse event during the off-treatment phase. Most adverse events were mild to moderate in severity. The three most frequent adverse events were arthralgia, nasopharyngitis, and back pain. The incidence of rashes was greater in the previously treated placebo group (n = 3; 2%) than the previously treated denosumab group (n = 0). There were no reports of osteonecrosis of the jaw.

Serious adverse events were reported by nine participants (7.0%) in the previously treated placebo group and seven participants (5.5%) in the previously treated denosumab group. The most common serious adverse events were neoplasms, which were reported by four participants (3%) in the previously treated placebo group and three participants (2%) in the previously treated denosumab group. In the former placebo group, these events included two cases of breast cancer and one case each of benign gastrointestinal neoplasm and benign ovarian tumor. In the former denosumab group, these events included one case each of meningioma, metastatic carcinoid, and malignant melanoma.

No notable changes in mean albumin-adjusted serum calcium concentration and no trends in serum chemistry or hematology parameters were noted during the off-treatment phase.

TABLE 2. Summary of adverse events during the off-treatment phase

	Placebo, n (%)	Denosumab, n (%)	*P* value
N	128	128	
Any AE	98 (76.6)	108 (84.4)	0.2
AEs occurring in >10% of participants in either treatment group			
Arthralgia	22 (17.2)	20 (15.6)	0.9
Nasopharyngitis	15 (11.7)	19 (14.8)	0.6
Back pain	22 (17.2)	15 (11.7)	0.3
Serious AEs	9 (7.0)	7 (5.5)	0.8
Neoplasm	4 (3.1)	3 (2.3)	1.0
Musculoskeletal or connective tissue disorder	1 (0.8)	2 (1.6)	1.0
Cardiac disorder	1 (0.8)	1 (0.8)	1.0
Infections	1 (0.8)	1 (0.8)	1.0
Injury, poisoning, or procedural complication	1 (0.8)	1 (0.8)	1.0
Gastrointestinal disorder	2 (1.6)	0 (0.0)	0.5
Nervous system disorders	1 (0.8)	0 (0.0)	1.0
Deaths	0 (0.0)	0 (0.0)	

N, Number of participants who enrolled in the off-treatment phase and received at least one dose of investigational product during the treatment phase; n, number of participants reporting at least one event; AE, adverse event.

Fractures

During the on-treatment phase, centrally confirmed clinical fractures occurred in six participants (4%) in the placebo group and two participants (1%) in the denosumab group. During the off-treatment phase, centrally confirmed clinical fractures occurred in four participants (3%) in the previously treated placebo group and four participants (3%) in the previously treated denosumab group. No clinical vertebral fractures were reported.

Discussion

This off-treatment study evaluated the effects of denosumab discontinuation over 24 months after treatment with 60 mg denosumab every 6 months for 24 months on BMD, BTM, and safety in postmenopausal women with low bone mass. This is the first report of off-treatment effects after treatment with the approved clinical 60 mg denosumab dose. Denosumab significantly increased BMD and decreased BTM during the 24-month on-treatment phase. These effects of denosumab treatment on BTM were transiently reversed upon treatment discontinuation, and there were reductions in BMD at all measured sites. However, at the end of the off-treatment phase, the previously treated denosumab group maintained higher BMD than the previously treated placebo group at all measured anatomical sites. The temporal pattern of increases in the bone resorption marker sCTXI followed by increases in the bone formation marker PINP indicated that remodeling remained coupled during the off-treatment phase. The overall profiles of adverse events, serious adverse events, and the incidence of centrally confirmed clinical fractures were similar between the two treatment groups during the off-treatment phase.

These results are consistent with those observed upon discontinuation of denosumab in a phase 2 dose-ranging study (27). As part of that study, participants treated with 210 mg denosumab every 6 months for 24 months were discontinued from treatment and were given placebo injections for a total of 24 months. During the off-treatment phase, BMD at all anatomic sites decreased to an extent comparable to the gains in BMD during 24 months of denosumab treatment but still remained greater than the placebo-treated group. In the previously treated denosumab group, there were transient increases of BTM above month 0 concentrations that returned to month 0 concentrations by month 48.

The observation that the effects of denosumab treatment on BMD and BTM were reversible after treatment discontinuation is consistent with the effects of discontinuation of other antiosteoporotic medications that do not persist in bone, including estrogen therapy and estrogen receptor agonists/antagonists. Discontinuation of these therapies is associated with a return to pretreatment levels of BMD (12–16), BTM (17), or both (10, 11, 18–20). Despite this return to pretreatment levels, large observational studies of postmenopausal estrogen therapy discontinuation have not demonstrated an increase in fracture risk (29–32). Reversibility of BMD and concentrations of BTM have also been observed with the anabolic agent teriparatide (21, 22). The effects of discontinuation of the bisphosphonates on BMD and BTM appear to be influenced by the affinity of the compounds to hydroxyapatite and the recycling of bisphosphonates (7–11, 33–35). It should be noted that although the concentration of BTM increased above month 0 concentrations after discontinuation of denosumab, these increases were transient and resolved during the observation period.

Denosumab is an antibody whose biological activity does not endure in the absence of continued administration. Osteoporosis is a chronic condition, and, as is the case with other chronic diseases, continued treatment is required to sustain the benefits of therapy. This is particularly important for women with elevated fracture risk.

It is noteworthy that although the effects of denosumab on BMD were reversible after treatment discontinuation, the previously treated denosumab group retained higher BMD than the previously treated placebo group for all measured sites at the end of the off-treatment phase, and the BTM resolved to baseline levels. Thus, denosumab-treated participants who discontinued treatment still maintained a treatment benefit as measured by BMD, compared with control participants who received only calcium and vitamin D.

There were no observed differences in the overall profile of adverse events or serious adverse events between the two treatment groups during the off-treatment phase. Although the incidence of centrally confirmed clinical fractures (all nonvertebral) was too small to permit definitive comparison, it was apparently similar between the two treatment groups. Although no differences were found in safety events or fractures in the women with low BMD studied here, the possibility cannot be excluded that a different outcome would result in a population with severe osteoporosis.

Similar to other extension studies, one of the limitations of our study was that not all participants continued into the off-treatment phase. In addition, the clinical inferences that can be drawn are limited by the sample size and the characteristics of our study population. Whether the results presented here can be generalized to women with more severe disease or to men remains to be determined.

In conclusion, these data demonstrate that in postmenopausal women with low BMD, the effects of 60 mg

denosumab every 6 months for 24 months on BMD and BTM are reversible upon treatment discontinuation for 24 months, reflecting the biological mechanism of action of denosumab. Thus, continued therapy is required to maintain treatment effects.

Acknowledgments

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