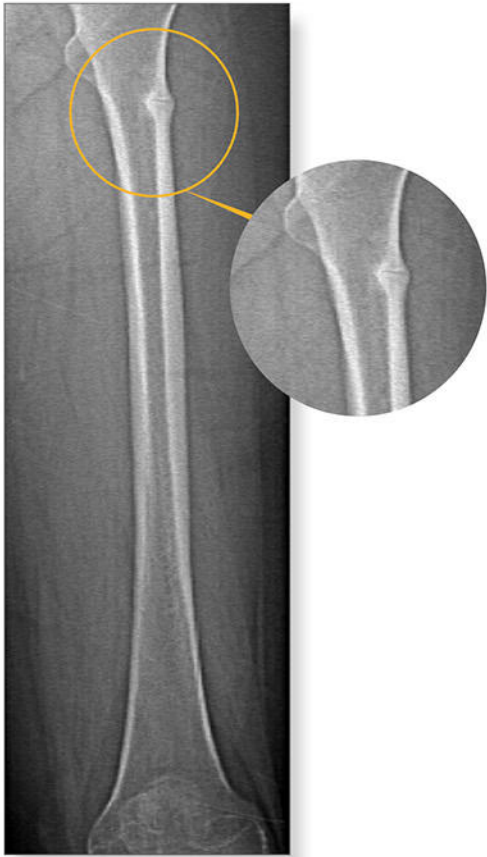
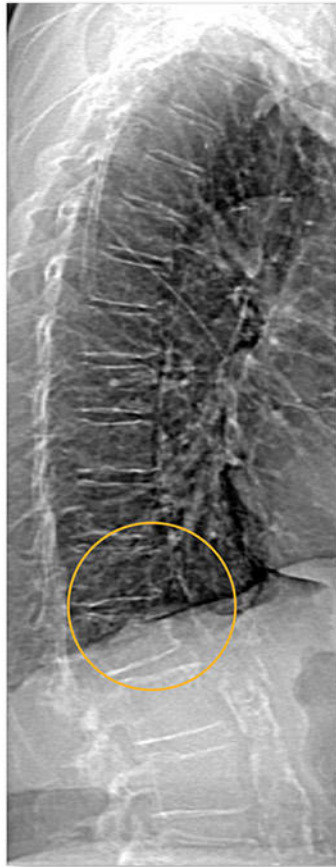


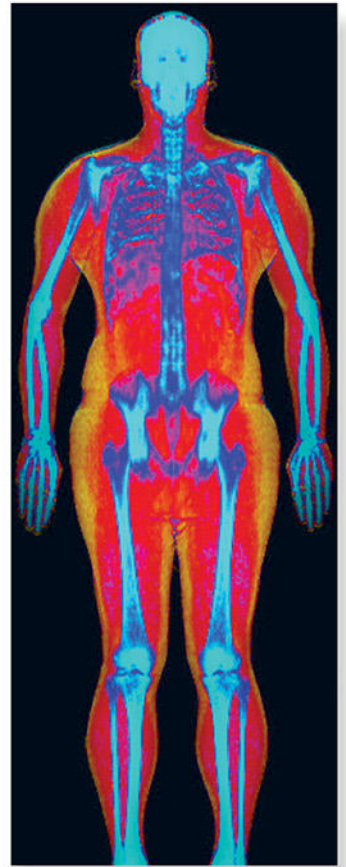
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FRAME Study: The Foundation Effect of Building Bone With 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab

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ABSTRACT

Romosozumab is a bone-forming agent with a dual effect of increasing bone formation and decreasing bone resorption. In FRActure study in postmenopausal woMen with ostEoporosis (FRAME), postmenopausal women with osteoporosis received romosozumab 210 mg s.c. or placebo once monthly for 12 months, followed by denosumab 60 mg s.c. once every 6 months in both groups for 12 months. One year of romosozumab increased spine and hip BMD by 13% and 7%, respectively, and reduced vertebral and clinical fractures with persistent fracture risk reduction upon transition to denosumab over 24 months. Here, we further characterize the BMD gains with romosozumab by quantifying the percentages of patients who responded at varying magnitudes; report the mean *T*-score changes from baseline over the 2-year study and contrast these results with the long-term BMD gains seen with denosumab during Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) and its Extension studies; and assess fracture incidence rates in year 2, when all patients received denosumab. Among 7180 patients ($n = 3591$ placebo, $n = 3589$ romosozumab), most romosozumab-treated patients experienced $\geq 3\%$ gains in BMD from baseline at month 12 (spine, 96%; hip, 78%) compared with placebo (spine, 22%; hip, 16%). For romosozumab patients, mean absolute *T*-score increases at the spine and hip were 0.88 and 0.32, respectively, at 12 months (placebo: 0.03 and 0.01) and 1.11 and 0.45 at 24 months (placebo-to-denosumab: 0.38 and 0.17), with the 2-year gains approximating the effect of 7 years of continuous denosumab administration. Patients receiving romosozumab versus placebo in year 1 had significantly fewer vertebral fractures in year 2 (81% relative reduction; $p < 0.001$), with fewer fractures consistently observed across other fracture categories. The data support the clinical benefit of rebuilding the skeletal foundation with romosozumab before transitioning to antiresorptive therapy. © 2018 The Authors. *Journal of Bone and Mineral Research* Published by Wiley Periodicals, Inc.

KEY WORDS: OSTEOPOROSIS; ANABOLICS; FRACTURE RISK ASSESSMENT

Introduction

Romosozumab is a monoclonal antibody that binds and inhibits sclerostin. Through sclerostin inhibition, this bone-forming agent has the dual effect of increasing bone formation and decreasing bone resorption,^(1,2) resulting in rapid and large

gains in bone mass and density and improved bone structure.^(3–5) In the phase 3 FRActure study in postmenopausal woMen with ostEoporosis (FRAME), 1 year of romosozumab treatment reduced new vertebral and clinical fracture risk compared with placebo in postmenopausal women with osteoporosis, with relative risk reductions (RRRs) of 73%

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Public clinical trial registration: <http://clinicaltrials.gov/show/NCT01575834>. A Multicenter, International, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Assess the Efficacy and Safety of Romosozumab Treatment in Postmenopausal Women With Osteoporosis.

Additional Supporting Information may be found in the online version of this article.

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($p < 0.001$) and 36% ($p = 0.008$), respectively, and was well tolerated.⁽⁶⁾ Romosozumab also resulted in large gains in BMD, with mean percent increases over placebo of 13% at the lumbar spine and 6% at the total hip (both $p < 0.001$) after 1 year.

In FRAME, all patients received denosumab in the second year and, over the cumulative 2-year study period, treatment with romosozumab led to continuous fracture risk reduction, with BMD differences between groups at month 12 overall maintained at month 24.⁽⁶⁾ At 24 months, there was a 75% relative reduction in the risk of new vertebral fracture in patients who received romosozumab followed by denosumab compared with those who received placebo followed by denosumab ($p < 0.001$), with a persistent benefit across other fracture categories as well. Although the primary analysis was designed to assess the sequence of romosozumab-to-denosumab versus placebo-to-denosumab, the results suggested a persistent benefit during the denosumab period in the second year from the large bone mass accrual achieved with romosozumab in the first year; the current analysis aimed to explore this concept further.

This analysis further characterized the BMD gains observed during the FRAME study by comparing the proportion of patients achieving BMD gains of varying magnitudes at the lumbar spine and total hip in response to romosozumab compared with placebo during year 1. It also summarized absolute *T*-score changes from baseline over the 2-year course of the study, after each group received romosozumab or placebo and after both groups received 1 year of denosumab. We placed the changes in BMD observed with romosozumab and then denosumab in the context of changes seen in the Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) and its Extension studies with denosumab alone, during which continued BMD gains were observed over 10 years of treatment, to qualitatively assess the magnitude of BMD changes with romosozumab relative to the only osteoporosis treatment shown to increase BMD over such an extended period.⁽⁷⁾ We further evaluated the clinical importance of the BMD gains from 1 year of romosozumab by comparing fracture incidence rates observed in the second year of the study, during which all patients received denosumab—a time when differences in fracture rates reflected the impact of having initially received romosozumab versus placebo before transitioning to denosumab.

Patients and Methods

Study design

This secondary, post-hoc analysis was based on FRAME (ClinicalTrials.gov, NCT01575834), a phase 3, international, randomized, double-blind, placebo-controlled, parallel-group trial in postmenopausal women with osteoporosis.

FRAME has been described in detail elsewhere.⁽⁶⁾ Women were eligible for this study if they were between 55 and 90 years old, had a *T*-score of -2.5 to -3.5 at the total hip or femoral neck, and at least two vertebrae in the L₁ through L₄ region and at least one hip that could be evaluated by DXA. Exclusion criteria have been described in detail.⁽⁶⁾ Women were randomized 1:1 to receive romosozumab 210 mg s.c. or placebo once monthly (QM) for 12 months, after which both groups transitioned to denosumab 60 mg s.c. once every 6 months (Q6M) for an additional 12 months. All patients received calcium and vitamin D supplementation throughout the study. The coprimary endpoints of the study were the subject incidence of new

vertebral fracture through month 12 and through month 24; secondary endpoints included subject incidence of other fracture types. In FRAME, BMD was measured at the lumbar spine and total hip in all patients at months 12 and 24, and additionally at months 6 and 18 in a subset of 128 patients (66 romosozumab, 62 placebo) in a DXA substudy; BMD was also measured at the lumbar spine and total hip at month 6 in an additional 162 patients from Argentina (92 romosozumab, 70 placebo; assessed to meet in-country requirements).

The current analysis also used BMD data from FREEDOM and its Extension. FREEDOM, the pivotal fracture study for denosumab, has been described.⁽⁸⁾ In that study, postmenopausal women aged 60 to 90 years with a *T*-score at the lumbar spine or total hip ≤ -2.5 were randomized 1:1 to receive denosumab 60 mg s.c. Q6M or placebo for 3 years; patients who missed ≤ 1 dose of investigational product were eligible to enter the open-label Extension, during which all patients received denosumab 60 mg s.c. Q6M for up to an additional 7 years.⁽⁷⁾ In FREEDOM and its Extension, BMD was measured in all patients at months 12 and 24 (total hip) and months 36, 48, 60, 72, 96, and 120 (lumbar spine and total hip), and additionally at months 6, 12, and 24 (lumbar spine and total hip) in a subset of 441 patients from FREEDOM (232 denosumab, 209 placebo) in a DXA substudy.

The FRAME trial was conducted in accordance with the World Medical Association Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. The trial protocol was approved by an ethics committee or institutional review board at each trial center. Patients provided written informed consent.

Outcome measures

A responder analysis assessed the percentage of patients with a percent change from baseline in BMD by DXA of varying magnitudes (ie, $\geq 3\%$, $\geq 6\%$, and $\geq 10\%$; chosen empirically, with 3% representing the approximate least significant change) at the lumbar spine and total hip at month 12, as well as patients who did not have BMD increases ($\leq 0\%$); mean absolute change from baseline in lumbar spine and total hip BMD *T*-scores during the first 2 years in patients from FRAME and throughout 10 years in patients from FREEDOM and FREEDOM Extension; and subject incidence of fractures in the second year of FRAME, including new vertebral, clinical, major osteoporotic, nonvertebral, major nonvertebral, and hip fractures.

Statistical analysis

For BMD response in FRAME, based on percent change from baseline at month 12, missing BMD values were imputed by carrying forward the last postbaseline observation. For BMD *T*-score changes from baseline, comparisons between treatment groups in FRAME were based on a linear mixed effect repeated measures model, adjusting for treatment, visit baseline value, age (< 75 versus ≥ 75 years), and prevalent vertebral fracture (yes versus no) randomization stratification variables, using observed data without imputation. In a qualitative, cross-study comparison of BMD gains in patients treated with romosozumab followed by denosumab in FRAME compared with those from FREEDOM and its Extension treated with denosumab alone, all available data at months 6, 12, 18, 24, 36, 48, 60, 72, 96, and 120 were used to assess mean change from baseline in lumbar spine and total hip BMD *T*-score.

For fracture efficacy, the current analysis focused on the RRRs in FRAME in the second year alone, when all patients were treated with the same active therapy—denosumab; relative fracture risk reductions through month 12 and through

month 24 of FRAME have been reported.⁽⁶⁾ Analyses of new vertebral fracture endpoints in the second year of FRAME included all randomized patients who had at least one radiograph at or prior to the month-12 visit and at least one radiograph obtained after the month-12 visit. The risk ratio was determined using the Mantel-Haenszel method, and the treatment comparison was assessed by a logistic regression model that was stratified by age and prevalent vertebral fracture. Analyses of other fracture endpoints included all randomized patients who were still on study after the month-12 visit. Treatment comparisons were based on a Cox proportional hazards model stratified by age and prevalent vertebral fracture.

Results

Subject disposition

There were 7180 patients in the FRAME study ($n = 3591$ placebo, $n = 3589$ romosozumab). Baseline characteristics were balanced between groups and have been described in detail.⁽⁶⁾ Overall,

the mean age was 70.9 years, 18.3% of patients had a prevalent vertebral fracture, and 21.7% of patients had a history of nonvertebral fracture (Supporting Table 1). Baseline mean BMD T -score was -2.7 at the lumbar spine, -2.5 at the total hip, and -2.8 at the femoral neck. For comparative purposes, there were 7808 patients in the FREEDOM study ($n = 3906$ placebo, $n = 3902$ denosumab), among whom mean age was 72.3 years; mean BMD T -score was -2.8 at the lumbar spine, -1.9 at the total hip, and -2.2 at the femoral neck; 23.6% had a prevalent vertebral fracture; and 38.8% of patients had a history of nonvertebral fracture (Supporting Table 1).⁽⁸⁾

BMD responder analysis

After 12 months of romosozumab, at the lumbar spine, 96% of patients achieved gains $\geq 3\%$ from baseline, 89% of patients achieved gains $\geq 6\%$, and 68% of patients achieved gains $\geq 10\%$, compared with 22%, 6%, and 1% of patients receiving placebo achieving these gains (Fig. 1A). Only 1.1% ($n = 34$) of patients receiving romosozumab failed to increase lumbar spine BMD at

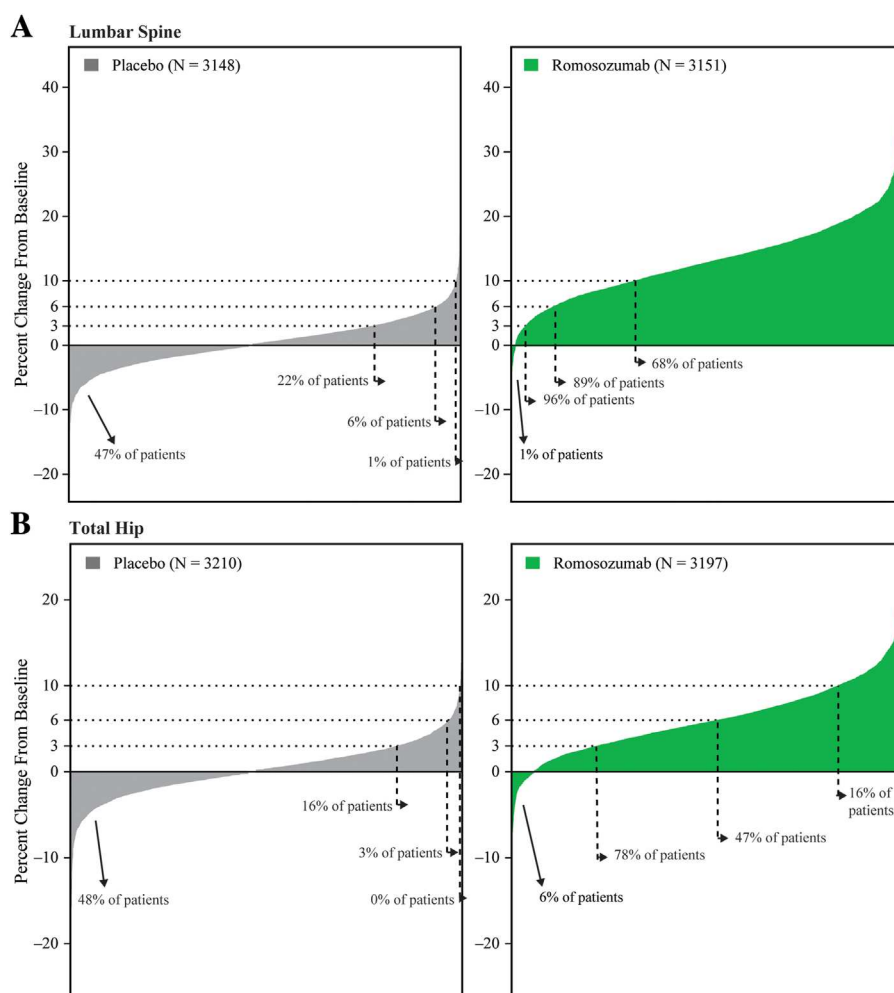


Fig. 1. Percent change in BMD from baseline to month 12 by individual subject. Data are percent change in BMD from baseline to month 12 at the (A) lumbar spine and (B) total hip. Missing data were imputed by last observation carried forward. The x-axis represents each individual subject. Dotted horizontal lines reflect 3%, 6%, and 10% response relative to baseline. Dotted lines through the plot with arrowheads below the x-axis represent the percentage of patients with the indicated changes in BMD ($\leq 0\%$, $\geq 3\%$, $\geq 6\%$, and $\geq 10\%$). N = number of patients with values at baseline and at least one postbaseline visit at or before month 12.

month 12, with only 0.2% of patients ($n = 6$) having a decline of 3% or more. Among patients who failed to gain BMD, one-half (52.9%) received fewer than six doses of romosozumab. Among patients who received placebo, 47% ($n = 1481$) did not increase BMD at the lumbar spine, and 15.6% ($n = 490$) had a decline of 3% or more.

At the total hip, 78% of patients receiving romosozumab achieved gains $\geq 3\%$ from baseline, 47% of patients achieved gains $\geq 6\%$, and 16% of patients achieved gains $\geq 10\%$, compared with 16%, 3%, and 0% of patients receiving placebo achieving similar gains (Fig. 1B). Six percent ($n = 189$) of patients receiving romosozumab failed to increase total hip BMD at month 12, with 1% of patients ($n = 31$) having a decline of 3% or more. Among patients who failed to gain BMD, 34% ($n = 62$) did not receive all 12 doses of romosozumab. Among patients who received placebo, 47% ($n = 1526$) failed to increase BMD, and 12% ($n = 369$) had a decline of 3% or more. BMD response at the femoral neck was similar to the total hip (data not shown).

Among patients who received romosozumab, 0.4% ($n = 11$) of patients did not increase BMD at both the lumbar spine and total hip at month 12. Only one patient had a decline of 3% or more at both the lumbar spine and total hip; she had received only four doses of romosozumab. In contrast, among those receiving placebo, 26% ($n = 808$) of patients lost BMD at both the lumbar spine and total hip, and 3% ($n = 90$) had a decline of 3% or more at both sites.

BMD gains with romosozumab were similar regardless of baseline age, T -score, or geographic region (data not shown).

BMD T -score changes

Mean (95% CI) change in lumbar spine BMD T -score at month 12 was 0.88 (95% CI, 0.87 to 0.89) for the romosozumab group and 0.03 (95% CI, 0.01 to 0.04) for the placebo group. At month 24, after both treatment groups received denosumab for 1 year, the mean change was 1.11 (95% CI, 1.10 to 1.13; romosozumab-to-denosumab group) and 0.38 (95% CI, 0.36 to 0.39; placebo-to-denosumab group). Mean (95% CI) change in total hip BMD T -score at month 12 was 0.32 (95% CI, 0.32 to 0.33) for the romosozumab group and 0.01 (95% CI, 0.01 to 0.02) for the placebo group. At month 24, the mean change was 0.45 (95% CI, 0.44 to 0.46; romosozumab-to-denosumab group) and 0.17 (95% CI, 0.17 to 0.18; placebo-to-denosumab group). Differences between groups at both the lumbar spine and total hip were statistically significant at all time points measured ($p < 0.001$).

FRAME and FREEDOM T -score changes

Next, we qualitatively compared the results in this analysis with the BMD gains from denosumab, which have been characterized in the pivotal phase 3 fracture trial, FREEDOM, and its Extension for up to 10 years of treatment. At the lumbar spine, the improvements from baseline in BMD T -score observed in patients treated with romosozumab for 1 year in FRAME were similar to the BMD gains observed with 4.5 years of continuous denosumab treatment in the FREEDOM and FREEDOM Extension studies (Fig. 2A). With the sequence of romosozumab for 1 year followed by denosumab for 1 year, patients from FRAME achieved BMD T -score gains similar to those observed in patients from FREEDOM and FREEDOM Extension studies after 7 years of denosumab.

At the total hip, 1 year of romosozumab produced BMD gains similar to those seen with 3 years of continuous denosumab treatment (Fig. 2B), and with the sequence of romosozumab for

1 year followed by denosumab for 1 year, patients from FRAME experienced BMD gains similar to those observed in patients from FREEDOM after 7 years of denosumab treatment.

Influence of prior romosozumab exposure on fracture rates during denosumab exposure

In the second year of the FRAME study, when all patients were receiving denosumab, overall fracture rates were low; ie, lower than during year 1 in subjects receiving placebo. However, in year 2, fracture rates were consistently lower in patients who had received romosozumab in the first year compared with those who had received placebo. Within the second year, for patients who had received romosozumab first, RRRs of fracture were 81% for vertebral fractures ($p < 0.001$, Fig. 3A), 32% for clinical fractures ($p = 0.052$, Fig. 3B), 25% for nonvertebral fractures ($p = 0.16$, Fig. 3C), 55% for hip fractures ($p = 0.18$, Fig. 3D), 39% for major osteoporotic fractures ($p = 0.034$), and 32% for major nonvertebral fractures ($p = 0.092$; Supporting Table 2).

Discussion

Bone mass and structure are main determinants of bone strength.^(9–16) Thus, a treatment approach employing a bone-forming agent prior to antiresorptive therapy may provide benefits for patients at high risk for fracture. Indeed, it is increasingly appreciated that some patients at imminent risk of fracture—ie, within 1 to 2 years, including those with recent prior fracture^(17–32)—may benefit from this approach. As shown in the FRAME study, bone-forming therapy with romosozumab provides an opportunity for rapid bone mass accrual and structural improvements, demonstrated by BMD gains and fracture risk reduction observed within 1 year of therapy. Indeed, substantial BMD responses were observed with romosozumab treatment in FRAME among the majority of patients at the lumbar spine and total hip, with 96% and 78% of patients achieving BMD gains of 3% or more from baseline at these sites, respectively, and larger BMD gains seen in a majority patients.

These BMD increases resulted in large T -score improvements attained with romosozumab—and romosozumab followed by denosumab—treatment, with mean changes from baseline over one full T -score at the lumbar spine and nearly 0.5 at the total hip after only 2 years. If patients had been treated with denosumab alone, similar improvements in T -score would have required a much longer treatment duration. On average, lumbar spine and total hip BMD gains, with a 2-year treatment sequence of romosozumab for 1 year followed by denosumab for 1 year, were comparable to approximately 7 years of treatment with denosumab alone, the only therapy known to lead to continuous improvements in BMD, putting the BMD gains with romosozumab (and romosozumab followed by denosumab) into perspective.

There were fewer fractures in the second year of FRAME among patients who had received romosozumab first. This difference in fracture rates occurred despite all patients being treated with denosumab in the second year and despite similar BMD improvements (both percent change and absolute T -score increases) in the second year. This observation supports the notion that achieving a higher BMD with romosozumab treatment within 1 year not only quickly reduces fracture risk but also leads to a persistent benefit when transitioning to antiresorptive therapy. New vertebral and major osteoporotic fracture incidence showed a significant difference between the

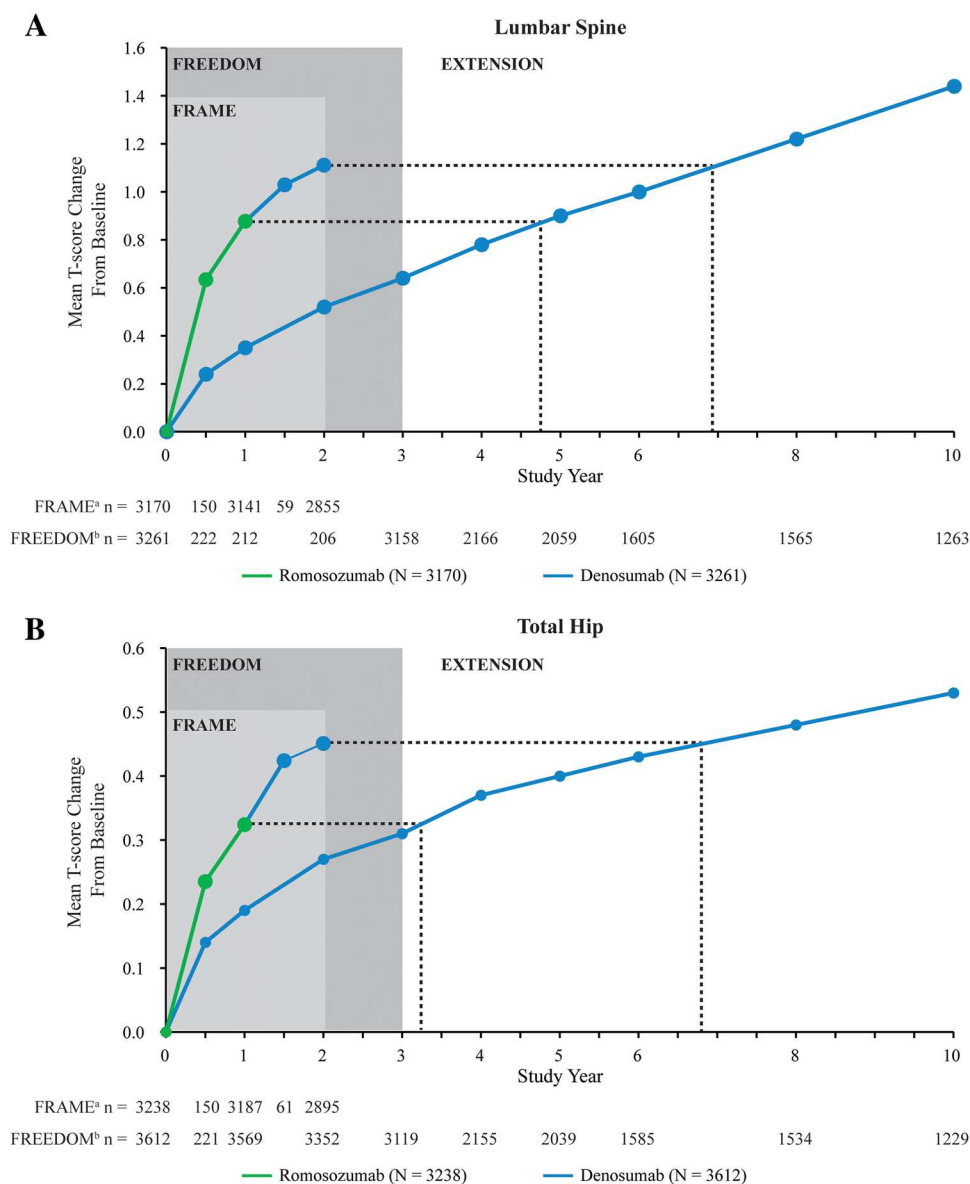


Fig. 2. BMD T-score increases at the (A) lumbar spine and (B) total hip in FRAME relative to FREEDOM and FREEDOM Extension. ^aBMD was measured more frequently (months 6 and 18) in a subset of patients from FRAME who participated in a DXA substudy; additionally, BMD was measured at month 6 in women from Argentina. ^bBMD was measured more frequently in a subset of patients from FREEDOM who participated in a DXA substudy. N = number of patients with a baseline and at least one postbaseline DXA BMD measurement; n = number of patients with evaluable data at the time point of interest.

groups in the second year alone, with other fracture types showing a similar trend, suggesting that a fundamental change in bone strength occurred during year 1 with romosozumab treatment prior to antiresorptive therapy. With romosozumab, that benefit may result from the rapid and substantial bone mass accrual, achieving more robust bone mass and improved bone structure prior to transitioning to the follow-on antiresorptive therapy. In support of this, as has been shown in preclinical studies, romosozumab administration for 12 months in ovariectomized cynomolgus monkeys increased cortical and trabecular bone mass and thickness, and improved bone strength.^(4,5,33) Improvements in cortical thickness and increases in estimated bone strength of both cortical and trabecular bone at the spine and hip using CT and finite element analysis have

also been observed in patients with postmenopausal osteoporosis receiving romosozumab.^(34,35)

These data add to our understanding of the value of administering sequential therapy, starting with a bone-forming agent, for the treatment of osteoporosis, an increasingly relevant and important topic in the management of this chronic condition. It has been documented that the sequence of a bone-forming agent followed by antiresorptive therapy has the potential to provide substantially larger BMD improvements than treatment with an antiresorptive agent first.⁽³⁶⁾ Expanding on that observation, our current analysis demonstrates that the sequence of romosozumab followed by denosumab offers patients a rapid benefit in reducing fracture risk, and then an additional benefit when receiving an antiresorptive agent such

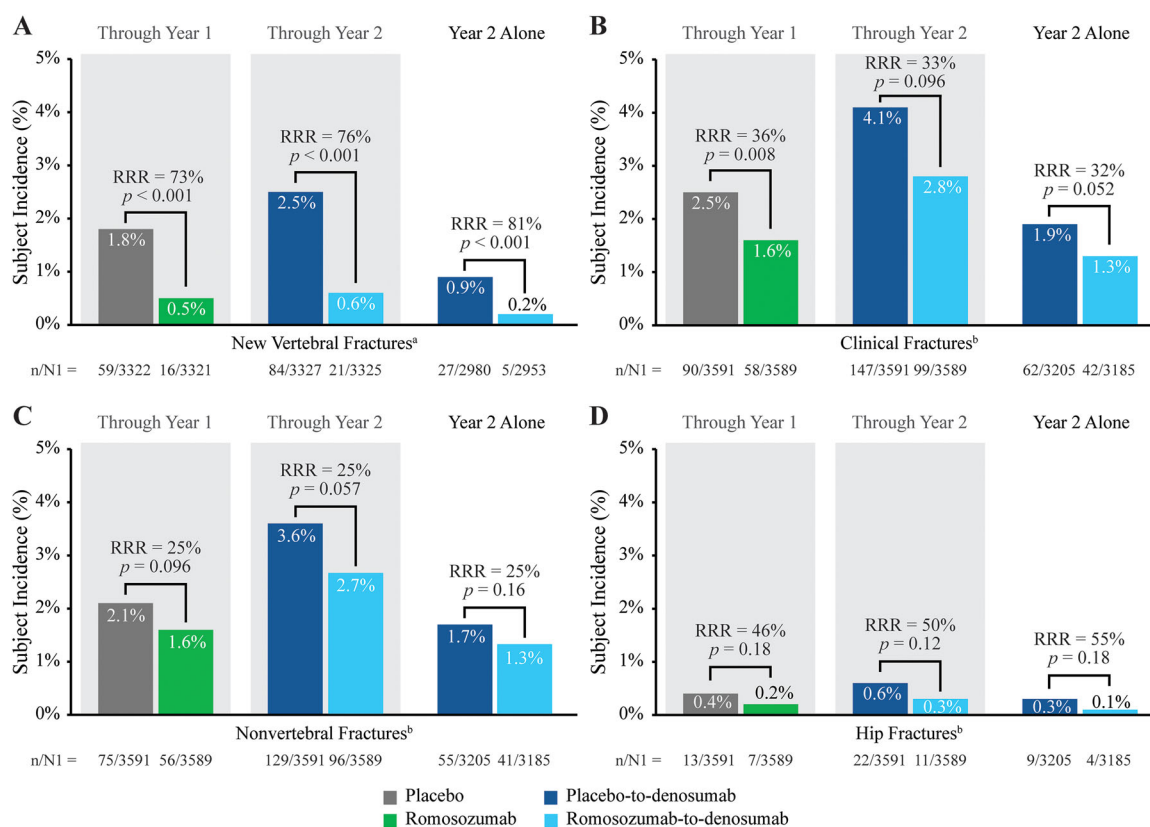


Fig. 3. Subject incidence of fracture in patients who received placebo-to-denosumab and romosozumab-to-denosumab in FRAME. Subject incidence of (A) new vertebral, (B) clinical, (C) nonvertebral, and (D) hip fractures during the FRAME study through year 1, through year 2, and during year 2 alone. ^aRisk ratio based on Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables; p values were based on a logistic regression model, adjusting for age and prevalent vertebral fracture stratification variables; missing data handled using last observation carried forward. ^bHazard ratio and nominal p values were based on a Cox proportional hazards model, adjusting for age and prevalent vertebral fracture stratification variables. Values of p for new vertebral, clinical, nonvertebral, and hip fractures through year 1 and through year 2 were adjusted; p values for new vertebral, clinical, nonvertebral, and hip fractures in year 2 alone were nominal. RRR = relative risk reduction; n/N1 = number of patients with fractures/number of patients in the analysis set.

as denosumab, as demonstrated by additional reductions in fracture risk between groups in our study despite the same follow-on therapy. The sequence of romosozumab followed by denosumab would allow for BMD gains within a short period of time not seen previously with other therapeutics.

This sequential approach to osteoporosis treatment may also be relevant to physicians seeking options for treating to a T-score target in osteoporosis, because it would allow attainment of the target BMD faster.⁽³⁷⁾ In addition, although not directly assessed, the study suggests that absolute BMD is more relevant as a predictor of fracture risk than change in BMD (percent or absolute change), as the BMD increases in year 2 of the study were similar in both groups on denosumab, yet fracture rates were lower in those who received romosozumab first. Although here we report on 1 year of denosumab following 1 year of romosozumab, ongoing treatment of osteoporosis is warranted in patients at high risk of fracture; the effects of romosozumab and denosumab are reversible if discontinued without follow-on therapy, as has been observed for all osteoporosis treatments over variable offset timeframes.

This study has a number of strengths, including a sufficiently large sample size to test the study hypothesis, comparison with placebo treatment during year 1 of the

study, complete data on all study endpoints (including adjudication of all fractures), and quality control of all BMD measures. There were also some limitations, including the post-hoc nature of these analyses without adjustment for multiple comparisons for the fracture analyses in the second year alone, and overall low fracture rates in the study limiting the power to detect between-group differences. However, the reductions in fracture risk in the second year of FRAME for patients treated with romosozumab in the first year is consistent with the results of the primary analysis for the study, in which fracture risk reduction was observed over the 24-month study period for patients who received romosozumab in the first year.⁽⁶⁾ We were also unable to perform a quantitative correlation between BMD attained and fracture rates in the FRAME study because of the low rates of fracture events in the study available for analysis, particularly in the second year, as well as the narrow range of T-scores at baseline and after treatment due to enrollment criteria. However, previous studies have shown that BMD attained on therapy correlates with fracture rates,⁽³⁸⁾ and preclinical data with romosozumab show that BMD achieved with therapy is highly correlated with ex vivo bone strength. Last, indirect comparisons in BMD changes between FRAME and FREEDOM

rely on a qualitative comparison across studies; however, adjusting for key baseline characteristics (eg, baseline BMD, age, and prevalent vertebral fracture) had no impact on the conclusions.

Conclusion

One year of treatment with the bone-forming agent romosozumab results in large improvements in BMD, with nearly all patients responding to therapy, providing a stronger skeletal foundation and leading to fewer fractures upon transition to antiresorptive treatment with denosumab. Our data further support the potential clinical benefit of treatment with romosozumab and the added benefit of the treatment sequence of romosozumab followed by denosumab, which may offer particular value for patients with osteoporosis at imminent risk of fracture.

Disclosures

FC has received grants/research support from Amgen and Eli Lilly; has served as a consultant for Merck, Radius, and Tarsa; has served on a speakers' bureau for Amgen, Eli Lilly, and Radius; and has served on an advisory board for Amgen, Eli Lilly, Merck, and Radius. DBC, CEM, and AG are employees of and have stocks in Amgen Inc. SF has received grants/research support from MSD, UCB, AMGEN, Novartis; and has served as a consultant for Amgen, UCB, Radius, Labatec, and AgNovos. AK has received grants/research support from Amgen and Shire; and has received speaker honoraria from Amgen and Eli Lilly. NEL has served as a consultant for Amgen, Pfizer, Radius, and Regeneron; and has served on a speakers' bureau for Amgen, Novartis, and Radius. KL has nothing to disclose. TM has received grants/research support from Daiichi-Sankyo and Astellas Pharma; has served as a consultant for Chugai, and Teijin Pharma; has served on a speakers' bureau for Ono Pharmaceutical; and has served on an advisory board for Amgen. CL is an employee and shareholder of UCB.

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