The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 2, 397–409
doi:10.1210/clinem/dgaa851
Clinical Research Article

Clinical Research Article

Denosumab Safety and Efficacy Among Participants in the FREEDOM Extension Study With Mild to Moderate Chronic Kidney Disease

Aaron Broadwell,[1] Arkadi Chines,[2] Peter R. Ebeling,[3] Edward Franek,[4] Shuang Huang,[2] Shawna Smith,[2] David Kendler,[5] Osvaldo Messina,[6] and Paul D. Miller[7]

[1]Rheumatology and Osteoporosis Specialists, Shreveport, Louisiana 71101, USA; [2]Amgen Inc, Thousand Oaks, California 91320, USA; [3]Monash University, Clayton, Victoria 3800, Australia; [4]Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw 02-106, Poland; [5]University of British Columbia, Vancouver, British Columbia V6T 1Z4, Canada; [6]University of Buenos Aires, Buenos Aires C1053 CABA, Argentina; and [7]Colorado Center for Bone Research, Lakewood, Colorado 80227, USA

ORCiD numbers: 0000-0003-3556-3279 (A. Broadwell); 0000-0001-7679-3965 (D. Kendler).

Abbreviations: AE, adverse event; BMD, bone mineral density; CCr, creatinine clearance; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; MDRD, Modification of Diet in Renal Disease; MedDRA, Medical Dictionary for Regulatory Activities; ONJ, osteonecrosis of the jaw; Q6M, every 6 months; SAE, serious adverse event; SC, subcutaneously; RANKL, receptor activator of nuclear factor κ-B ligand.

Received: 8 April 2020; Editorial Decision: 12 November 2020; First Published Online: 19 November 2020; Corrected and Typeset: 15 December 2020.

Abstract

Context: The effects of long-term exposure to denosumab in individuals with renal insufficiency are unknown.

Objective: This post hoc analysis evaluates the long-term safety and efficacy of denosumab in individuals with mild-to-moderate chronic kidney disease (CKD) (stages 2 and 3) using data from the pivotal phase 3, double-blind, 3-year FREEDOM (NCT00089791) and open-label, 7-year extension (NCT00523341) studies.

Participants and Methods: Women age 60 to 90 years with a bone mineral density (BMD) T-score of less than –2.5 to greater than –4.0 at the total hip or lumbar spine were randomly assigned 1:1 to receive denosumab 60 mg subcutaneously every 6 months (long-term arm) or placebo (cross-over arm) in FREEDOM; eligible participants could enroll in the extension to receive denosumab 60 mg subcutaneously every 6 months. Change in estimated glomerular filtration rate (eGFR) from study baseline and annualized rates of fracture and adverse events (AEs) were the main outcome measures.

Results: Most participants (1259/1969 [64%] long-term arm; 1173/1781 [66%] crossover arm) with baseline CKD stage 2 or 3 remained within the same CKD subgroup at study completion; less than 3% progressed to CKD stage 4. Participants in all eGFR subgroups showed

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

similar, persistent BMD gains over time and a low incidence of fractures. The percentage of participants reporting serious AEs was similar among renal subgroups (normal, CKD stage 2, CKD stage 3a, CKD stage 3b) both for the long-term (54% vs 52% vs 57% vs 58%) and crossover (43% vs 42% vs 43% vs 68%) arms, except CKD stage 3b subgroup, crossover arm. **Conclusion:** The safety and efficacy of denosumab did not differ among participants with mild to moderate CKD.

Freeform/Key Words: denosumab, chronic kidney disease, safety, fracture, bone mineral density

Aging is associated with a gradual decline in renal function, so the average level of renal function among community-dwelling individuals older than 70 years is at or below the threshold used to define chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] < 90 mL/min) (1-3). It is estimated that 85% of women with osteoporosis have mild to moderate renal impairment, defined as an estimated creatinine clearance (CCr) of less than or equal to 60 mL/min, whereas 24% have severe renal compromise (CCr < 35 mL/min) (4). Because bone quality and renal function both decline with age, osteoporosis and CKD are common comorbid conditions that reduce the quality of life and contribute to morbidity and mortality in older individuals (5-9). Both conditions have a negative impact on bone health due to reductions in bone mineral density (BMD), abnormal bone turnover, and increased risk of fracture (10-12). Mild to moderate CKD is associated with a significantly increased risk of vertebral, hip, and radial fractures compared with age-matched individuals with normal renal function (13-16).

Given the prevalence of osteoporosis and CKD among older individuals, it is important to understand the safety and efficacy of osteoporosis therapies in patients with renal insufficiency and any effects of these agents on intrinsic renal function. When treatment choices are considered, the side effects and risk of administration must be weighed against the accuracy of diagnosis and benefit of treatment. There may be uncertainties regarding the safety of medications in the context of altered metabolism in CKD. Almost half of all medications used, including bisphosphonates, are eliminated by the kidney and therefore may accumulate beyond normal levels in patients with reduced renal function (17). The levels of bone turnover markers present in patients with renal osteodystrophy range from severely suppressed to markedly elevated, which could also influence the choice of osteoporosis treatment (ie, antiresorptive or anabolic).

Denosumab is a human monoclonal antibody targeting receptor activator of nuclear factor κ-B ligand (RANKL) that inhibits osteoclasts to decrease bone resorption and increase BMD (18). Denosumab is not metabolized or excreted by the kidney, and 3-year data from the pivotal phase 3, placebo-controlled FREEDOM trial in postmenopausal women with osteoporosis showed similar efficacy and safety of denosumab between participants with and without renal impairment (19). However, the effects of long-term exposure to denosumab in individuals with renal insufficiency are unknown. Here, using 10-year data from the FREEDOM trial and its open-label extension, in which participants in the long-term denosumab and placebo-to-denosumab crossover arms received up to 10 and 7 years of continuous denosumab therapy, respectively, we assessed the safety and efficacy of denosumab in individuals with different levels of renal function and changes in renal function over time.

Materials and Methods

Study design and participants

The designs of the FREEDOM trial (NCT00089791) and its open-label extension (NCT00523341) have been described previously (18, 20). FREEDOM was a phase 3, randomized, double-blind, 3-year, placebo-controlled trial conducted at 214 centers worldwide. Enrolled individuals were postmenopausal women age 60 to 90 years with lumbar spine or total hip BMD T-scores between –4.0 and –2.5. Participants were randomly assigned to receive placebo or 60 mg denosumab subcutaneously (SC) every 6 months (Q6M) for 3 years. At the end of 3 years, participants who missed no more than one dose of the investigational product could enroll in the open-label extension to receive denosumab 60 mg SC Q6M for an additional 7 years. All participants were instructed to take daily calcium (≥ 1000 mg) and vitamin D (≥ 400 IU). Women randomly assigned to receive denosumab in FREEDOM could receive up to 10 years of denosumab treatment ("long-term arm"); women randomly assigned to receive placebo in FREEDOM could receive up to 7 years of denosumab treatment ("crossover arm"). Informed consent was obtained from each participant. The studies were conducted in accordance with the principles set out in the Declaration of Helsinki and were formally approved by the appropriate institutional review board, ethical review committee, or equivalent at each study site.

In the present analysis, the long-term arm included all individuals who were randomly assigned to denosumab in FREEDOM and received at least one dose of denosumab in the open-label extension; the crossover arm included all individuals randomly assigned to placebo in FREEDOM and received at least one dose of denosumab in the open-label extension. Participants were further grouped according to baseline eGFR, normalized to body surface area and calculated using the Modification of Diet in Renal Disease (MDRD) study equation, as follows: normal renal function, eGFR greater than or equal to 90 mL/min/1.73 m^2; CKD stage 2, eGFR 60 to 89 mL/min/1.73 m^2; CKD stage 3a, eGFR 45 to 59 mL/min/1.73 m^2; CKD stage 3b, eGFR 30 to 44 mL/min/1.73 m^2; and CKD stage 4, eGFR 15 to 29 mL/min/1.73 m^2 (21, 22). The MDRD equation was well validated and was used to estimate eGFR; because this analysis did not differentiate based on sex or race, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using splines was not used. Baseline assessments for the long-term and crossover arms were conducted at FREEDOM and open-label extension baselines, respectively.

Outcome measures

Vertebral fractures were identified by a central facility (Bioclinica) using lateral thoracic and lumbar spine radiographs. Nonvertebral fractures excluded those of the skull, face, mandible, metacarpus, finger phalanges, toe phalanges, and pathological fractures and fractures associated with a high severity of trauma and required confirmation by diagnostic imaging or a radiologist's report. In the long-term denosumab arm, new vertebral fracture rates were calculated for year 1 (FREEDOM baseline to 12 months), year 2 (> 12-24 months), year 3 (> 24-36 months), years 4 and 5 (> 36-60 months), year 6 (> 60-72 months), years 7 and 8 (> 72-96 months), and years 9 and 10 (> 96-120 months); in the crossover arm, new vertebral fracture rates were calculated for years 1 and 2 (open-label extension baseline to 24 months), year 3 (> 24-36 months), years 4 and 5 (> 36-60 months), and years 6 and 7 (>60-84 months). Nonvertebral fracture rates were calculated for each year of the 10 treatment years in the long-term arm and 7 treatment years in the crossover arm. BMD was measured by dual-energy x-ray absorptiometry of the lumbar spine and proximal femur. BMD measurements were obtained at baseline and years 1, 2, 3, 4, 5, 6, 8, and 10 for the long-term arm and baseline and years 1, 2, 3, 5, and 7 in the crossover arm. FREEDOM year 1 and 2 lumbar spine BMD was measured in a substudy with a limited number of participants; BMD was measured in all participants at baseline and year 3 only.

Safety was evaluated on the basis of treatment-emergent adverse event (AE) and serious adverse event (SAE) incidence. The Medical Dictionary for Regulatory Activities version 13.0 (MedDRA v13.0) was used to code and report AEs. Cases of osteonecrosis of the jaw (ONJ) were reviewed by an independent external adjudication committee. Albumin-corrected serum calcium was measured at study baseline and 6-month intervals thereafter during FREEDOM, and at baseline, every 6 months for 2 years, and every 12 months thereafter during the open-label extension. In-study hypocalcemia was reported by the investigator and defined as a combination of the following preferred MedDRA terms: *blood calcium decreased*, *calcium deficiency*, *calcium ionized decreased*, and *hypocalcemia*. The maximum hypocalcemia toxicity grade was calculated using the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE; grade 1, < lower limit of normal-8.0 mg/dL [2.0 mmol/L]; grade 2, < 8.0-7.0 mg/dL [< 2.0-1.75 mmol/L]). The change in eGFR subgroup from baseline to last in-study visit for each participant was assessed and summarized.

Statistical analyses

This analysis reports the annualized incidence rate of new vertebral fractures and the annualized, cumulative incidence rate of nonvertebral fractures based on Kaplan-Meier estimate. BMD values were summarized using descriptive statistics and plotted as mean with 95% CI. The outcomes were evaluated both for the long-term and crossover arms.

Results

Participant characteristics

The FREEDOM extension study enrolled 4550 women (2343 long-term, 2207 crossover). Of these, 2342 and 2200 women in the long-term and crossover arms had an eGFR assessment at FREEDOM and extension baselines, respectively, and were included in the present analysis. Less than 20% of individuals in either arm had normal renal function at baseline, and the majority in the long-term (1969/2342; 84%) and crossover (1781/2200; 81%) arms had mild or moderate renal insufficiency (CKD stage 2 or 3) prior to receiving denosumab. Few participants (N = 4 long-term; N = 5 crossover) had CKD stage 4 at baseline; none had CKD stage 5. The individuals with CKD stage 4 were not included in the analysis of annualized incidence rates of new vertebral and nonvertebral fractures, percentage change in BMD from baseline, and postbaseline shift in hypocalcemia grade. In both treatment arms, individuals with poorer

renal function were generally older and had lower BMD T-scores. Participant characteristics in each treatment arm by baseline renal function are provided in Table 1.

Fracture incidence and change in bone mineral density with long-term denosumab

For years 1 through 3 of FREEDOM, the annualized incidence rate of new vertebral fractures was 2.5%, 1.7%, 0.9%, and 1.6% for placebo-treated participants and 0.6%, 0.3%, 1.2%, and 0% for denosumab-treated participants with normal renal function, CKD stage 2, CKD stage 3a, and CKD stage 3b at baseline, respectively. In the extension, the annualized incidence rate of new vertebral fractures was 0.9%, 0.8%, 0.8%, and 0.7% for long-term denosumab-treated participants and 1.7%, 1.7%, 1.4%, and 1.7% for crossover denosumab-treated participants with normal renal function, CKD stage 2, CKD stage 3a, and CKD stage 3b at extension baseline, respectively (Fig. 1A). For nonvertebral fractures, the annualized cumulative incidence rate over the 3 years of FREEDOM was 2.4%, 2.0%, 1.7%, and 4.0% for placebo-treated participants and 2.2%, 1.8%, 1.7%, and 3.0% for denosumab-treated participants with normal renal function, CKD stage 2, CKD stage 3a, and CKD stage 3b at baseline, respectively. In the extension, the annualized cumulative incidence rate of nonvertebral fractures was 2.3%, 2.5%, 2.2%, and 2.7% for long-term denosumab-treated participants and 3.7%, 2.5%, 2.3%, and 2.4% for crossover denosumab-treated participants with normal renal function, CKD stage 2, CKD stage 3a, and CKD stage 3b at extension baseline, respectively (Fig. 1B).

In the long-term denosumab arm, BMD increased from FREEDOM baseline by 22.0%, 21.7%, 21.7%, and 23.7% at the lumbar spine and by 9.7%, 9.4%, 9.8%, and 7.4% at the total hip among individuals with normal renal function, CKD stage 2, CKD stage 3a, and CKD stage 3b, respectively. In the crossover arm after 7 years of denosumab treatment, BMD increased from extension baseline by 17.1%, 17.0%, 16.8%, and 14.9% at the lumbar spine and by 8.2%, 7.5%, 7.6%, and 6.2% at the total hip among individuals with normal renal function, CKD stage 2, CKD stage 3a, and CKD stage 3b, respectively (Fig. 2).

Shift in renal function from baseline

Among participants with normal renal function at baseline, 45.8% in the long-term arm and 59.4% in the crossover arm maintained normal renal function at the last in-study visit, whereas 48.5% and 35.5%, respectively, progressed to CKD stage 2. Among women treated for 3 years with placebo in FREEDOM, 62.8% maintained normal renal function and 35.3% progressed to CKD stage 2. Among those with mild to moderate renal impairment at baseline, the majority in the long-term (1259/1969; 63.9%) and crossover (1173/1781; 65.9%) denosumab arms remained within the same CKD stage subgroup at the last in-study visit. The majority of placebo-treated participants with CKD stage 2 or 3 at baseline (2421/3212; 75.4%) also remained within the same CKD stage subgroup at the end of 3 years. Less than 3% of individuals in either denosumab arm progressed from CKD stage 2 or 3 to CKD stage 4 (Table 2); no participants initiated renal replacement therapy.

Incidence of hypocalcemia and other adverse events

The percentages of participants reporting AEs and SAEs were similar among renal subgroups for both the long-term and crossover arms. Overall, the percentages of women reporting AEs and SAEs were similar among renal subgroups both for the long-term and crossover arms; however, a higher percentage of participants with SAEs was observed in the CKD stage 3b subgroup compared with other subgroups in the crossover arm. Seven women in the long-term arm (< 0.3%) and 5 women in the crossover arm (< 0.3%) developed ONJ. Hypocalcemia as an AE occurred in 6 participants in the long-term arm (< 0.3%) and 10 participants in the crossover arm (< 0.5%), and only 1 participant (in the crossover arm) developed hypocalcemia classified as an SAE (Table 3). None of the individuals in the long-term arm developed hypocalcemia in the first 36 months of the FREEDOM study. In the crossover arm, 1 woman with normal renal function, 3 women with CKD stage 2, and 1 woman with CKD stage 3a developed hypocalcemia in the first 6 months of treatment with denosumab. Among participants showing a decrease from baseline in albumin-corrected calcium, the majority of individuals in both treatment arms (> 90%) shifted within grade 0 of the CTCAE v3.0 criteria. A shift in hypocalcemia from grade 0 to 1 was observed in 3.0%, 3.1%, 3.1%, and 6.1% of participants in the long-term arm with normal renal function, CKD stage 2, CKD stage 3a, and CKD stage 3b, respectively, and in 5.8%, 3.5%, 4.7%, and 3.0% of participants in the crossover arm with normal renal function, CKD stage 2, CKD stage 3a, and CKD stage 3b, respectively. Less than 2% of participants in either arm had a maximum postbaseline shift in hypocalcemia from grade 0 to 2 (Fig. 3).

Discussion

Our results demonstrate that denosumab was equally effective at increasing BMD and reducing fracture risk in

Table 1. Participant characteristics in each treatment arm by baseline renal function

	Long-term denosumab arm Baseline renal function					Crossover denosumab arm Baseline renal function				
	Normal (N = 369)	CKD stage 2 (N = 1644)	CKD stage 3a (N = 292)	CKD stage 3b (N = 33)	CKD stage 4 (N = 4)	Normal (N = 414)	CKD stage 2 (N = 1495)	CKD stage 3a (N = 253)	CKD stage 3b (N = 33)	CKD stage 4 (N = 5)
Age, y, median (range)	70 (60-85)	72 (60-89)	74 (62-87)	76 (68-90)	79 (74-82)	74 (63-90)	75 (63-93)	77 (63-92)	78 (67-86)	78 (70-87)
Years since menopause, mean (SD)	22.0 (7.6)	23.4 (7.0)	26.4 (7.3)	28.8 (7.7)	33.8 (3.5)	26.0 (7.3)	26.4 (7.3)	28.5 (7.7)	31.4 (6.8)	30.2 (5.9)
Race/ethnicity, Whites or Caucasians, n (%)	346 (93.8)	1543 (93.9)	247 (84.6)	28 (84.8)	4 (100.0)	376 (90.8)	1411 (94.4)	232 (91.7)	33 (100.0)	5 (100.0)
Prevalent vertebral fracture, n (%)	100 (27.1)	388 (23.6)	63 (21.6)	8 (24.2)	0 (0.0)	105 (25.4)	362 (24.2)	67 (26.5)	14 (42.4)	1 (20.0)
Corrected calcium, mg/dL, mean (SD)	9.69 (0.44)	9.75 (0.41)	9.79 (0.45)	9.89 (0.47)	9.80 (0.59)	9.47 (0.36)	9.55 (0.36)	9.65 (0.37)	9.62 (0.42)	9.72 (0.26)
BMD T-score, mean (SD)										
Lumbar spine	–2.81 (0.62)	–2.84 (0.68)	–2.86 (0.67)	–2.39 (1.05)	–2.83 (0.86)	–2.92 (0.75)	–2.81 (0.75)	–2.67 (0.78)	–2.48 (1.03)	–2.74 (0.52)
Total hip	–1.85 (0.77)	–1.83 (0.79)	–1.93 (0.78)	–2.22 (0.83)	–2.28 (0.81)	–1.95 (0.81)	–1.92 (0.81)	–1.99 (0.84)	–2.29 (0.72)	–2.44 (0.81)
Femoral neck	–2.08 (0.71)	–2.10 (0.71)	–2.17 (0.73)	–2.48 (0.70)	–2.43 (0.61)	–2.12 (0.76)	–2.16 (0.70)	–2.23 (0.77)	–2.63 (0.59)	–2.62 (0.53)
Prior use of osteoporosis medications, n (%)	107 (29.0)	508 (30.9)	88 (30.1)	7 (21.2)	0 (0.0)	412 (99.5)	1489 (99.6)	252 (99.6)	33 (100.0)	5 (100.0)
Bisphosphonate (oral)	33 (8.9)	199 (12.1)	23 (7.9)	2 (6.1)	0 (0.0)	69 (16.7)	187 (12.5)	33 (13.0)	6 (18.2)	1 (20.0)
Calcitriol	26 (7.0)	141 (8.6)	34 (11.6)	2 (6.1)	0 (0.0)	411 (99.3)	1489 (99.6)	252 (99.6)	33 (100.0)	5 (100.0)
Hormone replacement therapy	18 (4.9)	36 (2.2)	1 (0.3)	0 (0.0)	0 (0.0)	21 (5.1)	97 (6.5)	15 (5.9)	2 (6.1)	0 (0.0)
Estrogens	16 (4.3)	34 (2.1)	1 (0.3)	0 (0.0)	0 (0.0)	18 (4.3)	92 (6.2)	15 (5.9)	2 (6.1)	0 (0.0)
Other[a]	23 (6.2)	94 (5.7)	11 (3.8)	0 (0.0)	0 (0.0)	20 (4.8)	95 (6.4)	13 (5.1)	1 (3.0)	1 (20.0)

Normal renal function = eGFR greater than or equal to 90 mL/min/1.73 m^2; CKD stage 2 = eGFR 60 to 89 mL/min/1.73 m^2; CKD stage 3a = eGFR 45 to 59 mL/min/1.73 m^2; CKD stage 3b = eGFR 30 to 44 mL/min/1.73 m^2; CKD stage 4 = eGFR 15 to 29 mL/min/1.73 m^2. One participant in the long-term denosumab arm and 7 participants in the crossover denosumab arm did not have an eGFR assessment at baseline. Data were summarized at FREEDOM baseline for long-term denosumab arm and at the extension baseline for crossover denosumab arm.

Abbreviations: BMD, bone mineral density; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N, number of participants with an eGFR evaluation at study baseline; n, number of participants with observed data.

[a]Includes calcitonin, selective estrogen receptor modulators, parathyroid hormone or its derivatives, intravenous bisphosphonate, and fluoride.

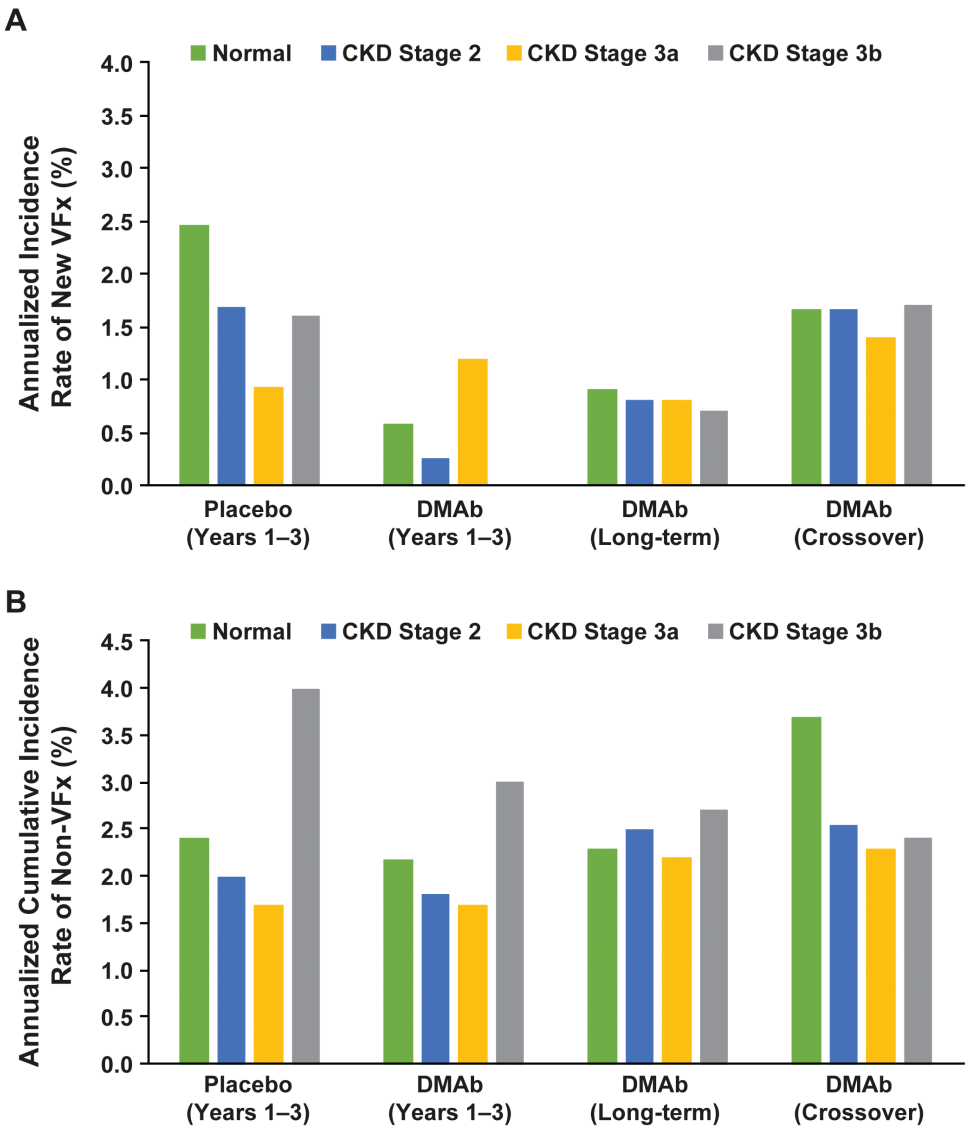

Figure 1. Annualized incidence rates of fractures by baseline estimated glomerular filtration rate (eGFR). A, Annualized incidence rate (%) of new vertebral fractures. B, Annualized cumulative incidence rate (%) of nonvertebral fractures based on Kaplan-Meier estimate. Bars (from left to right) show FREEDOM placebo arm, FREEDOM denosumab (DMAb)-treated arm, FREEDOM extension long-term denosumab-treated arm, and crossover denosumab-treated arm (randomly assigned to placebo in FREEDOM and received denosumab in the extension). Chronic kidney disease (CKD) stage was calculated according to eGFR at FREEDOM baseline, except for the crossover arm, where CKD stage was calculated according to eGFR at the extension baseline. Normal renal function = eGFR greater than or equal to 90 mL/min/1.73 m^2; CKD stage 2 = eGFR 60 to 89 mL/min/1.73 m^2; CKD stage 3a = eGFR 45 to 59 mL/min/1.73 m^2; CKD stage 3b = eGFR 30 to 44 mL/min/1.73 m^2. VFx, vertebral fracture.

women with normal renal function vs those with mild to moderate renal insufficiency. The magnitude and persistence of BMD gain and fracture reduction over time were similar for all renal subgroups and consistent with the overall results reported for the total study population in the FREEDOM and extension studies (18, 20), as well as 3-year findings of a post hoc analysis of FREEDOM data evaluating individuals stratified by level of renal function (19). Despite the aging of the study population, long-term treatment with denosumab was not associated with a further decline in renal function from baseline in the majority of participants, and there were no major differences in rates of AEs or SAEs, including hypocalcemia, by stage of CKD over the 7- or 10-year treatment periods.

Given the high prevalence of osteoporosis and decline in renal function among aging individuals, it is important to recognize and treat osteoporosis in the context of CKD. Indeed, low BMD in patients with CKD is associated with a 1.5- to 2-fold greater risk of fracture than that in the general population (23). Diagnosing and treating osteoporosis in the setting of CKD is complex because of the unique mechanisms responsible for low BMD in each disease and abnormalities in bone and mineral metabolism that develop with progressive renal decline, termed *chronic*

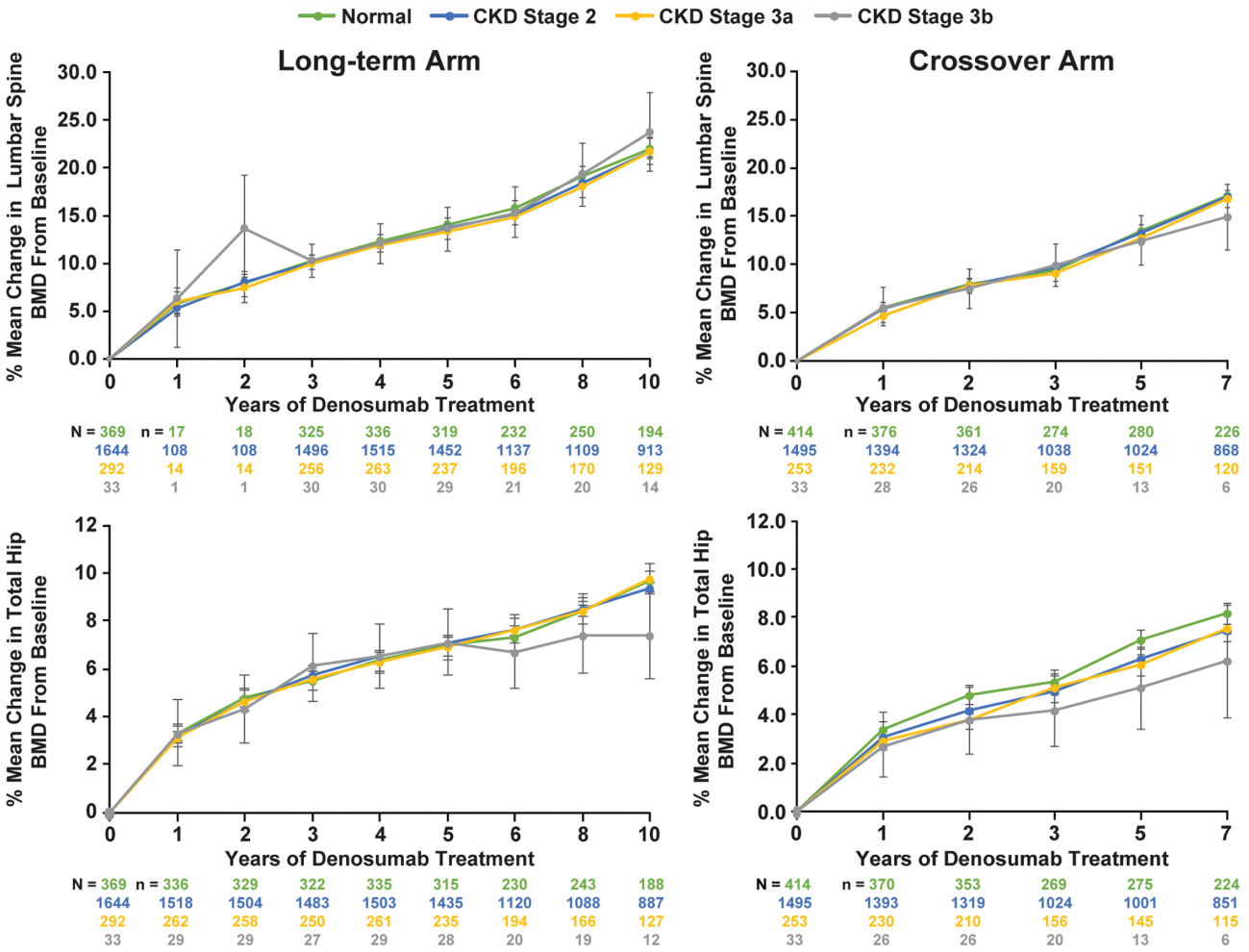

Figure 2. Percentage change in lumbar spine and total hip bone mineral density (BMD) from baseline by baseline estimated glomerular filtration rate (eGFR) in the long-term and crossover arms. Graphs show the least square means and 95% CIs. Chronic kidney disease (CKD) stage was calculated according to eGFR at FREEDOM and extension baseline for the denosumab-treated long-term and crossover arms, respectively. Note that for the long-term arm, lumbar spine BMD was measured in a FREEDOM substudy at year 1 and 2 with a limited number of participants; lumbar spine BMD was measured in all participants at baseline and year 3 only. Normal renal function = eGFR greater than or equal to 90 mL/min/1.73 m^2; CKD stage 2 = eGFR 60 to 89 mL/min/1.73 m^2; CKD stage 3a = eGFR 45 to 59 mL/min/1.73 m^2; CKD stage 3b = eGFR 30 to 44 mL/min/1.73 m^2. N = number of participants with an eGFR evaluation at study baseline; n = number of participants with observed data.

kidney disease–mineral and bone disorder (CKD-MBD). In its 2017 updated guideline, Kidney Disease: Improving Global Outcomes (KDIGO) recommends osteoporosis treatment decisions for patients with CKD stage 3a to 5D take into account the magnitude and reversibility of the biochemical abnormalities and progression of CKD, with consideration of a bone biopsy prior to osteoporosis treatment to understand the underlying bone pathology (22). Although rarely performed for CKD stages 0 to 3, bone biopsy is needed in advanced CKD to diagnose osteoporosis, which cannot be diagnosed on the basis of BMD or the presence of fragility fractures in these patients, and to exclude adynamic renal bone disease (24, 25). The present post hoc analysis of a large, randomized clinical trial demonstrates the long-term safety and efficacy of denosumab for osteoporosis treatment in individuals with normal renal function to CKD stage 3 and an absence of clear abnormalities in mineral metabolism. Unfortunately, our analysis had limited power to assess fracture risk reduction and BMD gain in individuals with more severe impairment of renal function (CKD stages 4 and 5).

Bisphosphonates are widely used to prevent fractures in women with postmenopausal osteoporosis, and data from pivotal trials and their extension studies have shown no effects of treatment with oral alendronate, risedronate, and ibandronate on renal function (26-30). Reports comparing alendronate with placebo in individuals with CKD stages 3 to 5 showed variable results for BMD improvement with alendronate over placebo in individuals with mild to moderate CKD (26, 28). Regarding fracture, the risks of clinical fracture and vertebral fracture were reduced with alendronate treatment to a similar degree in those with

Table 2. Shift in CKD stage from baseline to last visit with up to10-year follow-up period

	CKD stage at last visit					
	Normal n (%)	CKD stage 2 n (%)	CKD stage 3a n (%)	CKD stage 3b n (%)	CKD stage 4 n (%)	CKD stage 5 n (%)
Long-term denosumab arm (N = 2342)						
CKD stage at study baseline						
Normal (n = 369)	169 (45.8)	179 (48.5)	17 (4.6)	3 (0.8)	1 (0.3)	0 (0.0)
CKD stage 2 (n = 1644)	188 (11.4)	1110 (67.5)	279 (17.0)	61 (3.7)	4 (0.2)	2 (0.1)
CKD stage 3a (n = 292)	6 (21.0)	89 (30.5)	133 (45.5)	56 (19.2)	8 (2.7)	0 (0.0)
CKD stage 3b (n = 33)	0 (0.0)	6 (18.2)	10 (30.3)	16 (48.5)	1 (3.0)	0 (0.0)
CKD stage 4 (n = 4)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (50.0)	0 (0.0)
Crossover denosumab arm (N = 2200)						
CKD stage at study baseline						
Normal (n = 414)	246 (59.4)	147 (35.5)	4 (1.0)	1 (0.2)	0 (0.0)	0 (0.0)
CKD stage 2 (n = 1495)	154 (10.3)	1026 (68.6)	244 (16.3)	40 (2.7)	2 (0.1)	0 (0.0)
CKD stage 3a (n = 253)	2 (0.8)	74 (29.2)	128 (50.6)	38 (15.0)	2 (0.8)	0 (0.0)
CKD stage 3b (n = 33)	0 (0.0)	2 (6.1)	5 (15.2)	19 (57.6)	6 (18.2)	1 (3.0)
CKD stage 4 (n = 5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)	1 (20.0)	0 (0.0)
Placebo arm (N = 3858)						
CKD stage at study baseline						
Normal (n = 637)	400 (62.8)	225 (35.3)	11 (1.7)	1 (0.2)	0 (0.0)	0 (0.0)
CKD stage 2 (n = 2712)	287 (10.6)	2175 (80.2)	229 (8.4)	20 (0.7)	1 (< 0.1)	0 (0.0)
CKD stage 3a (n = 439)	6 (1.4)	184 (41.9)	214 (48.8)	34 (7.7)	1 (0.2)	0 (0.0)
CKD stage 3b (n = 61)	0 (0.0)	11 (18.0)	13 (21.3)	32 (52.5)	4 (6.6)	1 (1.6)
CKD stage 4 (n = 9)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)	6 (66.7)	0 (0.0)

CKD stage at study baseline was calculated according to eGFR at FREEDOM baseline, except for the crossover arm, where CKD stage was calculated according to eGFR at the extension baseline. Normal renal function = eGFR greater than or equal to 90 mL/min/1.73 m^2; CKD stage 2 = eGFR 60 to 89 mL/min/1.73 m^2; CKD stage 3a = eGFR 45 to 59 mL/min/1.73 m^2; CKD stage 3b = eGFR 30 to 44 mL/min/1.73 m^2; CKD stage 4 = eGFR 15 to 29 mL/min/1.73 m^2.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N, number of participants with an eGFR evaluation at study baseline; n, number of participants with observed data.

Table 3. Incidence of adverse events in each treatment arm by baseline renal function

Adverse event, n (%)	Long-term denosumab arm Baseline renal function					Crossover denosumab arm Baseline renal function				
	Normal (N = 369)	CKD stage 2 (N = 1644)	CKD stage 3a (N = 292)	CKD stage 3b (N = 33)	CKD stage 4 (N = 4)	Normal (N = 414)	CKD stage 2 (N = 1495)	CKD stage 3a (N = 253)	CKD stage 3b (N = 33)	CKD stage 4 (N = 5)
Any AE	363 (98.4)	1622 (98.7)	289 (99.0)	33 (100.0)	4 (100.0)	378 (91.3)	1411 (94.4)	239 (94.5)	31 (93.9)	5 (100.0)
SAE	200 (54.2)	847 (51.5)	166 (56.8)	19 (57.6)	2 (50.0)	177 (42.8)	633 (42.3)	108 (42.7)	22 (66.7)	2 (40.0)
Fatal AE	14 (3.8)	68 (4.1)	23 (7.9)	1 (3.0)	2 (50.0)	17 (4.1)	57 (3.8)	20 (7.9)	7 (21.2)	0 (0.0)
AE leading to discontinuation of drug	44 (11.9)	139 (8.5)	30 (10.3)	3 (9.1)	0 (0.0)	37 (8.9)	118 (7.9)	23 (9.1)	4 (12.1)	1 (20.0)
AE leading to study discontinuation	37 (10.0)	107 (6.5)	26 (8.9)	3 (9.1)	0 (0.0)	30 (7.2)	93 (6.2)	16 (6.3)	4 (12.1)	1 (20.0)
Positively adjudicated ONJ events[a]	1 (0.3)	6 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Positively adjudicated AFF events	0 (0.0)	1 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hypocalcemia										
AE	2 (0.5)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	6 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Normal renal function = eGFR greater than or equal to 90 mL/min/1.73 m^2; CKD stage 2 = eGFR 60 to 89 mL/min/1.73 m^2; CKD stage 3a = eGFR 45 to 59 mL/min/1.73 m^2; CKD stage 3b = eGFR 30 to 44 mL/min/1.73 m^2; CKD stage 4 = eGFR 15 to 29 mL/min/1.73 m^2.

Preferred terms were coded using MedDRA version 13.0.

Abbreviations: AE, adverse event; AFF, atypical femoral fracture; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N, number of participants with an eGFR evaluation at study baseline; n, number of participants with observed data; ONJ, osteonecrosis of the jaw; SAE, serious adverse event.

[a]In the crossover denosumab arm in the FREEDOM extension, there were 6 ONJ events. The present analysis reports 5 ONJ events in the crossover arm because 1 participant did not have an eGFR evaluation at study baseline.

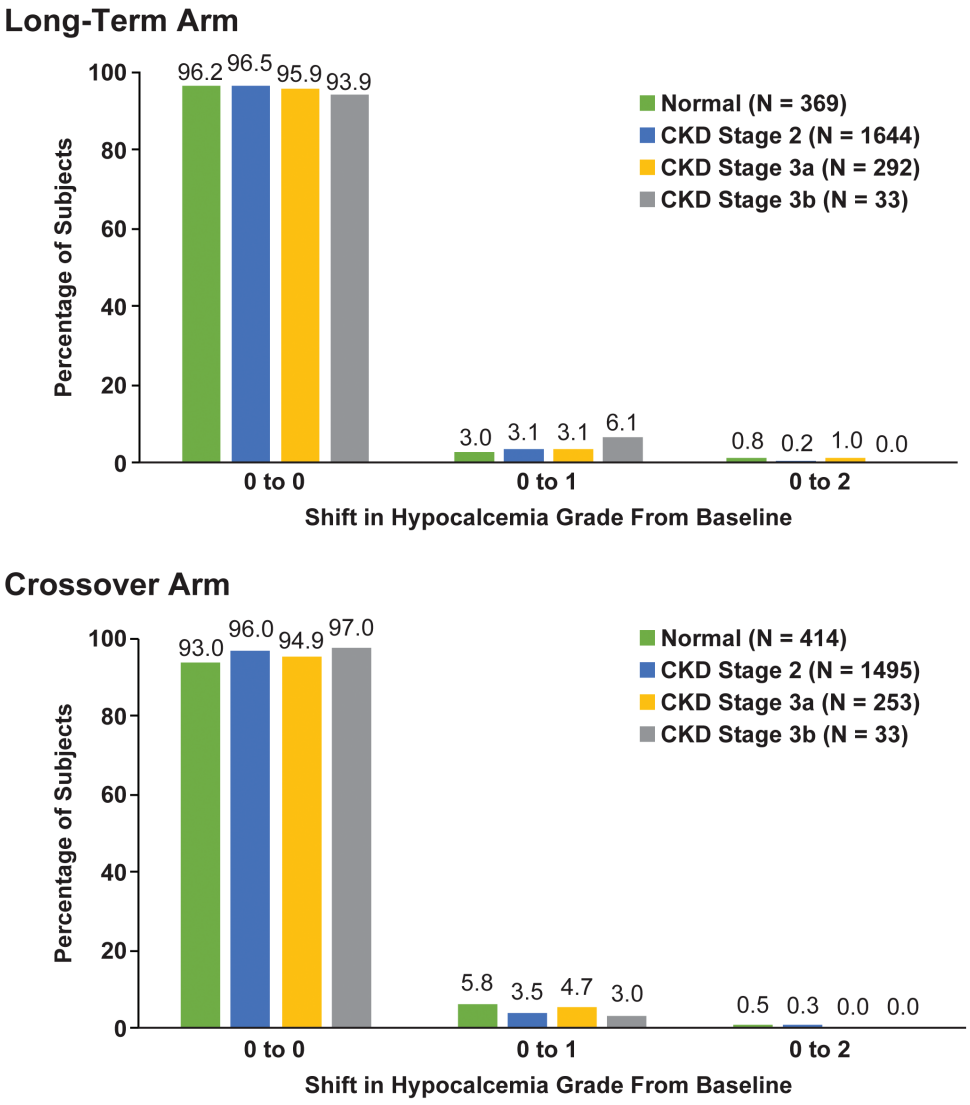

Figure 3. Maximum postbaseline shift in hypocalcemia grade in the long-term and crossover arms. Chronic kidney disease (CKD) stage was calculated according to estimated glomerular filtration rate (eGFR) at FREEDOM and extension baseline for the denosumab-treated long-term and crossover arms, respectively. Normal renal function = eGFR greater than or equal to 90 mL/min/1.73 m^2; CKD stage 2 = eGFR 60 to 89 mL/min/1.73 m^2; CKD stage 3a = eGFR 45 to 59 mL/min/1.73 m^2; CKD stage 3b = eGFR 30 to 44 mL/min/1.73 m^2. Hypocalcemia grade was based on the Common Terminology Criteria for Adverse Events, version 3.0: grade 1 = less than the lower limit of normal to 8.0 mg/dL (2.0 mmol/L); grade 2 = less than 8.0 to 7.0 mg/dL (< 2.0-1.75 mmol/L). N = number of participants with an eGFR evaluation at study baseline.

and without impaired renal function (26). A pooled analysis of 9 clinical trials suggested the safety and efficacy of risedronate in osteoporotic women with an age-related decline in renal function (27). However, no study has reported data for a bisphosphonate treatment duration longer than 3 years. Because of their clearance by the kidneys and reports of renal impairment and acute renal failure associated with the use of intravenous zoledronic acid, all bisphosphonates carry a warning for use in patients with severe renal impairment (CCr < 30 mL/min) (31). Additional data are needed to assess the safety of bisphosphonates in patients with moderate to severe CKD, as well as the potential for empiric bisphosphonate dose reductions to lessen retention of these drugs in patients with significantly impaired renal excretion.

In addition to the greater gains in BMD achieved with denosumab over bisphosphonates (32, 33), there may be benefits of denosumab over other osteoporosis treatments in the setting of renal impairment, given that denosumab is not metabolized or excreted by the kidneys. In our analysis, long-term denosumab treatment was not associated with a decline in renal function, which supports previous findings after 3 years of denosumab treatment (19). Because there is no negative impact of denosumab on renal function and the drug is not removed during dialysis, there is no need for dose adjustment in patients

with impaired renal function (34). Furthermore, given the mechanism of action of denosumab, there is no bone retention of the drug even with long-term use. In the event that a patient with CKD has a contraindication or needs to discontinue denosumab, treatment with another antiresorptive agent would be needed to avoid the rebound in bone turnover and increased fracture risk after denosumab discontinuation (35). Additional studies are needed to address antiresorptive treatment in patients with more severe CKD; however, the long-term data presented here support the safety and efficacy of denosumab in participants with mild to moderate CKD.

Any antiresorptive treatment for osteoporosis can reduce serum calcium levels, and hypocalcemia is a known AE in patients receiving denosumab. Care should be taken to ensure that patients are calcium and vitamin D replete prior to initiating therapy and to supplement with calcium and vitamin D during treatment. However, vitamin D supplementation may not be sufficient to overcome the risk of hypocalcemia in patients with advanced CKD because of the lack of conversion of 25-hydroxyvitamin D in the diseased kidney (36). In the present analysis, less than 1% of participants developed hypocalcemia, and only one case was classified as severe. This observation is likely because the FREEDOM and extension trials excluded individuals with hyperparathyroidism or hypoparathyroidism, hypocalcemia, and vitamin D deficiency, and participants were instructed to take calcium and vitamin D supplementation daily. In the published literature, the incidence of hypocalcemia following denosumab administration to CKD patients is approximately 13% to 15% (34, 37). Hypocalcemia is more common in patients with more advanced CKD and is observed more commonly after the first denosumab dose (38-40). Importantly, with aggressive adherence to preventive measures, such as calcium and calcitriol supplementation, use of high-calcium dialysate, and weekly blood test monitoring for calcium in the first month after initiating denosumab, episodes of hypocalcemia may be avoided. In the study by Block et al, calcium and vitamin D supplementation was added during the trial, and no participant who received adequate supplementation developed hypocalcemia (34).

Several limitations of this study should be considered. First, the majority of participants had mild CKD classified as CKD stage 2, very few had CKD stage 4, and none had CKD stage 5. However, the 3-year FREEDOM analysis reported by Jamal et al included a relatively larger number of individuals with CKD stage 4 (N = 73) and demonstrated that treatment efficacy and safety did not differ by renal function (19). Second, owing to the criteria applied for participation in FREEDOM and the extension study, patients were excluded if they had a diagnosis of either secondary hyperparathyroidism or CKD requiring dialysis. This is an important limitation of most clinical trials evaluating osteoporosis therapies, because included individuals with reduced eGFR likely have age-related declines in renal function rather than intrinsic renal disease with known renal pathology (eg, diabetes, systemic lupus erythematosus) or proteinuria. Thus, results from our study population may not be generalizable to the typical CKD patient population, in which abnormal mineral metabolism is common and dialysis is often required to compensate for poor renal function. Additional studies are needed to investigate the safety and efficacy of antiresorptive treatments in the setting of advanced kidney disease and renal pathology, specifically how gains in BMD can be achieved without further perturbation of the mineral balance. Third, the present analysis was descriptive in nature and did not evaluate statistical significance. Finally, given the 10-year duration of the study, there was a decline over time in the number of participants who remained in the analysis.

In conclusion, in this post hoc analysis of women treated with denosumab for up to 10 years, the safety and efficacy of denosumab did not substantially differ among participants with mild to moderate CKD. Furthermore, long-term exposure to denosumab does not appear to have a meaningful effect on renal function in women with postmenopausal osteoporosis.

Acknowledgments

Kate Smigiel, PhD (Amgen Inc.) and Jidnyasa Mulekar (CACTUS on behalf of Amgen) provided medical writing assistance.

Financial Support: This work was supported by Amgen Inc.

Clinical Trial Information: NCT00089791 and NCT00523341 (registered <August 16, 2004 and August 31, 2007>).

Additional Information

Correspondence and Reprint Requests: Aaron Broadwell, MD, Rheumatology and Osteoporosis Specialists, 820 Jordan St, Ste 201, Shreveport, LA 71101, USA. E-mail: abroadwell@rosdrs.com.

Disclosure Summary: A.B. has received grant/research support from Janssen; has served as a consultant for Janssen, Pfizer, and AbbVie; and has served on a speaker's bureau for AbbVie, Janssen, Celgene, Amgen, Mallinckrodt, UCB, and Pfizer. A.C., S.H., and S.S. are employees and stockholders of Amgen Inc. P.R.E. has received grant/research support from Eli Lilly and Amgen and has served as a consultant and received speaking fees from Amgen. E.F. has served on a speaker's bureau for Amgen, Eli Lilly, and MSD. D.K. has received grant/research support from Amgen, Radius, and Eli Lilly and has provided consultant/speaker bureau/advisory activities for Amgen, Pfizer, and Eli Lilly. O.M. has received grants and speaking fees from Pfizer, Amgen, and Eli Lilly. P.D.M. has received grant/research support from Shire Pharmaceuticals, Regeneron, Merck, and Eli Lilly; has served as a consultant for Amgen, Alexion,

and Eli Lilly; and has served on scientific advisory boards for Amgen, Shire Pharmaceuticals, and Radius Health.

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

References

1. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis*. 2016;**23**(1):19-28.
2. Schaeffner ES, Ebert N, Delanaye P, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med*. 2012;**157**(7):471-481.
3. Murphy D, McCulloch CE, Lin F, et al; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med*. 2016;**165**(7):473-481.
4. Klawansky S, Komaroff E, Cavanaugh PF Jr, et al. Relationship between age, renal function and bone mineral density in the US population. *Osteoporos Int*. 2003;**14**(7):570-576.
5. Dukas LC, Schacht E, Mazor Z, Stähelin HB. A new significant and independent risk factor for falls in elderly men and women: a low creatinine clearance of less than 65 ml/min. *Osteoporos Int*. 2005;**16**(3):332-338.
6. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. *Bone*. 2006;**38**(2 Suppl 1):S4-S9.
7. Roux C, Wyman A, Hooven FH, et al; GLOW investigators. Burden of non-hip, non-vertebral fractures on quality of life in postmenopausal women: the Global Longitudinal study of Osteoporosis in Women (GLOW). *Osteoporos Int*. 2012;**23**(12):2863-2871.
8. Khairallah P, Nickolas TL. Management of osteoporosis in CKD. *Clin J Am Soc Nephrol*. 2018;**13**(6):962-969.
9. Looker AC, Orwoll ES, Johnston CC Jr, et al. Prevalence of low femoral bone density in older U.S. adults from NHANES III. *J Bone Miner Res*. 1997;**12**(11):1761-1768.
10. Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int*. 2000;**58**(1):396-399.
11. Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM. Hip fracture in patients with non-dialysis-requiring chronic kidney disease. *J Bone Miner Res*. 2016;**31**(10):1803-1809.
12. Yenchek RH, Ix JH, Shlipak MG, et al; Health, Aging, and Body Composition Study. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol*. 2012;**7**(7):1130-1136.
13. Dukas L, Schacht E, Stähelin HB. In elderly men and women treated for osteoporosis a low creatinine clearance of < 65 ml/min is a risk factor for falls and fractures. *Osteoporos Int*. 2005;**16**(12):1683-1690.
14. Ensrud KE, Lui LY, Taylor BC, et al; Osteoporotic Fractures Research Group. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med*. 2007;**167**(2):133-139.
15. Fried LF, Biggs ML, Shlipak MG, et al. Association of kidney function with incident hip fracture in older adults. *J Am Soc Nephrol*. 2007;**18**(1):282-286.
16. Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol*. 2006;**17**(11):3223-3232.
17. Whittaker CF, Miklich MA, Patel RS, Fink JC. Medication safety principles and practice in CKD. *Clin J Am Soc Nephrol*. 2018;**13**(11):1738-1746.
18. Cummings SR, San Martin J, McClung MR, et al; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;**361**(8):756-765.
19. Jamal SA, Ljunggren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res*. 2011;**26**(8):1829-1835.
20. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinol*. 2017;**5**(7):513-523.
21. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;**39**(2 Suppl 1):S1-S266.
22. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl (2011)*. 2017;**7**(1):1-59.
23. Goldenstein PT, Jamal SA, Moysés RM. Fractures in chronic kidney disease: pursuing the best screening and management. *Curr Opin Nephrol Hypertens*. 2015;**24**(4):317-323.
24. Miller PD. The role of bone biopsy in patients with chronic renal failure. *Clin J Am Soc Nephrol*. 2008;**3**(Suppl 3):S140-S150.
25. Miller PD. Fragility fractures in chronic kidney disease: an opinion-based approach. *Cleve Clin J Med*. 2009;**76**(12):715-723.
26. Jamal SA, Bauer DC, Ensrud KE, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the Fracture Intervention Trial. *J Bone Miner Res*. 2007;**22**(4):503-508.
27. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res*. 2005;**20**(12):2105-2115.
28. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Effect of alendronate on vascular calcification in CKD stages 3 and 4: a pilot randomized controlled trial. *Am J Kidney Dis*. 2010;**56**(1):57-68.
29. Chesnut CH III, Skag A, Christiansen C, et al; Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res*. 2004;**19**(8):1241-1249.
30. Eisman JA, Civitelli R, Adami S, et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. *J Rheumatol*. 2008;**35**(3):488-497.
31. Miller PD, Jamal SA, Evenepoel P, Eastell R, Boonen S. Renal safety in patients treated with bisphosphonates for osteoporosis: a review. *J Bone Miner Res*. 2013;**28**(10):2049-2059.

32. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res*. 2009;**24**(1):153-161.
33. Lyu H, Jundi B, Xu C, et al. Comparison of denosumab and bisphosphonates in patients with osteoporosis: a meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab*. 2019;**104**(5):1753-1765.
34. Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone Miner Res*. 2012;**27**(7):1471-1479.
35. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: a post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *J Bone Miner Res*. 2018;**33**(2):190-198.
36. Dusso AS. Kidney disease and vitamin D levels: 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and VDR activation. *Kidney Int Suppl (2011)*. 2011;**1**(4):136-141.
37. Huynh AL, Baker ST, Stewardson AJ, Johnson DF. Denosumab-associated hypocalcaemia: incidence, severity and patient characteristics in a tertiary hospital setting. *Pharmacoepidemiol Drug Saf*. 2016;**25**(11):1274-1278.
38. Dave V, Chiang CY, Booth J, Mount PF. Hypocalcemia post denosumab in patients with chronic kidney disease stage 4-5. *Am J Nephrol*. 2015;**41**(2):129-137.
39. Jalleh R, Basu G, Le Leu R, Jesudason S. Denosumab-induced severe hypocalcaemia in chronic kidney disease. *Case Rep Nephrol*. 2018;**2018**:7384763.
40. Festuccia F, Jafari MT, Moioli A, et al. Safety and efficacy of denosumab in osteoporotic hemodialysed patients. *J Nephrol*. 2017;**30**(2):271-279.