ORIGINAL ARTICLE

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

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ABSTRACT

BACKGROUND

Romosozumab, a monoclonal antibody that binds sclerostin, increases bone formation and decreases bone resorption.

METHODS

We enrolled 7180 postmenopausal women who had a T score of –2.5 to –3.5 at the total hip or femoral neck. Patients were randomly assigned to receive subcutaneous injections of romosozumab (at a dose of 210 mg) or placebo monthly for 12 months; thereafter, patients in each group received denosumab for 12 months, at a dose of 60 mg, administered subcutaneously every 6 months. The coprimary end points were the cumulative incidences of new vertebral fractures at 12 months and 24 months. Secondary end points included clinical (a composite of nonvertebral and symptomatic vertebral) and nonvertebral fractures.

RESULTS

At 12 months, new vertebral fractures had occurred in 16 of 3321 patients (0.5%) in the romosozumab group, as compared with 59 of 3322 (1.8%) in the placebo group (representing a 73% lower risk with romosozumab; P<0.001). Clinical fractures had occurred in 58 of 3589 patients (1.6%) in the romosozumab group, as compared with 90 of 3591 (2.5%) in the placebo group (a 36% lower risk with romosozumab; P=0.008). Nonvertebral fractures had occurred in 56 of 3589 patients (1.6%) in the romosozumab group and in 75 of 3591 (2.1%) in the placebo group (P=0.10). At 24 months, the rates of vertebral fractures were significantly lower in the romosozumab group than in the placebo group after each group made the transition to denosumab (0.6% [21 of 3325 patients] in the romosozumab group vs. 2.5% [84 of 3327] in the placebo group, a 75% lower risk with romosozumab; P<0.001). Adverse events, including instances of hyperostosis, cardiovascular events, osteoarthritis, and cancer, appeared to be balanced between the groups. One atypical femoral fracture and two cases of osteonecrosis of the jaw were observed in the romosozumab group.

CONCLUSIONS

In postmenopausal women with osteoporosis, romosozumab was associated with a lower risk of vertebral fracture than placebo at 12 months and, after the transition to denosumab, at 24 months. The lower risk of clinical fracture that was seen with romosozumab was evident at 1 year. (Funded by Amgen and UCB Pharma; FRAME ClinicalTrials.gov number, NCT01575834.)

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A list of the principal investigators in the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) is provided in the Supplementary Appendix, available at NEJM.org.

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Osteoporosis can lead to fragility fractures, which result in clinical burden and increased mortality.[1,2] Even after a fracture, fewer than 25% of patients receive pharmacologic treatment for osteoporosis.[3-5] After the discovery that sclerostin deficiency causes rare genetic conditions that are characterized by high bone mass and resistance to fracture,[6,7] sclerostin became a therapeutic target for the treatment of osteoporosis. Sclerostin, a negative regulator of bone formation that is secreted by osteocytes,[8] inhibits Wnt signaling, down-regulating this stimulus for osteoblast development and function.[9]

Romosozumab (Amgen and UCB Pharma) is a monoclonal antibody that binds and inhibits sclerostin, with a dual effect of increasing bone formation and decreasing bone resorption.[10,11] In a phase 2 trial involving postmenopausal women with low bone mass, treatment with romosozumab for 1 year (at a dose of 210 mg, administered subcutaneously monthly) significantly increased bone mineral density, with increases in levels of bone-formation markers over the first 6 to 9 months of treatment and persistent decreases in levels of bone-resorption markers.[10] On the basis of those results, we undertook a phase 3 trial that evaluated the effects of 1 year of romosozumab treatment on the risk of fracture among women with postmenopausal osteoporosis. Given evidence that bone mineral density is maintained or potentially increased after the transition from treatment with a bone-forming agent to treatment with an antiresorptive agent,[12,13] we also assessed follow-on therapy with denosumab as sequential treatment for osteoporosis.

Methods

Trial Design

The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) was an international, randomized, double-blind, placebo-controlled, parallel-group trial. Women were randomly assigned, in a 1:1 ratio, with the use of an interactive voice-response system, to receive romosozumab in a blinded fashion at a dose of 210 mg or placebo. Randomization was stratified according to age (<75 years vs. ≥75 years) and prevalent vertebral fracture (yes vs. no). Romosozumab or placebo was administered subcutaneously once monthly for 12 months, followed by open-label denosumab at a dose of 60 mg (Prolia, Amgen), which was administered subcutaneously every 6 months for an additional 12 months (Fig. 1). Patients, investigators, and sponsors remained unaware of the initial treatment assignment.

Trial Oversight

The trial protocol, available with the full text of this article at NEJM.org, was approved by an ethics committee or institutional review board at each trial center. Patients provided written informed consent. Amgen and UCB Pharma designed the trial, and Amgen was responsible for trial oversight. An external independent data and safety monitoring committee monitored unblinded safety data. Amgen conducted the data analyses according to a prespecified statistical analysis plan.

Three of the authors (one academic author and two employees of Amgen) vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of the trial to the protocol. The authors had access to the data, with agreements relating to data confidentiality. The first two authors wrote the first draft of the manuscript, with assistance from professional medical writers who were funded by Amgen. All the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication.

Patients

Ambulatory postmenopausal women, 55 to 90 years of age, with a T score of −2.5 to −3.5 at the total hip or femoral neck were eligible for participation. Patients had to have at least two vertebrae in the L1 through L4 region and at least one hip that could be evaluated by means of dual-energy x-ray absorptiometry. Women who had a history of hip fracture, any severe or more than two moderate vertebral fractures, a history of metabolic bone disease or conditions affecting bone metabolism, osteonecrosis of the jaw, a 25-hydroxyvitamin D level of less than 20 ng per milliliter, current hypercalcemia or hypocalcemia, or recent use of drugs affecting bone metabolism (within defined washout periods; see the protocol) were excluded. For patients in whom the baseline serum 25-hydroxyvitamin D level was 40 ng per milliliter or less, a loading dose of 50,000 to 60,000 IU of vitamin D was administered at the

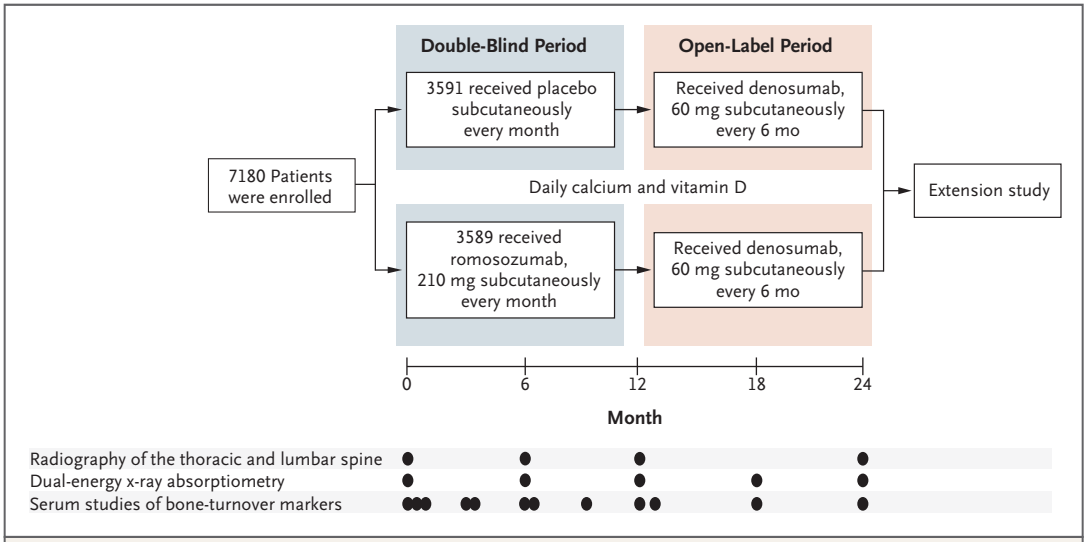


Figure 1. Trial Regimens and Assessments.

Women were randomly assigned, in a 1:1 ratio, to receive subcutaneous injections of 210 mg of romosozumab or placebo once monthly for 12 months during the double-blind phase of the trial. Patients then received open-label denosumab, administered subcutaneously at a dose of 60 mg every 6 months for an additional 12 months; the initial group assignment was still blinded. Patients were stratified according to age (<75 years vs. ≥75 years) and prevalent vertebral fracture (yes vs. no). In a substudy of the overall population that involved 128 patients, bone mineral density was assessed at baseline and every 6 months. In a substudy of the overall population that involved 129 patients, the levels of bone-turnover markers were assessed at baseline, at day 14, and at months 1, 3, 3+14 days, 6, 6+14 days, 9, 12, 13, 18, and 24. After the 24-month trial period, patients continue to receive open-label denosumab in a 1-year extension study (data not shown).

time the trial regimen was started. All patients received daily calcium (500 to 1000 mg) and vitamin D_3 or D_2 (600 to 800 IU).

PROCEDURES

Lateral radiographs of the spine were obtained at scheduled visits (Fig. 1) or if back pain occurred that was suggestive of vertebral fracture. Radiographs were assessed with the use of the Genant grading scale (grades range from 0 to 3, with higher grades indicating greater severity)[14] (see the Supplementary Appendix, available at NEJM.org) at a central imaging vendor (BioClinica). Patients were considered to have new vertebral fractures if there was an increase of at least one grade in previously normal vertebrae; determination that preexisting fractures had worsened also required an increase of at least one grade. The staff at the central imaging vendor, who were unaware of the treatment assignments, confirmed nonvertebral fractures by diagnostic imaging or by review of the radiologist's report. Fractures of the skull, facial bones, metacarpals, fingers, and toes, pathologic fractures, and fractures that were associated with severe trauma were excluded.

In a substudy involving 128 patients, the bone mineral density at the lumbar spine and proximal femur was evaluated by means of dual-energy x-ray absorptiometry (Lunar or Hologic) at baseline and every 6 months (Fig. 1). 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 measured in a substudy involving 129 patients (Fig. 1).

Adverse events were reported by trial-site physicians. Serious adverse events that were potentially cardiovascular-related, including deaths, and potential cases of osteonecrosis of the jaw and atypical femoral fracture were identified with the use of prespecified search strategies and adjudicated by independent committees. Adverse events of interest included those that were relevant to the injection of a monoclonal antibody or to calcium homeostasis and events that were

considered to be potentially related to hyperostosis (as seen with excessive bone growth in genetic syndromes of sclerostin deficiency).[6,15] Anti-romosozumab antibodies were assessed at baseline and at months 1, 3, 6, 12, 15, and 24.

PRIMARY AND SECONDARY END POINTS

The coprimary end points were the cumulative incidences of new vertebral fracture at 12 months and at 24 months. Prespecified secondary end points included the cumulative incidence of clinical fracture (a composite of nonvertebral fracture and symptomatic vertebral fracture), nonvertebral fracture, major nonvertebral fracture, new or worsening vertebral fracture, hip fracture, major osteoporotic fracture, and multiple new or worsening vertebral fractures at 12 months and at 24 months.

STATISTICAL ANALYSIS

Assuming an incidence of vertebral fracture of 2.1% in the placebo group, we calculated that the trial would have more than 99% power to detect a 65% lower risk of new vertebral fracture in the romosozumab group over a period of 12 months and a 62% lower risk in the romosozumab group over a period of 24 months. Assuming an incidence of clinical fracture of 3.9% and an incidence of nonvertebral fracture of 3.5% in the placebo group, we calculated that the trial would have 94% power to detect a 40% lower risk of clinical fracture and 91% power to detect a 40% lower risk of nonvertebral fracture in the romosozumab group at 12 months. A fixed-sequence testing procedure was used for the coprimary end points and selected secondary end points to adjust for multiple comparisons and maintain an overall significance level of 0.05 (Fig. S1 in the Supplementary Appendix). If statistical significance was not reached at any point in the sequence, the remaining end points would be considered to be exploratory, and both the nominal and adjusted P values would be reported.

We used an intention-to-treat approach for all the analyses for the assessment of the treatment effect. Analyses of vertebral-fracture end points included all the patients who underwent randomization and had a baseline radiograph and at least one radiograph obtained after the baseline visit. When a radiograph assessment after baseline was missing, the status was imputed with the status from the last nonmissing visit after baseline; a post hoc multiple-imputation approach to handle missing data was also undertaken as a sensitivity analysis.

For vertebral fracture, the risk ratio was determined on the basis of the Mantel–Haenszel method, and the treatment comparison was assessed with the use of a logistic-regression model that was stratified according to age (<75 years vs. ≥75 years) and prevalent vertebral fracture (yes vs. no). Analyses of other fracture end points included all the patients who underwent randomization. The cumulative incidence was summarized with the use of Kaplan–Meier estimates, and treatment comparisons were based on a Cox proportional-hazards model that was stratified according to age and prevalent vertebral fracture.

A total of 11 subgroup categories, including those defined according to age, history of fracture, T score, and geographic region, were prespecified for assessment of new vertebral, clinical, and nonvertebral fracture end points at 12 months and at 24 months. Treatment-by-subgroup interactions were assessed with the use of the same statistical approach that was used to test the main treatment effect, without adjustment for multiple comparisons.

Percentage changes from baseline in bone mineral density and in the levels of bone-turnover markers were assessed in patients who had a baseline measurement and at least one assessment after the baseline visit. Bone mineral density was analyzed with the use of an analysis-of-covariance model with adjustment for baseline bone mineral density, machine type, and interaction between baseline bone mineral density and machine type. We imputed missing values by carrying forward the last observation, and a sensitivity analysis was performed with the use of a repeated-measures model. A Wilcoxon rank-sum test was used to assess the treatment difference with regard to the percentage change from baseline in the levels of bone-turnover markers.

The safety analysis included all the patients who underwent randomization and received at least one dose of placebo or romosozumab in the 12-month double-blind period. Incidence rates at 24 months were cumulative and included all the events in the double-blind period and all the events in the open-label period that occurred in patients who received at least one dose of denosumab.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=3591)	Romosozumab (N=3589)
Age — yr	70.8±6.9	70.9±7.0
Age ≥75 yr — no. (%)	1121 (31.2)	1119 (31.2)
Ethnic group — no. (%)†		
Hispanic	1416 (39.4)	1427 (39.8)
Non-Hispanic	2175 (60.6)	2162 (60.2)
Body-mass index‡	24.74±4.42	24.66±4.30
Bone mineral density T score		
Lumbar spine	−2.71±1.04	−2.72±1.04
Total hip	−2.46±0.47	−2.48±0.47
Femoral neck	−2.74±0.29	−2.76±0.28
Prevalent vertebral fracture — no. (%)	645 (18.0)	672 (18.7)
No. of prevalent vertebral fractures		
1	496 (13.8)	506 (14.1)
≥2	149 (4.1)	166 (4.6)
Grade of most severe vertebral fracture§		
Mild	378 (10.5)	378 (10.5)
Moderate	263 (7.3)	293 (8.2)
Severe	4 (0.1)	1 (<0.1)
Previous nonvertebral fracture at ≥45 yr of age — no. (%)	782 (21.8)	778 (21.7)
Geographic region — no. (%)¶		
Latin America	1534 (42.7)	1550 (43.2)
Central or Eastern Europe	1050 (29.2)	1043 (29.1)
Western Europe, Australia, or New Zealand	497 (13.8)	482 (13.4)
Asia Pacific	419 (11.7)	410 (11.4)
North America	91 (2.5)	104 (2.9)
FRAX score‖	13.4±8.5	13.4±8.8
Median serum P1NP (IQR) — μg/liter**	52.3 (38.7–63.2)	50.3 (36.2–65.9)
Median serum β-CTX (IQR) — ng/liter**	517 (322–677)	551 (338–706)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. Additional details are provided in Table S1 in the Supplementary Appendix. β-CTX denotes β-isomer of C-terminal telopeptide of type I collagen, IQR interquartile range, and P1NP procollagen type 1 N-terminal propeptide.

† Ethnic group was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The grade of the most severe vertebral fracture was assessed with the use of the Genant grading scale.[14]

¶ The 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.

‖ The score on the Fracture Risk Assessment Tool (FRAX), developed by the World Health Organization (www.shef.ac.uk/frax/) indicates the 10-year risk of major osteoporotic fracture.

** Data shown are for the patients who enrolled in the bone-turnover marker and biomarker substudy and who had P1NP or β-CTX measurements both at baseline and at a postbaseline visit (62 patients in each group in the P1NP analysis, and 62 patients in the placebo group and 61 in the romosozumab group in the β-CTX analysis).

RESULTS

PATIENTS

A total of 7180 patients underwent randomization; 6390 patients (89.0%) completed 12 months of the trial, and 6026 (83.9%) completed 24 months (Fig. S2 in the Supplementary Appendix). The reasons for discontinuation were similar in the two trial groups. The demographic and clinical characteristics of the patients at baseline were balanced in the two groups (Table 1). The mean age of the patients was 70.9 years. The

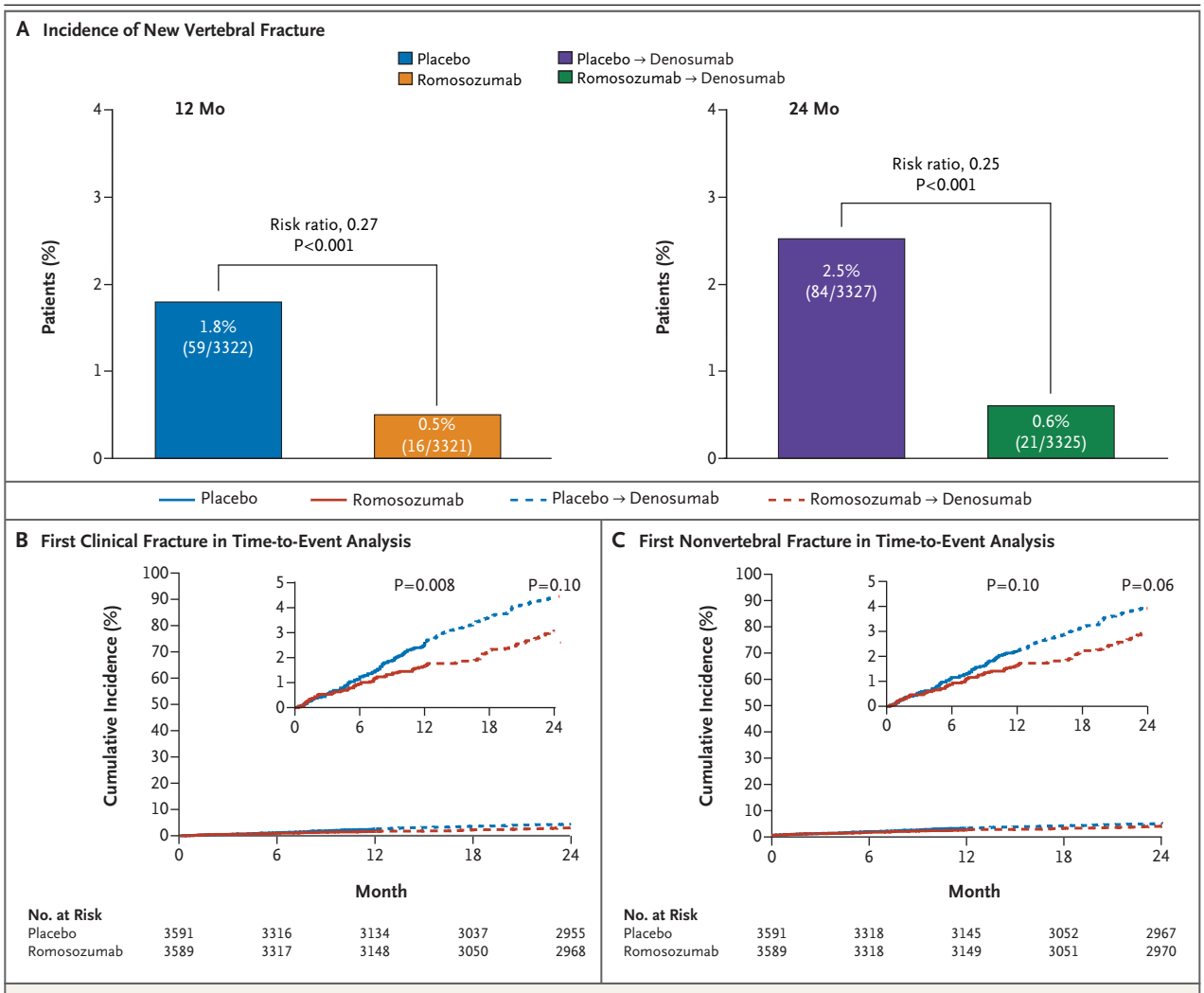


Figure 2. Incidence of New Vertebral, Clinical, and Nonvertebral Fractures.

The coprimary end points were the cumulative incidences of new vertebral fracture at 12 months and at 24 months (Panel A). The risk ratio was assessed among patients in the romosozumab group as compared with those in the placebo group at 12 months (end of the double-blind period) and at 24 months (by which time patients in both groups had received open-label denosumab for 12 months). Data from patients who underwent randomization and had a baseline radiograph and at least one radiograph obtained after the baseline visit are included here. Kaplan–Meier curves of the first clinical fracture (Panel B) and the first nonvertebral fracture (Panel C) from the time-to-event analysis are shown, including the double-blind period through 12 months and the period with open-label denosumab from 12 to 24 months. The insets show the same data on an enlarged y axis. Data from patients who withdrew from the trial or who reached the end of the reporting period without having a fracture were censored at the last observation time. P values are for results at 12 months and 24 months and are based on a Cox proportional-hazards model with adjustment for age and prevalent vertebral fracture, adjusted for multiple comparisons.

mean bone mineral density 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 patients (18.3%) had a prevalent vertebral fracture (the majority of which were mild in severity), and 1560 (21.7%) had a previous nonvertebral fracture. The geographic regions with the highest enrollment were Latin America (3084 patients) and Central or Eastern Europe (2093 patients).

12-MONTH FRACTURE EFFICACY

Romosozumab was associated with a risk of new vertebral fracture that was 73% lower than the risk with placebo at 12 months (incidence, 0.5% [16 of 3321 patients] in the romosozumab group vs. 1.8% [59 of 3322] in the placebo group; risk ratio, 0.27; 95% confidence interval [CI], 0.16 to 0.47; P<0.001) (Fig. 2A, and Table S2 in the Supplementary Appendix). By 6 months,

new vertebral fractures had occurred in 14 patients in the romosozumab group and in 26 in the placebo group. Between 6 months and 12 months, fractures occurred in 2 additional patients in the romosozumab group, as compared with 33 additional patients in the placebo group. Romosozumab was also associated with a risk of clinical fracture that was 36% lower than the risk with placebo at 12 months; fractures occurred in 58 of 3589 patients (1.6%) in the romosozumab group vs. 90 of 3591 (2.5%) in the placebo group (hazard ratio, 0.64; 95% CI, 0.46 to 0.89; P=0.008) (Fig. 2B, and Table S2 in the Supplementary Appendix).

Nonvertebral fractures constituted the majority (>85%) of clinical fractures. Nonvertebral fractures occurred in 56 patients (1.6%) in the romosozumab group and in 75 (2.1%) in the placebo group (hazard ratio, 0.75; 95% CI, 0.53 to 1.05; P=0.10) (Fig. 2C, and Table S2 in the Supplementary Appendix). Owing to the lack of statistical significance for the nonvertebral end point and the prespecified testing sequence, all other 12-month fracture end-point analyses were considered to be exploratory (Table S2 in the Supplementary Appendix).

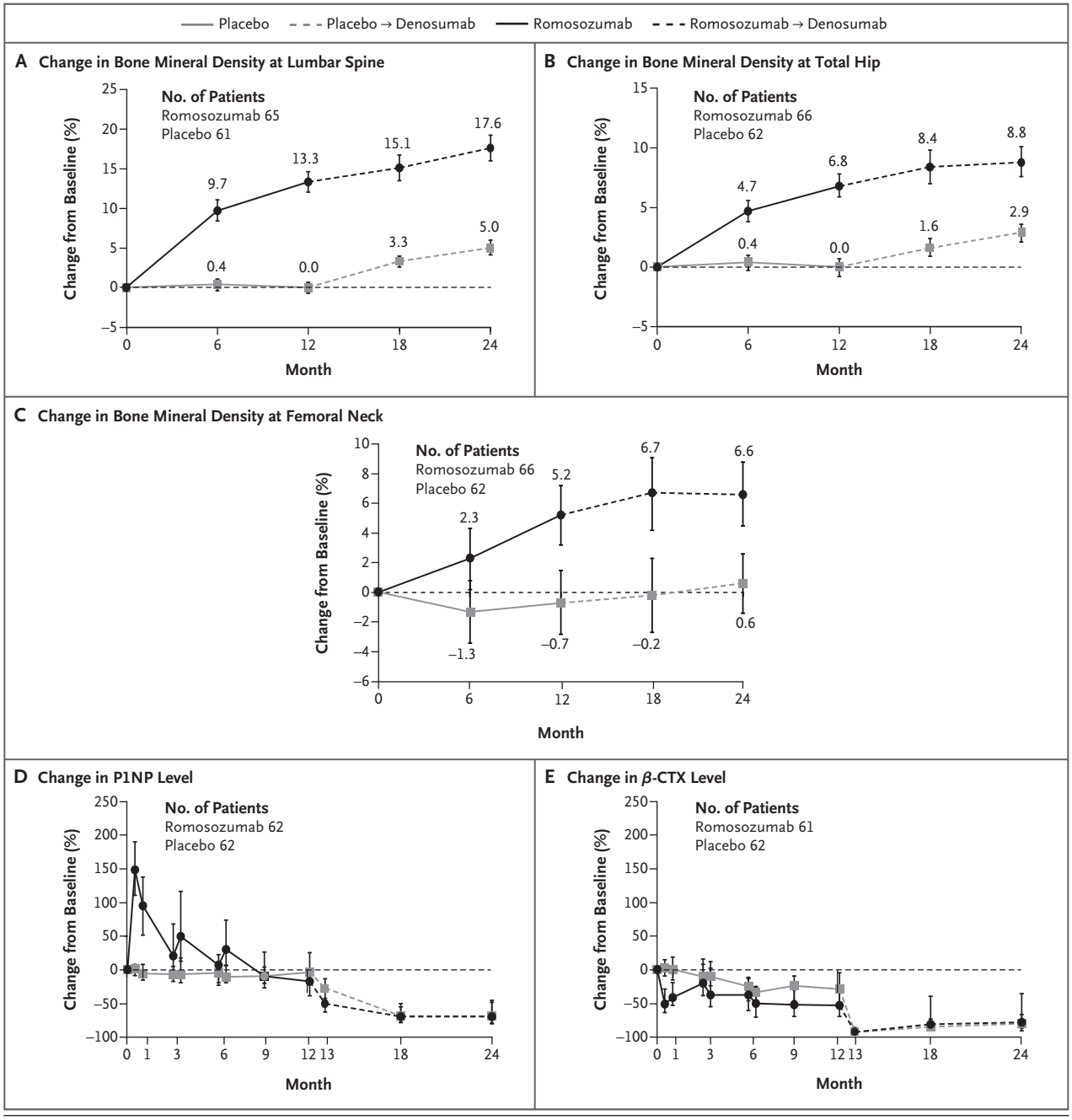
The treatment effect in prespecified subgroups was consistent with regard to new vertebral, clinical, and nonvertebral fractures (data not shown), except with regard to clinical and nonvertebral fractures across geographic regions, for which significant treatment-by-region interactions were observed (P=0.03 and P=0.04, respectively). These findings were evaluated in a post hoc analysis that showed that the incidence of nonvertebral fracture in the region of Latin America was 1.5% (24 of 1550 patients) in the romosozumab group versus 1.2% (19 of 1534) in the placebo group (hazard ratio, 1.25; 95% CI, 0.68 to 2.27). By contrast, among the patients outside the region of Latin America, the incidence was 1.6% (32 of 2039) in the romosozumab group versus 2.7% (56 of 2057) in the placebo group, representing a risk that was 42% lower in the romosozumab group (hazard ratio, 0.58, 95% CI, 0.37 to 0.89; P=0.04 for the treatment-by-region interaction). The corresponding baseline 10-year risk of major osteoporotic fracture, as assessed by the Fracture Risk Assessment Tool (FRAX; developed by the World Health Organization [www.shef.ac.uk/frax/]), was 8.7% in Latin America and 17.0% elsewhere.

Figure 3 (facing page). Percentage Change from Baseline in Bone Mineral Density and Levels of Bone-Turnover Markers.

Shown are the least-squares mean percentage changes in bone mineral density at the lumbar spine (Panel A), total hip (Panel B), and femoral neck (Panel C) for the 128 patients who were enrolled in the substudy on bone mineral density who had a baseline measurement and at least one measurement obtained after the baseline visit (two patients [one in each group] were missing the baseline assessment for the lumbar spine). Least-squares mean differences between the groups for each time point are shown in Table S3 in the Supplementary Appendix; estimated between-group mean differences may differ from those derived from the presented least-squares mean estimates owing to rounding. P<0.001 for the between-group comparisons of the mean percentage change from baseline at all time points for all skeletal sites. The median percentage-change values for the levels of serum procollagen type 1 N-terminal propeptide (P1NP; Panel D) and the β-isomer of C-terminal telopeptide of type I collagen (β-CTX; Panel E) are shown for patients who were enrolled in the substudy of bone-turnover markers. I bars indicate pointwise 95% confidence intervals for the values of bone mineral density and interquartile ranges for the levels of bone-turnover markers for patients who had a baseline measurement and at least one measurement obtained after the baseline visit; the numbers of patients in each group with missing data at baseline are provided in Table S1 in the Supplementary Appendix. Between-group comparisons of the percentage change in bone mineral density were analyzed with the use of analysis-of-covariance models with adjustment for baseline bone mineral density, machine type, and interaction of baseline bone mineral density with machine type. 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. For the comparisons of the mean percentage change from baseline in P1NP values: P<0.001 for the comparisons at 14 days and at months 1, 3, 3 plus 14 days, 6 plus 14 days, and 13; and at month 6, P=0.33; month 9, P=0.95; month 12, P=0.006; month 18, P=0.74; and month 24, P=0.81. For the comparisons of the mean percentage change from baseline in β-CTX levels: P<0.001 for the comparisons at 14 days and at months 1, 6 plus 14 days, 9, and 12; and at month 3, P=0.25; month 3 plus 14 days, P=0.005; month 6, P=0.08; month 13, P=0.82; month 18, P=0.06; and month 24, P=0.04. For P1NP and β-CTX levels, the comparisons were calculated with the use of the Wilcoxon rank-sum test.

24-MONTH FRACTURE EFFICACY

All the patients made the transition to denosumab in the second year. The cumulative 24-month incidence of new vertebral fracture was lower in the group that had originally received romosoz-



umab (21 of 3325 patients [0.6%]) than in the group that had originally received placebo (84 of 3327 [2.5%]), with a 75% lower risk in the romosozumab group (risk ratio, 0.25; 95% CI, 0.16 to 0.40; P<0.001) (Fig. 2A). In the second year, 5 patients in the group that had originally received romosozumab and 25 in the group that had originally received placebo had a new vertebral fracture.

There was no significant difference in the risk of nonvertebral fracture at 24 months (96 of 3589 patients [2.7%] in the romosozumab group and 129 of 3591 [3.6%] in the placebo group; hazard ratio, 0.75; 95% CI, 0.57 to 0.97; nominal P=0.03; adjusted P=0.06). Owing to the prespecified testing sequence, treatment comparisons for other fracture end points at 24 months were considered to be exploratory. There was no

significant difference in the risk of clinical fracture between the group that had originally received romosozumab and the group that had originally received placebo (99 patients and 147 patients, respectively; hazard ratio, 0.67; 95% CI, 0.52 to 0.87; nominal P=0.002; adjusted P=0.10) (Fig. 2B). Details are provided in Table S2 in the Supplementary Appendix.

BONE DENSITY AND MARKERS OF BONE TURNOVER

Romosozumab increased bone mineral density by 6 months, and at 12 months the percentage change from baseline was greater with romosozumab than with placebo at the lumbar spine, by 13.3 percentage points (95% CI, 11.9 to 14.7), at the total hip, by 6.9 percentage points (95% CI, 5.6 to 8.1), and at the femoral neck, by 5.9 percentage points (95% CI, 4.3 to 7.4) (P<0.001 for all comparisons) (Fig. 3A, 3B, and 3C). Bone mineral density continued to increase in the romosozumab group after the transition to denosumab (P<0.001 for all comparisons between the group that had originally received romosozumab and the group that had originally received placebo) (Fig. 3A, 3B, and 3C).

The levels of the bone-formation marker P1NP increased rapidly in the romosozumab group (maximum peak on day 14) and returned to baseline levels by 9 months. The levels of the bone-resorption marker β-CTX decreased early during treatment (maximum decline on day 14) and remained below the levels in the placebo group at 12 months (Fig. 3D and 3E). At prespecified time points when the levels were also measured 14 days after dosing of romosozumab or placebo, transient increases in the P1NP level and decreases in the β-CTX level in the romosozumab group were observed. Denosumab treatment reduced the levels of P1NP and β-CTX similarly in each group.

ADVERSE EVENTS AND SAFETY

The incidence of adverse events and serious adverse events was balanced in the two groups, as was the incidence of events that were categorized as osteoarthritis, hyperostosis, cancer, hypersensitivity, and adjudicated serious cardiovascular events (Table 2). Serious adverse events that were potentially indicative of hypersensitivity occurred in 7 patients in the romosozumab group in the first year. Injection-site reactions, which were mostly mild in severity, were reported over the 12-month period in 187 patients (5.2%) in the romosozumab group and in 104 (2.9%) in the placebo group.

Two events that occurred in patients in the romosozumab group were adjudicated as being consistent with the definition of osteonecrosis of the jaw. One event occurred after 12 months of romosozumab treatment in the context of ill-fitting dentures, and the other event occurred after 12 months of romosozumab treatment and one dose of denosumab after a tooth extraction and subsequent osteomyelitis of the jaw. One event that was adjudicated as being consistent with the definition of atypical femoral fracture occurred 3.5 months after the first dose of romosozumab; the patient had reported a history of prodromal pain at the site of fracture beginning before enrollment.

During the first 15 months of the trial, binding anti-romosozumab antibodies developed in 646 patients in the romosozumab group (18.0%), and neutralizing antibodies developed in 25 patients in the romosozumab group (0.7%), with no detectable effect on efficacy or safety (Tables S4 and S5 in the Supplementary Appendix). The median albumin-corrected serum calcium levels were lower at 1 month in the romosozumab group than in the placebo group (median change from baseline, –2.2% vs. 0.0%).

DISCUSSION

In this phase 3 trial involving patients with osteoporosis, romosozumab was associated with a lower risk of new vertebral fractures than placebo at 12 months. The effect of romosozumab on the risk of vertebral fracture was rapid, with only 2 additional vertebral fractures (of a total of 16 such fractures in the romosozumab group) occurring in the second 6 months of therapy. The risk of clinical fracture (a composite of nonvertebral fracture and symptomatic vertebral fracture) was also significantly lower in the romosozumab group within 12 months after the start of treatment than in the placebo group. Because vertebral and clinical fractures are associated with increased morbidity and considerable health care costs,[16-18] a treatment that would reduce this risk rapidly could offer appropriate patients an important benefit.

Table 2. Adverse Events.*

Event	12 Months		24 Months	
	Placebo (N=3576)	Romosozumab (N=3581)	Placebo to Denosumab (N=3576)	Romosozumab to Denosumab (N=3581)
	number of patients (percent)			
Adverse event during treatment†	2850 (79.7)	2806 (78.4)	3069 (85.8)	3053 (85.3)
Arthralgia	429 (12.0)	467 (13.0)	565 (15.8)	585 (16.3)
Nasopharyngitis	438 (12.2)	459 (12.8)	546 (15.3)	557 (15.6)
Back pain	378 (10.6)	375 (10.5)	516 (14.4)	463 (12.9)
Serious adverse event	312 (8.7)	344 (9.6)	540 (15.1)	565 (15.8)
Adjudicated serious cardiovascular event‡	41 (1.1)	44 (1.2)	79 (2.2)	82 (2.3)
Death	23 (0.6)	29 (0.8)	47 (1.3)	52 (1.5)
Adjudicated cardiovascular death‡	15 (0.4)	17 (0.5)	29 (0.8)	31 (0.9)
Event leading to discontinuation of trial regimen	94 (2.6)	103 (2.9)	110 (3.1)	122 (3.4)
Event leading to discontinuation of trial participation	50 (1.4)	44 (1.2)	56 (1.6)	52 (1.5)
Event of interest§				
Hypocalcemia	0	1 (<0.1)	3 (0.1)	6 (0.2)
Hypersensitivity¶	245 (6.9)	242 (6.8)	331 (9.3)	314 (8.8)
Injection-site reaction‖	104 (2.9)	187 (5.2)	106 (3.0)	188 (5.2)
Hyperostosis	27 (0.8)	19 (0.5)	40 (1.1)	35 (1.0)
Cancer	69 (1.9)	59 (1.6)	100 (2.8)	105 (2.9)
Osteoarthritis	315 (8.8)	281 (7.8)	431 (12.1)	396 (11.1)
Osteonecrosis of the jaw‡	0	1 (<0.1)	0	2 (<0.1)
Atypical femoral fracture‡	0	1 (<0.1)	0	1 (<0.1)

* The population for this analysis included all the patients who underwent randomization and received at least one dose of placebo or romosozumab in the 12-month double-blind period. At month 12, patients made the transition to denosumab for the second year of the trial.
† The events listed are the most frequent adverse events in the double-blind period that occurred in 10% or more of the patients in either group.
‡ The events listed include adverse events that were adjudicated as positive by an independent adjudication committee. Cardiovascular deaths include fatal events that were adjudicated as being cardiovascular-related or undetermined (presumed to be cardiac-related).
§ Events of interest were those that were identified by prespecified *Medical Dictionary for Regulatory Activities* search strategies.
¶ Seven patients in the romosozumab group had serious adverse events during the 12-month double-blind period. Events that were reported by the investigator as being related to romosozumab included dermatitis, allergic dermatitis, and macular rash, all of which resolved; the drug was withdrawn or withheld in these cases.
‖ The most frequent adverse events of injection-site reactions (occurring in >0.1% of the patients) in the romosozumab group during the 12-month double-blind period included injection-site pain (in 1.7% of the patients), erythema (1.5%), bruising (0.8%), pruritus (0.7%), swelling (0.4%), hemorrhage (0.4%), rash (0.3%), and hematoma (0.2%).

Although all patients made the transition to denosumab in the second year of the trial, the risk of fracture was lower in the group that had received romosozumab in the first year than in the group that had received placebo. Fewer additional vertebral fractures occurred in the second year in patients who had been originally assigned to romosozumab than in those who had been originally assigned to placebo (5 vs. 25 fractures) — a pattern that was also observed across other fracture types. These findings imply that romosozumab was associated with a lower underlying fracture risk even after the transition to denosumab.

In the trial population, the rate of nonvertebral fracture in the placebo group was lower than expected, which was driven by a geographic region with high enrollment (Latin

America) in which the incidence in the placebo group at 12 months was one third the expected rate, with no detectable treatment effect. The regional-subgroup data warrant cautious interpretation owing to a lack of adjustment for multiple comparisons and the possibility of type I error. However, the low rate of nonvertebral fracture in the placebo group in the Latin American geographic region is consistent with the low mean baseline FRAX score that was observed in the patients enrolled in that region and with recent epidemiologic reports.[19,20] In a post hoc analysis that included patients outside Latin America, a higher rate of nonvertebral fracture was observed in the placebo group (2.7%, vs. 1.2% in the placebo group in Latin America), and 12 months of romosozumab treatment resulted in a risk of fracture that was 42% lower than the risk with placebo. These findings merit further evaluation.

The results regarding bone-turnover markers confirm those reported previously[10] and support the dual effect of romosozumab in increasing bone formation and decreasing bone resorption by means of sclerostin inhibition. Sclerostin blocks canonical Wnt signaling, which results in decreased osteoblast-mediated bone formation[21,22] and increased bone resorption,[23] both of which are counteracted by romosozumab.[11,24] The transient increases in the P1NP level after repeated dosing may provide insight into the observed gains in bone mineral density over the treatment period. This effect of romosozumab on bone formation and resorption translated into large increases in bone mineral density at the spine and hip, and clinically significant increases were seen as early as 6 months, as reported previously.[10] Additional gains were observed after the transition to denosumab.

Adverse events were balanced in the two groups. Serious adverse events of hypersensitivity reactions were observed in the romosozumab group, although these events were uncommon. Cases of osteonecrosis of the jaw and an atypical femoral fracture were observed, albeit rarely, in patients with confounding factors that may have contributed to the event or that raise questions about causality.

In conclusion, romosozumab is a monoclonal antibody that increases bone formation and decreases bone resorption. One year of romosozumab treatment in postmenopausal women with osteoporosis resulted in a lower risk of vertebral and clinical fractures than the risk with placebo. Substantial gains in bone mineral density at the spine and hip with romosozumab provided a foundation for an ongoing reduction in the risk of fracture during sequential treatment with denosumab.

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APPENDIX

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REFERENCES

1. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761-7.
2. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285:785-95.
3. Harrington JT, Broy SB, Derosa AM, Licata AA, Shewmon DA. Hip fracture patients are not treated for osteoporosis: a call to action. Arthritis Rheum 2002;47:651-4.
4. Panneman MJ, Lips P, Sen SS, Herings RM. Undertreatment with anti-osteoporotic drugs after hospitalization for fracture. Osteoporos Int 2004;15:120-4.
5. Wilk A, Sajjan S, Modi A, Fan CP, Mavros P. Post-fracture pharmacotherapy for women with osteoporotic fracture: analysis of a managed care population in the USA. Osteoporos Int 2014;25:2777-86.
6. Balemans W, Ebeling M, Patel N, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Hum Mol Genet 2001;10:537-43.

7. Brunkow ME, Gardner JC, Van Ness J, et al. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. Am J Hum Genet 2001;68:577-89.
8. Poole KE, van Bezooijen RL, Loveridge N, et al. Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. FASEB J 2005;19:1842-4.
9. Li X, Zhang Y, Kang H, et al. Sclerostin binds to LRP5/6 and antagonizes canonical Wnt signaling. J Biol Chem 2005; 280:19883-7.
10. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med 2014;370:412-20.
11. Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. J Bone Miner Res 2011;26:19-26.
12. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet 2015; 386:1147-55.
13. Lindsay R, Scheele WH, Neer R, et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. Arch Intern Med 2004;164:2024-30.
14. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
15. Beighton P, Durr L, Hamersma H. The clinical features of sclerosteosis: a review of the manifestations in twenty-five affected individuals. Ann Intern Med 1976; 84:393-7.
16. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. J Am Geriatr Soc 2003; 51:364-70.
17. Cauley JA. Public health impact of osteoporosis. J Gerontol A Biol Sci Med Sci 2013;68:1243-51.
18. Puffer S, Torgerson DJ, Sykes D, Brown P, Cooper C. Health care costs of women with symptomatic vertebral fractures. Bone 2004;35:383-6.
19. Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 2012;23:2239-56.
20. Zerbini CA, Szejnfeld VL, Abergaria BH, McCloskey EV, Johansson H, Kanis JA. Incidence of hip fracture in Brazil and the development of a FRAX model. Arch Osteoporos 2015;10:224.
21. Semënov M, Tamai K, He X. SOST is a ligand for LRP5/LRP6 and a Wnt signaling inhibitor. J Biol Chem 2005;280: 26770-5.
22. van Bezooijen RL, Svensson JP, Eefting D, et al. Wnt but not BMP signaling is involved in the inhibitory action of sclerostin on BMP-stimulated bone formation. J Bone Miner Res 2007;22:19-28.
23. Wijenayaka AR, Kogawa M, Lim HP, Bonewald LF, Findlay DM, Atkins GJ. Sclerostin stimulates osteocyte support of osteoclast activity by a RANKL-dependent pathway. PLoS One 2011;6(10):e25900.
24. Ominsky MS, Niu QT, Li C, Li X, Ke HZ. Tissue-level mechanisms responsible for the increase in bone formation and bone volume by sclerostin antibody. J Bone Miner Res 2014;29:1424-30.