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Effects of Denosumab on Fracture and Bone Mineral Density by Level of Kidney Function

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ABSTRACT

The incidences of osteoporosis and chronic kidney disease (CKD) both increase with increasing age, yet there is a paucity of data on treatments for osteoporosis in the setting of impaired kidney function. We examined the efficacy and safety of denosumab (DMAb) among subjects participating in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Study. We estimated creatinine clearance (eGFR) using Cockcroft-Gault and classified levels of kidney function using the modified National Kidney Foundation classification of CKD. We examined incident fracture rates; changes in bone mineral density (BMD), serum calcium, and creatinine; and the incidence of adverse events after 36 months of follow-up in subjects receiving DMAb or placebo, stratified by level of kidney function. We used a subgroup interaction term to determine if there were differences in treatment effect by eGFR. Most (93%) women were white, and the mean age was 72.3 ± 5.2 years; 73 women had an eGFR of 15 to 29 mL/min; 2817, between 30 to 59 mL/min; 4069, between 60 to 89 mL/min, and 842 had an eGFR of 90 mL/min or greater. None had stage 5 CKD. Fracture risk reduction and changes in BMD at all sites were in favor of DMAb. The test for treatment by subgroup interaction was not statistically significant, indicating that treatment efficacy did not differ by kidney function. Changes in creatinine and calcium and the incidence of adverse events were similar between groups and did not differ by level of kidney function. It is concluded that DMAb is effective at reducing fracture risk and is not associated with an increase in adverse events among patients with impaired kidney function.

KEY WORDS: IMPAIRED KIDNEY FUNCTION; DENOSUMAB; FRACTURES; BONE MINERAL DENSITY

Introduction

Aging is associated with decreases in bone quality and kidney function; consequently, osteoporosis and kidney insufficiency are common comorbid conditions in older men and women.[1–3] For example, data from the National Health and Nutrition Examination Survey (NHANES) III reports that 85% of women with osteoporosis have mild to moderate kidney impairment.[4] Despite the high prevalence of both conditions, treatment options for osteoporosis in people with kidney disease are limited. Nitrogen-containing oral bisphosphonates, currently the most widely used drugs in the treatment of osteoporosis, are excreted by the kidney and are not recommended by the US Food and Drug Administration for the treatment of osteoporosis in patients with stage 4 to 5 chronic kidney disease (CKD), defined as a glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m^3.[5,6] This is based on early bisphosphonate kidney toxicity data in rats and a lack of randomized, controlled trial data

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from patients with severe decreases in GFR.[7] With intravenous bisphosphonates, rare cases of kidney failure requiring dialysis and/or fatal outcome have been reported in osteoporotic patients with preexisting kidney dysfunction or other risk factors such as advanced age, concomitant nephrotoxic medication, or dehydration in the postinfusion period, emphasizing the need for clinicians to select the appropriate patients for this treatment modality.[8]

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL). By blocking the binding of RANKL to RANK, denosumab decreases the number and activity of osteoclasts, decreases bone resorption, and increases bone mineral density (BMD).[9,10] In postmenopausal women with osteoporosis, as compared with placebo, 36 months of denosumab treatment significantly increased spine, hip, and radial BMD and decreased the incidence of new vertebral, nonvertebral, and hip fractures.[11] Denosumab does not depend on kidney clearance for metabolism or excretion. This observation raises the possibility that it could be used in patients who have both osteoporosis and impaired kidney function. To determine the safety and efficacy of denosumab in these patients, we conducted a secondary data analysis among postmenopausal women with varying levels of kidney function participating in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Trial, a multicentre randomized, placebo-controlled trial designed to reduce osteoporotic fractures in postmenopausal women.[11]

Material and Methods

Participants

Women were enrolled in the FREEDOM Trial if they were between 60 and 90 years of age with a BMD T-score of greater than −4.0 and less than −2.5 at the lumbar spine or total hip. Women were excluded if they had current hyper- or hypoparathyroidism, current hypocalcemia (albumin-adjusted serum calcium concentration below 2.13 mmol/L) or vitamin D deficiency (25-hydroxyvitamin D level less than 30 nmol/L). There were no exclusion criteria based on serum measures of kidney function or urinary protein.

A total of 7808 women were randomly assigned to treatment; 3902 received denosumab (DMAb), and 3906 received placebo. All women gave informed consent, and the study was approved by the relevant institutional review boards. Further details of the FREEDOM Trial are described in a prior publication.[11]

Fractures

We included all clinical fractures occurring over 36 months confirmed by either a radiologist or a radiology report with the exception of fractures of the skull, face, mandible, metacarpals, fingers, and toes. We also excluded pathologic fractures and those caused by high trauma. We included all vertebral fractures occurring over the 36 months of follow-up. Vertebral fractures were assessed by review of lateral spine radiographs, taken annually, using a semiquantitative technique that has been described in detail in a prior publication.[11]

Bone mineral density

BMD was measured by dual-energy X-ray absorptiometry (DXA) at study entry at the hip and lumbar spine and then yearly at the hip sites and at 36 months at the lumbar spine sites in the FREEDOM Trial. For the purposes of our analyses, we examined the percent change in BMD at the total hip, femoral neck, and lumbar spine sites at 36 months compared with baseline.

Adverse events

All physicians at study sites reported adverse events that were coded as preferred terms in the *Medical Dictionary for Regulatory Activities* system. For the purposes of our analyses, we examined changes in serum creatinine and calcium, overall adverse events, serious adverse events related to infection, and cardiovascular events over 36 months of follow-up by level of kidney function.

Laboratory evaluations

All women who participated in the FREEDOM Trial had extensive laboratory testing, the details of which have been described elsewhere.[11] Included in these tests were measurements of serum albumin-adjusted calcium, phosphate, creatinine, and 1,25-dihydroxyvitamin D_3 at study entry. Serum creatinine and albumin-adjusted calcium also were measured every 6 month until study completion.

We estimated baseline glomerular filtrations rates (eGFRs) from data obtained at study entry using two equations: (1) the Cockcroft-Gault equation (CG),[12] that is, {(140 – age)[lean body mass (kg)]/[serum creatinine (mg/dL)]} × 0.8 and (2) the four-variable modification of diet in kidney disease equation (MDRD),[13,14] that is, eGFR (mL/min/1.73 m^2) = 186 × [serum creatinine (mg/dL)]$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female) × 1.210 (if African American). We defined stages of kidney function based on the modified National Kidney Foundation classification of chronic kidney disease (K/DOQI Guidelines 2002).[5] Based on this classification, stage 1 (normal kidney function or kidney damage with normal or increased GFR) is an eGFR of 90 mL/min or more, stage 2 (kidney damage with mild decrease in GFR) is an eGFR between 60 to 89 mL/min, stage 3 (moderate decrease in GFR) is an eGFR between 30 to 59 mL/min, and stage 4 (severe decrease in GFR) is an eGFR between 15 to 29 mL/min.

Statistical analysis

The aim of our analysis was to determine the relationship between baseline kidney function, measured by eGFR, and the effect of denosumab compared with placebo on fracture risk reduction and change in BMD. We considered the eGFR calculated by the CG as the primary predictor and the eGFR calculated by the MDRD in a sensitivity analysis to address misclassification bias. Logistic regression analysis was performed to determine the treatment effect on the incidence of new vertebral fractures over 3 years by level of kidney function, and Cox proportional hazards models were performed to determine the treatment effect on nonvertebral fracture by level of kidney function. Analyses of covariance (ANCOVA) models were used to determine treatment effect on BMD changes by level of kidney function. All analyses included a treatment-by-kidney-function

interaction term to examine the effect of denosumab (DMAb) by level of kidney function; note that if the test for treatment-by-kidney-function subgroup interaction is statistically significant, this would indicate that fracture risk reduction or the difference in the mean percent changes in BMD in subjects treated with DMAb compared with placebo differed by level of kidney function. Analyses were conducted unadjusted and then adjusted for potential confounders. Specifically included in our adjusted model were fracture since age 45, prevalent vertebral fractures, self-reported health status, baseline calcium intake, current smoking, femoral neck BMD *T*-score, and years since menopause. When we considered the MDRD equation, we also adjusted for weight. Note that in our results, we present the data obtained using the adjusted model. We considered $p < .05$ to be statistically significant and did not adjust for multiple comparisons. Analyses were conducted using SAS 9.2 statistical software (SAS Institute, Inc., Cary, NC, USA).

Results

Statistical analyses were performed on all patients randomized with baseline and at least one postbaseline observation of interest (7393 subjects for new vertebral fracture, 7808 subjects for nonvertebral fracture, and 6363 subjects for lumbar spine BMD). By the CG, 73 women had stage 4 CKD; 2817 had stage 3, 4069 had stage 2 CKD, and the remaining 842 women had stage 1 CKD. By the MDRD, 17 women had stage 4 CKD, 1078 stage 3 CKD, 5413 had stage 2 CKD, and the remaining 1298 women had stage 1 CKD. None of our subjects had stage 5 CKD.

Baseline characteristics were balanced between the treatment and placebo groups within each level of kidney function, and there were no substantial differences in the distribution of baseline variables using the MDRD compared with CG. Compared with women with stage 1 CKD, those with stage 4 CKD were older, weighed less, had poorer health status and physical function, and had lower BMD *T*-scores at the femoral neck and total hip (Table 1).

Overall, compared with placebo, denosumab reduced the incidence of new vertebral fractures [odds ratio (OR) = 0.30; 95% confidence interval (CI) 0.23–0.39) as well as the incidence of nonvertebral fractures over 36 months (OR = 0.78, 95% CI 0.66–0.93). Denosumab was associated with an 8.8% (95% CI 8.6–9.1) increase in lumbar spine BMD, a 5.2% (95% CI 5.0–5.4) increase in femoral neck BMD, and a 6.4% (95% CI 6.3–6.5) increase in total-hip BMD over 36 months.

When we examined fracture risk, both vertebral and nonvertebral, by stage of CKD, by the CG, the treatment-by-subgroup interaction term was not statistically significant, indicating that the reduction in fracture risk did not differ by level of kidney function. The incidence of vertebral fractures was lower among those randomized to DMAb compared with placebo for all stages of CKD but did not reach statistical significance among those with stage 4 CKD. Similarly the incidence of nonvertebral fractures was lower among those randomized to DMAb compared with placebo but was not statistically significant for stages 3 and 4 CKD (Table 2). Owing to the small number of hip fractures (43 in the placebo group and 26 in the denosumab group), we did not examine differences in hip fractures by stage of CKD.

Similarly, the treatment-by-subgroup interaction in BMD increase was not statistically significant, indicating that the increases in BMD did not differ by level of kidney function, and the magnitude of increase in BMD was not substantially different

Table 1. Baseline Characteristics of the Study Subjects by eGFR using Cockcroft-Gault

Characteristic	Stage 4 CKD eGFR 15 to 29 mL/min ($N = 73$)	Stage 3 CKD eGFR 30 to 59 mL/min ($N = 2817$)	Stage 2 CKD eGFR 60 to 89 mL/min ($N = 4069$)	Stage 1 CKD eGFR $\geq$ 90 mL/min ($N = 842$)
Age (years)	80.0 (±5.5)	75.1 (±4.9)	71.1 (±4.5)	68.4 (±4.3)
Weight (kg)	52.7 (±10.3)	57.9 (±8.2)	65.7 (± 8.8)	75.7 (±10.5)
Years since menopause	33.5 (±9.0)	27.1 (±7.1)	22.8 (±7.0)	20.7 (±6.9)
Taking calcium supplements at baseline, *n* (%)	73 (100)	2798 (99.3)	4048 (99.5)	834 (99.0)
Current smoker, *n* (%)	9 (12.3)	263 (9.3)	375 (9.2)	82 (9.7)
No alcohol consumption, on average, over past 5 years, *n* (%)	50 (68.5)	1667 (59.2)	2144 (52.7)	475 (56.4)
EQ5D[a] health index status score	0.62 (0.28)	0.73 (0.25)	0.75 (0.23)	0.73 (0.22)
OPAQ[b] physical function score	67.1 (19.3)	79.3 (18.2)	80.6 (17.6)	78.0 (18.9)
Low-trauma fracture since age 45, *n* (%)	35 (47.9)	1250 (44.4)	1790 (44.0)	387 (46.0)
Prevalent vertebral fracture, *n* (%)	18 (24.7)	683 (24.2)	941 (23.1)	201 (23.9)
Serum albumin-adjusted calcium (mg/dL)	9.9 (±0.5)	9.8 (±0.4)	9.8 (±0.4)	9.7 (±0.4)
Serum creatinine (mg/dL)	1.5 (±0.3)	0.9 (±0.2)	0.8 (±0.1)	0.6 (±0.1)
Serum vitamin D (nmol/L)	61.8 (±34.0)	63.1 (±82.2)	56.9 (±63.3)	53.5 (±24.5)
Lumbar spine BMD *T*-score	−2.48 (±0.99)	−2.83 (±0.77)	−2.83 (±0.65)	−2.82 (±0.59)
Femoral neck BMD *T*-score	−2.80 (0.61)	−2.38 (0.68)	−2.06 (0.69)	−1.83 (0.73)
Total-hip BMD *T*-score	−2.79 (0.56)	−2.17 (0.77)	−1.78 (0.77)	−1.49 (0.81)

N = number of randomized subjects. Data are presented as mean (SD) unless otherwise indicated.
[a]EQ5D = EuroQol-5 Dimensions.
[b]OPAQ = Osteoporosis Assessment Questionnaire Short Version.

Table 2. Effect of Denosumab, Compared with Placebo, on Fractures—Crude Incidence and Odds Ratios—Over 36 Months, by Stage of Kidney Function Estimated by CG and MDRD[a]

Fracture type	Stage 4 CKD by CG			Stage 3 CKD by CG			Stage 2 CKD by CG			Stage 1 CKD by CG		
	Placebo	DMAb	Odds ratio	Placebo	DMAb	Odds ratio	Placebo	DMAb	Odds ratio	Placebo	DMAb	Odds ratio
Vertebral	3/33	1/31	0.31 (0.02–5.08)	92/1309	38/1332	0.38 (0.26–0.59)	137/1952	34/1924	0.23 (0.15–0.34)	32/394	13/413	0.33 (−0.16–0.66)
Nonvertebral	2/37	1/36	0.51 (0.04–7.26)	106/1399	93/1418	0.88 (0.66–1.16)	157/2048	115/2021	0.69 (0.54 to 0.89)	28/418	29/424	0.89 (0.51–1.52)
	Stage 4 by MDRD			Stage 3 by MDRD			Stage 2 by MDRD			Stage 1 by MDRD		
Vertebral	0/9	0/5		25/477	16/538	0.53 (0.28–1.02)	180/2594	52/2539	0.27 (0.20–0.38)	59/611	18/619	0.25 (0.14–0.44)
Nonvertebral	0/9	0/8		41/505	46/573	1.04 (0.67–1.60)	198/2737	150/2676	0.75 (0.60–0.93)	54/654	42/644	0.64 (0.42–0.98)

[a]$p \geq .05$ for treatment by subgroup interaction.

by stage of CKD compared with the overall increase in BMD at all sites (Table 3).

Sensitivity analyses using the MDRD demonstrated similar findings; the treatment-by-subgroup interaction was not statistically significant considering new vertebral fractures, nonvertebral fractures (Table 2), and BMD.

Comparing DMAb with placebo, there were no significant differences in the change in serum creatinine by stage of CKD from baseline to year 1. From baseline to year 2 and baseline to year 3, there were a few small (<2 mmol/L) but significant differences in the change in serum creatinine by stage of CKD (Table 4). There were no differences in the incidence of adverse events, serious adverse events, infection-related serious adverse events, or cardiovascular serious adverse events between those treated by DMAb compared with placebo stratified by stage of CKD (by the CG or MDRD; Table 5). In addition, we found no difference in eGFR or change in eGFR using either the CG or the MDRD from baseline to 36 months among those randomized to DMAb compared with those randomized to placebo. For example, the creatinine clearance by CG at baseline was 66.5 mL/min (± 18.5) among those randomized to placebo and 66.6 mL/min (± 19.0) among those randomized to DMAb. At 36 months, creatinine clearance was 64.5 mL/min (± 18.2) in the placebo group (mean change of -2.7 ± 11.0 ml/min) and 63.9 mL/min (± 18.1) in the DMAb group (mean change of -3.4 ± 10.8 mL/min). The changes in creatinine clearance compared with baseline and among DMAb and placebo groups were not significantly different.

Discussion

Our analysis demonstrated that 36 months of treatment with denosumab at 60 mg subcutaneously every 6 months compared with placebo is safe and effective among subjects with stages 1 to 4 CKD. We found no significant interaction between efficacy of treatment and stage of renal function. This suggests that efficacy may be similar. However, the subgroups with more severe renal dysfunction are small, limiting our power to find differences in efficacy in those with stage 3 and 4 CKD. In addition, we found no clinically important differences in the change in serum creatinine by stage of CKD. There were no differences in serum calcium, adverse events, serious adverse events, serious infection, or cardiovascular serious adverse events by stage of CKD over the 36–month study period.

The magnitude of fracture risk reduction and increases in BMD associated with DMAb treatment did not differ by level of kidney function and was similar to the overall results reported in the FREEDOM Trial total randomized population.[11] However, in the case of CKD stage 4 in particular, there was limited power to assess the fracture risk reduction and increases in BMD among subjects with more significant impairment of kidney function.

Table 3. Effect of Denosumab, Compared with Placebo, on BMD Over 36 Months, by Stage of Kidney Function Estimated by CG

Outcome	Stage 4 CKD eGFR 15 to 29 mL/min ($N = 73$)	Stage 3 CKD eGFR 30 to 59 mL/min ($N = 2817$)	Stage 2 CKD eGFR 60 to 89 mL/min ($N = 4069$)	Stage 1 CKD/normal eGFR ≥ 90 mL/min ($N = 842$)
Lumbar spine BMD, % change	5.0 (−0.8–10.8)	8.9 (8.4–9.3)*	9.0 (8.6–9.4)*	8.1 (7.2–8.9)*
Femoral neck BMD, % change	5.9 (3.3–8.5)*	5.1 (4.7–5.5)*	5.2 (4.9–5.5)*	5.6 (4.9–6.3)*
Total-hip BMD, % change	5.9 (3.0–8.7)*	6.4 (6.1–6.7)*	6.4 (6.2–6.7)*	5.8 (5.2–6.3)*

N = number of randomized subjects. A difference in BMD% change > 0 in favor of denosumab.
*$p \leq .0002$.

Table 4. Change in Serum Creatinine (mmol/L) from Baseline by Stage of CKD Estimated by CG

	Stage 4 CKD		Stage 3 CKD		Stage 2 CKD		Stage 1 CKD	
	Placebo	DMAb	Placebo	DMAb	Placebo	DMAb	Placebo	DMAb
Year 1	−6.9 (±22.9), $N = 33$	−4.6 (±32.8), $N = 28$	−2.3 (±11.4), $N = 1280$	−2.3 (±10.7), $N = 1302$	0.76 (±8.4), $N = 1908$	0.76 (±7.6), $N = 1896$	3.1 (±6.9), $N = 387$	3.1 (±7.6), $N = 404$
Year 2	1.53 (±32.0), $N = 27$	6.1 (±33.6), $N = 21$	1.53 (±11.4), $N = 1176$	0.76 (±10.9), $N = 1222$	2.3 (±7.6), $N = 1792$	2.3 (±7.6), $N = 1806$	3.81 (±6.1), $N = 374$	5.34* (±7.6), $N = 388$
Year 3	−8.4 (±23.6), $N = 19$	−12.9 (±22.9), $N = 16$	−3.1 (±12.9), $N = 1104$	−1.53** (±12.9), $N = 1141$	0.76 (±8.4), $N = 1700$	1.53* (±8.4), $N = 1732$	3.1 (±8.4), $N = 357$	3.8 (±7.6), $N = 372$

N = number of randomized subjects who had serum samples available for analysis.
*$p = .01$.
**$p = .02$.

Table 5. Incidence of Adverse Events by Stage of CKD Estimated by CG

	Stage 4 CKD		Stage 3 CKD		Stage 2 CKD		Stage 1 CKD	
	Placebo, $N = 37$	DMAb, $N = 36$	Placebo, $N = 1392$	DMAb, $N = 1410$	Placebo, $N = 2034$	DMAb, $N = 2015$	Placebo, $N = 410$	DMAb, $N = 423$
Adverse events, *n* (%)	35 (94.6)	35 (97.2)	1307 (93.9)	1308 (92.8)	1875 (92.2)	1869 (92.8)	387 (94.4)	391 (92.4)
Serious adverse events, *n* (%)	13 (35.1)	15 (41.7)	351 (25.2)	392 (27.8)	509 (25)	502 (25.0)	99 (24.1)	95 (22.5)
Serious adverse events of infection, *n* (%)	1 (2.7)	4 (11.1)	49 (3.5)	60 (4.3)	66 (3.2)	79 (3.9)	17 (4.1)	16 (3.8)
Cardiovascular serious adverse events, *n* (%)	3 (8.1)	4 (11.1)	88 (6.3)	88 (6.3)	71 (3.5)	78 (3.9)	16 (3.9)	16 (3.8)

N = number of randomized subjects who received 1 dose or more of investigational product.

For example, there were only four vertebral fractures and three nonvertebral fractures in the 73 subjects with stage 4 CKD. In addition, given the small number of hip fractures, we could not comment specifically on differences in hip fracture by stage of CKD.

Our findings are consistent with other secondary analyses of studies assessing bisphosphonates, selective estrogen receptor modulators, and teriparatide that have demonstrated increases in BMD, reductions in the incidence of vertebral fractures, and an acceptable safety profile regardless of level of kidney function.[7,15–17] These studies include the Fracture Intervention Trial (FIT; 581 women with eGFR by CG of less than 45 mL/min), the Multiple Outcomes of Raloxifene Evaluation (MORE) trial (1480 women with a creatinine clearance of less than 45 mL/min), the Fracture Prevention Trial using teriparatide (731 women with eGFR between 30 and 79 mL/min), and a pooled analysis of nine risedronate studies (571 women with eGFR by CG of less than 30 mL/min). While these are all post hoc analyses, these studies provide important clinical information because age-related decreases in kidney function are common and are associated with bone loss and fractures.[18–21]

Denosumab may have certain advantages when used in patients with kidney dysfunction. One important advantage of denosumab compared with bisphosphonates is that there is no impact on kidney function, and because DMAb is not excreted by the kidney, there is no need for dose adjustment in patients with impaired kidney function. In addition, based on the mechanism of action, there are no concerns about bone retention of this agent with long-term use. All antiresorptives can reduce serum calcium levels, particularly in severe kidney dysfunction (eGFR $<$ 30 mL/min). Therefore, in patients with severe kidney dysfunction, particular attention should be paid to ensuring that patients are calcium and vitamin D replete prior to initiating therapy and supplementing with calcium and vitamin D during treatment. In addition, patients with severe kidney disease (eGFR $<$ 30 mL/min) also may have metabolic bone diseases that may mimic osteoporosis clinically but be other forms of renal bone disease where management may differ from that of osteoporosis.[23,24]

Our study has limitations. Although parathyroid hormone (PTH) was not measured in all subjects at baseline, women were excluded if they had a current diagnosis of hyperparathyroidism, which is seen often in individuals with intrinsic kidney disease and reduced GFR,[22] and this limits our ability to generalize our findings to these groups. We were unable to use a direct measure of GFR. Instead, we used two indirect measures of kidney function, the CG and MDRD estimates, both based on measured serum creatinine. Note that use of these equations resulted in substantial differences in the number of subjects classified with stages 3 and 4 CKD likely owing to the fact that the MDRD does not consider lean body mass, whereas the CG does. To partially account for this, we adjusted our analyses for body weight when using the MDRD. Yet the overall effect of denosumab treatment on BMD, fracture, and safety was similar, irrespective of the formula used, and importantly, there were was no evidence of a treatment-by-subgroup interaction using either the CG or the MDRD. None of the women had stage 5 CKD, so we cannot comment on the safety or efficacy of denosumab at that level of kidney function. Women were excluded from participating in this trial if they had hypocalcemia or vitamin D deficiency, so data on the safety and efficacy of denosumab cannot be generalized to those with laboratory abnormalities of mineral metabolism.

In conclusion, our post hoc analysis of subjects with stage 1 to 4 CKD suggests that DMAb is safe and likely effective at reducing fracture risk and increasing BMD in women with postmenopausal osteoporosis and stage 1 to 3 CKD. Although the sample size of subjects with stage 4 CKD was small, our analysis suggests that the benefits are directionally similar.

Disclosures

SAJ serves on advisory boards for Amgen, Novartis, and Warner Chillcott and receives lecture fees from Novartis and Amgen. OL serves on advisory boards for and receives speaker fees from Amgen, Eli Lilly, and Novartis. CS-B, OIE, and YY are employees of Amgen, Inc., and own stock or stock options in Amgen, Inc. SRC receives consulting fees from Amgen and Eli Lilly, lecture fees from Novartis and Eli Lilly, and grant support from Amgen and Eli Lilly. MRM receives grant support, advisor fees, and/or speakers' bureau fees from Amgen, Eli Lilly, Merck, Novartis, and Warner Chillcott. SG receives research grant support from Novartis and Warner Chillcott; serves as a clinical trial investigator for Amgen, Eli Lilly, Merck Sharp & Dohme, Novartis, Proctor & Gamble, Servier, and Wyeth Research; and receives consulting and speaker fees from Daichii Sankyo, Eli Lilly, Merck Sharp & Dohme, Novartis, Warner Chillcott, and Servier. PRE receives speakers fees and grant support from and serves on advisory boards for Amgen, Merck, and Novartis and speakers fees from Eli Lilly and Sanofi-Aventis. EF serves on an advisory board for Amgen and receives speaker fees from Amgen, Novartis, Roche, and Servier. SB has received research funding and consulting fees from Amgen and also serves as the senior clinical investigator of the Fund for Scientific Research, Flanders, Belgium (F.W.O.-Vlaanderen). PDM has received grant support from Warner Chillcott, Genentech, Amgen, Eli Lilly, Merck, and Novartis and also has served as a consultant and/or on speaker and advisory boards for Warner Chillcott, Genentech, Amgen, Eli Lilly, Merck, Novartis, and GlaxoSmithKline.

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