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Effect of Romosozumab Treatment in Postmenopausal Women With Osteoporosis and Knee Osteoarthritis: Results From a Substudy of a Phase 3 Clinical Trial

Nancy E. Lane,[1] Donald Betah,[2] Cynthia Deignan,[2] Mary Oates,[2] Zhenxun Wang,[2] Jen Timoshanko,[3] Aliya A. Khan,[4] and Neil Binkley[5]

Objective. Romosozumab is a bone-forming agent approved for osteoporosis treatment. Here we report results of the protocol-specified, noninferiority osteoarthritis substudy of the fracture study in postmenopausal women with osteoporosis (FRAME), which evaluated the effect of romosozumab versus placebo on knee osteoarthritis in patients with a clinical history of osteoarthritis.

Methods. Women in FRAME with a history of knee osteoarthritis were eligible for enrollment in the osteoarthritis substudy; key inclusion criteria were osteoarthritis-related signal knee pain, morning stiffness lasting less than 30 minutes, knee crepitus, and knee osteoarthritis confirmed by x-ray within 12 months. The protocol-specified outcomes were change from baseline through month 12 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, incidence of worsening knee osteoarthritis, and treatment-emergent adverse events (TEAEs) with romosozumab versus placebo. In a post hoc analysis, percentage change from baseline to month 12 in bone mineral density (BMD) was assessed.

Results. Of 7180 women in FRAME, 347 participated in the osteoarthritis substudy (placebo, 177; romosozumab, 170). At month 12, no significant difference in progression of knee osteoarthritis was observed with romosozumab versus placebo (least squares mean total WOMAC score: –2.2 vs. –1.3; $P = 0.71$). Incidence of worsening symptoms of knee osteoarthritis was comparable between romosozumab (17.1%) and placebo (20.5%) (odds ratio 0.9 [95% confidence interval: 0.5, 1.7]; $P = 0.69$). Incidence of TEAEs of osteoarthritis was numerically lower with romosozumab (13 [7.7%]) versus placebo (21 [12.0%]). BMD gains were higher with romosozumab.

Conclusion. Romosozumab treatment did not impact knee pain or function in postmenopausal women with osteoporosis and knee osteoarthritis and resulted in significant BMD gains in these women.

INTRODUCTION

Osteoarthritis and osteoporosis are two of the most common skeletal diseases in the elderly and often occur concomitantly, with both associated with high economic and societal burden (1–3). Osteoarthritis is a slowly progressive degenerative disorder of joints characterized by cartilage damage, subchondral sclerosis, osteophyte formation, muscle weakness, and inflammation of synovial tissue and tendon (4,5). Osteoporosis is a metabolic disease characterized by loss of bone mineral density (BMD), disorders of bone microarchitecture, and decreased bone strength, leading to increased susceptibility to fractures (6–9). The relationship between osteoarthritis and osteoporosis is complex, with increased fracture risk reportedly associated with osteoarthritis (10).

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Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/.

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Romosozumab is an osteoanabolic with a dual effect of increasing bone formation while decreasing bone resorption (11,12). Romosozumab binds to and inhibits sclerostin (12), which is widely viewed as an osteocyte-specific protein but is also expressed in articular chondrocytes (13). Sclerostin expression is focally increased in cartilage in osteoarthritis while being decreased in the subjacent subchondral bone (13).

Treatment with monthly subcutaneous romosozumab at 210 mg for 12 months in postmenopausal women with osteoporosis produced significantly larger gains in lumbar spine and total hip BMD (11,14) and reduced fracture risk compared with treatment with placebo in fracture study in postmenopausal women with osteoporosis (FRAME) (15) or with alendronate in ARCH (16). These improvements were maintained when romosozumab was followed by an antiresorptive, specifically denosumab (a fully human monoclonal antibody against RANKL) in FRAME (15) or alendronate (an oral bisphosphonate) in Active-controlled fracture study in postmenopausal women with osteoporosis (ARCH) (16). Further analysis of FRAME and ARCH data showed that 12 months of treatment with romosozumab compared with placebo in FRAME or alendronate in ARCH resulted in significantly greater gains in hip cortical and trabecular bone parameters, including cortical thickness, cortical volumetric BMD (vBMD), cortical surface BMD, and trabecular vBMD (Lewiecki et al: unpublished observations) and lumbar spine trabecular vBMD, bone mineral content, and bone strength (17,18).

The efficacy of romosozumab in promoting bone formation and reducing fracture risk by influencing changes of bone microarchitecture has been clearly established. However, to date, there are no data from a randomized clinical trial directly addressing whether romosozumab treatment might impact clinical progression of osteoarthritis. This possibility arises from three factors: 1) the target of romosozumab, sclerostin, is also expressed in articular chondrocytes (12,13); 2) sclerostin expression has been shown to be focally increased in cartilage in osteoarthritis (13); and 3) worsening osteoarthritis is accompanied by promotion of bone mass at the bone margins to form osteophytes that increase joint pain (19,20). To evaluate the effect of romosozumab on the clinical progression of osteoarthritis, FRAME included a protocol-specified, noninferiority osteoarthritis substudy to assess the effect of 12 months of treatment with romosozumab compared with placebo on the progression of osteoarthritis of the knee in postmenopausal women with osteoporosis and knee osteoarthritis. The knee was selected for evaluation because it represents an anatomic location where osteoarthritis results in significant morbidity and because the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) has been well validated as a patient-reported outcomes instrument to assess clinical progression of osteoarthritis in the knee and hip (21).

In this article, we report results for the FRAME protocol-specified osteoarthritis substudy assessing change in knee pain and physical function, worsening symptoms of knee osteoarthritis, and treatment-emergent adverse events (TEAEs) of osteoarthritis (FRAME Osteoarthritis Substudy). We also report results from a post hoc analysis assessing change in BMD at the lumbar spine, total hip, and femoral neck in the FRAME Osteoarthritis Substudy.

PATIENTS AND METHODS

Study design and patients. FRAME (ClinicalTrials.gov identifier NCT01575834) (15) randomized 7180 postmenopausal women aged 55 to 90 years with a T score of –2.5 to –3.5 at the total hip or femoral neck to receive double-blinded monthly subcutaneous romosozumab doses of 210 mg or placebo for 12 months, after which both groups received an open-label subcutaneous denosumab dose of 60 mg every 6 months for an additional 12 months (Figure 1A). The coprimary end points were the cumulative incidences of new vertebral fractures at 12 and 24 months, and key secondary end points included incidences of clinical and nonvertebral fractures; data for these outcomes were previously published (15). The trial protocol for FRAME was approved by an ethics committee or institutional review board at each trial center, and the study was conducted in compliance with ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent.

This article reports data from the protocol-specified FRAME osteoarthritis substudy, which assessed the effect of romosozumab treatment for 12 months on women in FRAME who had knee osteoarthritis. The planned sample size for the FRAME osteoarthritis substudy was up to 300 women (placebo, 150 women; romosozumab, 150) (Figure 1B). Women were included in the FRAME osteoarthritis substudy if they provided informed consent to participate in the substudy and had signal knee pain due to osteoarthritis on most days for 1 month or more within 3 months prior to randomization, morning stiffness lasting less than 30 minutes, presence of knee crepitus, or knee osteoarthritis confirmed by x-ray within 12 months prior to randomization. Women were excluded if they could not complete the WOMAC questionnaire or received intraarticular knee injection of corticosteroids or hyaluronan preparations within 3 months prior to randomization. Based on a previous study showing a link between excess weight and osteoarthritis, particularly in the knee joints (22), women were excluded if they had a body mass index (BMI) greater than 40 to control for that variable and confounding effect. Additionally, women were also excluded if they had a history of medical conditions, including knee arthroplasty (or were expected to require knee arthroplasty because of symptoms of osteoarthritis within 12 months of randomization), inflammatory arthritis (including rheumatoid arthritis or psoriatic arthritis), pseudogout or gouty arthropathy, meniscal or gouty arthropathy within 12 months prior to randomization, or knee fracture or other clinically significant trauma or knee surgery to the index knee, or if they had any other

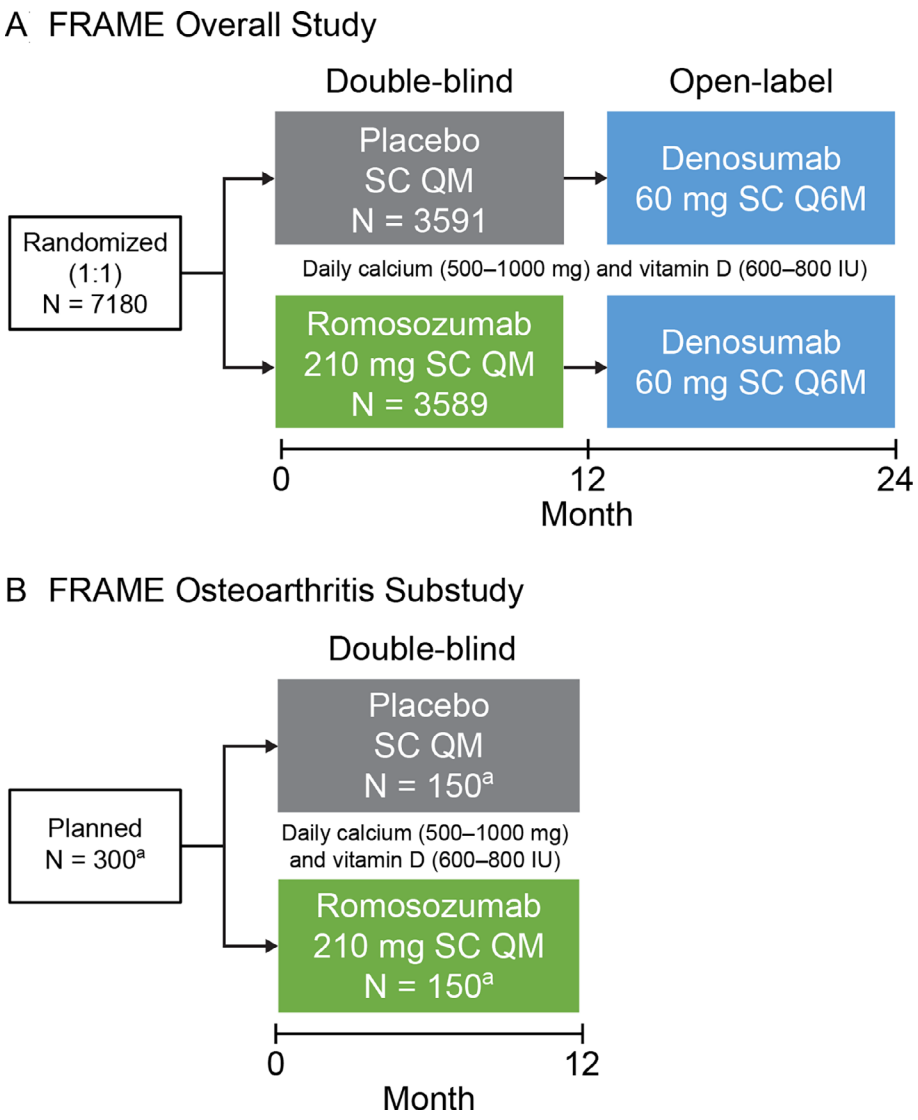

Figure 1. Study designs. **A**, FRAME overall study. **B**, Planned FRAME Osteoarthritis Substudy. N = number of women randomized or planned. [a]The planned sample size for the FRAME Osteoarthritis Substudy was up to 300 women (placebo, 150; romosozumab, 150); the actual number enrolled was 347 (placebo, 177; romosozumab, 170). A total of 343 women received at least one dose of the investigational product and had at least one WOMAC questionnaire result and were included in the current analysis (placebo, 175; romosozumab, 168). FRAME, Fracture Study in Postmenopousal Women With Osteoporosis; QM, monthly; Q6M, every 6 months; SC, subcutaneous; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

medical condition that, in the opinion of the investigator, could confound evaluation of the index knee.

Study outcomes. Protocol-specified assessments included change from baseline to month 12 in the WOMAC score (total, knee pain, and physical function), incidence of worsening knee osteoarthritis (defined as an increase in the WOMAC total score of ≥10 points) through month 12, and TEAEs of osteoarthritis (including newly diagnosed events or worsening of existing disease) through month 12. The WOMAC subscale and total scores were normalized to a 100-point scale, and the effect size cutoff value of 10 points between groups is consistent with the range of minimal clinically important difference (MCID) previously reported (21). Each normalized subscale score was calculated separately within the subscale by averaging scores of the questions answered, and the normalized total score was calculated by averaging the total questions answered. BMD percentage change from baseline to month 12 at the lumbar spine, total hip, and femoral neck was assessed as a post hoc analysis.

Statistical analysis. Considering a planned sample size of up to 300 women for the FRAME osteoarthritis substudy, we calculated that the substudy would have greater than or equal

to 90% power for testing noninferiority of romosozumab and placebo on the WOMAC total score change from baseline to month 12. The calculated statistical power is under the assumption of 7.5% dropout over the 12-month, double-blind, placebo-controlled study period and a 23-point standard deviation of the WOMAC total score change from baseline. The noninferiority testing is based on a two-sided 95% confidence interval (95% CI) for the treatment difference in the mean WOMAC total score change from baseline and a 10-point margin, which is the MCID for the total WOMAC score (21).

WOMAC score change from baseline was assessed by analysis of covariance (ANCOVA), and incidence of worsening knee osteoarthritis was assessed by logistic regression with adjustment for age, baseline BMI, and baseline WOMAC total score for both statistical models. BMD percentage change from baseline at the lumbar spine, total hip, and femoral neck was assessed by ANCOVA with adjustment for age and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction. All *P* values were nominal, and no adjustments for multiplicity were made for all statistical models.

RESULTS

Patients and baseline characteristics. Of the 7180 women enrolled in FRAME, 736 (placebo, 376; romosozumab, 360) were screened for the FRAME osteoarthritis substudy; 389 (placebo, 199; romosozumab, 190) did not meet the inclusion/exclusion criteria (Table 1). The most common reasons for exclusion from the substudy were lack of knee pain and morning stiffness (Table 1). Of the remaining 347 women (placebo, 177; romosozumab, 170), 343 (placebo, 175; romosozumab, 168) received one or more doses of the investigational product and had one or more WOMAC questionnaire results and therefore qualified for inclusion in the current analysis (Figure 2). The actual sample size for the substudy was higher than the planned 300 women (placebo, 150; romosozumab, 150).

Most baseline characteristics for women in the FRAME osteoarthritis substudy were consistent with baseline characteristics for the FRAME overall population (Table 2). Mean age was 71.9 years, and mean baseline T scores were –2.6 at the lumbar spine, –2.5 at the total hip, and –2.7 at the femoral neck. Less than 20% of the women had a prevalent vertebral fracture (19.0%) at baseline. However, differences in racial composition were noted between the FRAME osteoarthritis substudy population and the FRAME overall population, with a higher proportion of White women (84.3% vs. 57.3%) and lower proportions of women of other racial background (13.4% vs. 25.1%) and Asian women (0.9% vs. 12.1%) enrolled in the FRAME osteoarthritis substudy. Baseline WOMAC scores were determined for the FRAME osteoarthritis substudy patient population only and not for the FRAME overall population. In the FRAME osteoarthritis

Table 1. Reasons for exclusion from the FRAME osteoarthritis substudy

Reason for exclusion	Placebo N = 199 n (%)	Romosozumab N = 190 n (%)
No signal knee pain due to osteoarthritis on most days for at least 1 month within 3 months prior to randomization	98 (49.2)	91 (47.9)
No morning stiffness lasting <30 minutes	56 (28.1)	50 (26.3)
No knee osteoarthritis confirmed by knee x-ray within the past 12 months, to be read and interpreted by principal investigator or qualified delegate	30 (15.1)	20 (10.5)
Not available for protocol-required study visits or procedures, to the best of the participant's and investigator's knowledge	28 (14.1)	26 (13.7)
No knee osteoarthritis confirmed by knee x-ray, to be read and interpreted by principal investigator or qualified delegate	23 (11.6)	27 (14.2)
No presence of knee crepitus	18 (9.0)	14 (7.4)
Unable to complete the WOMAC	6 (3.0)	7 (3.7)
No informed consent for participation in this substudy	4 (2.0)	1 (0.5)
History of meniscal or gouty arthropathy within 12 months prior to randomization	1 (0.5)	0 (0.0)
Any other medical condition that in the opinion of the investigator could confound evaluation of the index knee	1 (0.5)	0 (0.0)
History of knee arthroplasty (either knee) or expected to require knee arthroplasty because of symptoms of osteoarthritis within 12 months of randomization	0 (0.0)	3 (1.6)
History of pseudogout or gouty arthropathy	0 (0.0)	1 (0.5)
Intraarticular knee injection of corticosteroids or hyaluronan preparations within 3 months prior to randomization	0 (0.0)	2 (1.1)

Note: N = number of women who did not meet the inclusion/exclusion criteria. n = number of women for each inclusion/exclusion criterion. Women could have more than one inclusion/exclusion criterion; therefore, incidence rates for individual criteria may not sum to the total for a given category.
Abbreviations: FRAME, fracture study in postmenopausal women with osteoporosis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

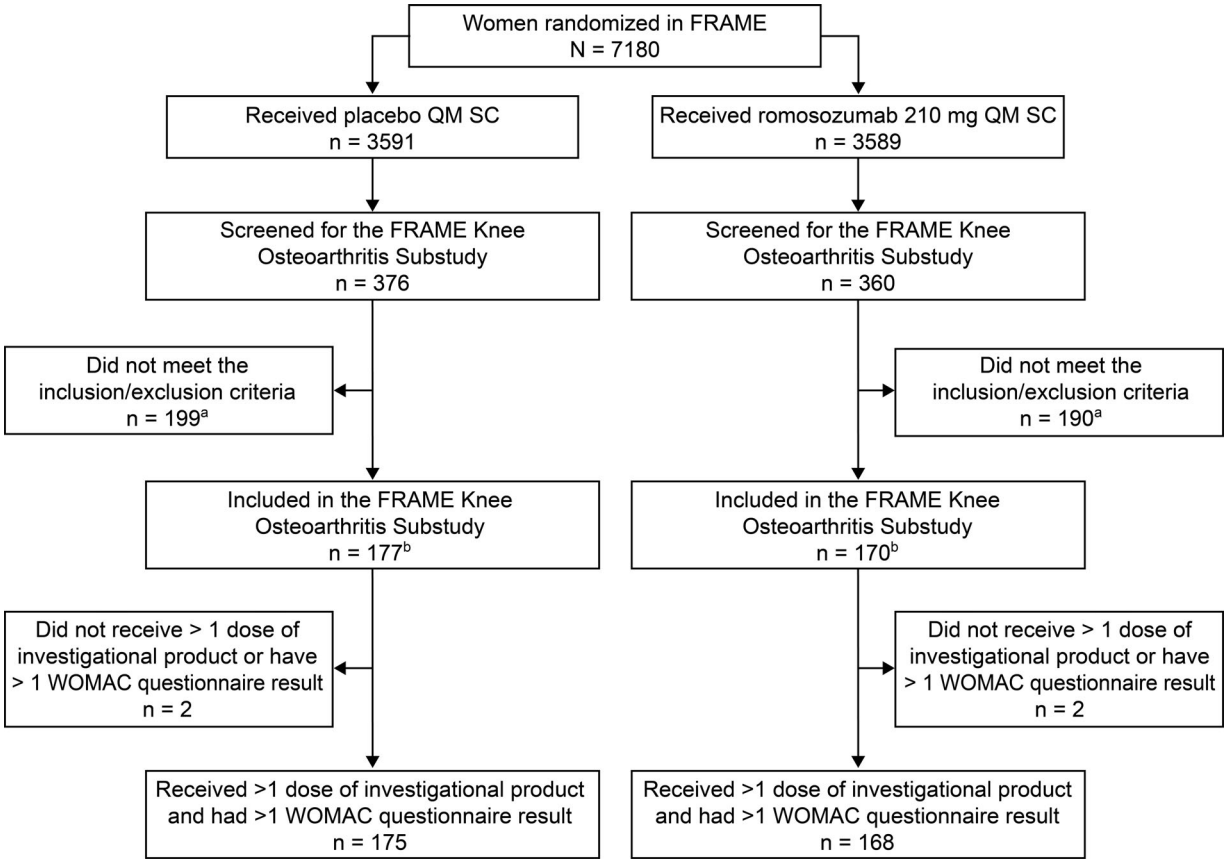

Figure 2. Patient disposition in the FRAME osteoarthritis substudy. [a]Reasons for exclusion from the substudy are shown in Table 1. [b]The planned sample size for the FRAME osteoarthritis substudy was up to 300 women (placebo, 150; romosozumab, 150); however, a total of 347 women participated in the substudy (placebo, 177; romosozumab, 170). FRAME, fracture study in postmenopausal women with osteoporosis; QM, monthly; SC, subcutaneous; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Baseline characteristics

	FRAME osteoarthritis substudy population[a]		FRAME overall population	
Characteristic	Placebo N = 175	Romosozumab N = 168	Placebo N = 3591	Romosozumab N = 3589
Age, mean ± SD years	71.9 ± 7.2	71.8 ± 6.9	70.8 ± 6.9	70.9 ± 7.0
Race, n (%)				
White	149 (85.1)	140 (83.3)	2052 (57.1)	2063 (57.5)
Other	22 (12.6)	24 (14.3)	901 (25.1)	900 (25.1)
Asian	2 (1.1)	1 (0.6)	441 (12.3)	425 (11.8)
Black or African American	2 (1.1)	3 (1.8)	74 (2.1)	77 (2.1)
American Indian or Alaska Native	0 (0)	0 (0)	63 (1.8)	64 (1.8)
Multiple	0 (0)	0 (0)	59 (1.6)	60 (1.7)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	1 (< 0.1)	0 (0)
T score, mean ± SD				
Lumbar spine	−2.7 ± 1.2	−2.6 ± 1.0	−2.7 ± 1.0	−2.7 ± 1.0
Total hip	−2.5 ± 0.5	−2.5 ± 0.5	−2.5 ± 0.5	−2.5 ± 0.5
Femoral neck	−2.7 ± 0.3	−2.8 ± 0.3	−2.7 ± 0.3	−2.8 ± 0.3
Prevalent vertebral fracture, n (%)	30 (17.1)	35 (20.8)	645 (18.0)	672 (18.7)
WOMAC score, mean ± SD				
Total	36.7 ± 25.0	39.4 ± 24.1	ND	ND
Pain	35.8 ± 25.8	37.1 ± 25.1	ND	ND
Physical function	37.0 ± 25.8	40.3 ± 25.1	ND	ND

Abbreviations: FRAME, fracture study in postmenopausal women with osteoporosis; ND, not determined; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[a]Women enrolled in the FRAME osteoarthritis substudy who received ≥1 dose of the investigational product and had ≥1 WOMAC questionnaire result.

Table 3. WOMAC score change from baseline to month 12

WOMAC score	Least squares mean (95% CI) change from baseline to month 12			
	Placebo N = 175	Romosozumab N = 168	Difference (romosozumab minus placebo)	Nominal *P* value
Total	−1.3 (−4.5, 1.9) [n = 122]	−2.2 (−5.4, 1.0) [n = 123]	−0.9 (−5.4, 3.7)	0.71
Pain	−0.6 (−4.1, 3.0) [n = 122]	−1.1 (−4.5, 2.3) [n = 128]	−0.6 (−5.5, 4.4)	0.82
Physical function	−1.0 (−4.5, 2.4) [n = 123]	−2.8 (−6.2, 0.6) [n = 123]	−1.8 (−6.6, 3.1)	0.47

Note: N = number of women enrolled in the FRAME osteoarthritis substudy who received ≥1 dose of the investigational product and had ≥1 WOMAC questionnaire result. n = number of women with evaluable data. *P* values were based on a two-sided test from the ANCOVA model adjusted for age, baseline BMI, and baseline WOMAC total score and were nominal without multiplicity adjustment.
Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; FRAME, fracture study in postmenopausal women with osteoporosis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

substudy population, the baseline total WOMAC score was 38.0, with a pain WOMAC score of 36.4 and a physical function WOMAC score of 38.7.

WOMAC score change from baseline to month 12. No significant difference in progression of knee pain or physical function was observed with 12 months of treatment with romosozumab versus placebo at month 12 (Table 3). The least squares (LS) mean for the WOMAC total score was –2.2 (95% CI –5.4, 1.0) with romosozumab versus –1.3 (95% CI –4.5, 1.9) with placebo (*P* = 0.71). The LS mean for the WOMAC pain score for romosozumab versus placebo was –1.1 (95% CI –4.5, 2.3) versus –0.6 (95% CI –4.1, 3.0) (*P* = 0.82), and the LS mean for the WOMAC physical function score for romosozumab versus placebo was –2.8 (95% CI –6.2, 0.6) versus –1.0 (95% CI –4.5, 2.4; *P* = 0.47).

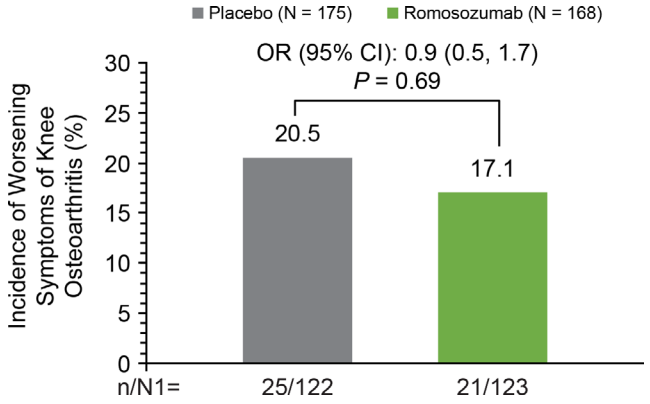

Figure 3. Incidence of worsening symptoms of knee osteoarthritis through month 12. N = number of women enrolled in the FRAME osteoarthritis substudy who received one or more doses of the investigational product and had one or more WOMAC questionnaire results. N1 = number of women enrolled in the FRAME osteoarthritis substudy with one or more doses of the investigational product and a nonmissing WOMAC total score at both baseline and post baseline. n = number of women with worsening symptoms of knee osteoarthritis. Based on the logistic regression model adjusted for age, baseline BMI, and baseline WOMAC total score; the *P* value is based on the test score. BMI, body mass index; CI, confidence interval; FRAME, fracture study in postmenopausal women with osteoporosis; OR, odds ratio; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Incidence of worsening symptoms of knee osteoarthritis at month 12. Incidence of worsening symptoms of knee osteoarthritis was comparable between romosozumab and placebo at month 12 (Figure 3), with romosozumab having a slightly lower numerical incidence of worsening symptoms than placebo (17.1% [21 of 123 women] with romosozumab and 20.5% [25 of 122 women] with placebo; odds ratio 0.9 [95% CI 0.5, 1.7]; *P* = 0.69).

Incidence of TEAEs of osteoarthritis through month 12. The incidence of all TEAEs of osteoarthritis was numerically lower with romosozumab than with placebo through

Table 4. Incidence of TEAEs of osteoarthritis through month 12

Event type	Placebo N = 175	Romosozumab N = 168
All TEAEs of osteoarthritis,[a] n (%)	21 (12.0)	13 (7.7)
Osteoarthritis	16 (9.1)	10 (6.0)
Spinal osteoarthritis	5 (2.9)	3 (1.8)
Arthritis	3 (1.7)	1 (0.6)
Monoarthritis	0 (0)	1 (0.6)

Note: N = number of women enrolled in the FRAME osteoarthritis substudy who received ≥1 dose of the investigational product and had ≥1 WOMAC questionnaire result. TEAEs of osteoarthritis were identified by the MedDRA Event of Interest search strategy during the double-blind period. Preferred terms were coded using MedDRA version 18.1.
Abbreviations: FRAME, fracture study in postmenopausal women with osteoporosis; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[a]TEAEs included newly diagnosed events or worsening of existing disease.

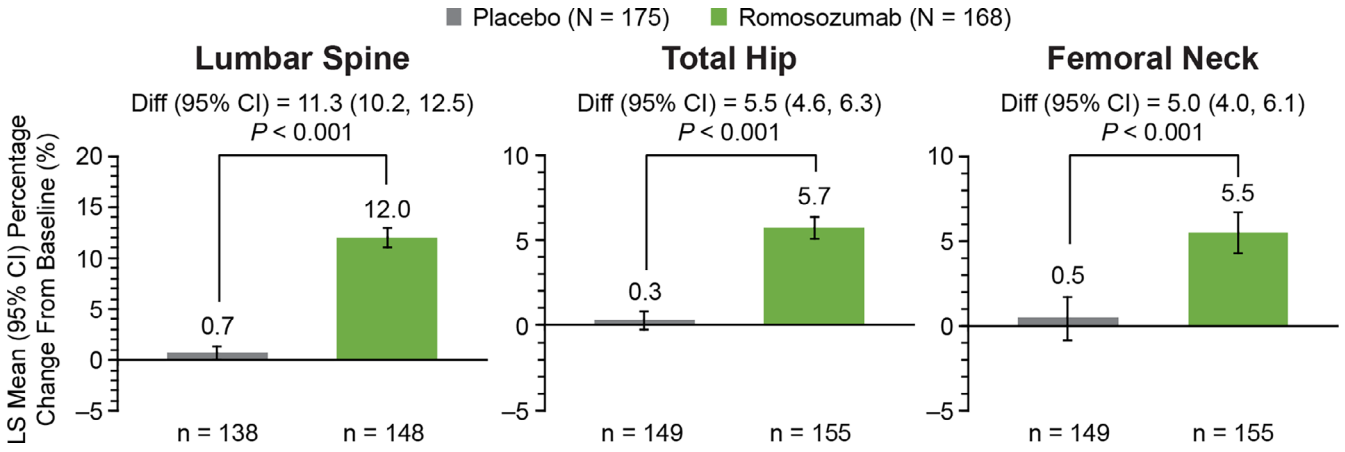

Figure 4. BMD percentage change from baseline to month 12 at the lumbar spine, total hip, and femoral neck. N = number of women enrolled in the FRAME osteoarthritis substudy who received one or more doses of the investigational product and had one or more WOMAC questionnaire results. n = number of women with evaluable data. Based on the ANCOVA model adjusted for age and prevalent vertebral fracture stratification variables, baseline value, machine type, and baseline value-by-machine type interaction. Missing values were imputed by carrying forward the last nonmissing postbaseline value. ANCOVA, analysis of covariance; BMD, bone mineral density; CI, confidence interval; Diff, difference for romosozumab minus placebo; FRAME, fracture study in postmenopausal women with osteoporosis; LS, least squares; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

month 12, with 13 (7.7%) TEAEs reported with romosozumab and 21 (12.0%) with placebo (Table 4). TEAEs of osteoarthritis reported with romosozumab and placebo included osteoarthritis (6.0% and 9.1%, respectively), spinal osteoarthritis (1.8% and 2.9%, respectively), arthritis (0.6% and 1.7%, respectively), and monoarthritis (0.6% and 0%, respectively).

BMD percentage change from baseline to month 12 at the lumbar spine, total hip, and femoral neck. At month 12, mean BMD gains were significantly higher with romosozumab than with placebo at the lumbar spine, total hip, and femoral neck (Figure 4). At the lumbar spine, a net mean BMD gain with romosozumab of 11.3% (12.0% romosozumab vs. 0.7% placebo; $P < 0.001$) was observed. Net mean BMD gains at the total hip of 5.5% (5.7% romosozumab vs. 0.3% placebo; $P < 0.001$) and at the femoral neck of 5.0% (5.5% romosozumab vs. 0.5% placebo; $P < 0.001$) were observed.

DISCUSSION

Results from our analysis of the impact of treatment with romosozumab for 12 months compared with placebo in postmenopausal women with osteoporosis and knee osteoarthritis showed no significant difference in progression of knee pain or physical function between treatment groups. Incidence of worsening symptoms of knee osteoarthritis was comparable between romosozumab and placebo, with romosozumab having a slightly lower numerical incidence of worsening symptoms than placebo. Incidence of TEAEs of osteoarthritis was numerically lower with romosozumab than with placebo. At month 12, treatment with romosozumab resulted in significantly greater BMD gains at the lumbar spine, total hip, and femoral neck compared with treatment with placebo.

The current substudy, included as part of a randomized clinical trial, was conducted to evaluate the effect of romosozumab treatment in postmenopausal women with osteoporosis and knee osteoarthritis, arising from the fact that romosozumab binds to and inhibits sclerostin and that sclerostin expression has been shown to be focally increased in cartilage in osteoarthritis (12,13). At a molecular level, there is a possibility that romosozumab inhibition of sclerostin might impair cartilage function in osteoarthritis or that increases in BMD could lead to bone microarchitectural changes that may result in worsening of osteoarthritis. However, results from our analysis showed that even though romosozumab led to the expected BMD gains, this was not associated with worsening of knee osteoarthritis.

Some US-based studies have reported a higher prevalence of knee osteoarthritis in Black patients compared with White patients (23–25), with few comparisons of knee osteoarthritis prevalence in other racial and ethnic groups. A comparison of knee osteoarthritis prevalence in White versus Black patients could not be evaluated in our analysis because the FRAME population enrolled a small number of Black women (151 of 7180 women [2.1%]) versus the large proportion of White women enrolled (4115 of 7180 women [57.3%]); of the 151 Black women, only five were enrolled in the knee osteoarthritis substudy compared with 289 White women. However, we observed that knee osteoarthritis incidence was higher among White women compared with Asian women or women of other ethnic

backgrounds. Our finding that White women had a higher prevalence of knee osteoarthritis than Asian women differs from findings from other studies. One study reported a higher prevalence of radiographic and symptomatic knee osteoarthritis in Chinese women aged 60 years and older in Beijing than in White women of the same age in the US (26). Another study reported a higher prevalence of age-adjusted knee osteoarthritis in Japanese women than in White women (27). The reason for the differences in findings from our analysis and published results is not clear. Of note, our analysis was descriptive and not designed to address racial and ethnic prevalence of knee osteoarthritis in the FRAME population. Our findings that romosozumab had no impact on progression of osteoarthritis of the knee in this group of patients and that these patients achieved significant BMD gains at all skeletal sites with 12 months of treatment warrant confirmation in protocol-specified studies with larger populations to further evaluate the safety of romosozumab in patients with osteoporosis and knee osteoarthritis. Additionally, studies evaluating romosozumab's safety in patients with hip arthritis, hand arthritis, or spine arthritis are needed because clinical characteristics of these conditions may be different from those of knee arthritis.

The strength of our analysis is that the impact of treatment with romosozumab on the progression of osteoarthritis of the knee in postmenopausal women with osteoporosis and knee osteoarthritis was evaluated in a protocol-specified, noninferiority substudy of a randomized controlled trial with standardized assessment of WOMAC scores and incidence of worsening knee osteoarthritis. Additionally, the preplanned noninferiority margin was determined by the MCID, which was 10 for the total WOMAC score (21). However, a limitation of our analysis is that knee radiographs were not obtained, raising the potential for misclassification of pain from musculoskeletal diseases at other sites, such as referred from the hip and the lumbar spine, as knee pain. An additional limitation is that patient use of nonsteroidal anti-inflammatory drugs (NSAIDs) at baseline, which might impact reporting of knee pain, was not captured in our analysis. Therefore, additional studies that include weight-bearing knee radiographs and baseline NSAID use would help confirm or refute the findings from our analysis.

Results from our analysis showed that romosozumab treatment did not impact knee pain or function in postmenopausal women with osteoporosis and knee osteoarthritis and also resulted in significant BMD gains in those women.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors had full access to all of the data in the study, and Drs. Lane, Oates, and Wang take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lane, Betah, Deignan, Oates.

Acquisition of data. Lane, Khan, Binkley.

Analysis and interpretation of data. Lane, Betah, Deignan, Oates, Wang, Timoshanko, Khan, Binkley.

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ROLE OF THE STUDY SPONSOR

Amgen Inc. and UCB Pharma had a role in the study design, analysis, and interpretation of the data. Publication was not contingent upon approval by Amgen Inc. or UCB Pharma.

ADDITIONAL DISCLOSURES

Authors Betah, Deignan Oates, and Wang are employees of Amgen Inc. Author Jen Timoshanko is an employee of UCB Pharma.

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