Bone 134 (2020) 115268

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Denosumab in postmenopausal women with osteoporosis and diabetes: Subgroup analysis of FREEDOM and FREEDOM extension

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ARTICLE INFO

Keywords:
Diseases and disorders of/related to bone
osteoporosis
Clinical trials
Therapeutics antiresorptive

ABSTRACT

Purpose: Diabetes and osteoporosis occur frequently in older adults and are both associated with increased fracture risk. Denosumab treatment reduced new vertebral, nonvertebral, and hip fractures over 3 years, with continued low fracture incidence for up to 10 years in postmenopausal women with osteoporosis. However, its effects in diabetic subjects with osteoporosis have not yet been investigated.

Methods: Post hoc analysis of the 3-year, placebo-controlled FREEDOM study and 7-year Extension included postmenopausal women with osteoporosis and diabetes. Effects on BMD, vertebral, and nonvertebral fracture incidence were evaluated.

Results: Of 7808 subjects in FREEDOM, 508 with diabetes received denosumab (n = 266) or placebo (n = 242). Among those, BMD increased significantly with denosumab versus placebo in FREEDOM, and continued to increase during the Extension in long-term (continuing denosumab) and crossover (placebo to denosumab) denosumab subjects. In FREEDOM, denosumab-treated subjects with diabetes had significantly lower new vertebral fracture rates (1.6%) versus placebo (8.0%) (RR: 0.20 [95% CI 0.07–0.61]; p = .001). Nonvertebral fracture incidence was higher with denosumab (11.7%) versus placebo (5.9%) (HR: 1.94 [95% CI 1.00–3.77]; p = .046), although there were fewer hip fractures with denosumab (World Health Organization, 2017 [1]) than placebo (4; nonsignificant). During the first 3 years in FREEDOM Extension, new vertebral and nonvertebral fracture incidences were low in long-term and crossover denosumab diabetic groups (≤6%), consistent with the overall Extension population; yearly nonvertebral fracture incidence was comparable to the FREEDOM placebo group.

Conclusion: Denosumab significantly increased BMD and decreased vertebral fracture risk in subjects with osteoporosis and diabetes. No reduction in nonvertebral fractures was observed.

1. Introduction

An estimated 422 million adults have diabetes worldwide [1], and prevalence increases with age, reaching 25% among those aged ≥65 years in the US [2]. Similarly, osteoporosis occurrence rises with age [3]; consequently, diabetes and osteoporosis are common in the elderly. People with diabetes have an increased fracture risk, despite higher bone mineral density (BMD) than those without diabetes [4]. The mechanisms underlying this apparent paradox are not fully elucidated, but poorer bone quality, diabetic complications, physical disability, and increased risk of falls may be contributing factors [5–7].

It is important to assess the skeletal effects of osteoporosis

Abbreviations: BMD, bone mineral density; CTX, C-terminal telopeptide; FREEDOM, Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months; PINP, procollagen type 1 N propeptide

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[1] At the time of the study

https://doi.org/10.1016/j.bone.2020.115268
Received 17 September 2019; Received in revised form 22 January 2020; Accepted 9 February 2020
Available online 10 February 2020

treatments in subjects with diabetes. Post hoc analyses of two randomized, placebo-controlled trials and one observational study in adults with osteoporosis and diabetes suggest that the beneficial effect of bisphosphonates [8] or teriparatide [9,10] on occurrence of nonvertebral and vertebral fractures in subjects with diabetes are similar to that in subjects without diabetes.

Denosumab is a fully human monoclonal antibody with high specificity to human RANK ligand that can reversibly reduce osteoclast number and activity and decrease bone resorption [11]. In the Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM; ClinicalTrials.gov: NCT00089791) study in postmenopausal women with osteoporosis, denosumab reduced risk of vertebral, nonvertebral, and hip fractures versus placebo [11]. FREEDOM Extension (ClinicalTrials.gov: NCT00523341) additionally demonstrated a low incidence of new vertebral, nonvertebral, and hip fractures for up to 10 years [12].

Analyses of key fracture endpoints from FREEDOM have been conducted in > 100 subgroups, some of which have previously been published [13–15]. In addition, the effects of denosumab treatment on the development of diabetes in pre-diabetic postmenopausal women have been studied, indicating that denosumab had no effect on the development of diabetes [13]. However, no randomized clinical trials have been performed to assess the effects of denosumab treatment among patients with osteoporosis and diabetes. Therefore, here we present findings from a post hoc analysis of the diabetic subgroup of FREEDOM and its long-term Extension, assessing the effects of denosumab on BMD and fracture incidence in postmenopausal women with osteoporosis and diabetes.

2. Methods

FREEDOM and its open-label Extension have been previously described [11,12]. FREEDOM was a phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-year study in postmenopausal women aged 60–90 years with lumbar spine or total hip BMD T-score less than −2.5 (either location) and at least −4.0 (both locations), randomized to placebo or 60 mg subcutaneous denosumab every 6 months. Participants who completed FREEDOM and did not discontinue treatment or miss more than one dose of investigational product were eligible to enter the 7-year extension study. In the FREEDOM Extension study, subjects who received denosumab during FREEDOM continued denosumab treatment (long-term denosumab group), while those previously receiving placebo were transitioned onto denosumab (crossover denosumab group).

Subjects with diabetes at FREEDOM baseline were retrospectively identified according to the American Diabetes Association diagnostic criteria (antidiabetic medication use and/or fasting glucose levels ≥126 mg/dL [7 mmol/L] at baseline) [16].

BMD was measured using dual-energy X-ray absorptiometry at lumbar spine (baseline, year 3) and proximal femur (baseline, annually) during FREEDOM, and both sites during the FREEDOM Extension study (baseline and years 1, 2, 3, 5, and 7). All scans were centrally read by Bioclinica (formerly SYNARC).

Vertebral fractures were identified by a central facility (Bioclinica) using the Genant semiquantitative grading scale [17] from lumbar spine and lateral thoracic radiographs obtained at baseline and annually in FREEDOM and years 2, 3, 5, and 7 in FREEDOM Extension. A fracture at baseline was defined as a vertebral body with a semiquantitative grade of at least 1. A new vertebral fracture was identified when there was at least 1 grade increase from a previous grade of 0 in any vertebra between T4 and L4, excluding fractures associated with high trauma severity or a pathologic fracture. Nonvertebral fractures were confirmed by diagnostic imaging or radiologist's report.

Bone turnover markers, C-terminal telopeptide (CTX; assessed by enzyme-linked immunosorbent assay [Nordic Bioscience Diagnostics A/S]) and procollagen type 1 N propeptide (PINP; assessed by radioimmunoassay [Orion Diagnostica Oy]), and serum 25-Hydroxyvitamin D (D2 and D3; assessed by radioimmunoassay [Covance Inc.]) were measured at FREEDOM baseline. Estimated glomerular filtration rate, derived using The Modification of Diet in Renal Disease Study (MDRD) equation, was calculated at FREEDOM baseline.

2.1. Statistical analysis

Analyses of BMD percentage changes included subjects with a BMD value at FREEDOM baseline and ≥1 postbaseline BMD value from FREEDOM or the FREEDOM Extension study using a repeated-measures, mixed-effects model adjusted for treatment, age stratification variable, visit, baseline value, machine type, treatment-by-visit interaction, and baseline value-by-machine type interaction.

Exposure-adjusted fracture rates and rate ratios were obtained using generalized estimating equation Poisson models; fracture rates are reported per 100 subject-years. Rate ratios relative to the first 3 years of denosumab treatment were adjusted for age, total hip BMD T-score, weight, and history of nonvertebral fracture. Analyses of fractures included subject incidence of new vertebral fracture and Kaplan-Meier estimates of nonvertebral fracture rates. Fracture rates were compared by length of denosumab exposure, regardless of whether exposure occurred during FREEDOM or the FREEDOM Extension study.

3. Results

3.1. Subgroup population

Of the 7808 randomized subjects in FREEDOM [11], 508 (6.5%) met the criteria for diabetes at baseline, of whom 266 (52.4%) received denosumab and 242 (47.6%) received placebo (Fig. 1). Subjects with diabetes were older, had higher body mass index, and lower serum CTX and PINP levels than those without diabetes, but baseline BMD T-scores, prevalent fracture rates, serum 25-Hydroxyvitamin D levels, and estimated glomerular filtration rates were similar (Table 1). Anti-diabetic medication use at baseline was also similar between subjects with diabetes who received denosumab and those who received placebo.

3.2. Bone mineral density

During FREEDOM, percentage change from baseline in lumbar spine, total hip, and femoral neck BMD was significantly higher following denosumab treatment versus placebo, irrespective of presence/absence of diabetes (Fig. 2; Table 2). During the FREEDOM Extension study, BMD increases from baseline were overall similar between subjects with/without diabetes at all skeletal sites in the long-term denosumab and crossover denosumab groups (Fig. 2; Table 2).

3.3. Fractures

During FREEDOM, denosumab significantly reduced new vertebral fracture risk versus placebo in subjects with diabetes (cumulative

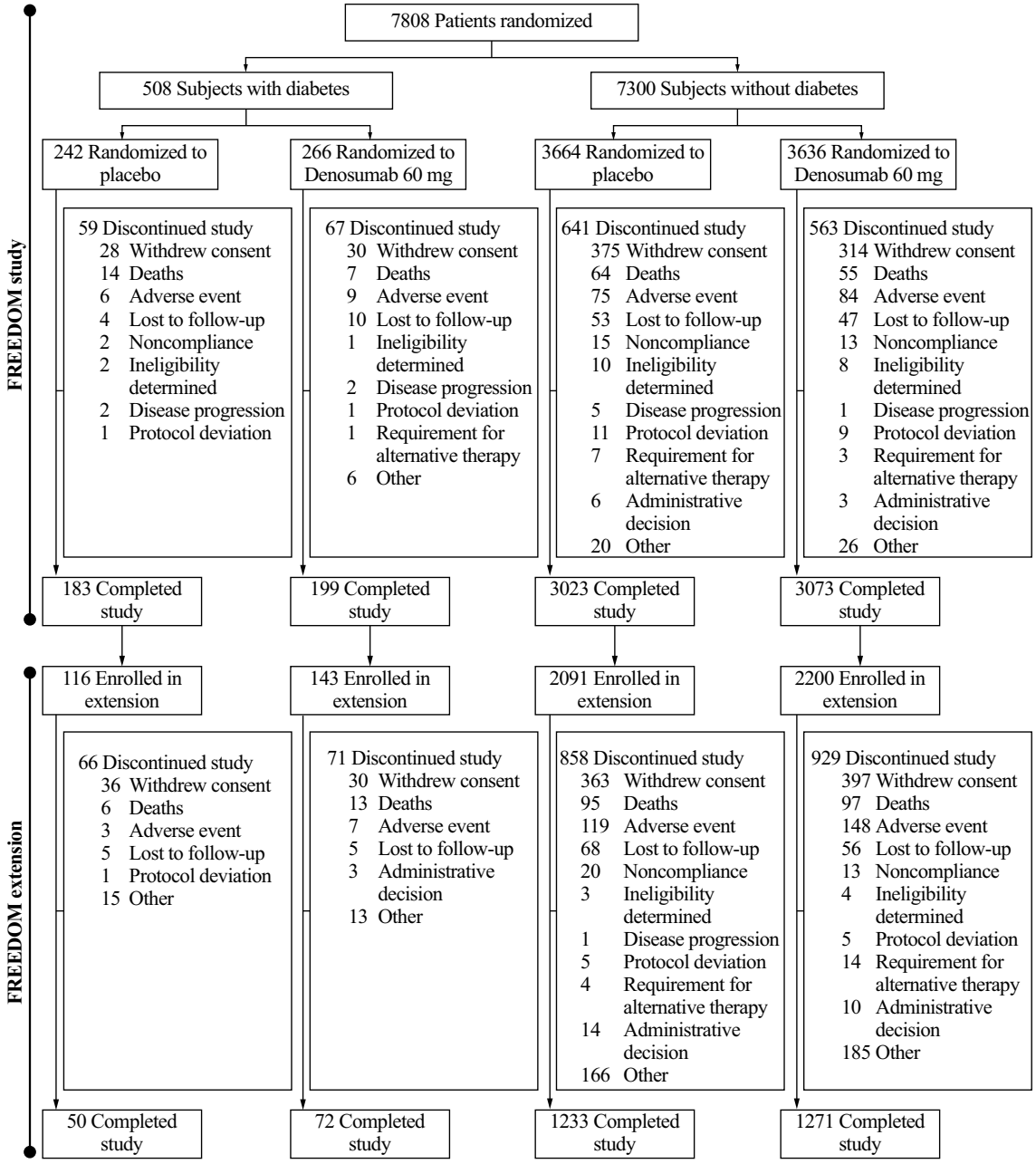

Fig. 1. Subject disposition in FREEDOM and FREEDOM extension.

incidence: 1.6% [denosumab group] vs 8.0% [placebo group]; risk ratio: 0.20; 95% CI 0.07–0.61; $p = .001$) (Table 3; Fig. 3A and B). A higher cumulative incidence of nonvertebral fractures was observed in denosumab-treated (11.7%) versus placebo-treated subjects (5.9%) with diabetes (HR: 1.94; 95% CI 1.00–3.77; $p = .046$), with most occurring in the forearm and ribs, whereas there were four hip fractures in the placebo group and one in the denosumab group (nonsignificant) (Table 4); this pattern was not observed in denosumab- and placebo-treated subjects without diabetes (hazard ratio for denosumab vs placebo: 0.74; 95% CI 0.62–0.89; $p = .001$) (Fig. 3C and D). The qualitative interaction between treatment and diabetes subgroups was significant ($p = .025$). The majority of nonvertebral fractures in denosumab-treated subjects were observed during the second year while the incidence of nonvertebral fractures was low and comparable between denosumab- and placebo-treated subjects during years 1 and 3 (Fig. 3C). The rate of nonvertebral fracture in the placebo group was lower in subjects with diabetes compared with subjects without diabetes (Fig. 3C and D).

In contrast, during the FREEDOM Extension study the annualized subject incidence of both new vertebral and nonvertebral fractures

Table 1
Subject demographics and clinical characteristics at FREEDOM study baseline by diabetes status.

Characteristic	Subjects with diabetes[a]		Subjects without diabetes[a]		Overall FREEDOM $N = 7808$
	Placebo N = 242	Denosumab N = 266	Placebo $N = 3664$	Denosumab $N = 3636$	
Age (years), mean ± SD	73.5 ± 5.0	73.5 ± 5.1	72.3 ± 5.3	72.3 ± 5.3	72.3 ± 5.2
Age group (years), n (%)					
< 70	40 (16.5)	48 (18.1)	988 (27.0)	982 (27.0)	2058 (26.4)
70–74	100 (41.3)	120 (45.1)	1542 (42.1)	1517 (41.7)	3279 (42.0)
≥75	102 (42.1)	98 (36.8)	1134 (30.9)	1137 (31.3)	2471 (31.6)
Body mass index (kg/m^2), mean ± SD, n[b]	27.9 ± 4.6	28.3 ± 4.8	25.8 ± 4.1, $n = 3643$	25.9 ± 4.0, $n = 3620$	26.0 ± 4.2, $n = 7771$
Prevalent vertebral facture, n (%)	48 (19.8)	59 (22.2)	867 (23.7)	870 (23.9)	1844 (23.6)
Prior nonvertebral fractures, n (%)	97 (40.1)	101 (38.0)	1410 (38.5)	1423 (39.1)	3031 (38.8)
BMD T-score, mean ± SD, n[b]					
Lumbar spine	−2.8 ± 0.7, $n = 241$	−2.7 ± 0.8, $n = 265$	−2.8 ± 0.7, $n = 3661$	−2.8 ± 0.7, $n = 3632$	−2.8 ± 0.7, $n = 7799$
Total hip	−1.9 ± 0.8, $n = 240$	−1.8 ± 0.8, $n = 262$	−1.9 ± 0.81, $n = 3650$	−1.9 ± 0.8, $n = 3617$	−1.9 ± 0.8, $n = 7769$
Femoral neck	−2.2 ± 0.8, $n = 240$	−2.2 ± 0.7, $n = 262$	−2.2 ± 0.71, $n = 3650$	−2.2 ± 0.7, $n = 3617$	−2.2 ± 0.7, $n = 7769$
Bone turnover markers, median (IQR), n[b]					
Serum CTX (ng/mL)	0.43 (0.29–0.64), $n = 231$	0.41 (0.28–0.60), $n = 260$	0.55 (0.39–0.73), $n = 3560$	0.54 (0.39–0.72), $n = 3543$	0.54 (0.38–0.72), $n = 7594$
PINP (μg/mL)	51.0 (41.8–71.5), $n = 32$	43.2 (33.5–50.7), n = 29	54.2 (41.9–69.2), $n = 445$	54.8 (41.7–69.9), $n = 517$	54.2 (41.5–69.4), $n = 1023$
25-Hydroxyvitamin D (ng/mL), mean ± SD, n[b]	21.2 ± 10.3	22.8 ± 11.4	24.2 ± 37.5, $n = 3662$	23.2 ± 12.5, $n = 3635$	23.6 ± 27.2, $n = 7805$
Estimated glomerular filtration rate (mL/min), mean ± SD, n[b]	81.2 ± 21.5	78.7 ± 19.7	78.9 ± 17.7, $n = 3663$	78.9 ± 17.7, n = 3635	78.9 ± 18.0, $n = 7806$
Fasting glucose (mg/dL), mean ± SD, n[b]	150.5 ± 54.2, $n = 236$	147.0 ± 44.5, n = 260	92.1 ± 9.7, $n = 3566$	92.1 ± 9.5, $n = 3517$	95.8 ± 21.0, $n = 7579$
Anti-diabetic medication use, n (%)	182 (75.2)	192 (72.2)	N/A	N/A	374 (4.8)
Sulfonylureas	124 (51.2)	137 (51.5)	N/A	N/A	261 (3.3)
Biguanides	64 (26.4)	83 (31.2)	N/A	N/A	147 (1.9)
Insulins	30 (12.4)	28 (10.5)	N/A	N/A	58 (0.7)
α-Glucosidase Inhibitors	7 (2.9)	7 (2.6)	N/A	N/A	14 (0.2)
Meglitinides (Glinides)	5 (2.1)	6 (2.3)	N/A	N/A	11 (0.1)
Thiazolidinediones	7 (2.9)	5 (1.9)	N/A	N/A	12 (0.2)

Abbreviations: BMD, bone mineral density; CTX, C-terminal telopeptide; IQR, interquartile range; N/A, not applicable; PINP, procollagen type 1 N propeptide; SD, standard deviation.

[a] Subjects with diabetes were defined based on use of antidiabetic medication and/or fasting glucose levels ≥126 mg/dL (7 mmol/L) at baseline.

[b] For instances where baseline values were available from fewer subjects than the total N in the subgroup.

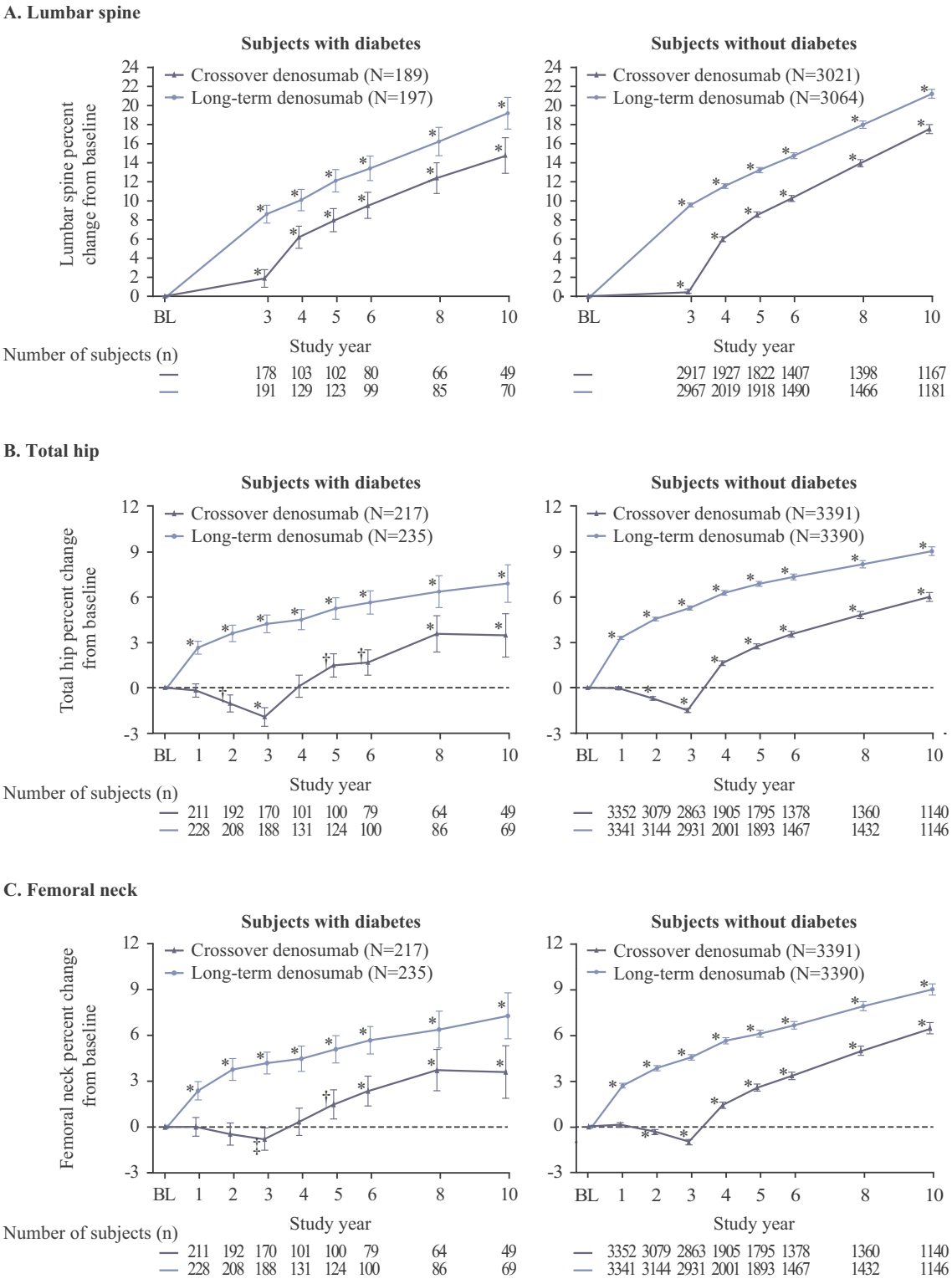

Fig. 2. BMD over the course of FREEDOM and FREEDOM extension. Percentage changes from FREEDOM baseline in BMD are shown for the lumbar spine (A), total hip (B), and femoral neck (C). $^{*}p < .0001$, $^{\dagger}p < .01$, $^{\ddagger}p < .05$ compared with baseline. Subjects with diabetes are defined as use of antidiabetic medication at baseline and/or fasting glucose levels ≥126 mg/dL (/L) at baseline. BL, baseline; BMD, bone mineral density.

Table 2
Percentage change from baseline to year 3 in BMD in the FREEDOM study.

Skeletal site	Subjects with diabetes[a]		Subjects without diabetes[a]	
	Placebo	Denosumab	Placebo	Denosumab
Lumbar spine	*n* = 178	*n* = 191	*n* = 2917	*n* = 2967
	1.9% (1.0, 2.8)*	8.6% (7.7, 9.5)*,‡	0.5% (0.3, 0.7)*	9.6% (9.4, 9.8)*,‡
Total hip	*n* = 170	*n* = 188	*n* = 2863	*n* = 2931
	−1.9% (−2.5, −1.3)*	4.2% (3.6, 4.8)*,‡	−1.5% (−1.6, −1.4)*	5.3% (5.1, 5.4)*,‡
Femoral neck	n = 170	n = 188	n = 2863	n = 2931
	−0.8% (−1.5, −0.1)†	4.2% (3.5, 4.9)*,‡	−1.0% (−1.2, −0.8)*	4.6% (4.4, 4.7)*,‡

Abbreviation: BMD, bone mineral density.
Data are least-squares mean (95% confidence interval) with change from baseline based on a repeated-measures, mixed-effects model adjusting for treatment, age stratification variable, visit, baseline value, machine type, treatment-by-visit interaction, and baseline value-by-machine-type interaction; n = number of subjects with BMD at baseline and Year 1 in the FREEDOM study.
[a] Subjects with diabetes were defined based on use of antidiabetic medication and/or fasting glucose levels ≥126 mg/dL (7 mmol/L) at baseline.
* $p < .0001$ compared with baseline.
† $p < .05$ compared with baseline.
‡ $p < .05$ compared with placebo.

Table 3
Cumulative incidence of fracture at year 3 in subjects with diabetes[a] in the FREEDOM study.

	Fracture type					
	New vertebral		Nonvertebral		Hip	
	Placebo *N* = 226	Denosumab *N* = 245	Placebo N = 242	Denosumab N = 266	Placebo N = 242	Denosumab N = 266
Incidence, n (%)	18 (8.0)	4 (1.6)	13 (5.9)[b]	27 (11.7)[b]	4 (1.7)[b]	1 (0.4)[b]
Risk or hazard ratio (95% CI)	0.20 (0.07–0.61)[c]		1.94 (1.00–3.77)[d]		0.23 (0.03–2.02)[d]	
p value	0.001		0.046		0.145	

Abbreviation: CI, confidence interval.
[a] Subjects with diabetes were defined based on use of antidiabetic medication and/or fasting glucose levels ≥126 mg/dL (7 mmol/L) at baseline.
[b] Fracture incidence for nonvertebral and hip fracture are Kaplan-Meier estimates.
[c] Risk ratio adjusted using the Mantel-Haenszel method for age stratification variable.
[d] Hazard ratio calculated based on the Cox proportional hazards model and stratified by age.

remained low in the long-term denosumab group with diabetes, similar to the crossover denosumab group (those subjects with diabetes receiving placebo during FREEDOM and after receiving denosumab during FREEDOM extension) (Fig. 3A and C), and hip fracture incidence was negligible. The nonvertebral fracture incidence in subjects with diabetes during the first 3 years of exposure to denosumab in the crossover denosumab group ($n = 116$) was also lower than in denosumab-treated subjects ($n = 266$) during the first 3 years of FREEDOM and similar to that of placebo ($n = 242$) (Fig. 4a). Eventually, the nonvertebral fracture incidence during the first 3 years of FREEDOM Extension was comparable between long-term denosumab-treated subjects with and without diabetes, and comparable to placebo-treated subjects with diabetes during the first 3 years of FREEDOM (Fig. 4b).

Consistently, exposure-adjusted nonvertebral fracture rates in denosumab-treated subjects with diabetes in the FREEDOM Extension study crossover denosumab group over years 1–7 (1.52; 95% CI 0.70–2.89) and in the long-term denosumab group over years 4–10 (1.72; 95% CI 0.92–2.94) were similar to that of placebo-treated subjects with diabetes (2.00; 95% CI 1.07–3.43) and lower than denosumab-treated subjects with diabetes over years 1–3 (FREEDOM) (4.13; 95% CI 2.76–5.92) (Table 5).

4. Discussion

In this post hoc analysis, denosumab treatment was associated with significantly greater BMD increases and significantly lower new vertebral fracture rates versus placebo in postmenopausal women with osteoporosis and diabetes from FREEDOM, which was similar to findings in the broader FREEDOM population [11]. Hip fractures were rare (four in the placebo group vs one in the denosumab group). Unlike in the overall FREEDOM population, nonvertebral fracture incidence in the subgroup with diabetes was higher among denosumab-treated versus placebo-treated subjects during the first 3 years. These differences mainly occurred with regards to rib and forearm fractures in year 2. It was not replicated in the crossover denosumab group, and did not continue long-term. In general, continuous BMD increases and sustained low rates of new vertebral and nonvertebral fractures (and negligible hip fracture incidence) were observed in subjects with diabetes in both long-term denosumab and crossover denosumab groups during the FREEDOM Extension study, consistent with the broader FREEDOM Extension study population [18]. Exposure-adjusted nonvertebral fracture rates in subjects with diabetes in the FREEDOM Extension long-term and crossover denosumab groups were similar to

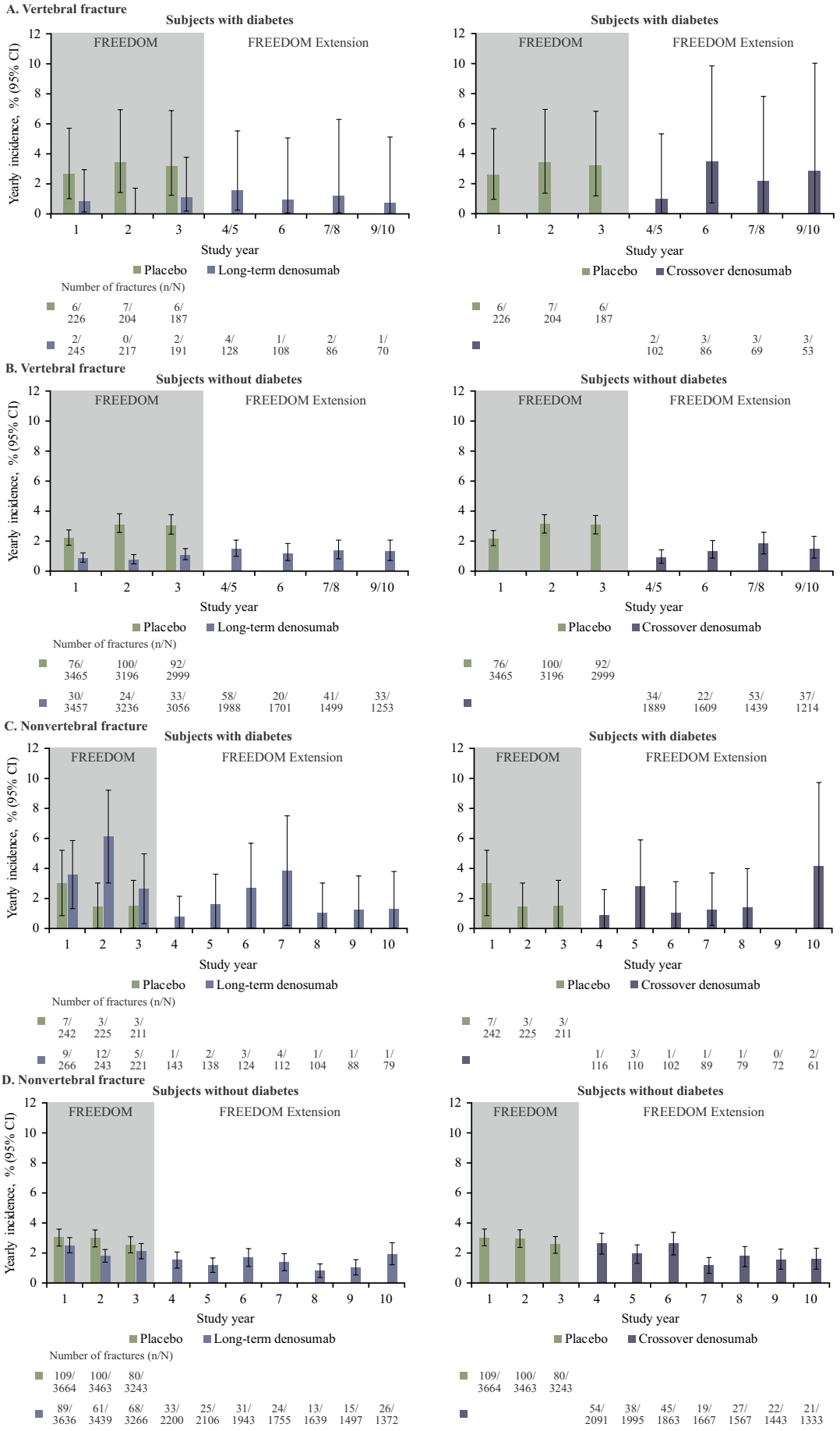

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Fig. 3. Incidence of Vertebral Fracture in Subjects With Diabetes[a] (A) and Without Diabetes (B) in FREEDOM and FREEDOM Extension. Incidence of Nonvertebral Fracture in Subjects With Diabetes[a] (C) and Without Diabetes (D) in FREEDOM and FREEDOM Extension.
[a]Subjects with diabetes were defined based on use of antidiabetic medication and/or fasting glucose levels ≥126 mg/dL (7 mmol/L) at baseline.
CI, confidence interval.

Table 4
Nonvertebral fracture locations occurring in ≥1% subjects in the FREEDOM study.

	Subjects with diabetes[a]		Subjects without diabetes	
	Placebo N = 242	Denosumab N = 266	Placebo N = 3664	Denosumab N = 3636
Number of subjects reporting nonvertebral fractures, n (%)	13 (5.4)	27 (10.2)	280 (7.6)	211 (5.8)
Radius	2 (0.8)	8 (3.0)	111 (3.0)	86 (2.4)
Ribs	0 (0.0)	8 (3.0)	20 (0.5)	19 (0.5)
Humerus	5 (2.1)	7 (2.6)	40 (1.1)	31 (0.9)
Ulna	0 (0.0)	4 (1.5)	38 (1.0)	30 (0.8)
Hip	4 (1.7)	1 (0.4)	39 (1.1)	25 (0.7)
Other[b]	3 (1.2)	6 (2.3)	87 (2.4)	62 (1.7)

Includes only nonvertebral fractures with low trauma severity.
[a] Subjects with diabetes were defined based on use of antidiabetic medication and/or fasting glucose levels ≥126 mg/dL (7 mmol/L) at baseline.
[b] Other types of fracture included fibula, metatarsus, clavicle, patella, tarsus, tibia, sacrum, scapula, acetabulum, carpus, femur distal, illium, ischo-pubic branch, ischium, periprosthetic fracture of the femur, pubis, and sternum.

those of placebo-treated subjects with diabetes in FREEDOM.

The reasons for the finding of a higher incidence of nonvertebral fracture in the subgroup of subjects with diabetes over the first 3 years of treatment with denosumab compared with placebo-treated subjects in FREEDOM are unclear. Unexpectedly, the nonvertebral fracture rate observed in placebo-treated subjects with diabetes in FREEDOM was lower than anticipated, ie, was similar to that in denosumab-treated subjects without diabetes and lower than in placebo-treated subjects without diabetes (6.1% vs. 6.2% and 8.2%, respectively). The nonvertebral fracture rate in subjects with diabetes from a post hoc subgroup analysis of combined data from two randomized placebo-controlled trials, the Fracture Intervention Trial (FIT) of alendronate and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT), was also higher, namely 10% [8]. Furthermore, the incidence of nonvertebral fracture during the first 3 years of exposure to denosumab in the FREEDOM Extension study was lower than observed in denosumab-treated subjects in FREEDOM and similar to that observed during placebo treatment. Secondly, to leverage the broadest possible sample size for denosumab exposure, an exposure-adjusted analysis of nonvertebral fracture rates was conducted to account for the different duration of exposure between denosumab and placebo. This analysis showed that the rate of nonvertebral fracture in crossover denosumab subjects in the FREEDOM Extension study was lower than that observed in denosumab-treated subjects and similar to the fracture rate in patients treated with placebo in FREEDOM. Finally, the number of subjects included in this analysis of diabetes was small (266 in the denosumab group and 242 in the placebo group), thus limiting the ability to draw definitive conclusions regarding fracture rates.

Lower rates of bone remodeling have been reported in subjects with diabetes [19,20]. In our study, baseline serum concentrations of biomarkers of bone formation and resorption were slightly lower in subjects with diabetes, compared with subjects without diabetes. The role of significant inhibition of bone remodeling with denosumab on the diabetes background remains to be established. However, this is unlikely to explain the finding of higher nonvertebral fracture rates in subjects with diabetes during FREEDOM, as vertebral fracture rates were reduced with denosumab treatment to a similar extent in both subjects with and without diabetes, and the nonvertebral fracture rates were similar between subjects with and without diabetes with long-term suppression of bone turnover, i.e. in both long-term and crossover denosumab arms for up to 10 years in FREEDOM Extension.

Some [21], but not all [20], studies have found an increase in cortical porosity in subjects with type 2 diabetes, which might contribute to the increased fracture risk despite higher BMD in this population [21]. Denosumab treatment in postmenopausal women leads to greater reductions in cortical porosity compared with placebo [22], alendronate [23], or teriparatide [24]. Therefore, an improvement in cortical porosity with denosumab would be expected to have beneficial effects on nonvertebral fracture, and denosumab treatment was actually associated with a 20% relative risk reduction in nonvertebral fracture in the broader FREEDOM population [11]. The nonvertebral fractures observed in the FREEDOM denosumab group of postmenopausal women with diabetes occurred at skeletal locations which are less common fragility fracture sites, with nearly a third of such fractures being rib fractures. With the exception of one rib fracture patient, for whom the nature of trauma was unknown, all rib fractures were sustained after a fall from a standing height. Diabetes is associated with a higher risk of falling [6,25], which might contribute to upper body fractures, such as those observed in denosumab-treated subjects with diabetes in this analysis (rib, radius, and ulna). A role for the RANK/RANK ligand pathway has recently been implicated in muscle strength and function [26–29], with some indications that denosumab may reduce the incidence of falls.

This post hoc analysis has several limitations. As a post hoc subgroup analysis, it is subject to selection bias, inflated type I error rate, and small subject numbers (denosumab group: $n = 266$; placebo group: $n = 242$), hampering the ability to draw definitive conclusions regarding fracture rates [30]. FREEDOM and its Extension were not designed to assess effects on fracture incidence in subjects with diabetes, thus randomization was not stratified by this condition. Furthermore, because falls were only reported as adverse events by the investigators and not proactively recorded, the incidence of falls, either associated with fracture or not, was not adjusted for in the statistical analysis and remains a limitation of the study. Additionally, the study population was not representative, comprising only postmenopausal women with fewer overweight and obese subjects than would be expected in the general population of subjects with diabetes [31]. Lastly, diabetes status was not ascertained using glycated hemoglobin (HbA1c), nor was

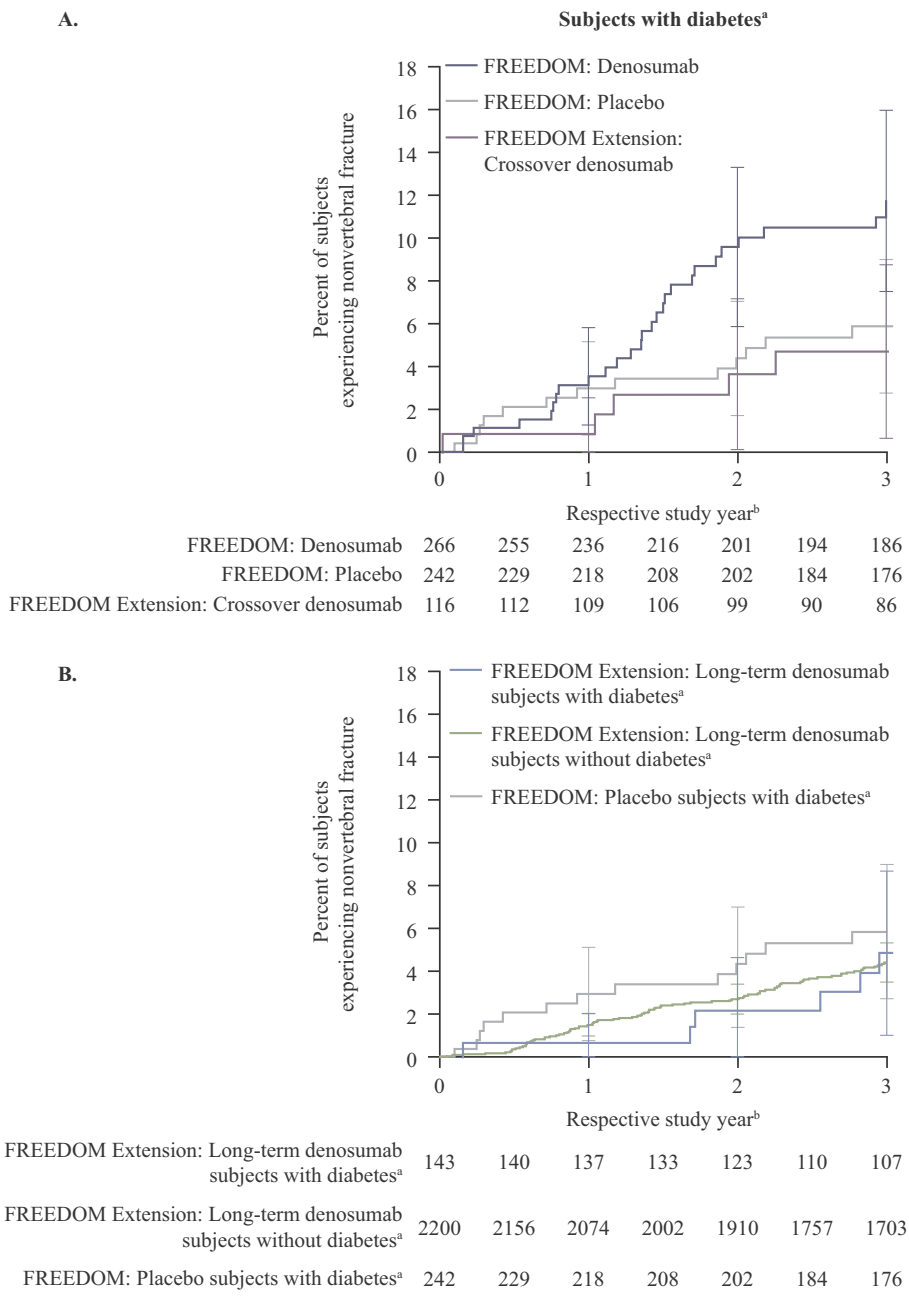

Fig. 4. Time to nonvertebral fracture in subjects with diabetes[a] over 3 years of FREEDOM (study years 1–3) and crossover denosumab subjects in the first 3 years of FREEDOM extension (study years 4–6) receiving denosumab treatment (A) and subjects with or without diabetes[a] in the first 3 years of FREEDOM extension (study years 4–6) receiving denosumab treatment versus FREEDOM (study years 1–3) placebo subjects with diabetes[a] (B).
[a]Subjects with diabetes were defined based on use of antidiabetic medication and/or fasting glucose levels ≥126 mg/dL (7 mmol/L) at baseline.
[b]Respective study years 1–3 correspond to the first 3 years of the FREEDOM study (study years 1–3) and FREEDOM extension study (study years 4–6).

HbA1c measured during the study, thus limiting the ability to assess the impact of glycemic control on fracture risk. Therefore, findings from this analysis and others [8,10] may not necessarily elucidate the effects of osteoporosis medications on diabetes-associated bone fragility.

In conclusion, in subjects with osteoporosis and diabetes, denosumab treatment led to continued BMD increases, reduced vertebral fracture rates, and an overall low long-term fracture incidence, comparable with those in the broader FREEDOM and FREEDOM Extension study populations. Nonvertebral fracture incidence was elevated specifically during the second year of FREEDOM but returned to levels comparable to placebo during the subsequent 7 years of follow-up.

Disclosures

SF has received research support from Amgen, Agnovos, Alexion, and UCB and consulting honoraria from Amgen, Labatec, UCB Pharma, Alexion, and Agnovos all outside the submitted work. RE has received research grants from Alexion, Amgen, and Ultragenyx and consulting fees from ImmunoDiagnostic Systems, GlaxoSmithKline, and Amgen, all outside the submitted work. NN has received consulting fees from Amgen and MSD, all outside the submitted work. AS has received research grants from Hologic and consulting fees from Janssen Pharmaceuticals and Amgen, all outside the submitted work). LH has

Table 5
Exposure-adjusted analysis of nonvertebral fractures by length of denosumab exposure in subjects with diabetes.

	Placebo	Denosumab			
	Years 1–3	Years 1–3	Years 4–7	Years 4–10	Years 1–7
Long-term denosumab subjects					
N[a]	–	266	143	143	–
Number of nonvertebral fractures	–	29	10	13	–
Fracture rate per 100 subject-years, (95% CI)[b]	–	4.13 (2.76–5.92)	2.02 (0.97–3.71)	1.72 (0.92–2.94)	–
Rate ratio (95% CI)[b]		[Referent]	0.50 (0.25–0.99)	0.42 (0.22–0.82)	
p value			$p = .047$	$p = .011$	
Crossover denosumab subjects					
N[a]	242	116	89	–	116
Number of nonvertebral fractures	13	5	4	–	9
Fracture rate per 100 subject-years (95% CI)[b]	–	1.60 (0.52–3.73)	1.44 (0.39–3.69)	–	1.52 (0.70–2.89)
Rate ratio (95% CI)[b]		[Referent]	0.97 (0.29–3.24)		N/A
p value			$p = .967$		
Rate ratio (95% CI)[b]	2.00 (1.07–3.43)	0.75 (0.30–3.41)	0.73 (0.27–1.98)	–	0.75 (0.37–1.55)
p value (versus placebo)	[Referent]	$p = .534$	$p = .538$		$p = .440$

Abbreviations: BMD, bone mineral density; CI, confidence interval.

[a] Number of subjects with diabetes who completed FREEDOM (i.e., completed their 3-year visit and did not discontinue investigational product), did not miss > 1 dose of investigational product, and who enrolled in FREEDOM Extension. In addition, crossover denosumab subjects completed 3 years of the extension and did not miss > 1 dose of denosumab during the first 3 years of the Extension study.

[b] Fracture rates and rate ratios were obtained using generalized estimating equation Poisson models; fracture rates are per 100 subject-years. Rate ratios relative to the first 3 years of denosumab treatment were adjusted for age, total hip BMD T-score, weight, and history of non-vertebral fracture. Fracture rates were compared by length of denosumab exposure, regardless of whether exposure occurred during FREEDOM or the FREEDOM Extension study.

received research support from Amgen and Novartis and consulting fees from Alexion, Amgen, Novartis, Radius, Shire, and UCB, all outside the submitted work. AC, AW, and NP are all Amgen employees with stock options. SRC has received consulting fees from Amgen, outside the submitted work.

Funding

This study was sponsored by Amgen Inc.

Clinical trial registration

The FREEDOM trial (NCT00089791) and its extension (NCT00523341) are both registered with ClinicalTrials.gov.

Acknowledgments

The authors thank Hannah Greenwood, PhD, Stephanie Weng, PhD, and Fiona Woodward, PhD (Fishawack Communications Inc.), whose work was funded by Amgen Inc., and Lisa Humphries, PhD (Amgen Inc.) for providing medical writing assistance. Additionally, the authors thank Shuang Huang, PhD (Amgen Inc.) for statistical support. Research on bone health in diabetes by SF, RE, NN, and LCH is supported by the European Union's Horizon 2020 research and innovation program under the MARIE SKŁODOWSKA-CURIE grant agreement no. 860898 (FIDELIO).

Author's roles

Data analysis: AW. Data interpretation: SF, RE, NN, AS, LCH, AC, AW, NP, and SRC. Drafting manuscript: SF and NP. All authors contributed to the development of subsequent drafts and approved the final version for submission. SF, AC, and AW take responsibility for the integrity of the data analysis.

Data availability

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.

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