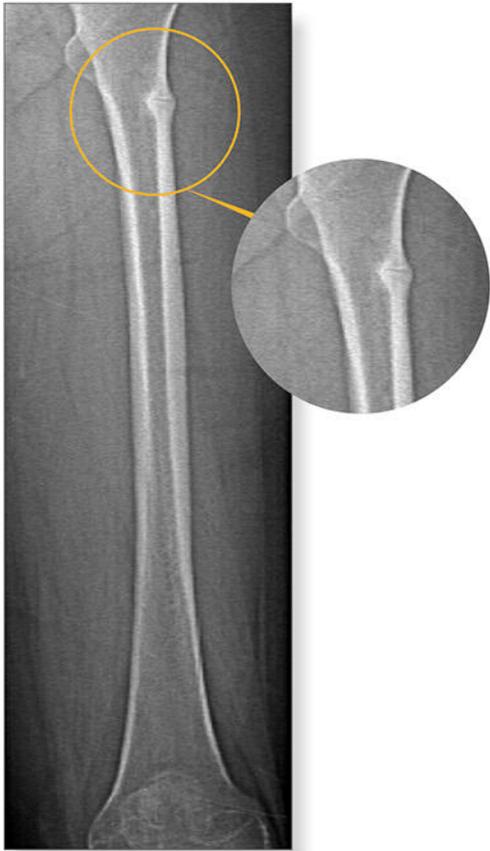


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One Year of Romosozumab Followed by Two Years of Denosumab Maintains Fracture Risk Reductions: Results of the FRAME Extension Study

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ABSTRACT

Romosozumab, a humanized monoclonal antibody that binds and inhibits sclerostin, has the dual effect of increasing bone formation and decreasing bone resorption. As previously reported in the pivotal FRActure study in postmenopausal women with osteoporosis (FRAME), women with a *T*-score of ≤ -2.5 at the total hip or femoral neck received subcutaneous placebo or romosozumab once monthly for 12 months, followed by open-label subcutaneous denosumab every 6 months for an additional 12 months. Upon completion of the 24-month primary analysis period, eligible women entered the extension phase and received denosumab for an additional 12 months. Here, we report the final analysis results through 36 months, including efficacy assessments of new vertebral, clinical, and nonvertebral fracture; bone mineral density (BMD); and safety assessments. Of 7180 women enrolled, 5743 (80%) completed the 36-month study (2851 romosozumab-to-denosumab; 2892 placebo-to-denosumab). Through 36 months, fracture risk was reduced in subjects receiving romosozumab versus placebo for 12 months followed by 24 months of denosumab for both groups: new vertebral fracture (relative risk reduction [RRR], 66%; incidence, 1.0% versus 2.8%; $p < 0.001$), clinical fracture (RRR, 27%; incidence, 4.0% versus 5.5%; $p = 0.004$), and nonvertebral fracture (RRR, 21%; incidence, 3.9% versus 4.9%; $p = 0.039$). BMD continued to increase for the 2 years with denosumab treatment in both arms. The substantial difference in BMD achieved through 12 months of romosozumab treatment versus placebo was maintained through the follow-up period when both treatment arms received denosumab. Subject incidence of adverse events, including positively adjudicated serious cardiovascular adverse events, were overall balanced between groups. In conclusion, in postmenopausal women with osteoporosis, 12 months of romosozumab led to persistent fracture reduction benefit and ongoing BMD gains when followed by 24 months of denosumab. The sequence of romosozumab followed by denosumab may be a promising regimen for the treatment of osteoporosis. © 2018 American Society for Bone and Mineral Research.

KEY WORDS: ROMOSUZUMAB; DENOSUMAB; BONE MINERAL DENSITY; FRACTURE RISK; POSTMENOPAUSAL OSTEOPOROSIS

Introduction

The consequences of osteoporosis, namely fractures, result in substantial clinical and economic burden among postmenopausal women.^(1,2) After a fracture, the risk of second fracture is five times higher in the next year,⁽³⁾ and recent fracture and other characteristics such as older age and low bone mineral

density (BMD) can put patients at high risk for fracture both over a longer-term horizon (eg, 10 years), as well as over shorter-term horizons.^(4–12) However, even in patients in whom there is urgency to treat, there is a large treatment gap in osteoporosis, with only about 20% of patients receiving treatment following a fracture.^(13–15) Limited options for bone-forming therapy are currently available. Although the bone-forming agents

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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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teriparatide and abaloparatide are US Food and Drug Administration (FDA) approved for the treatment of postmenopausal women with osteoporosis,^(16–18) agents with a different mechanism of action stand to offer additional therapeutic benefits. Patients receiving bone-forming therapy should receive follow-on therapy with an antiresorptive agent to maintain or further increase BMD, given that BMD increases attained with bone-forming agents are reversible and osteoporosis—a chronic and progressive disease—requires ongoing management and, as reported, cessation of romosozumab therapy results in decrease in BMD toward baseline.^(19,20)

Romosozumab (Amgen Inc. and UCB Pharma), a humanized monoclonal antibody that binds and inhibits sclerostin, has the dual effect of increasing bone formation and decreasing bone resorption.^(21,22) The pivotal FRActure study in postmenopausal women with osteoporosis (FRAME) was a large, international fracture endpoint trial that enrolled 7180 postmenopausal women with osteoporosis. In FRAME, patients received blinded romosozumab or placebo for 1 year, after which all patients received denosumab for an additional year. The primary analysis results from this study have been published, reporting that 12 months of treatment with romosozumab significantly reduced the risk of vertebral fractures (73% relative risk reduction [RRR], $p < 0.001$) and clinical fractures (36% RRR, $p = 0.008$) within 1 year compared with placebo.⁽²³⁾ Substantial BMD gains were observed in the first year (13% increase from baseline at the spine and 7% at the hip), with continued BMD gains and ongoing risk reduction of vertebral fractures (75% RRR, $p < 0.001$) and clinical fractures (33% RRR, nominal $p = 0.002$ and adjusted $p = 0.096$) through 24 months with romosozumab followed by denosumab.⁽²³⁾ Risk reduction of nonvertebral fractures did not reach statistical significance through 12 months (25% RRR, $p = 0.096$) or through 24 months (25% RRR, nominal $p = 0.029$ and adjusted $p = 0.057$), largely due to regional differences in nonvertebral fracture rates and a particularly low rate of nonvertebral fractures in Latin American subjects, who constituted 43% of the enrolled population.^(23,24) Adverse events were balanced between the groups, with one atypical femoral fracture (AFF) and two cases of osteonecrosis of the jaw (ONJ) positively adjudicated in subjects initially treated with romosozumab.⁽²³⁾ Positively adjudicated serious cardiovascular adverse events were also balanced between the treatment groups.⁽²³⁾

Following the 24-month study period, a 12-month extension investigated whether the benefits of the initial treatment with romosozumab would be maintained with continued treatment with denosumab for an additional 12 months. Here we report efficacy and safety results from the final analysis of FRAME through 36 months, where 12 months of romosozumab or placebo were followed by 24 months of denosumab treatment.

Subjects and Methods

Study design

FRAME was an international, randomized, double-blind, placebo-controlled, parallel-group, phase 3, 36-month study undertaken in 222 centers in 25 countries worldwide. The FRAME study design (Supporting Fig. 1) and details of the eligibility criteria have been previously reported.⁽²³⁾ Briefly, ambulatory postmenopausal women aged 55 to 90 years, with 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 evaluable by dual-energy X-ray absorptiometry (DXA) were

eligible for inclusion. Women were excluded from the study if they had a history of hip fracture, any severe or more than two moderate vertebral fractures, history of ONJ, history of metabolic bone disease or conditions affecting bone metabolism, recent use of drugs affecting bone metabolism, current hypercalcemia or hypocalcemia, or 25-hydroxyvitamin D levels less than 20 ng/mL.

Subjects were randomized 1:1 (stratified by age [<75 years versus ≥ 75 years] and prevalent vertebral fracture) to receive blinded subcutaneous romosozumab 210 mg or placebo once monthly for 12 months, followed by open-label subcutaneous denosumab 60 mg (Prolia[®]; Amgen Inc., Thousand Oaks, CA, USA) every 6 months for an additional 12 months, blinded to initial treatment assignment. Women who received denosumab at the 12-month and 18-month study visits and who completed the 24-month study period were eligible to receive open-label subcutaneous denosumab 60 mg every 6 months for a further 12 months for a total study duration of 36 months (Supporting Fig. 1). All subjects received daily calcium (500 to 1000 mg) and vitamin D (600 to 800 IU) supplementation from screening through the end of study, with some receiving a vitamin D loading dose of 50,000 to 60,000 IU within 7 days of starting the study drug when the baseline serum 25-hydroxyvitamin D level was 40 ng per milliliter or less.

The results of the primary analysis at 24 months have been reported.⁽²³⁾ Here we report efficacy and safety results through 36 months for the final analysis. Endpoints included subject incidence of new vertebral fracture, clinical fracture, non-vertebral fracture, and other fracture categories through 36 months and percentage changes from baseline in BMD at 36 months. All endpoints reported through 36 months were prespecified but considered exploratory. Safety was evaluated throughout the study.

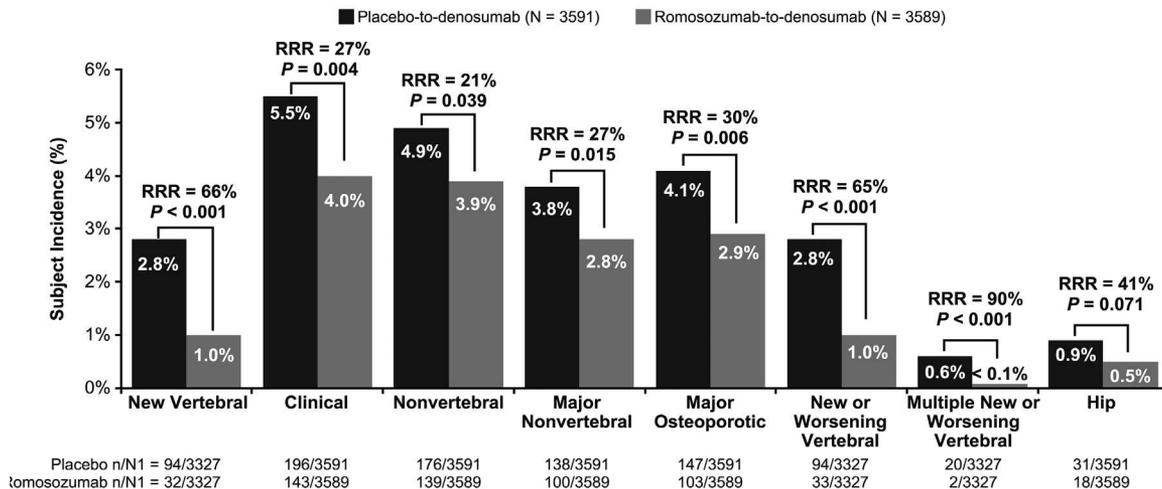
The study protocol was approved by the ethics committee or institutional review board at each center, and the study was conducted in accordance with International Conference on Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All subjects provided written informed consent. This trial is registered at ClinicalTrials.gov (NCT01575834).

Study procedures

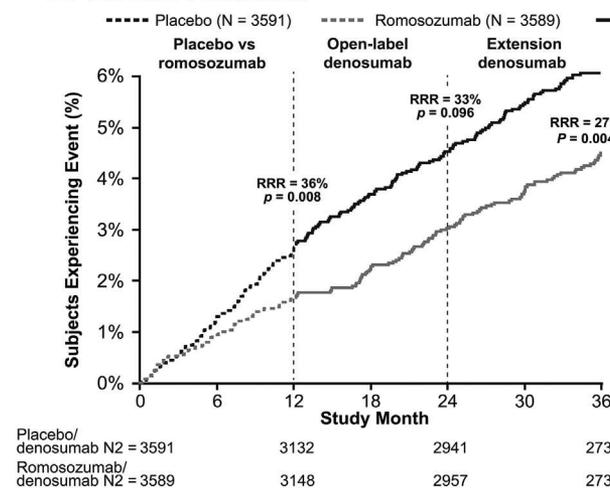
Procedures for this study have been described.⁽²³⁾ Briefly, lateral spine radiographs (thoracic and lumbar spine) were taken at select scheduled visits or when a subject experienced back pain suggestive of vertebral fracture, and assessed, blinded to the initial treatment assignment, at a central imaging vendor (BioClinica, Newark, CA, USA) using the Genant semiquantitative grading scale.⁽²⁵⁾

New vertebral fractures were defined as at least one grade increase in previously normal vertebrae; at least one grade increase was also required for worsening of preexisting fractures. The central imaging vendor, also blinded to the initial treatment assignment, confirmed nonvertebral fractures using radiologists' reports or diagnostic images. Nonvertebral fractures excluded fractures of the skull, facial bones, metacarpals, fingers, and toes, and pathologic fractures, or those associated with severe trauma. Clinical fractures included nonvertebral fractures and clinical vertebral fractures defined as radiographically confirmed new or worsening vertebral fractures associated with back pain deemed by the investigator to be consistent with a vertebral fracture event. BMD was assessed in all subjects at

A. Key Fracture Endpoints Through 36 Months



B. Clinical Fractures



C. Nonvertebral Fractures

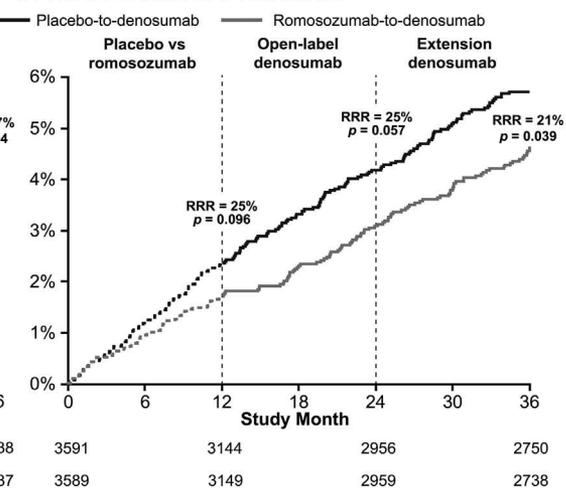


Fig. 1. Effect of romosozumab treatment for 12 months followed by denosumab for 24 months on fracture. Subject incidence of key fracture endpoints (A), time to first clinical fracture (B), and time to first nonvertebral fracture (C) through 36 months for the overall population are shown. Nonvertebral fractures exclude fractures of the skull, facial bones, metacarpals, fingers, and toes, pathologic fractures and fractures associated with high trauma. Major nonvertebral fractures include fractures of the pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip. Major osteoporotic fractures include clinical vertebral, hip, forearm, and humerus (regardless of trauma severity) and exclude pathologic fractures. For new vertebral fracture, new or worsening vertebral fracture, and multiple new or worsening vertebral fracture, the risk ratio and RRR were based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables; *p* values were based on logistic regression model stratified by age and prevalent vertebral fracture. For all other fracture endpoints, the hazard ratio, relative risk reduction, and *p* values were based on a Cox proportional hazards model stratified by age and prevalent vertebral fracture, without multiplicity adjustment. For time to first clinical fracture (B) and time to first nonvertebral fracture (C), *p* values for 12-month and 24-month periods are adjusted values based on a sequential testing procedure and nominal for month 36. Data displayed for 12-month and 24-month periods are as reported for the primary analysis. N = number of subjects randomized; n = number of subjects with fractures; N1 = number of subjects in the analysis set; N2 = number of subjects at risk at the specified time point; RRR = relative risk reduction.

baseline and at 12, 24, and 36 months. The findings of a substudy assessing BMD every 6 months up to 24 months have been reported.⁽²³⁾ Serum concentrations of the bone turnover markers procollagen type 1 N-terminal propeptide (P1NP) and β -isomer of C-terminal telopeptide of type I collagen (β -CTX) were assessed at month 36 as part of the bone turnover marker substudy, as published.⁽²³⁾

Adverse events were reported by physicians at the study centers. Potential cases of AFF and ONJ identified with the use of prespecified search strategies and serious adverse events that

were potentially cardiovascular-related, including deaths, were adjudicated by their respective independent committees.

Statistical analysis

All efficacy analyses assessing treatment effect used an intention-to-treat approach. Analyses for vertebral fracture endpoints included all randomized subjects with a baseline and at least one postbaseline radiograph. Any missing postbaseline spinal radiograph assessment was imputed using

the status from the last available postbaseline visit. For the other fracture endpoints, all randomized subjects were included.

For the incidence of new vertebral fracture, new or worsening vertebral fracture, and multiple new or worsening vertebral fractures, the risk ratio was determined based on the Mantel-Haenszel method, with treatment comparison assessed using a logistic regression model stratified by age (<75 years versus ≥ 75 years) and prevalent vertebral fracture stratification variables. For other fracture endpoints, treatment comparisons were based on a Cox proportional hazards model stratified by age and prevalent vertebral fracture stratification variables. Values of p for the 12-month and 24-month periods were adjusted values using a sequential testing procedure based on the odds ratio for the new vertebral and new or worsening vertebral fracture endpoints, and RRR for the other fracture endpoints, except major osteoporotic fracture, as reported in the primary analysis.⁽²³⁾ Although prespecified, the 36-month endpoints are considered exploratory; therefore, p values are nominal.

Percentage change from baseline in BMD was assessed for subjects who had a baseline and at least one postbaseline measurement. Percentage change from baseline in BMD was analyzed using an ANCOVA model adjusted for treatment, age, and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction, with missing values imputed by carrying forward the last postbaseline observation. The percentages of subjects with T -scores > -2.5 , > -2.0 , and > -1.5 at the lumbar spine and total hip at baseline, 12, 24, and 36 months were determined.

Similar to analyses reported in the primary FRAME results and subsequent post hoc analyses of results by geographic region,^(23,24) we undertook post hoc analyses of nonvertebral fracture efficacy in the Latin American population compared with the remaining study population, which was referred to as Rest-of-World, given the observed nonvertebral fracture rate in the placebo group was unexpectedly low in Latin America.

The safety analysis included all the subjects who underwent randomization and received at least one dose of placebo or romosozumab in the 12-month double-blind period. The subject incidence rates for the 36-month study period included all events that occurred in the 12-month double-blind period and all events that occurred in the open-label and extension periods for those subjects who received at least one dose of denosumab.

Results

Subjects

Of 7180 randomized subjects, 6045 (84.2%) entered the 12-month extension period, and 5743 (80.0%) completed the 36 months of study (2851 [79.4%] romosozumab followed by denosumab [romosozumab-to-denosumab]; 2892 [80.5%] placebo followed by denosumab [placebo-to-denosumab]) (Supporting Fig. 2). The reasons for discontinuation were similar in the two groups through the 12-month, 24-month, and 36-month treatment periods (Supporting Fig. 2). The most common reasons for discontinuation through the 36-month study period were consent withdrawn (742 subjects; 10.3%), death (155 subjects; 2.2%), other (140 subjects; 1.9%), and adverse events (124 subjects; 1.7%).

Baseline demographic and clinical characteristics of subjects who entered the extension period were similar to the full randomized study population⁽²³⁾ and were balanced in the two treatment groups (Table 1). Mean age for the full randomized study population was 70.9 years. Mean T -scores were -2.72 at

the lumbar spine, -2.47 at the total hip, and -2.75 at the femoral neck. A total of 1317 subjects (18.3%) had at least one prevalent vertebral fracture (756 [10.5%] were mild in severity), and 1560 (21.7%) had a previous nonvertebral fracture. Latin America was the highest enrolling region (3084; 43.0%).

Fracture efficacy results

Through 36 months, fracture risk was significantly reduced in subjects who received romosozumab rather than placebo during the first 12 months of the study, even though all subjects received denosumab during study years 2 and 3. A significant reduction in risk was observed for new vertebral fracture by 66%, clinical fracture by 27%, and nonvertebral fracture by 21% in subjects who received romosozumab-to-denosumab compared with placebo-to-denosumab (all $p < 0.05$; Fig. 1A–C; Supporting Table 1). Similarly, the risk of fracture was significantly reduced for other fracture types including major nonvertebral, major osteoporotic, new or worsening vertebral, and multiple new or worsening vertebral fracture in subjects who had received romosozumab-to-denosumab versus placebo-to-denosumab (Fig. 1A; Supporting Table 1). The incidence of hip fracture was low, with numerically fewer hip fractures and RRR of 41% in subjects who had received romosozumab-to-denosumab versus placebo-to-denosumab, through 36 months ($p = 0.071$; Fig. 1A; Table 1).

The RRR of new vertebral fractures through 24 and 36 months between the romosozumab-to-denosumab and placebo-to-denosumab groups was similar in magnitude to the effect observed after 12 months of treatment, even after all subjects transitioned to active therapy with denosumab in years 2 and 3 of the study (Fig. 2). Subjects who had received romosozumab-to-denosumab had significantly reduced risk of new vertebral fracture through 12 months (73% reduction; $p < 0.001$), 24 months (75% reduction; $p < 0.001$), and 36 months (66% reduction; $p < 0.001$) (Fig. 2) compared with subjects who received placebo-to-denosumab.

Although romosozumab reduced vertebral fractures and increased BMD consistently across regions, reduction in nonvertebral fracture rate was not observed in Latin America, where the population had unexpectedly low baseline risk.^(23,24) Similar to findings from the primary analysis, a reduction in new vertebral fractures was observed consistently in both Latin American and Rest-of-World subjects through 36 months (62% reduction; $p = 0.003$ and 68% reduction; $p < 0.001$, respectively; Supporting Fig. 3). Reductions in clinical and nonvertebral fractures were seen in the Rest-of-World subjects who had received romosozumab-to-denosumab compared with placebo-to-denosumab (34% reduction; $p = 0.002$ and 28% reduction; $p = 0.017$, respectively; Supporting Fig. 3), but not in Latin America (11% reduction in clinical fractures; $p = 0.55$ and 4% reduction in nonvertebral fractures; $p = 0.84$, respectively), against a background of low observed fracture risk in that population as previously reported.⁽²⁴⁾

BMD

Mean BMD percentage changes from baseline at the lumbar spine, total hip, and femoral neck were significantly greater in subjects who had received romosozumab-to-denosumab versus placebo-to-denosumab at 36 months (Fig. 3A–C). BMD increased significantly each year in both treatment arms while receiving denosumab. BMD gains observed with romosozumab versus placebo at 12 months were maintained through 36 months.

Table 1. Baseline Demographic and Clinical Characteristics for FRAME and Extension

Characteristic	Primary analysis subjects		Extension subjects	
	Placebo-to-denosumab (N = 3591)	Romosozumab-to-denosumab (N = 3589)	Placebo-to-denosumab (N1 = 3042)	Romosozumab-to-denosumab (N1 = 3003)
Age (years), mean ± SD	70.8 ± 6.9	70.9 ± 7.0	70.5 ± 6.8	70.6 ± 6.9
<75 years, n (%)	2470 (68.8)	2479 (68.8)	2140 (70.3)	2111 (70.3)
≥75 years, n (%)	1121 (31.2)	1119 (31.2)	902 (29.7)	892 (29.7)
Geographic region, n (%) ^a				
Latin America	1534 (42.7)	1550 (43.2)	1331 (43.8)	1349 (44.9)
Central or Eastern Europe	1050 (29.2)	1043 (29.1)	838 (27.5)	828 (27.6)
Western Europe, Australia, or New Zealand	497 (13.8)	482 (13.4)	428 (14.1)	402 (13.4)
Asia Pacific	419 (11.7)	410 (11.4)	369 (12.1)	338 (11.3)
North America	91 (2.5)	104 (2.9)	76 (2.5)	86 (2.9)
Ethnic group, n (%) ^b				
Hispanic	1416 (39.4)	1427 (39.8)	1237 (40.7)	1239 (41.3)
Non-Hispanic	2175 (60.6)	2162 (60.2)	1805 (59.3)	1764 (58.7)
Body mass index (kg/m ²), mean ± SD	24.7 ± 4.4	24.7 ± 4.3	24.7 ± 4.4	24.7 ± 4.3
T-score, mean ± SD				
Lumbar spine	-2.71 ± 1.04	-2.72 ± 1.04	-2.72 ± 1.04	-2.74 ± 1.04
Total hip	-2.46 ± 0.47	-2.48 ± 0.47	-2.46 ± 0.47	-2.48 ± 0.47
Femoral neck	-2.74 ± 0.29	-2.76 ± 0.28	-2.74 ± 0.30	-2.76 ± 0.28
Prevalent vertebral fracture, n (%)	645 (18.0)	672 (18.7)	540 (17.8)	549 (18.3)
Number of prevalent vertebral fractures, n (%)				
1	496 (13.8)	506 (14.1)	421 (13.8)	408 (13.6)
≥2	149 (4.1)	166 (4.6)	119 (4.0)	141 (4.7)
Grade of most severe vertebral fracture, n (%) ^c				
Mild	378 (10.5)	378 (10.5)	323 (10.6)	306 (10.2)
Moderate	263 (7.3)	293 (8.2)	214 (7.0)	243 (8.1)
Severe	4 (0.1)	1 (<0.1)	3 (<0.1)	0 (0)
Previous nonvertebral fracture at ≥45 years of age, n (%)	782 (21.8)	778 (21.7)	644 (21.2)	629 (20.9)
FRAX 10-year probability of major osteoporotic fracture, median (IQR) ^d	10.9 (7.1–16.7)	10.8 (7.1–17.0)	10.8 (7.0–16.4)	10.6 (6.9–16.6)
25-hydroxyvitamin D (ng/mL), median (IQR)	27.2 (23.6–32.3)	27.2 (23.6–32.5)	27.4 (23.6–32.6)	27.3 (23.6–32.7)

Percentage based on number of subjects in respective analysis.

FRAME = FRActure study in postmenopausal woMen with ostEoporosis; N = number of subjects randomized for the primary analysis; N1 = number of subjects who entered the extension; SD = standard deviation; FRAX = Fracture Risk Assessment Tool.

^aThe countries included within the respective regions are as follows (listed in order of enrollment, from highest to lowest, within each region)—Latin America: Colombia, Brazil, Argentina, Dominican Republic, and Mexico; Central or Eastern Europe: Poland, Czech Republic, Hungary, Lithuania, Estonia, Latvia, and Romania; Western Europe, Australia, or New Zealand: United Kingdom, Denmark, Germany, Spain, New Zealand, Switzerland, Belgium, and Australia; Asia Pacific: Japan, China (Hong Kong), and India; and North America: United States and Canada.

^bEthnic group was self-reported.

^cThe grade of the most severe vertebral fracture was assessed with the use of the Genant semiquantitative grading scale.

^dThe FRAX was used to estimate the 10-year probability of major osteoporotic fracture.

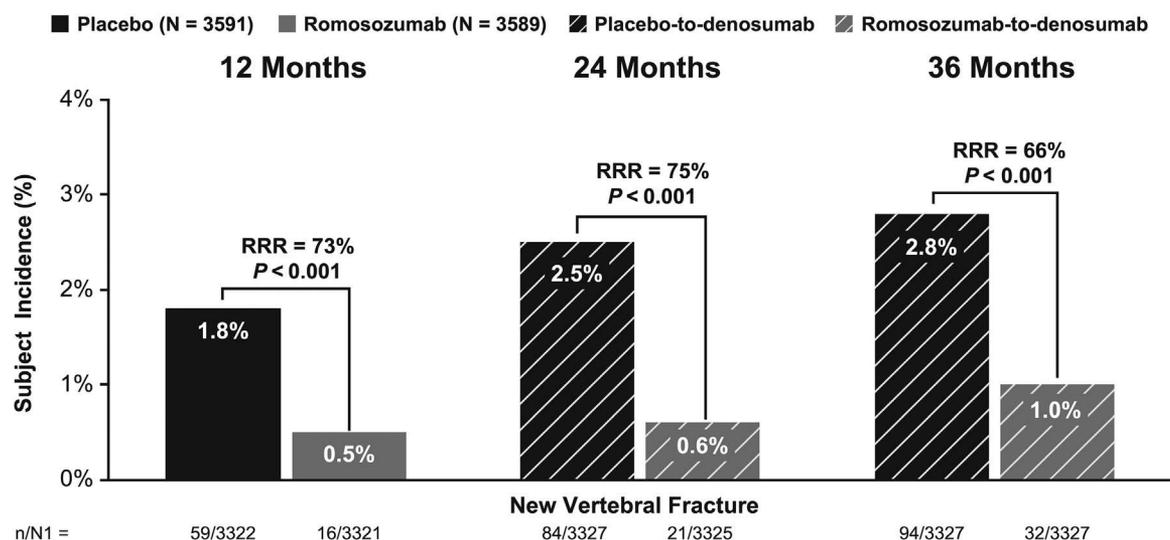


Fig. 2. Subject incidence of new vertebral fracture through 12, 24, and 36 months for the overall population are shown. The RRR was assessed among subjects in the romosozumab group as compared with those in the placebo group at 12 months (end of the double-blind period) and at 24 and 36 months (by which time subjects in both groups had received open-label denosumab for 12 and 24 months, respectively) based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables. *p* values were based on a logistic regression model adjusted for age and prevalent vertebral fracture stratification variables. *p* values for 12-month and 24-month periods are adjusted values based on a sequential testing procedure and nominal for 36 months, without multiplicity adjustment. Data displayed for 12-month and 24-month periods are as reported for the primary analysis. N = number of subjects randomized; n = number of subjects with fractures; N1 = number of subjects in the analysis set; RRR = relative risk reduction.

Differences in relative increases from baseline in BMD for subjects who had received romosozumab-to-denosumab versus placebo-to-denosumab at 36 months were 10.5% (95% CI, 10.2% to 10.8%) at the lumbar spine, 5.2% (95% CI, 5.0% to 5.4%) at the total hip, and 4.8% (95% CI, 4.5% to 5.0%) at the femoral neck (all *p* < 0.001 compared with placebo-to-denosumab). Among patients who initially received romosozumab in the first year, BMD continued to increase significantly each year.

At baseline, 62.8% and 60.5% of romosozumab-to-denosumab and placebo-to-denosumab subjects, respectively, had an osteoporotic lumbar spine *T*-score (−2.5 or less). After 36 months, fewer subjects who had received romosozumab remained osteoporotic at this skeletal site (20.3% romosozumab-to-denosumab and 42.9% placebo-to-denosumab) (Supporting Table 2). Similarly, fewer subjects with a total hip *T*-score of −2.5 to −3.5 at baseline (53.1% romosozumab-to-denosumab and 51.9% placebo-to-denosumab) were osteoporotic at 36 months (14.3% romosozumab-to-denosumab and 30.0% placebo-to-denosumab). Mean ± SD *T*-scores at the lumbar spine improved over the 36-month study period, from −2.73 ± 1.04 to −1.50 ± 1.18 in the romosozumab-to-denosumab group and −2.71 ± 1.04 to −2.18 ± 1.13 in the placebo-to-denosumab group from baseline to 36 months. Improvements in *T*-score at the total hip were also observed from −2.48 ± 0.47 to −1.96 ± 0.49 in the romosozumab-to-denosumab group and −2.46 ± 0.47 to −2.22 ± 0.48 in the placebo-to-denosumab from baseline to 36 months. Analyzing the number of patients in each group who achieved a BMD *T*-score above −2.0 or −1.5 showed similar trends (Supporting Table 2).

Bone turnover markers

Bone turnover markers, P1NP and β-CTX, were measured in patients included in the bone turnover marker substudy who

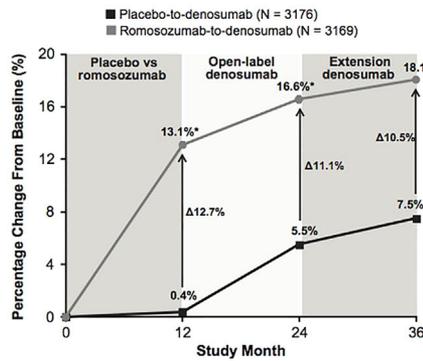
received romosozumab or placebo from 0 to 12 months and then received denosumab from 12 to 24 months. These data have been published.⁽²³⁾ P1NP and β-CTX were also measured at month 36 following continued denosumab treatment. P1NP and β-CTX levels that had been reduced to below baseline with denosumab treatment in the romosozumab-to-denosumab and the placebo-to-denosumab treatment groups at 24 months⁽²³⁾ remained suppressed below baseline with continued denosumab treatment from 24 to 36 months (data not shown).

Safety

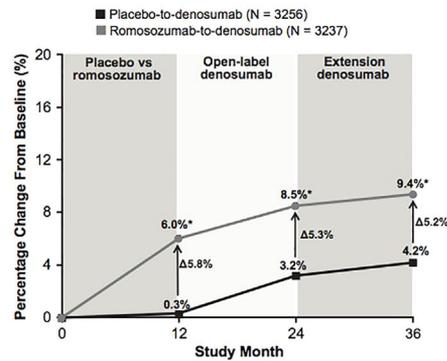
The incidence of adverse events and serious adverse events were balanced in the two groups through 36 months (Table 2). Serious cardiovascular adverse events and all fatal adverse events were adjudicated and the incidence of positively adjudicated serious cardiovascular adverse events, including fatal cardiovascular events, were balanced between treatment groups throughout the 36-month study period (Table 2).

The incidence of adverse events of interest categorized as hypocalcemia, hypersensitivity, malignancy, osteoarthritis, and hyperostosis was also generally similar between the groups through 36 months (Table 2). Adverse events of hypersensitivity were mostly mild and rarely led to study discontinuation. A total of 10 subjects in the romosozumab-to-denosumab treatment group and four in the placebo-to-denosumab treatment group reported serious adverse events of hypersensitivity through 36 months. The majority of these cases occurred in the first 24 months and have been reported: seven subjects in the romosozumab-to-denosumab treatment group and four in the placebo-to-denosumab treatment group.⁽²³⁾ Another three subjects reported serious adverse events of hypersensitivity between 24 and 36 months, including grade 3 dermatitis with secondary purulent lesions and grade 3 dermatitis in one

A. Lumbar Spine



B. Total Hip



C. Femoral Neck

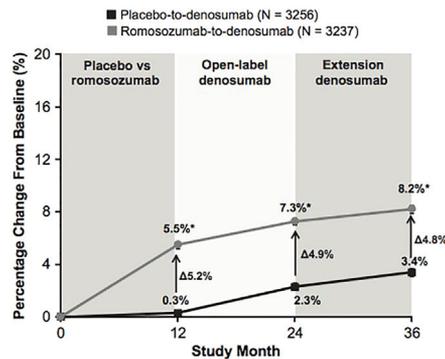


Fig. 3. Percentage change from baseline in BMD at the lumbar spine, total hip, and femoral neck at 36 months. Least-squares mean (95% CI) percentage changes in BMD at the lumbar spine (A), total hip (B), and femoral neck (C). Least squares mean percentage change from baseline in BMD and *p* values were based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction, without multiplicity adjustment. Missing values were imputed by the last-observation-carried-forward method, and a sensitivity analysis with the use of a repeated measures model showed similar results. *Nominal *p* < 0.001. N = number of subjects with a baseline and at least one postbaseline BMD assessment.

subject, grade 3 anaphylactic shock in one subject, and grade 2 necrosis of the skin in one subject, all in the romosozumab-to-denosumab treatment group; none led to study drug or study discontinuation and none were considered by the investigators to be related to investigational product. Injection site reactions, most of which were mild in severity and reported in the first 12 months,⁽²³⁾ were reported in 189 (5.3%) romosozumab-to-denosumab subjects and 107 (3.0%) placebo-to-denosumab subjects. There were no serious injection site reactions reported during the study.

No additional positively adjudicated cases of AFF or ONJ were observed since the reporting of the 24-month data, where one positively adjudicated AFF event and two positively adjudicated ONJ events had been reported and described in subjects who initially received romosozumab.⁽²³⁾

Discussion

In postmenopausal women with osteoporosis, BMD continued to increase over 36 months following 12 monthly doses of romosozumab and transition to denosumab every 6 months for up to 24 months. The magnitude of initial BMD improvement achieved in women receiving romosozumab versus placebo in the first 12 months was maintained through 36 months, when romosozumab was followed by denosumab for 24 months

(10.5% at lumbar spine, 5.2% at total hip, and 4.8% at femoral neck at 36 months), even though the placebo group also received denosumab for 24 months. Importantly, these BMD gains observed in patients who initially received romosozumab were associated with significant reductions in new vertebral and clinical fracture risk compared with women who initially received placebo, and these fracture risk reductions were also maintained with continued denosumab administration through 36 months. At 36 months, very low fracture rates were observed in women treated with romosozumab for the first 12 months of the study.

These observations suggest that attaining a higher BMD and improving bone microarchitecture within 1 year of romosozumab treatment^(26–31) is associated with rapid fracture risk reduction, which is sustained upon transition to antiresorptive therapy, and support the clinical benefit of rebuilding skeletal mass and structure (ie, the foundation effect) with romosozumab for 12 months resulting in fewer fractures upon transition to denosumab.⁽³²⁾ This sequence of therapy—a bone-forming agent first, followed by an antiresorptive agent—may be particularly beneficial for patients at high risk for fracture.⁽²⁰⁾ Indeed, there is a growing body of literature suggesting that some high-risk patients may be at imminent risk of fracture (ie, in the next 1 to 2 years) on the basis of clinical characteristics such as recent fracture, older age, and lower BMD,^(4–12) and these

Table 2. Subject Incidence of Adverse Events Through 36 Months

	Placebo-to-denosumab (N = 3576) n (%)	Romosozumab-to-denosumab (N = 3581) n (%)
All treatment-emergent adverse events	3182 (89.0)	3156 (88.1)
Most frequent treatment-emergent adverse events ^a		
Arthralgia	666 (18.6)	668 (18.7)
Nasopharyngitis	622 (17.4)	651 (18.2)
Back pain	577 (16.1)	521 (14.5)
Fall	544 (15.2)	489 (13.7)
Pain in extremity	407 (11.4)	418 (11.7)
Hypertension	421 (11.8)	395 (11.0)
Serious adverse events	733 (20.5)	728 (20.3)
Positively adjudicated serious cardiovascular adverse events ^b	124 (3.5)	128 (3.6)
Death	85 (2.4)	72 (2.0)
Adjudicated cardiovascular deaths ^b	50 (1.4)	43 (1.2)
Leading to study drug discontinuation	130 (3.6)	138 (3.9)
Leading to study discontinuation	64 (1.8)	64 (1.8)
Events of interest ^c		
Hypocalcemia	3 (<0.1)	9 (0.3)
Injection-site reaction	107 (3.0)	189 (5.3)
Hypersensitivity	375 (10.5) ^d	370 (10.3) ^d
Malignancy	121 (3.4)	126 (3.5)
Osteoarthritis	497 (13.9)	488 (13.6)
Hyperostosis	58 (1.6)	49 (1.4)
Atypical femoral fracture ^b	0 (0)	1 (<0.1)
Osteonecrosis of the jaw ^b	0 (0)	2 (<0.1)

The subject incidence rates include all events that occurred in the 12-month double-blind period and, in addition, all events that occurred in the open-label and extension periods for those subjects who received at least one dose of denosumab.

N = number of subjects randomized and received at least one dose of the study drug in the 12-month double-blind study period; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA query.

^aMost frequent adverse events occurring in $\geq 10\%$ of subjects in either treatment group.

^bIncludes adverse events adjudicated positive by an independent adjudication committee. Cardiovascular deaths include fatal events adjudicated as cardiovascular-related or undetermined (presumed cardiac-related).

^cIdentified by prespecified search strategies using MedDRA version 19.1. Hypocalcemia, injection site reaction, osteoarthritis, and hyperostosis (preferred term exostosis) include only treatment-emergent adverse events as a result of a narrow search/scope in SMQs. Hypersensitivity and malignancy include only treatment-emergent adverse events as a result of a narrow search/scope in SMQs.

^dSerious adverse events of hypersensitivity were reported in 10 subjects who had received romosozumab followed by denosumab and in 4 subjects who had received placebo followed by denosumab.

patients may particularly benefit from bone-forming therapy prior to antiresorptive therapy. The advantage of this sequential approach compared with starting with an antiresorptive agent was recently confirmed in another large fracture trial in which romosozumab for 12 months followed by alendronate versus alendronate alone resulted in superior fracture risk reductions for all fracture types.⁽³³⁾ As a result of BMD increases on therapy, fewer patients were considered to have osteoporosis at the end of the study (defined by *T*-score; from 62.8% at baseline to 20.3% at 36 months at the lumbar spine and 53.1% to 14.3% at the total hip in the romosozumab-to-denosumab group and from 60.5% at baseline to 42.9% at 36 months at the lumbar spine and 51.9% to 30.0% at the total hip in the placebo-to-denosumab group; Supporting Table 2) and, therefore, decreasing annual fracture incidence rates were observed overall as the study continued. Despite fracture risk reductions in both groups, the positive fracture relative risk reductions with romosozumab versus placebo persisted through 36 months. A recent qualitative analysis has reported that increases in *T*-score achieved in the first 2 years of FRAME approximated the BMD gains observed after roughly 7 years of continuous denosumab administration

in the FREEDOM trial and its Extension, and the observed reductions in new vertebral, major osteoporotic, and other fracture types support the beneficial effect of adding skeletal mass and an improvement in bone microarchitecture with romosozumab before transitioning to antiresorptive therapy with denosumab.⁽¹⁶⁾

The adverse events profile remained similar between the primary analysis at 24 months and the final analysis at 36 months. In particular, the incidence of hypocalcemia, hypersensitivity, malignancy, osteoarthritis, and hyperostosis was similar between the groups. No additional positively adjudicated cases of AFF or ONJ were observed since the reporting of the 24-month data. In this large study, no imbalance in adjudicated cardiovascular serious adverse events was detected between romosozumab and placebo either in the first 12 months or during follow-up through 36 months when all subjects had transitioned to denosumab.

As reported, through 12 months, romosozumab significantly reduced new vertebral fracture risk in Rest-of-World (74% reduction; $p < 0.001$) and Latin America (70% reduction; $p = 0.014$).⁽²⁴⁾ Through the 12-month time point for

nonvertebral fracture, risk reduction was observed in Rest-of-World (42% reduction; $p = 0.012$) whereas no treatment effect was observed in Latin America (25% relative risk increase; $p = 0.47$), where background nonvertebral fracture risk was low (1.2% in the placebo group).⁽²⁴⁾ These regional differences reported in the primary analysis⁽²³⁾ with respect to a lower nonvertebral fracture rate in Latin America compared with the Rest-of-World populations were also observed through 36 months, but the treatment-by-region interaction was not statistically significant at that time point. Consistent reduction in fracture rate across all key endpoints, including nonvertebral fracture, was observed in a large active-controlled phase 3 study (NCT01631214) of romosozumab versus alendronate,⁽³³⁾ where a large subset of patients from countries in Latin America were also included, likely due to the higher risk postfracture population enrolled in that study.

One limitation of the study is lack of follow-up after study completion, after which patients resumed routine care with their physicians. As osteoporosis is a chronic disease, ongoing management of patients at high risk for fracture is required to prevent future fractures. Both romosozumab and denosumab are reversible treatments for osteoporosis, as are all osteoporosis therapies over variable timeframes. Upon denosumab discontinuation, bone turnover markers transiently increase to above baseline levels, BMD returns toward baseline, and overall fracture risk returns to that of an untreated population, with an increased risk of multiple vertebral fractures, particularly in patients with a history of vertebral fracture.^(34–36) Guidelines suggest that high-risk patients continue to be treated^(37,38) and recommend continued therapy with denosumab for up to 10 years or follow-on bisphosphonate therapy, unless contraindicated, after denosumab discontinuation to mitigate the transient increase in bone turnover.^(36,38,39) Although many patients in FRAME reached a low-risk status due to substantial BMD gains on study, the benefits of therapy would be expected to wane without ongoing treatment with denosumab or an alternative antiresorptive therapy, as was shown in a recent case series.⁽³⁹⁾

In conclusion, the 3-year FRAME trial shows the positive effect of 12 doses of romosozumab to rapidly improve BMD and to decrease fracture risk, a benefit that can be maintained up to 36 months when romosozumab is followed by denosumab. This may offer patients at high risk of fracture—because of one or more clinical characteristics, including previous fracture, advanced age, and very low BMD—a valuable treatment approach, with both early and persistent fracture risk reduction benefits, and add to the body of evidence supporting the sequence of a bone-forming agent followed by an antiresorptive therapy for such high-risk patients.

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