A 24-Month Study Evaluating the Efficacy and Safety of Denosumab for the Treatment of Men With Low Bone Mineral Density: Results From the ADAMO Trial

Bente L. Langdahl, Christence Stubbe Teglbjærg, Pei-Ran Ho, Roland Chapurlat, Edward Czerwinski, David L. Kendler, Jean-Yves Reginster, Alan Kivitz, E. Michael Lewiecki, Paul D. Miller, Michael A. Bolognese, Michael R. McClung, Henry G. Bone, Östen Ljunggren, Bo Abrahamsen, Ugis Gruntmanis, Yu-Ching Yang, Rachel B. Wagman, Faisal Mirza, Suresh Siddhanti, and Eric Orwoll*

Context: One in 4 men in the United States aged >50 years will have an osteoporosis-related fracture. Fewer data are available on osteoporosis treatment in men than in women.

Objective: The purpose of this study was to evaluate denosumab therapy in men with low bone mineral density (BMD).

Design: This was a phase 3 study with 2 treatment periods: a previously reported 12-month double-blind, placebo-controlled phase and a 12-month open-label phase.

Setting: This was a multicenter study conducted in North America and Europe.

Participants: A total of 228 men entered the open-label phase and 219 completed the study.

Intervention: Men from the original denosumab (long-term) and placebo (crossover) groups received 60 mg of denosumab sc every 6 months.

Main Outcome Measures: BMD, serum collagen type I C-telopeptide, and safety were measured.

Results: During the open-label phase, continued BMD increases occurred with long-term denosumab treatment (2.2% lumbar spine, 0.9% total hip, 1.3% femoral neck, 1.3% trochanter, and 0.2% 1/3 radius), resulting in cumulative 24-month gains from baseline of 8.0%, 3.4%, 3.4%, 4.6%, and 0.7%, respectively (all $P < .01$). The crossover group showed BMD gains after 12 months of denosumab treatment similar to those of the long-term denosumab group during the first treatment year. Significant reductions in serum collagen type I C-teleopeptide were observed after denosumab administration. Adverse event rates were similar between groups, and no new safety signals were identified.

Conclusions: In men with low BMD, denosumab treatment for a second year continued to increase BMD, maintained reductions in bone resorption, and was well tolerated. BMD increased in men initiating denosumab during the second year. These effects were similar to those previously seen in postmenopausal women with osteoporosis and in men with prostate cancer receiving androgen deprivation therapy. **(*J Clin Endocrinol Metab* 100: 1335–1342, 2015)**

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* Author Affiliations are shown at the bottom of the next page.

Abbreviations: ADAMO, A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Denosumab Vs Placebo in Males with Osteoporosis; AE, adverse event; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; HALT, Hormone Ablation Bone Loss Trial; q6m, every 6 months; SAE, serious adverse event; sCTX, serum collagen type I C-telopeptide.

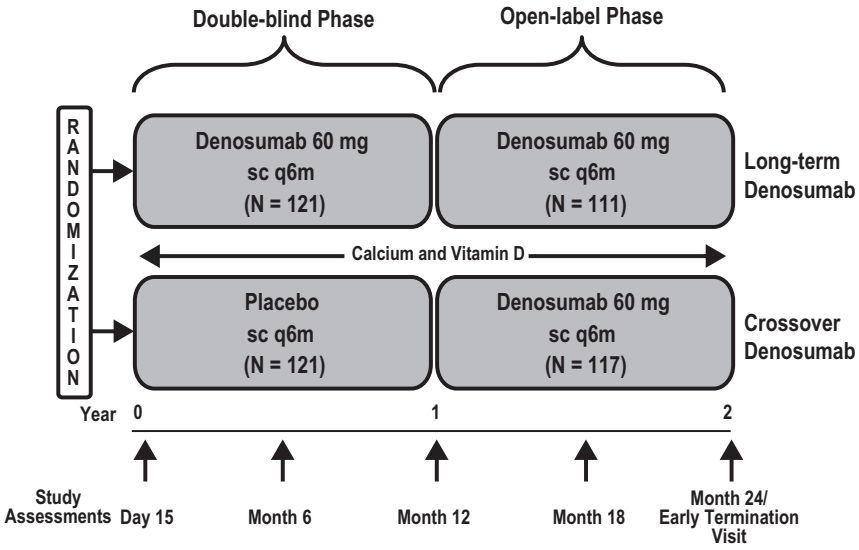

Figure 1. Study design.

The health burden of osteoporosis in men is expected to increase with an aging population and increasing life expectancy. One in 4 men in the United Stated aged >50 years will have a fracture due to osteoporosis (1). Both hip and vertebral fractures are associated with increased morbidity and mortality in men (2), and at any given age, mortality after hip fracture is higher in men than in women (3). Whereas the risk of osteoporosis-related fractures has been extensively studied for women, fewer published data for men are available.

There are a number of approved treatments for osteoporosis in men. The most commonly used are bisphosphonates. Oral bisphosphonates require long-term daily, once weekly, or once monthly dosing, with persistence and compliance waning as the treatment continues (4). Zoledronic acid is administered as a once yearly intravenous infusion (5). Whereas this assures that the patient is treated for at least 1 year, an infusion in a primary care setting may not always be feasible for patients, and other challenges may include iv access, infusion reactions, and the potential for renal compromise (5). Teriparatide (parathyroid hormone) is administered daily by self-injection, which can be inconvenient for patients (6).

Denosumab is a fully human monoclonal IgG_2 antibody that binds to RANKL. In women with postmenopausal osteoporosis, denosumab markedly reduced bone resorption, increased bone mineral density (BMD), and significantly reduced the risk of new vertebral and nonvertebral fractures, including hip fractures (7). Denosumab is approved in several countries as a treatment to increase bone mass in men with osteoporosis at high/increased risk for fracture (7). A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of denosumab vs placebo in males with osteoporosis (ADAMO) was undertaken to further define the response to therapy. The study comprised 2 consecutive 12-month phases. In the first 12 months, the study was double-blind and placebo-controlled and reported that denosumab therapy reduced bone resorption, increased BMD at all skeletal sites assessed, and was well tolerated (8). We now report the results from the second year of the ADAMO study, in which all patients were to receive open-label denosumab for 12 months.

Subjects and Methods

Study design

A multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial of men with low BMD was conducted at 27 study centers in Belgium, Canada, Denmark, France, Poland, Sweden, and the United States. The study comprised 2 12-month phases. The first 12-month phase was a double-blind, randomized trial comparing 60 mg of denosumab sc every 6 months (q6m) with placebo (Figure 1). At month 12, men entered the second phase. In this open-label phase, all participants (independent of randomization) were to receive 60 mg of denosumab sc q6m at months 12 and month 18. All participants were required to take daily supplements of ≥1000 mg elemental calcium and ≥800 IU vitamin D during the study. The study protocol was approved by an institutional review board or ethics committee for each site. All participants provided written informed consent.

The endpoints for the first phase of the study have been reported previously (8). The endpoints for the open-label phase (through month 24) were exploratory (percent changes in BMD of the lumbar spine, total hip, femoral neck, trochanter, and 1/3 radius and the percent change from baseline in serum type I collagen C-telopeptide [sCTX]) and safety. Safety was evaluated

Aarhus University Hospital (B.L.L.), DK-8000 Aarhus, Denmark; Center for Clinical and Basic Research (C.S.T.), 2750 Ballerup, Denmark; Amgen Inc. (P.-R.H., Y.-C.Y., R.B.W., F. M., S.S.), Thousand Oaks, California 91320; INSERM UMR 1033 (R.C.), Université de Lyon, Hôpital Edouard Herriot, F-69437, Lyon, France; Krakow Medical Center (E.C.), Krakow, 31-501 Poland; University of British Columbia (D.L.K.), Vancouver, British Columbia V6T 1Z4, Canada; University of Liège (J.-Y.R.), 4000 Liège, Belgium; Altoona Center for Clinical Research (A.K.), Duncansville, Pennsylvania 16635; New Mexico Clinical Research and Osteoporosis Center (E.M.L.), Albuquerque, New Mexico 87106; Colorado Center for Bone Research (P.D.M.), Lakewood, Colorado 80227; Bethesda Health Research Center (M.A.B.), Bethesda, Maryland 20817; Oregon Osteoporosis Center (M.R.M.), Portland, Oregon 97213; Michigan Bone and Mineral Clinic (H.G.B.), Detroit, Michigan 48236; Uppsala University (Ö.L.), 751 05 Uppsala, Sweden; University of Southern Denmark and Glostrup Hospital (B.A.), DK-5000 Odense and Copenhagen, Denmark; Dallas Veterans Affairs Medical Center and University of Texas Southwestern (U.G.), Dallas, Texas 75390; and Oregon Health and Science University (E.O.), Portland, Oregon 97239

as crude and exposure-adjusted participant incidence of adverse events (AEs).

Participants

Participants enrolled in the ADAMO trial were ambulatory men between the ages of 30 and 85 years. Details on the inclusion and exclusion criteria have been previously published (8). In brief, men were considered eligible if they had a T-score (based on male reference ranges) of ≤ -2.0 and ≥ -3.5 at the lumbar spine or femoral neck or a T-score of ≤ -1.0 and ≥ -3.5 at the lumbar spine or femoral neck with a prior major osteoporotic fracture and had at least 2 lumbar vertebrae, 1 hip, and 1 forearm evaluable by dual-energy x-ray absorptiometry (DXA). Key exclusion criteria included any severe or >1 moderate vertebral fracture (using a semiquantitative grading scale) (9), any vertebral fracture or clinical fracture diagnosed within 6 months before screening, diseases that affect bone metabolism, and vitamin D deficiency. Further, men were ineligible if they had received bisphosphonate treatment for 3 months or more cumulatively in the past 2 years, for 1 month or more in the past year, or at any time during the 3-month period before randomization. Men using anabolic steroids or testosterone, glucocorticoids, calcitonin, calcitriol, or vitamin D derivatives and other bone-active drugs in a 3-month period before screening were also excluded. Men with significantly impaired renal function, as determined by a derived glomerular filtration rate (using the Modification of Diet in Renal Disease formula) of <30 mL/min/1.73 m^2 calculated by a central laboratory, were also excluded.

Study assessments

BMD was assessed by DXA of the lumbar spine, hip, and forearm at screening and at months 6, 12, and 24. DXA scans were performed by a local DXA technologist and were submitted electronically to a central imaging center (Synarc, Inc.) for blinded analysis. All scans for an individual participant were performed on the same scanner (GE Lunar or Hologic bone densitometers). Lateral spine x-rays were performed at screening and at months 12 and 24 and were scored at the central imaging vendor (blinded to treatment allocation) using a semiquantitative grading scale (9) to detect vertebral fractures.

All participants had sCTX (Serum Crosslaps ELISA; IDS Nordic) measured from fasting blood samples drawn at each scheduled visit (except the screening visit) and assessed at the same central laboratory (Covance). Blood samples for assessment of anti-denosumab antibodies were obtained from all participants on day 1 (predose) and at months 12 and 24.

Safety was evaluated by assessing the nature, frequency, severity, relationship to investigational product, and outcome of all AEs, including fractures.

Statistical analyses

For the open-label phase, efficacy was analyzed for all participants who had at least 1 measurement at baseline of the double-blind phase and 1 measurement at a time point during the open-label phase. Observed data were used for the efficacy analyses. The means and 95% confidence intervals of percent changes in BMD from study baseline were estimated at months 12 and 24 using an ANCOVA model with treatment as main effect and minimum baseline BMD T-score (stratification factor) as a covariate. The percent change from months 12 to 24 was descriptive, and a one-sample *t* test within each treatment arm was performed to assess the significance of change from month 12. Percent changes from baseline in sCTX at each visit were summarized by median and interquartile range, and a sign test within each treatment arm was performed to assess the significance of change from study baseline. No direct statistical comparison was made between the 2 concurrent treatment arms in year 2 or from months 12 to 24.

Safety in the open-label phase was analyzed for all participants who received at least 1 dose of denosumab in the open-label phase. The crude participant incidence of AEs and exposure-adjusted participant incidence per 100 participant-years were evaluated by treatment group (long-term, crossover) and were descriptive. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 15.0) coding dictionary. Also summarized were the incidences of all clinical fractures, new vertebral fractures, and clinical osteoporosis-related fractures (defined as a radiological confirmed fracture excluding skull, face, mandible, metacarpals, finger phalanges, toe phalanges, and cervical vertebrae and not associated with high trauma severity or pathologic fracture).

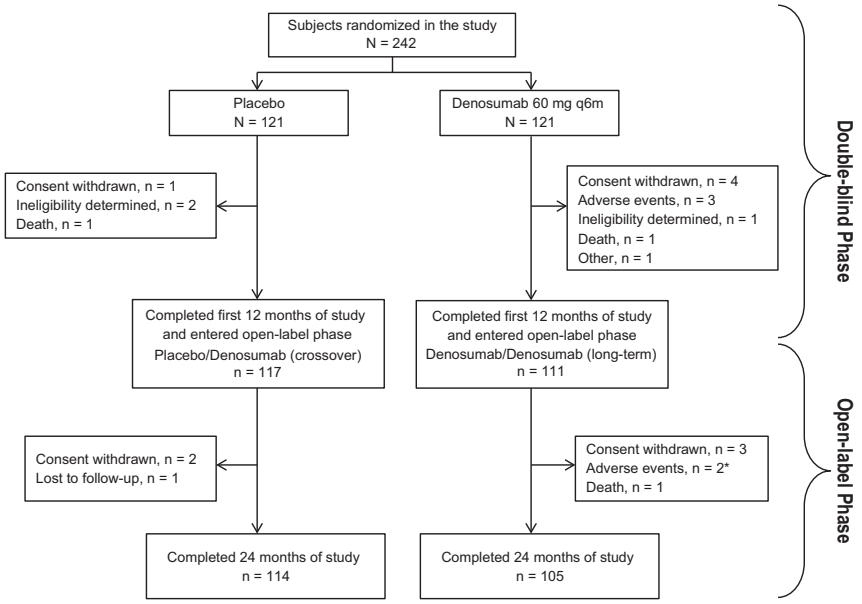

Figure 2. Participant disposition. *, One adverse event leading to early study discontinuation in the open-label phase commenced in the double-blind phase.

Results

Of the 242 men enrolled and randomly assigned to receive either denosumab (n = 121) or placebo (n = 121) (Figure 2), 228 (94%) entered the open-label phase. Of these, 111 continued to receive denosumab therapy (long-term group), and 117 crossed over from placebo to deno-

Table 1. Demographics and Characteristics of Randomized Participants

	Crossover Denosumab (n = 117)		Long-Term Denosumab (n = 111)	
	Double-Blind Phase Baseline	Open-Label Phase Baseline	Double-Blind Phase Baseline	Open-Label Phase Baseline
Age, y	65.1 (9.2)	66.1 (9.2)	65.0 (10.2)	66.0 (10.2)
Age group, n (%)				
<50 y	5 (4.3)	5 (4.3)	8 (7.2)	7 (6.3)
50–59 y	25 (21.4)	22 (18.8)	20 (18.0)	18 (16.2)
60–69 y	47 (40.2)	43 (36.8)	41 (36.9)	39 (35.1)
70–79 y	34 (29.1)	39 (33.3)	36 (32.4)	40 (36.0)
≥80 y	6 (5.1)	8 (6.8)	6 (5.4)	7 (6.3)
White race, n (%)	104 (88.9)	104 (88.9)	111 (100.0)	111 (100.0)
BMD T-score				
Lumbar spine	−2.0 (1.0)	−2.0 (1.0)	−1.9 (1.1)	−1.5 (1.1)
Total hip	−1.4 (0.7)	−1.4 (0.7)	−1.5 (0.6)	−1.3 (0.6)
Femoral neck	−1.9 (0.6)	−1.9 (0.6)	−1.9 (0.6)	−1.8 (0.6)
Trochanter	−1.3 (0.7)	−1.2 (0.7)	−1.2 (0.7)	−1.1 (0.7)
1/3 radius	−1.7 (1.2)	−1.7 (1.1)	−1.3 (1.3)	−1.3 (1.3)
Prevalent vertebral fracture, n (%)	23 (19.7)	24 (20.5)	26 (23.4)	26 (23.4)
sCTX, ng/mL	0.41 (0.20)	0.45 (0.22)	0.40 (0.18)	0.17 (0.10)
Total testosterone, ng/dL	355.7 (117.9)	NA	365.9 (122.4)	NA
eGFR, mL/min/1.73 m^2	79.2 (16.6)	78.5 (16.8)	78.8 (16.2)	76.6 (15.0)
CKD stage, n (%)[a]				
Stage 1	18 (16)	23 (20)	22 (20)	15 (14)
Stage 2	89 (77)	79 (68)	78 (70)	83 (75)
Stage 3	9 (8)	14 (12)	11 (10)	13 (12)
Stage 4	0 (0)	0 (0)	0 (0)	0 (0)
Stage 5	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NA, not assessed. n represents the numbers of participants enrolled in the open-label phase. Data are means (SD) unless otherwise noted.

[a] Stage 1, ≥90 mL/min/1.73 m^2; stage 2, ≥60 and <90 mL/min/1.73 m^2; stage 3, ≥30 and <60 mL/min/1.73 m^2; stage 4, ≥15 and <30 mL/min/1.73 m^2; stage 5, <15 mL/min/1.73 m^2.

sumab (crossover group). Reasons for not completing the 12-month double-blind phase and the open-label phase are summarized in Figure 2. A total of 219 of 228 participants (96%) completed the open-label phase; 95% and 97% were in the long-term and crossover groups, respectively. When considered in terms of the overall study, 219 of 242 participants (91%) completed the entire 24 months of the study.

Baseline demographics and characteristics for participants in the open-label phase are shown in Table 1 and were similar to those of the original enrolled cohorts (8) (data not shown). At the beginning of the open-label phase, mean (SD) sCTX in the long-term group was lower (0.17 [0.10] ng/mL), and the BMD T-score was improved, reflecting denosumab administration in the 12-month double-blind phase of the study.

Efficacy

BMD

During the 12-month open-label phase, continued increases in BMD occurred with long-term denosumab treatment at all skeletal sites evaluated (2.2% lumbar spine, 0.9% total hip, 1.3% femoral neck, 1.3% trochanter, and 0.2% 1/3 radius) for cumulative gains from baseline to month 24 of 8.0% (lumbar spine), 3.4% (total hip), 3.4% (femoral neck), 4.6% (trochanter), and 0.7% (1/3 radius) (all $P < .01$) (Figure 3). The crossover group showed significant gains in BMD at the lumbar spine (4.9%), total hip (1.7%), femoral neck (1.9%), trochanter (2.0%), and 1/3 radius (1.0%) in the open-label phase (all $P \leq .0001$), similar to those observed in the long-term denosumab group during the first year of treatment (lumbar spine, 5.8%; total hip, 2.3%; femoral neck, 2.2%; trochanter, 3.2%; and 1/3 radius, 0.6%).

Bone turnover markers

For the long-term group, a 60% reduction in sCTX noted in the first phase was observed at month 12 ($P < .0001$). At months 18 and 24, sCTX levels remained lower than baseline (57% and 50%, respectively; all $P < .0001$) (Figure 4). In the crossover group, there was no change in sCTX levels during the first 12-month phase of placebo administration, but during the second 12-month phase of denosumab administration there was a median decrease in sCTX of 68% at month 18 and 59% at month 24 ($P <$

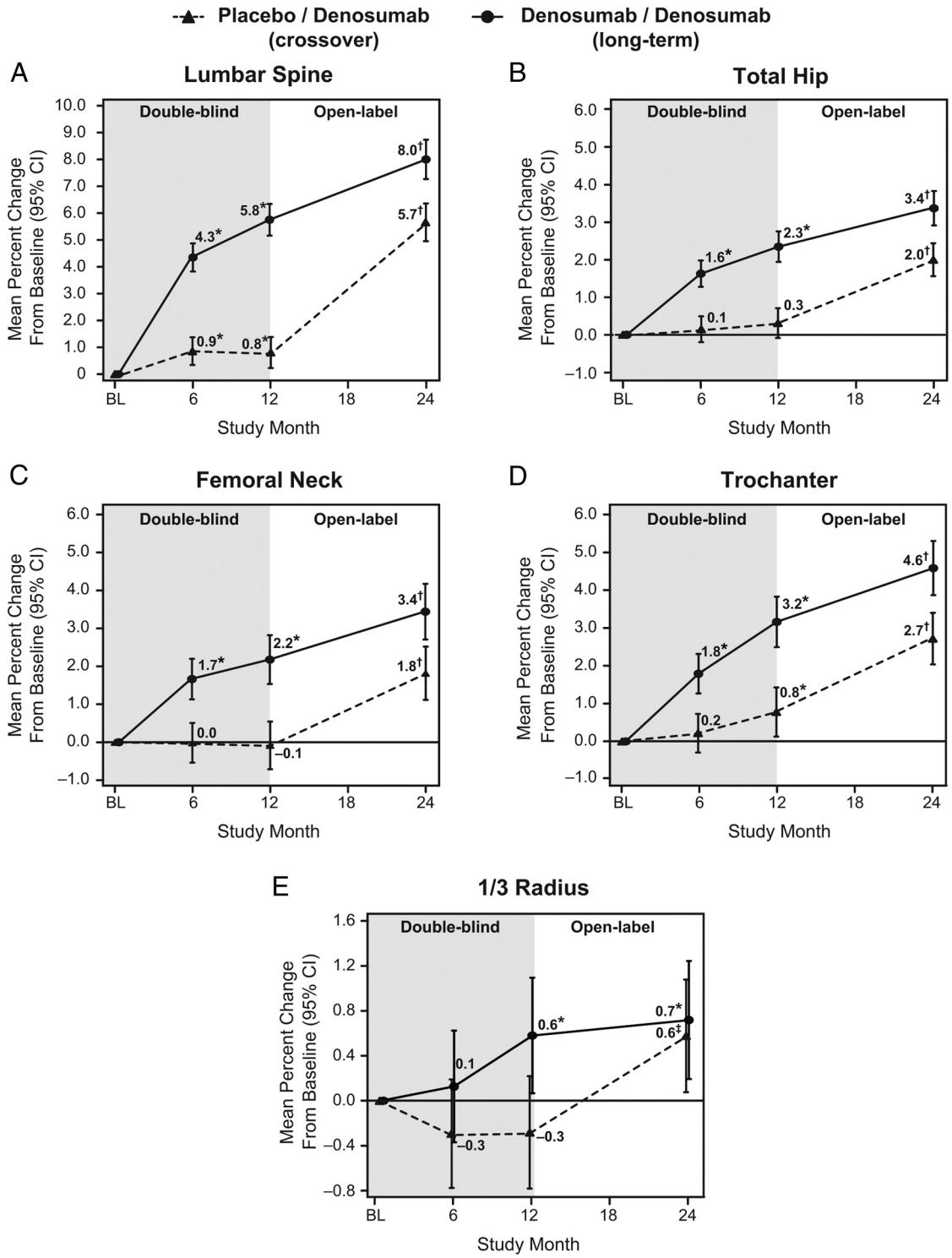

Figure 3. Percent change in BMD from baseline to month 24 at lumbar spine (A), total hip (B), femoral neck (C), trochanter (D), and 1/3 radius (E). Data are least-squares means and 95% confidence intervals (CIs). *, $P < .05$ vs double-blind baseline; †, $P < .0001$ vs double-blind baseline and open-label baseline; ‡, $P < .05$ vs double-blind baseline and open-label baseline. BL, baseline.

.0001), a response similar to that observed in the first 12-month phase in denosumab-treated men.

Anti-denosumab antibody assays

Anti-denosumab binding antibodies were not detected at any time point during 24 months of the study (data not shown).

Fractures

During the open-label phase, clinical fractures were reported in 4 men (2 rib and 2 foot) in the long-term denosumab treatment group (3.6%) (Table 2). Clinical osteoporotic fractures were reported in 2 men (2 rib) in the

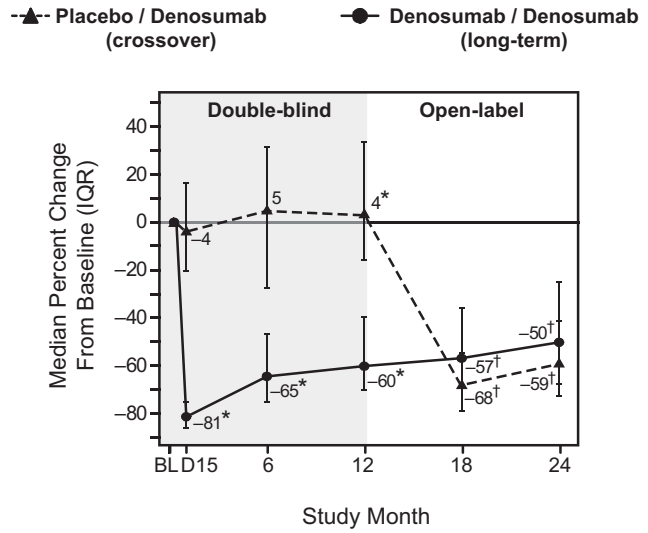

Figure 4. Percent change in sCTX from baseline to month 24. Data are medians and interquartile ranges. *, $P < .01$ vs double-blind baseline; †, $P < .0001$ vs double-blind baseline and open-label baseline. BL, baseline; D, day; IQR, interquartile range.

long-term group (1.8%). No new vertebral fractures were reported in either treatment group.

Safety

Of the 228 men who continued in the open-label phase, 227 participants received at least 1 dose of denosumab during the open-label phase (long-term group, n = 111; crossover group, n = 116) and were included in the safety analysis (217 received 2 doses of denosumab and 10 received 1 of the 2 scheduled doses of denosumab during the open-label phase).

The participant incidence of AEs, serious AEs (SAEs), and fatal AEs is summarized in Table 2. During the open-label phase, the participant incidence of overall AEs was 63% in the long-term group and 52% in the crossover group. Most AEs were mild or moderate in severity in both groups. SAEs occurred in 8.1% of the long-term group and 4.3% of the crossover group. No AEs were reported as serious for >1 participant in either group. The system organ class with the highest incidence of SAEs was infections and infestations; 5 of 111 men (4.5%) in the long-term group and 1 of 116 (0.9%) in the crossover group. Malignancy AEs were reported in 1 of 111 men (0.9%) in the long-term group (gastric cancer with metastases to the lung) and 2 of 116 men (1.7%) in the crossover group (bladder cancer and malignant lung neoplasm with metastases to central nervous system). The incidence of cardiac disorders, eczema, infections, acute pancreatitis, and AEs potentially associated with hypersensitivity was low and did not appear to increase over time (Table 2). One death caused by bacterial endocarditis was reported in the long-term group; an echocardiogram confirmed mitral valve endocarditis and blood cultures were positive for staphylococcus in a participant without previous valvular disease. There were no reports of hypocalcemia, osteonecrosis of the jaw, fracture healing complications, or atypical femoral fracture. The exposure-adjusted participant inci-

Table 2. Participant Incidence of AEs

		Denosumab		
	Placebo: Year 1 (n = 120)	**Year 1 (n = 120)**	**Crossover Year 2 (n = 116)[a]**	**Long-Term Year 2 (n = 111)[a]**
All AEs, n (%)	87 (73)	87 (73)	60 (52)	70 (63)
Serious AEs	11 (9)	13 (11)	5 (4)[b]	9 (8)[c]
Fatal	1 (1)	1 (1)	0	1 (1)
Leading to study discontinuation	0	4 (3)	0	1 (1)
AEs of interest, n (%)				
Potentially associated with hypersensitivity	3 (3)	3 (3)	2 (2)	2 (2)
Malignancies	0	4 (3)	2 (2)	1 (1)
Cardiac disorders	4 (3)	7 (6)	2 (2)	2 (2)
Vascular disorders	9 (8)	6 (5)	2 (2)	7 (6)
Eczema	0	2 (2)	0	0
Infection	27 (23)	25 (21)	23 (20)	21 (19)
Acute pancreatitis	1 (1)	1 (1)	0	0
Hypocalcemia	0	0	0	0
Osteonecrosis of the jaw	0	0	0	0
Atypical femoral fracture	0	0	0	0
Clinical fracture	2 (2)	1 (1)	0	4 (4)

n represents the numbers of participants who received ≥1 dose of the investigational product. AEs were coded using MedDRA, version 15.0.

[a] Number of participants who received ≥1 dose of denosumab in the open-label phase (year 2).

[b] Bladder cancer (1), bacterial pneumonia (1), malignant lung neoplasm and metastases to central nervous system (1), nodal rhythm (1), and transient ischemic attack (1).

[c] Arthralgia and infective arthritis (1), atrial fibrillation and pneumonia (1), carotid artery stenosis (1), cholecystitis (1), endocarditis (1), gastric cancer and metastases to lung (1), osteoarthritis (1), pyelonephritis (1), and urosepsis (1).

dence of AEs per 100 participant-years is summarized in Supplemental Table 1.

Discussion

The ADAMO study evaluated the efficacy and safety of 60 mg of denosumab sc q6m in a population of men with low BMD. BMD for all assessed skeletal sites continued to increase from month 12 to month 24 in the long-term group. In addition, those men who crossed over from placebo to denosumab at month 12 exhibited mean increases in BMD that were similar to those observed for men administered denosumab from baseline to month 12.

The continued increases in BMD through 2 years of treatment were comparable to those observed in previous studies of postmenopausal women with osteoporosis (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months [FREEDOM] study), suggesting that denosumab is effective regardless of sex. Moreover, the response to denosumab therapy that we observed was similar to that observed in men with prostate cancer receiving androgen deprivation therapy with low bone mass or a history of fragility fracture (Hormone Ablation Bone Loss Trial [HALT]) (7, 10). At 24 months in the double-blind, placebo-controlled HALT study, BMD of the lumbar spine had increased by 5.6% in the denosumab group compared with a loss of 1.0% in the placebo group ($P < .001$); significant increases in BMD at the total hip, femoral neck, and 1/3 radius were also observed (10). Thus, denosumab therapy appears to result in similar increases in BMD in men with low bone mass with and without hypogonadism. Our results also showed that denosumab treatment was associated with a rapid decrease in bone resorption and a significant reduction in bone turnover as observed by marked decreases in sCTX from as early as day 15 after treatment initiation, with reductions maintained through month 24. These results also were consistent with changes in sCTX reported in the FREEDOM and HALT studies (7, 10).

In FREEDOM, the primary efficacy analysis demonstrated that denosumab therapy decreased fracture risk, with relative risk reductions at month 36 for new vertebral, nonvertebral, and hip fractures of 68%, 20%, and 40%, respectively (7). A decrease in fracture risk was also observed in the HALT study, with a 62% decrease in the incidence of new vertebral fractures in the denosumab group relative to that in the placebo group at month 36 (10). Because a reduction in fracture risk was associated with increases in BMD in FREEDOM and HALT and because the mean increases in BMD in the current study were similar, it is reasonable to anticipate that 60 mg of denosumab q6m will reduce fracture risk in men with osteoporosis.

As in previous studies, denosumab was well tolerated throughout the 24-month study period. Most AEs in the open-label phase were either mild or moderate in severity. No new safety signals were identified in this open-label study phase. The overall rates of AEs of interest, including AEs potentially associated with hypersensitivity, infections, malignancies, cardiac disorders, eczema, and acute pancreatitis, were low and did not appear to increase over the duration of the study.

In summary, 2 years of denosumab therapy in men with low BMD was well tolerated and resulted in continued increases in BMD at all skeletal sites assessed and reductions in bone resorption. The increases in BMD and reductions in sCTX were similar to those observed in previous studies of denosumab treatment in postmenopausal women with osteoporosis and in men with prostate cancer receiving androgen deprivation therapy. It is reasonable to anticipate that the effect on fracture risk is likely to be similar in men with osteoporosis treated with denosumab.

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Address all correspondence and requests for reprints to: Bente Langdahl, PhD, DMSc, Department of Endocrinology and Internal Medicine THG, Aarhus University Hospital, DK-8000 Aarhus C, Denmark. E-mail: bente.langdahl@aarhus.rm.dk.

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