ORIGINAL ARTICLE

Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

Kenneth G. Saag, M.D., Jeffrey Petersen, M.D., Maria Luisa Brandi, M.D., Andrew C. Karaplis, M.D., Ph.D., Mattias Lorentzon, M.D., Ph.D., Thierry Thomas, M.D., Ph.D., Judy Maddox, D.O., Michelle Fan, Ph.D., Paul D. Meisner, Pharm.D., and Andreas Grauer, M.D.

ABSTRACT

BACKGROUND

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

METHODS

We enrolled 4093 postmenopausal women with osteoporosis and a fragility fracture and randomly assigned them in a 1:1 ratio to receive monthly subcutaneous romosozumab (210 mg) or weekly oral alendronate (70 mg) in a blinded fashion for 12 months, followed by open-label alendronate in both groups. The primary end points were the cumulative incidence of new vertebral fracture at 24 months and the cumulative incidence of clinical fracture (nonvertebral and symptomatic vertebral fracture) at the time of the primary analysis (after clinical fractures had been confirmed in ≥330 patients). Secondary end points included the incidences of nonvertebral and hip fracture at the time of the primary analysis. Serious cardiovascular adverse events, osteonecrosis of the jaw, and atypical femoral fractures were adjudicated.

RESULTS

Over a period of 24 months, a 48% lower risk of new vertebral fractures was observed in the romosozumab-to-alendronate group (6.2% [127 of 2046 patients]) than in the alendronate-to-alendronate group (11.9% [243 of 2047 patients]) (P<0.001). Clinical fractures occurred in 198 of 2046 patients (9.7%) in the romosozumab-to-alendronate group versus 266 of 2047 patients (13.0%) in the alendronate-to-alendronate group, representing a 27% lower risk with romosozumab (P<0.001). The risk of nonvertebral fractures was lower by 19% in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group (178 of 2046 patients [8.7%] vs. 217 of 2047 patients [10.6%]; P=0.04), and the risk of hip fracture was lower by 38% (41 of 2046 patients [2.0%] vs. 66 of 2047 patients [3.2%]; P=0.02). Overall adverse events and serious adverse events were balanced between the two groups. During year 1, positively adjudicated serious cardiovascular adverse events were observed more often with romosozumab than with alendronate (50 of 2040 patients [2.5%] vs. 38 of 2014 patients [1.9%]). During the open-label alendronate period, adjudicated events of osteonecrosis of the jaw (1 event each in the romosozumab-to-alendronate and alendronate-to-alendronate groups) and atypical femoral fracture (2 events and 4 events, respectively) were observed.

CONCLUSIONS

In postmenopausal women with osteoporosis who were at high risk for fracture, romosozumab treatment for 12 months followed by alendronate resulted in a significantly lower risk of fracture than alendronate alone. (Funded by Amgen and others; ARCH ClinicalTrials.gov number, NCT01631214.)

From the University of Alabama, Birmingham (K.G.S.); Amgen, Thousand Oaks, CA (J.P., J.M., M.F., A.G.); University of Florence, Florence, Italy (M.L.B.); McGill University, Montreal (A.C.K.); University of Gothenburg and Sahlgrenska University Hospital, Mölndal, Sweden (M.L.); Centre Hospitalier Universitaire de Saint-Étienne, Saint-Étienne, France (T.T.); and UCB Pharma, Brussels (P.D.M.). Address reprint requests to Dr. Saag at the Division of Clinical Immunology and Rheumatology, University of Alabama, Faculty Office Tower, Suite 820, 510 20th St. South, Birmingham, AL 35294-3408.

This article was published on September 11, 2017, and updated on September 18, 2017, at NEJM.org.

DOI: 10.1056/NEJMoa1708322

Fragility fractures are common and increase morbidity and mortality.[1,2] Romosozumab (Amgen and UCB Pharma) is a new bone-forming monoclonal antibody that binds to and inhibits sclerostin, with a dual effect of increasing bone formation and decreasing bone resorption.[3,4]

In a randomized, controlled trial,[5] 1 year of romosozumab treatment was associated with significantly lower risks of new vertebral fracture and clinical fracture (a composite of nonvertebral fracture and symptomatic vertebral fracture) than placebo among postmenopausal women with osteoporosis. That trial excluded patients with severe osteoporosis and thus enrolled a relatively low-risk population.[6-10] In that context, the risk of nonvertebral fracture was not significantly lower with romosozumab than with placebo.

Alendronate is an antiresorptive agent commonly used as first-line therapy for osteoporosis. In a trial involving postmenopausal women with prevalent fractures, the risks of vertebral and clinical (in particular, hip) fractures were lower with alendronate than with placebo.[10]

There are few head-to-head studies of osteoporosis therapy with fracture end points, and only one trial evaluating bone-building versus antiresorptive therapy was designed with fracture as the primary end point.[11] In the Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH), we compared the effectiveness of a treatment regimen starting with romosozumab and transitioning to alendronate with alendronate treatment alone in reducing the risk of fracture among postmenopausal women with osteoporosis and a previous fracture.

METHODS

TRIAL DESIGN

In this phase 3, multicenter, international, randomized, double-blind trial, women were randomly assigned, in a 1:1 ratio, with the use of an interactive voice-response system, to receive monthly subcutaneous romosozumab (210 mg) or weekly oral alendronate (Merck; 70 mg) for 12 months (Fig. 1). Randomization was stratified according to age (<75 vs. ≥75 years). After completion of the double-blind trial period, all the patients received open-label weekly oral alendronate (70 mg) until the end of the trial, with blinding to the initial treatment assignment maintained. Patients received daily calcium and vitamin D, as described previously.[5] In this trial designed to show the superiority of romosozumab over alendronate, the primary analysis was performed when clinical-fracture events had been confirmed in at least 330 patients and all the patients had completed the month 24 visit.

TRIAL OVERSIGHT

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

Three 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. All the authors had access to the data. The first and last authors wrote the first draft of the manuscript, with medical-writing assistance funded by Amgen and UCB Pharma. All the authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. Trial investigators signed agreements with the sponsors relating to data confidentiality.

PATIENTS

Ambulatory postmenopausal women 55 to 90 years of age who met at least one of the following criteria were eligible: a bone mineral density T score of –2.5 or less at the total hip or femoral neck and either one or more moderate or severe vertebral fractures or two or more mild vertebral fractures; or a bone mineral density T score of –2.0 or less at the total hip or femoral neck and either two or more moderate or severe vertebral fractures or a fracture of the proximal femur sustained 3 to 24 months before randomization. Women were excluded as described previously[5] and for an inability to take alendronate oral tablets or contraindications to alendronate, including a glomerular filtration rate below 35 ml per minute per 1.73 m^2 of body-surface area.

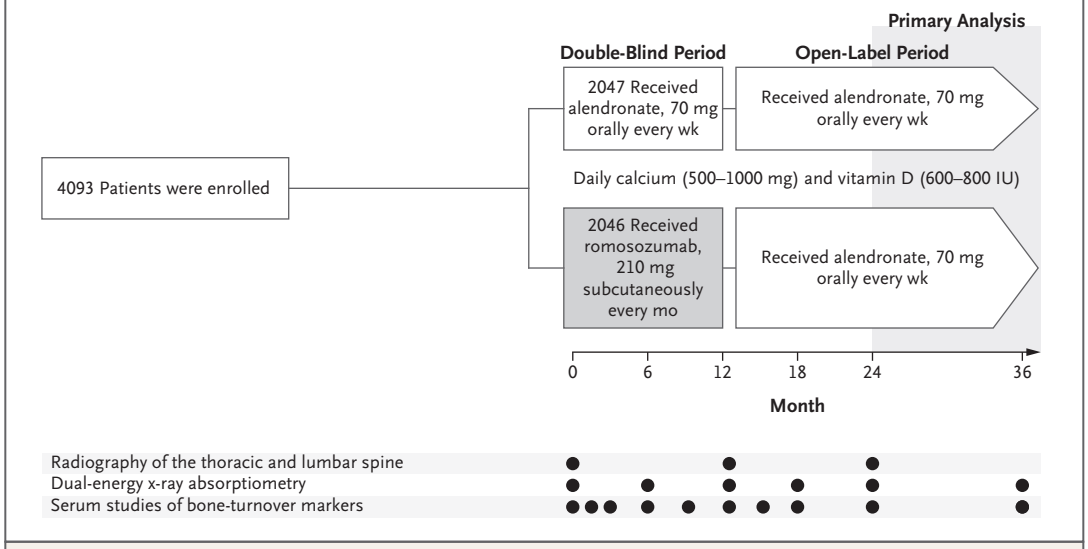

Figure 1. Trial Schema.

Women were randomly assigned, in a 1:1 ratio, to receive 210 mg of romosozumab by subcutaneous injection once monthly or 70 mg of alendronate orally every week for 12 months for the double-blind period of the trial, followed by open-label alendronate until the time of the primary analysis; the initial treatment assignment remained blinded. The primary analysis was performed when events of clinical fracture (nonvertebral and symptomatic vertebral fracture) had been confirmed in at least 330 patients and all the patients had completed the month 24 visit. The median follow-up at the time of the primary analysis was 2.7 years (interquartile range, 2.2 to 3.3). Bone mineral density was assessed at the lumbar spine and proximal femur in all the patients at baseline and every 12 months thereafter, and also at months 6 and 18 in a substudy of the total patient population that involved 167 patients. Levels of bone-turnover markers were assessed at baseline (day 1) and months 1, 3, 6, 9, 12, 15, 18, 24, and 36 or until the primary analysis, whichever came first, in a subgroup of 277 patients from the total patient population.

PROCEDURES

Lateral radiographs of the thoracic and lumbar spine were obtained at screening, at months 12 and 24, and every 12 months thereafter until the time of the primary analysis. Radiographs were assessed at a central imaging center, as described previously, as were nonvertebral fractures (additional details are provided in the Supplementary Appendix, available at NEJM.org).[5]

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 12 months thereafter; in a subgroup of 167 patients, assessment was also performed at months 6 and 18. Serum concentrations of the bone-turnover markers β-isomer of C-terminal telopeptide of type I collagen (β-CTX; LabCorp) and procollagen type 1 N-terminal propeptide (P1NP; Covance) were measured in a subgroup of 277 patients.

Adverse events were reported by individual trial sites. Serious cardiovascular adverse events were adjudicated by the Duke Clinical Research Institute, and potential cases of osteonecrosis of the jaw and atypical femoral fracture were adjudicated by independent committees. Serum was tested for anti-romosozumab antibodies at day 1 and until month 24; samples that were positive for binding antibodies were assessed for neutralizing antibodies.

PRIMARY AND SECONDARY END POINTS

The primary end points of this trial were the cumulative incidence of new vertebral fracture at 24 months and the cumulative incidence of clinical fracture (nonvertebral and symptomatic vertebral fracture) at the time of the primary analysis. Bone mineral density at the lumbar spine, total hip, and femoral neck at 12 and 24 months and the incidence of nonvertebral fracture at the time of the primary analysis were key secondary end points. Other fracture categories, including hip fracture, were evaluated as additional secondary end points.

STATISTICAL ANALYSIS

The trial was powered to show superiority, with 94% power to detect a 30% lower risk of clinical fracture in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group at the time of the primary analysis and 95% power to detect a 50% lower risk of new vertebral fracture over a period of 24 months. If the differences in both primary end points were significant with the use of the Hochberg procedure,[12] a fixed-sequence testing procedure was to be used for bone mineral density and the key secondary end point of nonvertebral fracture to adjust for multiple comparisons and to maintain an overall significance level of 0.05. The nonvertebral-fracture end point was tested by means of a group sequential approach at the time of the primary analysis with the use of a Lan–DeMets alpha spending function (Fig. S1 in the Supplementary Appendix). All remaining secondary and exploratory efficacy end points were analyzed at a significance level of 0.05 (two-sided).

All analyses of treatment effect used an intention-to-treat approach. Analyses of vertebral-fracture end points included all randomly assigned patients with a baseline radiograph and at least one radiograph obtained after baseline. 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 analysis of vertebral fractures was also performed for all randomly assigned patients with the use of a multiple-imputation method that included treatment group and the following baseline variables: age, years since menopause, body-mass index, number of prevalent vertebral fractures, worst vertebral fracture severity, and bone mineral density T score at the lumbar spine, total hip, and femoral neck.

For the incidence of clinical, nonvertebral, major nonvertebral, hip, osteoporotic, symptomatic vertebral, and major osteoporotic fractures, the treatment groups were compared on the basis of a Cox proportional-hazards model with adjustment for age (<75 vs. ≥75 years), the presence or absence of severe vertebral fracture at baseline, and baseline bone mineral density T score at the total hip. For the incidence of new vertebral and new or worsening vertebral fractures, risk ratios were determined by means of the Mantel–Haenszel method, with treatment comparison assessed with the use of a logistic-regression model with adjustment for age (<75 vs. ≥75 years), the presence or absence of severe vertebral fracture at baseline, and baseline bone mineral density T score at the total hip. A total of 11 subgroup categories were prespecified and analyzed for treatment-by-subgroup interactions, as described previously.[5]

Percentage changes from baseline in bone mineral density were assessed in patients who had a baseline measurement and at least one measurement after baseline. Between-group comparisons of the percentage change from baseline in bone mineral density were analyzed by means of a repeated-measures model with adjustment for treatment, age category, the presence or absence of severe vertebral fracture at baseline, visit, treatment-by-visit interaction, and baseline bone mineral density as fixed effects, with machine type and interaction between baseline bone mineral density and machine type as covariates, with the use of an unstructured variance–covariance structure. Percentage changes from baseline in bone-turnover markers were assessed in patients enrolled in the biomarker substudy, as described previously.[5]

The safety analysis included all randomly assigned patients who received at least one dose of romosozumab or alendronate in the double-blind period. Incidence rates at the time of the primary analysis were cumulative and included all events in the double-blind and open-label periods in patients who received at least one dose of open-label alendronate. Odds ratios and confidence intervals were estimated for serious cardiovascular adverse events with the use of a logistic-regression model.

RESULTS

PATIENTS

A total of 4093 patients underwent randomization; 3654 patients (89.3%) completed 12 months of the trial (Fig. S2 in the Supplementary Appendix), and 3150 (77.0%) completed the primary analysis period. The reasons for discontinuation were similar in the two treatment groups (Fig. S2 in the Supplementary Appendix). The demographic and clinical characteristics of the patients at baseline were balanced between the two groups (Table 1). The mean age of the patients was 74.3 years, 99.0% had a previous osteoporotic fracture at 45 years of age or older, 96.1% had a prevalent vertebral fracture, and the mean bone mineral density T scores were –2.96 at the lumbar spine, –2.80 at the total hip, and –2.90 at the femoral neck.

EFFICACY

Fracture

Over a period of 24 months, treatment with romosozumab followed by alendronate resulted in a 48% lower risk of new vertebral fractures than alendronate alone (6.2% [127 of 2046 patients] vs. 11.9% [243 of 2047 patients]; risk ratio, 0.52; 95% confidence interval [CI], 0.40 to 0.66; P<0.001) with the use of multiple imputation for missing fracture status (Fig. 2A); similarly, a 50% lower risk with romosozumab was observed with the use of the last observation carried forward (Table S1 in the Supplementary Appendix). At the time of the primary analysis, romosozumab followed by alendronate resulted in a 27% lower risk of clinical fracture than alendronate alone (hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001) (Fig. 2B). The cumulative incidence of clinical fracture in the romosozumab-to-alendronate group was 9.7% (198 of 2046 patients) versus 13.0% (266 of 2047 patients) in the alendronate-to-alendronate group.

At the time of the primary analysis, romosozumab followed by alendronate also resulted in a 19% lower risk of nonvertebral fracture than alendronate alone (hazard ratio, 0.81; 95% CI, 0.66 to 0.99; P=0.04) (Fig. 2C), with fractures occurring in 178 of 2046 patients (8.7%) in the romosozumab-to-alendronate group versus 217 of 2047 patients (10.6%) in the alendronate-to-alendronate group (Table S1 in the Supplementary Appendix). Hip fractures occurred in 41 of 2046 patients (2.0%) in the romosozumab-to-alendronate group as compared with 66 of 2047 patients (3.2%) in the alendronate-to-alendronate group at the time of the primary analysis, representing a 38% lower risk with romosozumab (hazard ratio, 0.62; 95% CI, 0.42 to 0.92; P=0.02).

Between-group differences in favor of romosozumab were observed by month 12, including in new vertebral fractures (risk ratio, 0.63; 95% CI, 0.47 to 0.85) and clinical fractures (hazard ratio, 0.72; 95% CI, 0.54 to 0.96). The risk of nonvertebral fracture was 26% lower with romosozumab than with alendronate, but the difference was not significant (P=0.06). Table S1 in the Supplementary Appendix shows details of these and other fracture end points.

Bone Mineral Density

Patients who received romosozumab had greater gains in bone mineral density from baseline at all measured sites and at all time points than patients who received alendronate alone. The differential greater gains achieved by month 12 with romosozumab were maintained at month 36, after the transition to alendronate (P<0.001 for all comparisons) (Fig. 3A and 3B, and Fig. S3 and Table S2 in the Supplementary Appendix). In a subgroup of patients assessed every 6 months, greater gains with romosozumab were observed beginning at month 6 (P<0.001 for all comparisons) (Table S3 in the Supplementary Appendix).

Bone-Turnover Markers

Romosozumab increased levels of the bone-formation marker P1NP and decreased levels of the bone-resorption marker β-CTX within 12 months (Fig. 3C and 3D). After the transition to alendronate, levels of P1NP and β-CTX decreased and remained below baseline levels at 36 months. In patients receiving alendronate alone, levels of P1NP and β-CTX decreased within 1 month and remained below baseline levels at 36 months.

SAFETY

The incidences of adverse events and serious adverse events were similar overall between the two treatment groups during the 12-month double-blind period, and cumulative incidences were similar between the two groups during the primary analysis period (Table 2). In the first 12 months, injection-site reactions (mostly mild in severity) were reported in more patients receiving romosozumab (90 of 2040 patients [4.4%]) than in those receiving alendronate (53 of 2014 patients [2.6%]).

An imbalance in adjudicated serious cardiovascular adverse events was observed during the double-blind period, with 50 patients (2.5%) in the romosozumab group and 38 (1.9%) in the alendronate group reporting these events (odds ratio, 1.31; 95% CI, 0.85 to 2.00). A total of 16 patients (0.8%) in the romosozumab group and 6 (0.3%) in the alendronate group reported cardiac ischemic events (odds ratio, 2.65; 95% CI, 1.03 to 6.77), and 16 patients (0.8%) in the romosozumab group and 7 (0.3%) in the alendronate group reported cerebrovascular events (odds ratio, 2.27; 95% CI, 0.93 to 5.22), whereas heart failure, noncoronary revascularization, and peripheral vascular ischemic events not requiring revascularization were numerically lower in the romosozumab group (Table 2). Cardiovascular risk

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

Characteristic	Alendronate (N=2047)†	Romosozumab (N=2046)†
Age — yr	74.2±7.5	74.4±7.5
Age ≥75 yr — no. (%)	1071 (52.3)	1073 (52.4)
Ethnic group — no. (%)‡		
Hispanic	662 (32.3)	631 (30.8)
Non-Hispanic	1385 (67.7)	1415 (69.2)
Geographic region — no. (%)§		
Central or Eastern Europe or Middle East	798 (39.0)	835 (40.8)
Latin America	727 (35.5)	674 (32.9)
Western Europe, Australia, or New Zealand	264 (12.9)	269 (13.1)
Asia–Pacific or South Africa	216 (10.6)	213 (10.4)
North America	42 (2.1)	55 (2.7)
Body-mass index¶	25.36±4.42	25.46±4.41
Bone mineral density T score		
Lumbar spine	–2.99±1.24	–2.94±1.25
Total hip	–2.81±0.67	–2.78±0.68
Femoral neck	–2.90±0.50	–2.89±0.49
Previous osteoporotic fracture at ≥45 yr of age — no. (%)	2029 (99.1)	2022 (98.8)
Prevalent vertebral fracture — no. (%)	1964 (95.9)	1969 (96.2)
Grade of most severe vertebral fracture‖		
Mild	73 (3.6)	68 (3.3)
Moderate	570 (27.8)	532 (26.0)
Severe	1321 (64.5)	1369 (66.9)
Previous nonvertebral fracture at ≥45 yr of age — no. (%)	770 (37.6)	767 (37.5)
Previous hip fracture — no. (%)**	179 (8.7)	175 (8.6)
FRAX score††	20.0±10.1	20.2±10.2
Median serum β-CTX (IQR) — ng/liter‡‡	230.0 (137.0–388.0)	276.0 (166.0–407.0)
Median serum P1NP (IQR) — μg/liter‡‡	44.7 (32.7–64.4)	50.6 (37.5–64.7)
Median 25-hydroxyvitamin D (IQR) — ng/ml	27.6 (24.0–34.2)	28.4 (24.0–34.8)

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. Percentages may not total 100 because of rounding. β-CTX denotes β-isomer of C-terminal telopeptide of type I collagen, IQR interquartile range, and P1NP procollagen type 1 N-terminal propeptide.

† Shown is the number of patients who were randomly assigned to the 12-month double-blind period of the trial.

‡ Ethnic group was reported by the patient.

§ The countries included within the respective regions are shown in the Supplementary Appendix.

¶ 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 (see the Supplementary Appendix).

** Previous hip fracture excludes pathologic or high-trauma hip fracture.

†† The score on the Fracture Risk Assessment Tool (FRAX),[2] developed by the World Health Organization (www.shef.ac.uk/frax/), indicates the 10-year probability of major osteoporotic fracture, expressed as a percentage and calculated with bone mineral density.

‡‡ Data shown are for the 266 patients (128 in the alendronate group and 138 in the romosozumab group) who enrolled in the biomarker substudy and who had measurements of bone-turnover markers both at baseline and at one or more visits after baseline.

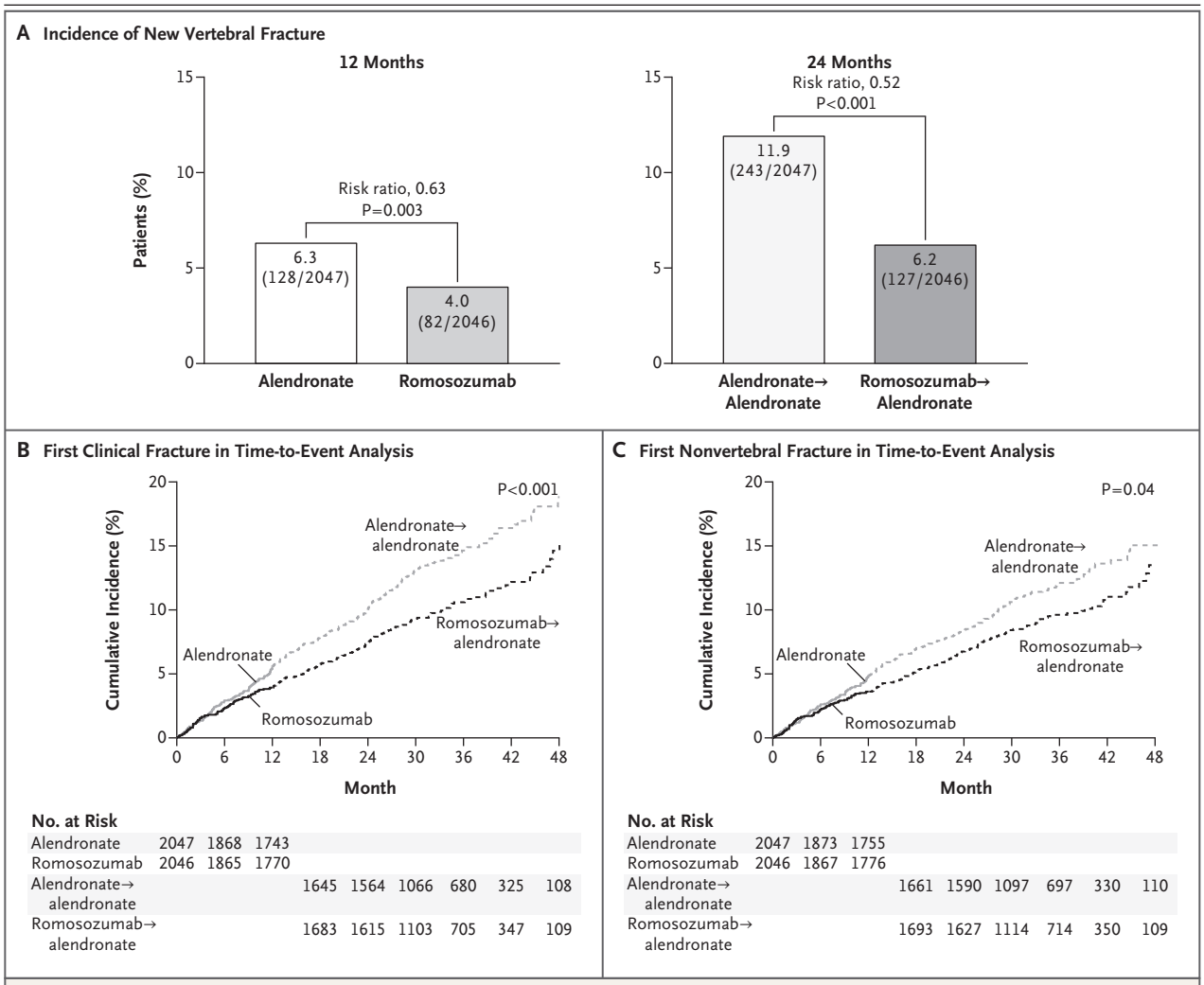

Figure 2. Incidence of New Vertebral, Clinical, and Nonvertebral Fracture.

The primary end points were the cumulative incidence of new vertebral fracture at 24 months (Panel A) and the cumulative incidence of clinical fracture at the time of the primary analysis (Panel B). For new vertebral fractures, the risk ratio was assessed among patients in the romosozumab group as compared with those in the alendronate group (at 12 months) and among patients in the romosozumab-to-alendronate group as compared with those in the alendronate-to-alendronate group (at 24 months). Risks presented are based on a multiple-imputation method for patients with missing fracture status. For Kaplan–Meier curves of the first clinical fracture and the first nonvertebral fracture (Panel C) in the time-to-event analysis, data from patients who withdrew or reached the end of the reporting period without having a fracture were censored at the last observation time. P values for clinical and nonvertebral fractures were calculated with the use of a Cox proportional-hazards model; P values for new vertebral fracture were calculated with the use of a logistic-regression model.

factors in patients with positively adjudicated cardiovascular events are shown in Table S4 in the Supplementary Appendix.

No adjudicated events of osteonecrosis of the jaw or atypical femoral fracture were reported in the 12-month double-blind period. During the open-label period, 2 events of osteonecrosis of the jaw (1 [<0.1%] in each treatment group) and 6 events of atypical femoral fracture (2 [<0.1%] in the romosozumab-to-alendronate group and 4 [0.2%] in the alendronate-to-alendronate group) were positively adjudicated.

During the first 18 months of the trial, binding anti-romosozumab antibodies were observed in 310 of 2028 patients (15.3%) in the romosozumab group; neutralizing antibodies were ob-

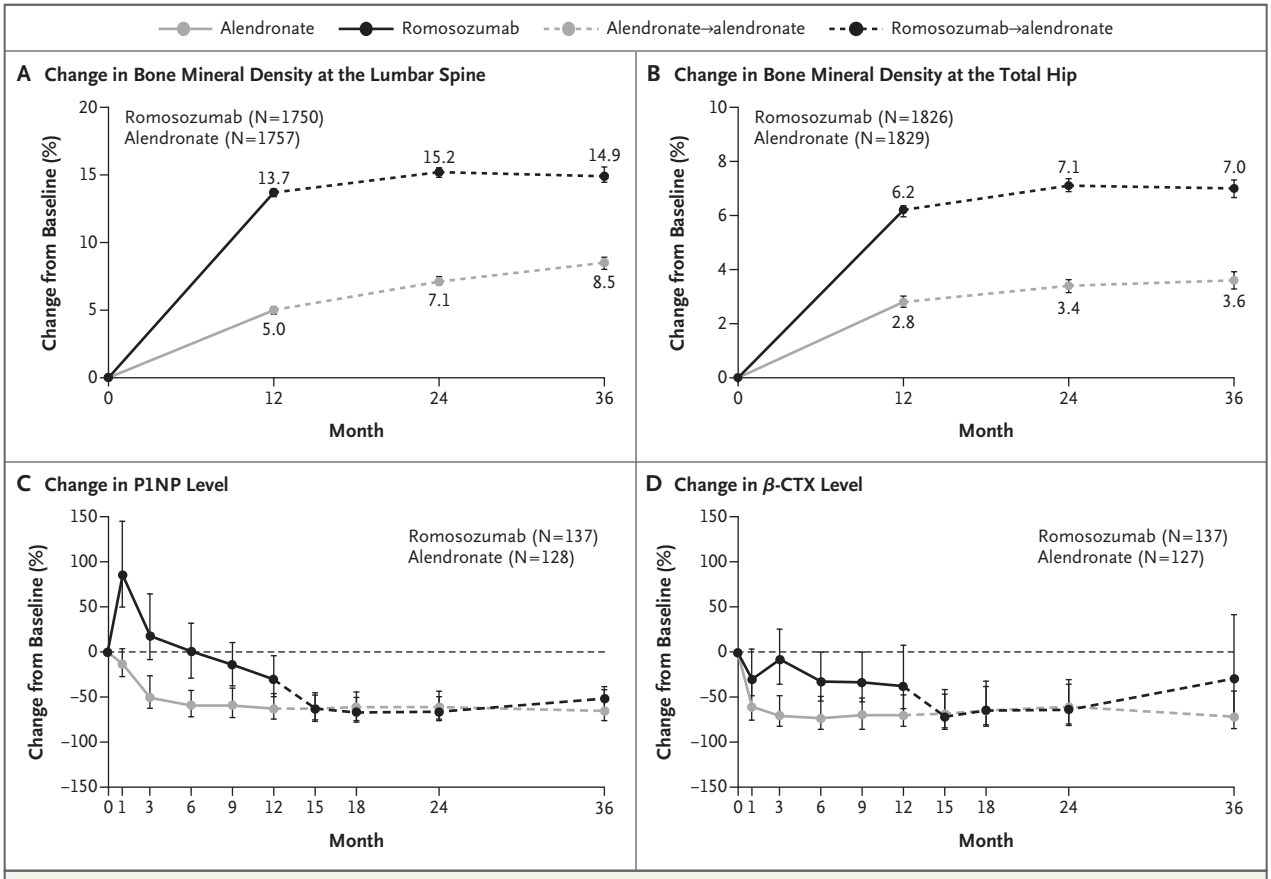

Figure 3. Percentage Change from Baseline in Bone Mineral Density and Levels of Bone-Turnover Markers.

The least-squares mean percentage changes in bone mineral density at the lumbar spine (Panel A) and total hip (Panel B) are shown for patients who had a baseline measurement and at least one measurement obtained at a postbaseline visit at or before month 36. Between-group comparisons of the percentage change in bone mineral density were analyzed with the use of a repeated-measures model; P<0.001 for all comparisons. The median percentage change from baseline in the levels of serum procollagen type 1 N-terminal propeptide (P1NP) (Panel C) and β-isomer of C-terminal telopeptide of type I collagen (β-CTX) (Panel D) are shown for a subgroup of 266 patients who had serial assessments of bone-turnover markers as part of the biomarker substudy and had a baseline measurement and at least one measurement after the baseline visit. The substudy population was representative of the overall trial population. Between-group comparisons of the percentage change from baseline in levels of P1NP and β-CTX were calculated with the use of the Wilcoxon rank-sum test; P<0.001 for the comparisons at months 1, 3, 6, 9, and 12. I bars indicate pointwise 95% confidence intervals for the values of bone mineral density and interquartile ranges for the levels of P1NP and β-CTX.

served in 12 patients (0.6%), with no detectable effect on relevant efficacy or safety (Tables S5 and S6 in the Supplementary Appendix).

DISCUSSION

In this phase 3 trial involving postmenopausal women with osteoporosis and a previous fracture, treatment with romosozumab for 12 months before alendronate was superior to alendronate alone with respect to the risks of a new vertebral, clinical, nonvertebral, and hip fracture. It is worth noting that romosozumab outperformed an effective drug; in large meta-analyses, alendronate has been shown to consistently reduce vertebral, nonvertebral, and hip fractures by up to 50%[13,14] among patients with osteoporosis. In our trial, the effect of romosozumab on the risk of fracture was rapid: the risks of new vertebral fracture and clinical fracture were significantly lower with romosozumab than with alendronate at 12 months, findings that imply both a near-term and persistent reduction in fracture risk with the initiation of romosozumab before anti-

Table 2. Adverse Events.

Event	Month 12: Double-Blind Period		Primary Analysis: Double-Blind and Open-Label Period*	
	Alendronate (N=2014)	Romosozumab (N=2040)	Alendronate to Alendronate (N=2014)	Romosozumab to Alendronate (N=2040)
	number of patients (percent)			
Adverse event during treatment	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Back pain†	228 (11.3)	186 (9.1)	393 (19.5)	329 (16.1)
Nasopharyngitis†	218 (10.8)	213 (10.4)	373 (18.5)	363 (17.8)
Serious adverse event	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Adjudicated serious cardiovascular event‡	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Noncoronary revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1)	0	5 (0.2)	2 (<0.1)
Death	21 (1.0)§	30 (1.5)	90 (4.5)§	90 (4.4)
Event leading to discontinuation of trial regimen	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
Event leading to discontinuation of trial participation	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)
Event of interest¶				
Osteoarthritis‖	146 (7.2)	138 (6.8)	268 (13.3)	247 (12.1)
Hypersensitivity	118 (5.9)	122 (6.0)	185 (9.2)	205 (10.0)
Injection-site reaction**	53 (2.6)	90 (4.4)	53 (2.6)	90 (4.4)
Cancer	28 (1.4)	31 (1.5)	85 (4.2)	84 (4.1)
Hyperostosis††	12 (0.6)	2 (<0.1)	27 (1.3)	23 (1.1)
Hypocalcemia	1 (<0.1)	1 (<0.1)	1 (<0.1)	4 (0.2)
Atypical femoral fracture‡	0	0	4 (0.2)	2 (<0.1)
Osteonecrosis of the jaw‡	0	0	1 (<0.1)	1 (<0.1)

* Incidence rates at the time of the primary analysis were cumulative and included all events in the double-blind and open-label period (to February 27, 2017) in patients who received at least one dose of open-label alendronate.

† Shown are events that occurred in 10% or more of the patients in either group during the double-blind period.

‡ Serious cardiovascular adverse events were adjudicated by the Duke Clinical Research Institute, and potential cases of osteonecrosis of the jaw and atypical femoral fracture were adjudicated by independent committees. Cardiovascular deaths include fatal events that were adjudicated as being cardiovascular-related or undetermined (and, therefore, possibly cardiovascular-related).

§ One patient had a non–treatment-related serious adverse event of pneumonia that was incorrectly flagged as death in the primary analysis snapshot and was not included in the analysis of fatal events.

¶ Events of interest were those that were identified by prespecified *Medical Dictionary for Regulatory Activities* search strategies.

‖ Prespecified events that were reported under osteoarthritis were osteoarthritis, spinal osteoarthritis, exostosis, arthritis, polyarthritis, arthropathy, monoarthritis, and interspinous osteoarthritis.

** The most frequent adverse events of injection-site reactions (occurring in >0.1% of the patients) in the romosozumab group during the double-blind period included injection-site pain (in 1.6% of the patients), erythema (1.3%), pruritus (0.8%), hemorrhage (0.5%), rash (0.4%), and swelling (0.3%).

†† Prespecified events reported under hyperostosis were exostosis (mostly reported as heel spurs), lumbar spinal stenosis, spinal column stenosis, cervical spinal stenosis, enostosis, extraskeletal ossification, and vertebral foraminal stenosis.

resorptive therapy in patients at high risk for fracture. Although the placebo-controlled Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) showed that 12 months of romosozumab had preventive effects with respect to vertebral and clinical but not nonvertebral fractures (potentially influenced by the lower baseline fracture risk),[5] the present trial assessed efficacy in a higher-risk population and showed broad beneficial effects on fracture risk as compared with a commonly used active drug.

Romosozumab rapidly increased bone mineral density, a finding consistent with those of previous studies.[5,15] We found significantly greater gains with romosozumab than with alendronate at the lumbar spine, total hip, and femoral neck by month 6. After the transition to alendronate, the significant difference between treatment groups was maintained. A plateau in bone mineral density was observed with ongoing alendronate therapy, a finding similar to results from other studies.[10]

Overall, adverse events and serious adverse events were balanced between the two groups. No cases of osteonecrosis of the jaw or atypical femoral fracture were identified during the period of romosozumab-alone treatment. Events were observed in the alendronate open-label period, with four events of atypical femoral fracture in the alendronate-to-alendronate group and two in the romosozumab-to-alendronate group. Adjudicated serious cardiovascular adverse events were more frequent in the romosozumab group than in the alendronate group during the double-blind period, with cardiac ischemic events and cerebrovascular events contributing to the imbalance.

There are theoretical considerations that sclerostin inhibition could be associated with cardiovascular risk. Sclerostin is constitutively expressed in the aorta[16-18] and up-regulated in foci of vascular and valvular calcification.[19-22] The function of sclerostin in the vasculature is unknown. Although sclerostin may function as a negative regulator of vascular calcification and sclerostin inhibition could promote vascular calcification, studies have shown conflicting results.[22,23] In long-term toxicology studies in rats[17] and monkeys,[17,24] there was no histologic or radiographic evidence of the development or exacerbation of vascular mineralization. Vascular calcification, although not specifically examined, has not been reported in *Sost* knockout mice or patients with sclerosteosis or van Buchem's disease.[25-28]

Further evaluation is needed to determine the cause of the observed imbalance in cardiovascular events. Such an imbalance was not seen in FRAME, a larger (7180 patients), placebo-controlled trial that enrolled a somewhat younger population with less advanced osteoporosis.[5] Another important contrast is the comparison drug. Alendronate has been associated with a reduction in the risk of cardiovascular disease in some studies[29] but not in two meta-analyses,[30,31] perhaps related to differences in the patient populations studied or the dosing of alendronate.[32]

Strengths of this trial include an active-comparator design involving patients with osteoporosis and a high risk of fracture. Limitations include the facts that the trial was not designed as a cardiovascular-outcomes trial and that it did not include a placebo control. Investigation is ongoing, including evaluation of cardiovascular risk factors; however, the small number of events makes interpretation difficult.

In conclusion, rapid gains in bone mineral density from bone-forming therapy with romosozumab were associated with a lower risk of fracture than with alendronate within 1 year and over the course of romosozumab followed by alendronate. Hip fractures were less frequent with romosozumab followed by alendronate than with alendronate alone, suggesting an important benefit and challenging the common treatment practice of first-line use of alendronate in women who have had a previous fracture. An imbalance in serious cardiovascular adverse events in comparison with alendronate was also found, which was not observed in a previous large, placebo-controlled trial.

Supported by Amgen, Astellas Pharma, and UCB Pharma.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their caregivers; the investigators and their teams who contributed to this trial; Deborah Wenkert (Amgen) for contributions to the trial execution and analysis planning; Rogely Boyce (Amgen), Li Chen (Amgen), Daria B. Crittenden (Amgen), Cesar Libanati (UCB Pharma), and Rajani Dinavahi (Amgen) for their careful review of earlier drafts of the manuscript; Wenjing Yang (Amgen) for statistical analysis support; and Lisa Humphries of Amgen and Martha Mutomba (contracted by Amgen) for medical writing and editorial assistance with an earlier draft of the manuscript.

REFERENCES

1. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761-7.
2. Kanis JA, Hans D, Cooper C, et al. Interpretation and use of FRAX in clinical practice. Osteoporos Int 2011;22:2395-411.
3. 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.
4. 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.
5. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375:1532-43.
6. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
7. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
8. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int 2000;11:83-91.
9. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756-65.
10. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet 1996; 348:1535-41.
11. Kendler D. Effects of 24 months treatment of teriparatide compared with risedronate on new fractures in postmenopausal women with severe osteoporosis: a randomized, double-dummy clinical trial (VERO trial). Presented at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, Florence, Italy, March 23–26, 2017.
12. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800-2.
13. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 2002;23: 508-16.
14. Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. Osteoporos Int 2005;16:468-74.
15. Keaveny TM, Crittenden DB, Bolognese MA, et al. Greater gains in spine and hip strength for romosozumab compared with teriparatide in postmenopausal women with low bone mass. J Bone Miner Res 2017;32:1956-62.
16. 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.
17. Chouinard L, Felx M, Mellal N, et al. Carcinogenicity risk assessment of romosozumab: a review of scientific weight-of-evidence and findings in a rat lifetime pharmacology study. Regul Toxicol Pharmacol 2016;81:212-22.
18. Didangelos A, Yin X, Mandal K, Baumert M, Jahangiri M, Mayr M. Proteomics characterization of extracellular space components in the human aorta. Mol Cell Proteomics 2010;9:2048-62.
19. Brandenburg VM, Kramann R, Koos R, et al. Relationship between sclerostin and cardiovascular calcification in hemodialysis patients: a cross-sectional study. BMC Nephrol 2013;4219.
20. Kramann R, Kunter U, Brandenburg VM, et al. Osteogenesis of heterotopically transplanted mesenchymal stromal cells in rat models of chronic kidney disease. J Bone Miner Res 2013;28:2523-34.
21. Rukov JL, Gravesen E, Mace ML, et al. Effect of chronic uremia on the transcriptional profile of the calcified aorta analyzed by RNA sequencing. Am J Physiol Renal Physiol 2016;310:F477-F491.
22. Zhu D, Mackenzie NC, Millán JL, Farquharson C, MacRae VE. The appearance and modulation of osteocyte marker expression during calcification of vascular smooth muscle cells. PLoS One 2011;6(5): e19595.
23. Claes KJ, Viaene L, Heye S, Meijers B, d'Haese P, Evenepoel P. Sclerostin: another vascular calcification inhibitor? J Clin Endocrinol Metab 2013;98:3221-8.
24. Ominsky MS, Boyd SK, Varela A, et al. Romosozumab improves bone mass and strength while maintaining bone quality in ovariectomized cynomolgus monkeys. J Bone Miner Res 2017;32:788-801.
25. Hamersma H, Gardner J, Beighton P. The natural history of sclerosteosis. Clin Genet 2003;63:192-7.
26. Li X, Ominsky MS, Niu QT, et al. Targeted deletion of the sclerostin gene in mice results in increased bone formation and bone strength. J Bone Miner Res 2008;23:860-9.
27. van Buchem F, Prick J, Jaspar H. Hyperostosis corticalis generalisata familiaris (van Buchem's disease). In: Excerpta medica. New York: Elsevier, 1976:1-205.
28. Vanhoenacker FM, Balemans W, Tan GJ, et al. Van Buchem disease: lifetime evolution of radioclinical features. Skeletal Radiol 2003;32:708-18.
29. Kang JH, Keller JJ, Lin HC. Bisphosphonates reduced the risk of acute myocardial infarction: a 2-year follow-up study. Osteoporos Int 2013;24:271-7.
30. Kim DH, Rogers JR, Fulchino LA, Kim CA, Solomon DH, Kim SC. Bisphosphonates and risk of cardiovascular events: a meta-analysis. PLoS One 2015; 10(4):e0122646.
31. Kranenburg G, Bartstra JW, Weijmans M, et al. Bisphosphonates for cardiovascular risk reduction: a systematic review and meta-analysis. Atherosclerosis 2016; 52:106-15.
32. Lu PY, Hsieh CF, Tsai YW, Huang WF. Alendronate and raloxifene use related to cardiovascular diseases: differentiation by different dosing regimens of alendronate. Clin Ther 2011;33:1173-9.