A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis

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Context: Globally, one in five men aged >50 years is predicted to experience an osteoporotic fracture. Because of the treatment gap in osteoporosis and the paucity of bone-forming agents for men, new osteoporosis treatments are needed.

Objective: To evaluate the safety and efficacy of romosozumab in men with osteoporosis.

Design: Phase III randomized BRIDGE study (placebo-controlled double-blind study evaluating the efficacy and safety of romosozumab in treating men with osteoporosis; ClinicalTrials.gov identifier, NCT02186171) for 12 months.

Setting: Thirty-one centers in Europe, Latin America, Japan, and North America.

Patients: Men aged 55 to 90 years with a baseline bone mineral density (BMD) T-score at the lumbar spine (LS), total hip (TH), or femoral neck of ≤ -2.5 or ≤ -1.5 with a history of a fragility nonvertebral or vertebral fracture.

Interventions: The subjects were randomized 2:1 to receive romosozumab 210 mg subcutaneously monthly or placebo for 12 months.

Main Outcome Measures: The primary efficacy endpoint was percentage change from baseline in LS BMD at month 12.

Results: In 245 subjects (163 romosozumab, 82 placebo), at month 12, the mean percentage change from baseline in the LS and TH BMD was significantly greater for the romosozumab group than for the placebo group (LS, 12.1% vs 1.2%; TH, 2.5% vs −0.5%; $P < 0.001$). Adverse events and serious adverse events were balanced between the two groups, with a numerical imbalance in the positively adjudicated cardiovascular serious adverse events [romosozumab, 8 (4.9%) vs placebo, 2 (2.5%)].

Conclusions: Treatment with romosozumab for 12 months increased the spine and hip BMD compared with placebo and was well tolerated in men with osteoporosis. **(*J Clin Endocrinol Metab* 103: 3183–3193, 2018)**

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Abbreviations: ANCOVA, analysis of covariance; BMD, bone mineral density; BTM, bone turnover marker; CTX, C-telopeptide of type 1 collagen; DXA, dual-energy X-ray absorptiometry; FN, femoral neck; LS, lumbar spine; P1NP, procollagen type 1 N-terminal propeptide; QM, once a month; TH, total hip.

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Osteoporosis affects 1 to 2 million men in the United States and 5.5 million men in the European Union, with 8 to 13 million men in the United States having osteopenia (1, 2). One in three fractures occur in men aged >60 years, with a lifetime osteoporosis fracture risk of 15%. The morbidity and mortality associated with fracture, in particular hip fracture, are greater for men than for women (3–5). Globally, the fracture incidence is expected to increase owing to the aging population (6). According to the Endocrine Society clinical practice guideline, pharmacological treatment is recommended for men aged >50 years who have experienced a spine or hip fracture, those with a T-score of ≤−2.5, and those with a high risk of fracture because of low bone mineral density (BMD) and/or clinical risk factors (7). Because of the large osteoporosis treatment gap (8), which is worse for men than for women (9), and because idiopathic male osteoporosis might have low bone turnover (10), a need exists for new strategies to improve osteoporosis care and for new treatment options for male osteoporosis, especially bone-forming agents.

Romosozumab is a humanized monoclonal antibody that binds and inhibits sclerostin. Sclerostin, which is secreted by osteocytes, has been shown to regulate bone formation. Inhibition of sclerostin by romosozumab is characterized by a dual effect—increasing bone formation and decreasing bone resorption (11, 12). Romosozumab has shown efficacy in the treatment of postmenopausal women with a low bone mass in a phase II study (11) and women with osteoporosis in a phase III study [FRAME (efficacy and safety of romosozumab treatment in postmenopausal women with osteoporosis)] (13). In FRAME, romosozumab treatment for 12 months was associated with a substantially greater increase from the baseline BMD at the lumbar spine (LS), total hip (TH), and femoral neck (FN), a significantly lower incidence of vertebral and clinical (nonvertebral plus symptomatic vertebral) fractures, and a numerically lower incidence of nonvertebral fractures compared with placebo (13). The present study evaluated the safety and efficacy of romosozumab in men with osteoporosis. This was a bridging study to extrapolate the fracture benefit observed in women with osteoporosis in FRAME to men by demonstrating that the BMD profile in the male population is comparable to that in the female population.

Materials and Methods

Study design

We performed a phase III BRIDGE study (placebo-controlled study evaluating the efficacy and safety of romosozumab in treating men with osteoporosis; ClinicalTrials.gov identifier, NCT02186171). Eligible subjects were randomized 2:1 to receive romosozumab 210 mg subcutaneously once a month (QM) or matched placebo for 12 months, with 500 to 1000 mg of calcium and 600 to 800 IU of vitamin D daily (Supplemental Fig. 1). Randomization was stratified by geographic region (Europe, North America, Latin America, and Japan). On completion of the 12-month treatment period, the subjects were followed up for an additional 3 months to evaluate the development of antibodies against romosozumab. Additional study details are available at EudraCT and ClinicalTrials.gov. The dosing strategy was modeled after that used in FRAME. Two phase I studies of men and women provided evidence of comparability between males and females in the pharmacokinetics of romosozumab (12, 14).

Study population

The key inclusion criteria were men aged 55 to 90 years; dual-energy X-ray absorptiometry (DXA) BMD T-score at the LS, TH, or FN of ≤–2.5 or ≤–1.5 with a history of fragility nonvertebral or vertebral fracture; and two or more vertebrae (L1 to L4) and one or more hip evaluable for DXA assessment. The key exclusion criteria were a T-score at the TH or FN of ≤–3.5, a history of hip fracture, the presence of metabolic or bone diseases or substantial laboratory abnormalities, or the current use of a medication affecting the bone metabolism (including oral and intravenous bisphosphonates, teriparatide, or any PTH analogs, and denosumab). The full exclusion criteria can be found in the Supplemental Materials.

Copies of the protocol and informed consent form were submitted to the independent ethics committee or institutional review board at each center for written approval. The present study was conducted in accordance with International Conference on Harmonization Good Clinical Practice and applicable regulatory requirements. All participants provided written informed consent before inclusion in the study.

Randomization and blinding

Randomization and the determination of treatment assignments occurred after all screening procedures had been performed and the subjects had met all the eligibility criteria. The subjects were randomized to the treatment assignment in a double-blind manner. Randomization, using a schedule prepared by the Amgen Central Randomization Group before the start of the study, was performed using an interactive voice response system. A subject's treatment assignment could be unblinded only when knowledge of the treatment was essential for further treatment of that patient during the present study.

Sample size considerations

The sample size was calculated using a two-sided, two-sample *t* test with a 5% significance level for the comparison of romosozumab with placebo by percentage change from baseline in the LS, TH, and FN BMD by DXA at month 12. A sample size of 225 subjects (150 romosozumab and 75 placebo) was expected to provide >99% power to assess the superiority for the LS, TH, and FN BMD changes at month 12, assuming a 10.0%, 4.0%, and 3.7% difference between romosozumab and placebo, respectively. This would also allow analysis of the safety and tolerability of romosozumab in men with osteoporosis. In addition, the present study used a 2:1 randomization of romosozumab to placebo subjects based on the recommendation of the Food and Drug Administration to expose ≥150 subjects to romosozumab, combined with the consideration of limiting the number of subjects exposed to placebo.

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Objectives

The primary objective of the present study was to evaluate the effect of treatment with romosozumab for 12 months compared with placebo on percentage change from baseline in the LS BMD as assessed by DXA in men with osteoporosis. The secondary objectives were to evaluate the effect of treatment with romosozumab compared with placebo on percentage change from baseline in (1) TH and FN BMD at 12 months and (2) LS, TH, and FN BMD at 6 months. The exploratory objectives were to evaluate the effect of treatment with romosozumab for 12 months compared with placebo on (1) the percentage change from baseline in the serum bone formation marker procollagen type 1 N-terminal propeptide (P1NP) and bone resorption marker C-telopeptide of type 1 collagen (CTX) and (2) the bone histologic findings and histomorphometry (15) in a bone biopsy substudy of a subset of subjects. The safety objective was to characterize the (1) safety and tolerability of treatment with romosozumab for 12 months compared with placebo, as determined by adverse events reported by the trial-site physicians, and (2) formation of anti-romosozumab antibodies during the 15-month trial period (12 months of treatment plus 3 months of follow-up). Potential cardiovascular-related serious adverse events, including deaths, and potential cases of osteonecrosis of the jaw and atypical femoral fracture were identified using predefined search strategies and adjudicated by their respective independent adjudication committees.

Outcome measures

BMD measurements were performed by DXA (GE Lunar, Madison, WI, or Hologic Inc., Marlborough, MA); the same instrument was used for all study procedures for a particular subject for the duration of the study. All DXA scans were submitted to and analyzed by a central imaging vendor (Synarc, Newark, CA), which provided instructions for the acquisition of bone scans. Quality control of DXA instruments included a completed quality assurance spine phantom form listing 25 most recent spine phantom scans and the calculated acceptable range. Cross-calibration used 20 volunteers scanned on old and upgraded systems and between two scanners at the relevant skeletal sites. BMD was measured at the LS and proximal femur. All T-scores were determined using reference data for whites and the mean BMD for a young, healthy, sex-matched adult population. Blood samples for evaluating bone turnover markers (BTMs) and anti-romosozumab antibodies were processed by a central laboratory and sent to an appropriate secondary laboratory or the study sponsor for analysis or distributed further to other laboratories. Additional information on anti-romosozumab antibodies is available in the Supplemental Materials. A subset of subjects underwent a transiliac crest bone biopsy at month 12; the methods are available in the Supplemental Materials.

Statistical analysis

Analysis of the primary efficacy endpoint of percentage change from baseline in the LS BMD at month 12 was conducted for subjects with a baseline and at least one postbaseline LS BMD measurement. An analysis of covariance (ANCOVA) model with last observation carried forward imputation was used. The ANCOVA model included treatment, baseline DXA BMD value, baseline testosterone level, and the stratification factor of geographic region (Europe, North America, Latin America, or Japan) as the main effects. Additional covariates of machine type (Hologic or GE Lunar) and machine type-by-baseline DXA BMD value interaction were included in the model to adjust for the effect of machine type on the baseline DXA BMD value. Summaries for the results included least squares mean point estimates of percentage change from baseline for each treatment arm. The two-sided 95% CI and associated *P* value were computed for the difference between the least squares means for romosozumab and placebo. A similar model was used for the primary efficacy endpoint stratified by subgroup: baseline testosterone level (<250 vs ≥ 250 ng/dL), baseline minimum T-score (≤ -2.5 vs > -2.5; minimum was defined as the lower value of the baseline BMD LS or FN T-score), baseline age (<70 vs ≥ 70 years), and baseline 10-year major osteoporotic fracture risk (less than the median vs the median or greater; the median was 7.62 for the overall study population). All subgroup analyses were *post hoc* analyses. In addition, percentage change from baseline in the TH and FN BMD at month 12 was evaluated by age subgroup (<70 vs ≥ 70 years).

For each secondary efficacy BMD endpoint, the percentage change from baseline in the DXA BMD used an ANCOVA model similar to that for the primary efficacy endpoint. The secondary efficacy endpoint hypotheses of different efficacy of romosozumab compared with placebo were tested, and the significance levels were adjusted using Hochberg methodology, using two-sided comparisons at an initial significance level of 0.05 for LS BMD at month 6 and FN and TH BMD at months 6 and 12. The analyses included subjects who had a baseline and at least one postbaseline DXA BMD measurement at the corresponding skeletal site. To control for multiplicity for assessment of the primary and secondary endpoints, a combination of hierarchical and Hochberg testing procedures was implemented.

For the exploratory endpoints assessing serum P1NP and CTX levels, descriptive statistics are presented stratified by treatment group at each visit for the absolute and percentage change from the baseline value. Graphs depicting the median and interquartile range by treatment group for percentage change over time are provided. The significance of the treatment difference for percentage change from baseline at each visit was assessed using a Van Elteren rank-sum test, adjusting for region as the stratification factor.

For the bone biopsy substudy, the bone histologic features and histomorphometry parameters are summarized descriptively. Cross-sectional evaluation of the histomorphometry parameters at month 12 was performed between treatment groups using the Wilcoxon rank-sum test to test for statistical significance.

For the 12-month treatment period, the subject incidence of all treatment-emergent adverse events was tabulated by system organ class and the preferred term coded by the Medical Dictionary for Regulatory Activities, version 18.1, for all subjects who had received at least one dose of the investigational product. Tabular data of the fatal adverse events, serious adverse events, adverse events leading to withdrawal from the investigational product, and events of interest are provided. The incidence and percentage of subjects who developed anti-romosozumab antibodies (binding and, if positive, neutralizing) at months 1, 3, 6, and 12 were tabulated stratified by treatment group. The analysis was

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repeated to include all results from the samples collected during the 3-month follow-up period.

Results

Subject disposition

A total of 245 subjects were enrolled in the present study; 163 were randomized to receive romosozumab 210 mg QM and 82 to placebo QM for 12 months (Table 1). The first subject was enrolled on 16 June 2014. The data cutoff date for the 12-month primary analysis was 27 January 2016. The subject disposition is shown in Fig. 1. The baseline demographic and disease characteristics were balanced between the two groups. Overall, the mean ± SD age was 72.1 ± 7.3 years, with 40.4% of subjects aged >75 years at enrollment. The mean body mass index was 25.1 ± 3.9 kg/m^2. The baseline T-scores were −2.3 ± 1.3 at the LS, −1.9 ± 0.6 at the TH, and −2.3 ± 0.5 at the FN. The regional distribution of the subjects was 66.1% in Europe, 14.3% in Latin America, 11.0% in Japan, and

Table 1. Baseline Characteristics

Characteristic	Romosozumab 210 mg QM (N = 163)	Placebo (N = 82)
Age, y	72.4 ± 7.4	71.5 (6.9)
Age <75 y, n (%)	93 (57.1)	53 (64.6)
Age ≥75 y, n (%)	70 (42.9)	29 (35.4)
BMD T-score		
LS	−2.22 ± 1.19	−2.33 ± 1.41
TH	−1.92 ± 0.59	−1.92 ± 0.65
FN	−2.34 ± 0.52	−2.30 ± 0.52
Serum P1NP, μg/L, median (IQR)	48.0 (33.6–59.7)	45.2 (34.3–57.9)
Serum CTX, ng/L, median (IQR)	346 (239–483)	350 (231–498)
Previous fracture,[a] n (%)	86 (52.8)	46 (56.1)
FRAX score with BMD[b]		
Major osteoporotic fracture	9.0 ± 5.2	8.6 ± 5.2
Major osteoporotic fracture, median (IQR)	7.7 (5.6–11.7)	7.2 (4.7–12.6)
Hip fracture	4.0 ± 3.3	3.6 ± 2.6
Hip fracture, median (IQR)	3.3 (1.8–4.9)	3.0 (1.6–4.8)
Previous osteoporosis medication, n (%)		
Oral bisphosphonate	1 (0.6)	5 (6.1)
PTH or PTH derivative	1 (0.6)	0 (0.0)
Calcitonin	2 (1.2)	2 (2.4)
Strontium ranelate	1 (0.6)	0 (0.0)
Fluoride	0 (0.0)	0 (0.0)
Calcitriol	5 (3.1)	2 (2.4)
Denosumab	3 (1.8)	3 (3.7)
History of smoking, n (%)		
Never	82 (50.3)	31 (37.8)
Former	54 (33.1)	34 (41.5)
Current	27 (16.6)	17 (20.7)
Cardiovascular risk factors,[c] n (%)	126 (77.3)	59 (72.0)
History of diabetes	55 (33.7)	33 (40.2)
History of hypertension	83 (50.9)	44 (53.7)
History of hypercholesterolemia	63 (38.7)	33 (40.2)
History of cardiovascular disease	108 (66.3)	54 (65.9)
History of central nervous system vascular disorder	15 (9.2)	10 (12.2)
Total testosterone, n (%)		
<250 ng/dL	39 (23.9)	14 (17.1)
≥250 ng/dL	123 (75.5)	68 (82.9)
Creatinine, μmol/L	88.3 (15.8)	90.8 (19.1)
25-hydroxyvitamin D, ng/mL	28.4 (8.9)	27.3 (6.7)

Data presented as mean ± SD, unless otherwise noted.

Abbreviations: FRAX, fracture risk assessment tool; IQR, interquartile range; N, number of subjects randomized.

[a]Included all vertebral fractures and nonvertebral fractures after 45 y of age.

[b]The score using the FRAX (16), developed by the World Health Organization (available at: www.shef.ac.uk/frax/) indicates the 10-y risk of a major osteoporotic fracture and hip fracture calculated with the BMD.

[c]A history of cardiovascular risk factors was assessed using the medical history electronic case report form relating to a history of diabetes, hypertension, hypercholesterolemia, cardiac disorder, vascular disorder, and central nervous system vascular disorders (high level group term in the Medical Dictionary for Regulatory Activities, version 18.1); the subjects could have more than one cardiovascular risk factor; therefore, subject incidence rates might not sum to the total.

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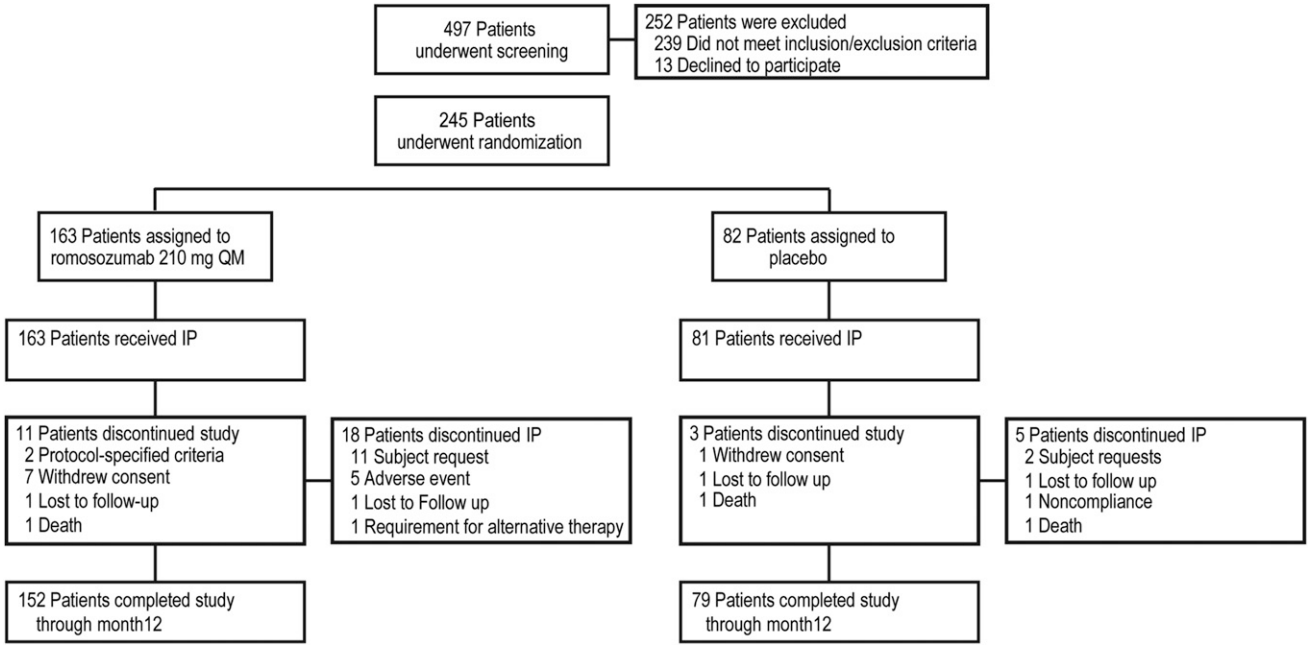

Figure 1. Consolidating standards of reporting trials diagram of BRIDGE showing flow of subjects screened for the study through week 12. IP, investigational product.

8.6% in North America. Of the 245 subjects, 73.5% were white, 11.0% were Asian, and 14.7% were "other." The romosozumab and placebo groups had a similar fracture risk (53% and 56% had a previous fracture, respectively), a similar FRAX (fracture risk assessment tool) with BMD 10-year fracture probability of a major osteoporotic fracture (clinical spine, hip, shoulder, and forearm; 9.0% and 8.6%, respectively), and a similar 10-year fracture probability of a hip fracture (4.0% and 3.6%, respectively).

Efficacy

After 12 months, the subjects receiving romosozumab had had a significantly greater mean increase from baseline in the LS BMD compared with the subjects receiving placebo (12.1% vs 1.2%; $P < 0.001$). Those receiving romosozumab also had significantly greater mean BMD increases from baseline (vs placebo) at the TH (2.5% vs −0.5%; $P < 0.001$) and FN (2.2% vs −0.2%; $P < 0.001$) at month 12 (Fig. 2). Statistically significant differences in LS, TH, and FN BMD were observed between the romosozumab and placebo groups as early as month 6 (LS, 9% vs 0.3%; and TH, 1.6% vs 0.2%; $P < 0.001$; FN, 1.2% vs 0.0%; $P = 0.0033$).

The percentage change from baseline in LS BMD at month 12 was evaluated by the baseline subgroups specified in the Statistical analysis section. The treatment effect of romosozumab vs placebo in the percentage change from baseline in LS BMD at month 12 was consistent for all subgroups assessed (Fig. 3). Although the *P* value for the treatment by subgroup interaction was statistically significant for testosterone level, no qualitative difference was found in the LS BMD change from baseline between the two subgroups. The subgroup of subjects with a testosterone level <250 ng/dL was relatively small; however, the difference in the percentage change from baseline in the LS BMD at 12 months between the romosozumab and placebo subgroups was still substantial. In addition, the treatment effect of romosozumab vs placebo in the mean percentage change from baseline in TH and FN BMD at month 12 was similar between the age subgroups: 2.6% for romosozumab vs −1.1 for placebo for age <70 years and 2.5% for romosozumab vs −0.3% for placebo for age ≥70 years at the TH and 2.6% for romosozumab vs 0.2% for placebo for age <70 years and 2.1% for romosozumab vs −0.5% for placebo for age ≥70 years at the FN.

As part of an exploratory objective, the percentage change from baseline in serum BTMs during the 12-month period was assessed. The P1NP levels increased early in subjects receiving romosozumab, peaking at month 1, when the median percentage change from baseline was 85.8% compared with 1.2% in the placebo group ($P < 0.001$; Fig. 4). By month 3, the median percentage change from baseline was 25.4% in the romosozumab group and −2.4% in the placebo group ($P < 0.001$). The median percentage change from baseline through the end of the study was −0.9% and −2.5% at month 6 ($P = 0.58$) and −19.7% and −6.2% at month 12 ($P = 0.0032$) for romosozumab and placebo,

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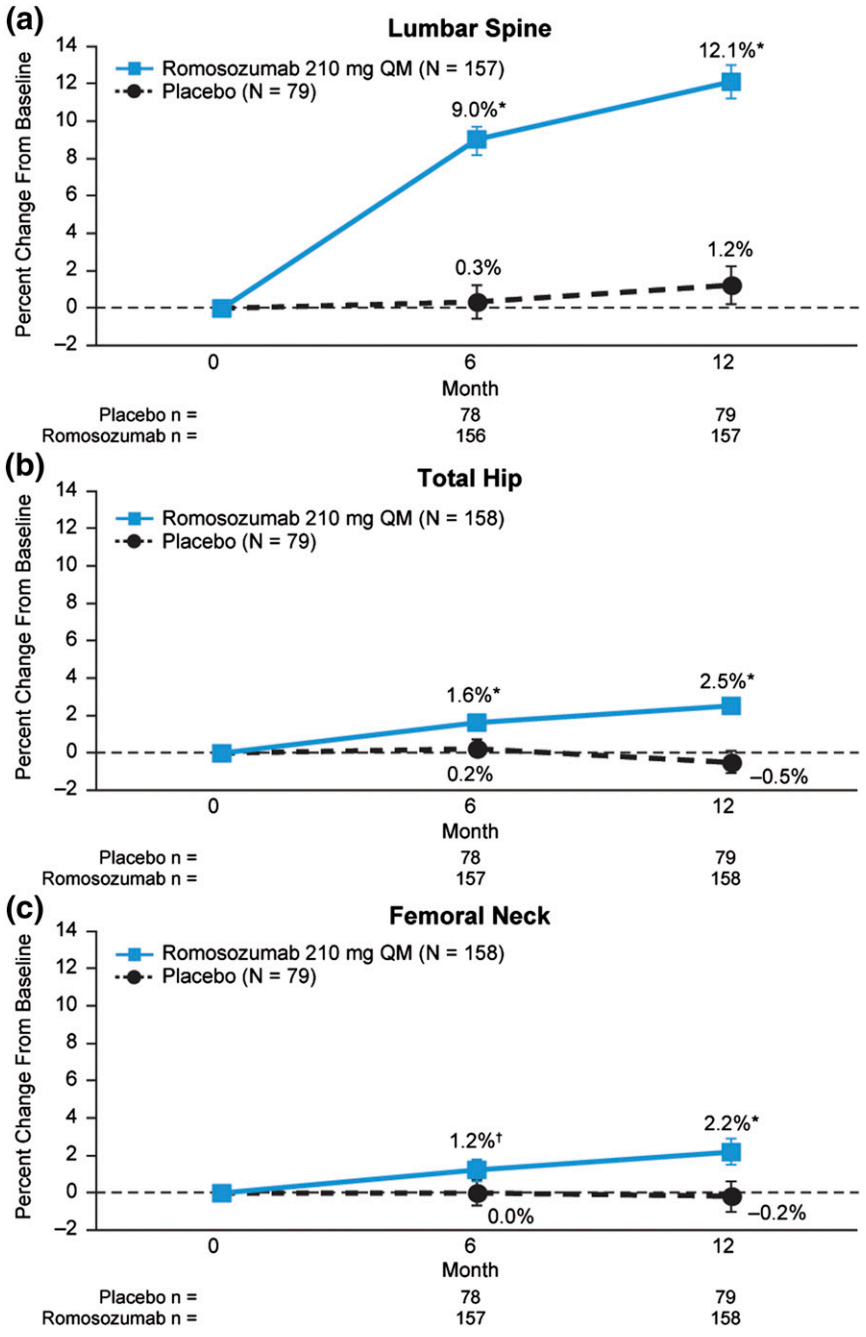

Figure 2. Percentage change from baseline in BMD stratified by visit. Percentage change from baseline in (a) LS, (b) TH, and (c) FN BMD stratified by visit. Data presented as least squares mean estimates with 95% CIs. *$P < 0.001$ vs placebo; †$P = 0.0033$. N, all randomized subjects with a baseline and one or more postbaseline measurements; n, number of subjects with values at baseline and at or before the time point of interest.

respectively. The CTX levels also changed early in the study in the subjects receiving romosozumab, with the greatest decrease at month 1, when the median change from baseline was −30.8% compared with −1.7% in those receiving placebo ($P < 0.001$; Fig. 4). The CTX levels in the romosozumab group remained less than those in the placebo group throughout the study: −16.8% vs −8.2% at month 3 ($P = 0.15$), −24.2% vs −5.8% at month 6 ($P < 0.001$), and −27.8% vs 0.7% at month 12 ($P < 0.001$).

Bone biopsy substudy

Twenty subjects (n = 11, romosozumab; n = 9, placebo) were enrolled in the bone biopsy substudy. Histomorphometric analyses at 12 months showed a reduction in bone resorption consistent with that previously observed in postmenopausal women with osteoporosis (Supplemental Materials).

Safety

The incidence rate of treatment-emergent adverse events was 75.5% in the romosozumab group and 80.2% in the placebo group (Table 2). Overall, 12.9% of the romosozumab group and 12.3% of the placebo group experienced a serious adverse event, and 3.1% and 1.2% experienced an adverse event leading to discontinuation of the investigational product, respectively. Incident fractures were reported in three subjects (1.8%) in the romosozumab group and two subjects (2.5%) in the placebo group. Injection-site reactions were reported for 5.5% of the subjects in the romosozumab group and 3.7% in the placebo group. The injection-site reactions reported in more than one subject included injection-site pain (n = 4) and injection-site erythema (n = 3) in the romosozumab group and injection-site pruritus (n = 2) in the placebo group. A numerical difference was found in the overall positively adjudicated cardiovascular serious adverse events between the romosozumab and placebo groups [8 (4.9%) vs 2 (2.5%), respectively; Table 2]. These included cardiac ischemic events [3 (1.8%) vs 0 (0.0%)], cerebrovascular events [3 (1.8%) vs 1 (1.2%)], and heart failure events [1 (0.6%) vs 0 (0.0%)] in the romosozumab and placebo groups, respectively (Table 2). In addition, one positively adjudicated cardiovascular death occurred in each treatment group through month 12 [0.6%, romosozumab (cardiorespiratory arrest); 1.2%, placebo (sudden death)]. During the 3-month follow-up period (months 12 to 15), one additional positively adjudicated cardiovascular death (unknown cause), which occurred in the first 12 months of the study, was reported for a subject

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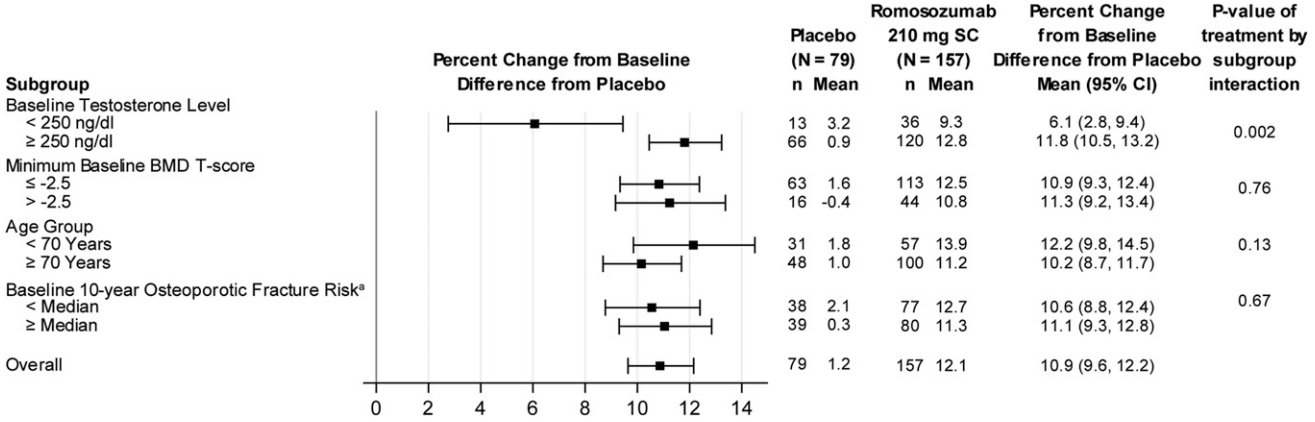

Subgroup	Placebo (N = 79) n	Mean	Romosozumab 210 mg SC (N = 157) n	Mean	Percent Change from Baseline Difference from Placebo Mean (95% CI)	P-value of treatment by subgroup interaction
Baseline Testosterone Level						
< 250 ng/dl	13	3.2	36	9.3	6.1 (2.8, 9.4)	0.002
≥ 250 ng/dl	66	0.9	120	12.8	11.8 (10.5, 13.2)	
Minimum Baseline BMD T-score						
≤ -2.5	63	1.6	113	12.5	10.9 (9.3, 12.4)	0.76
> -2.5	16	-0.4	44	10.8	11.3 (9.2, 13.4)	
Age Group						
< 70 Years	31	1.8	57	13.9	12.2 (9.8, 14.5)	0.13
≥ 70 Years	48	1.0	100	11.2	10.2 (8.7, 11.7)	
Baseline 10-year Osteoporotic Fracture Risk[a]						
< Median	38	2.1	77	12.7	10.6 (8.8, 12.4)	0.67
≥ Median	39	0.3	80	11.3	11.1 (9.3, 12.8)	
Overall	79	1.2	157	12.1	10.9 (9.6, 12.2)	

Figure 3. LS BMD by DXA percentage change from baseline to month 12 stratified by baseline subgroups. ANCOVA model adjusted for treatment, baseline DXA BMD, machine type, baseline testosterone level, geographic region (stratification factor), and machine type-by-baseline DXA BMD and using a variance structure allowing for heterogeneity between treatment groups. Minimum baseline BMD T-score was defined as the lower value of the LS and FN BMD T-scores. [a]Median baseline 10-year major osteoporotic fracture risk was 7.62 for the overall study population. N, number of subjects with a baseline and at least one postbaseline LS BMD measurement; SC, subcutaneously.

in the romosozumab group. That subject had previously had a positively adjudicated cardiovascular event (myocardial ischemia). Of the 10 subjects with positively adjudicated cardiovascular serious adverse events, all 8 in the romosozumab group and 1 of 2 in the placebo group had baseline cardiovascular risk factors. Two of the eight subjects in the romosozumab group and one of the two subjects in the placebo group with a positively adjudicated cardiovascular serious adverse event had positive findings in their cardiovascular medical history and were not taking cardioprotective drugs before the start of the present study. Overall, 126 subjects (77.3%) in the romosozumab group and 58 (71.6%) in the placebo group had positive findings in their cardiovascular-related medical history. Of these subjects, 93 (57.1%) in the romosozumab group and 50 (61.7%) in the placebo group had a baseline use of cardiovascular-related concomitant medications. No positively adjudicated cases of atypical femoral fracture or osteonecrosis of the jaw were reported.

Through month 15, all 163 subjects (100%) who received romosozumab had an on-study anti-romosozumab antibody test result. Of the 162 subjects with a postbaseline result, 28 (17.3%) had binding antibodies and 1 (0.6%) had neutralizing antibodies at any postbaseline visit through month 12 (Table 2). No subjects had binding antibodies at month 1. The percentage of subjects with binding antibodies at months 3, 6, and 12 was 4.4%, 16.9%, and 13.2%, respectively. During the 3-month follow up period, one subject who was positive for binding antibodies at month 12 tested positive for neutralizing antibodies at month 15. During the 15-month trial period, 35 subjects (19.6%) in the romosozumab group developed anti-romosozumab antibodies, 1 (0.6%) of whom had neutralizing antibodies. Anti-romosozumab antibodies had no detectable effect on efficacy or safety, because the percentage change in BMD at the lumbar spine from baseline to month 12 was similar in those with and without anti-romosozumab antibodies (12.6 and 12.8, respectively; Supplemental Table 1).

Discussion

In the present study of men with osteoporosis, romosozumab treatment for 12 months resulted in rapid and substantial BMD gains at the LS, TH, and FN compared with placebo. Evaluation of the BTMs showed early increases in bone formation and decreases in bone resorption in the subjects treated with romosozumab compared with placebo. Romosozumab was generally well tolerated. The overall subject incidence of adverse events (75.5% and 80.2%, respectively) and serious adverse events (12.9% and 12.3%, respectively) was comparable between the romosozumab and placebo groups. Although small numerical differences were observed in the positively adjudicated cardiovascular serious adverse events, more subjects with positively adjudicated cardiovascular serious adverse events and positive findings in their cardiovascular disease history were in the romosozumab group than in the placebo group. Among the subjects with positive findings in their cardiovascular disease history, the romosozumab group had fewer subjects using cardioprotective medications at baseline compared with the placebo group. Based on the subgroup analyses, romosozumab is effective for the treatment of a spectrum of men with osteoporosis, including those with hypogonadism.

Osteoporosis therapies have been studied extensively in women and to a lesser extent in men. Even in the

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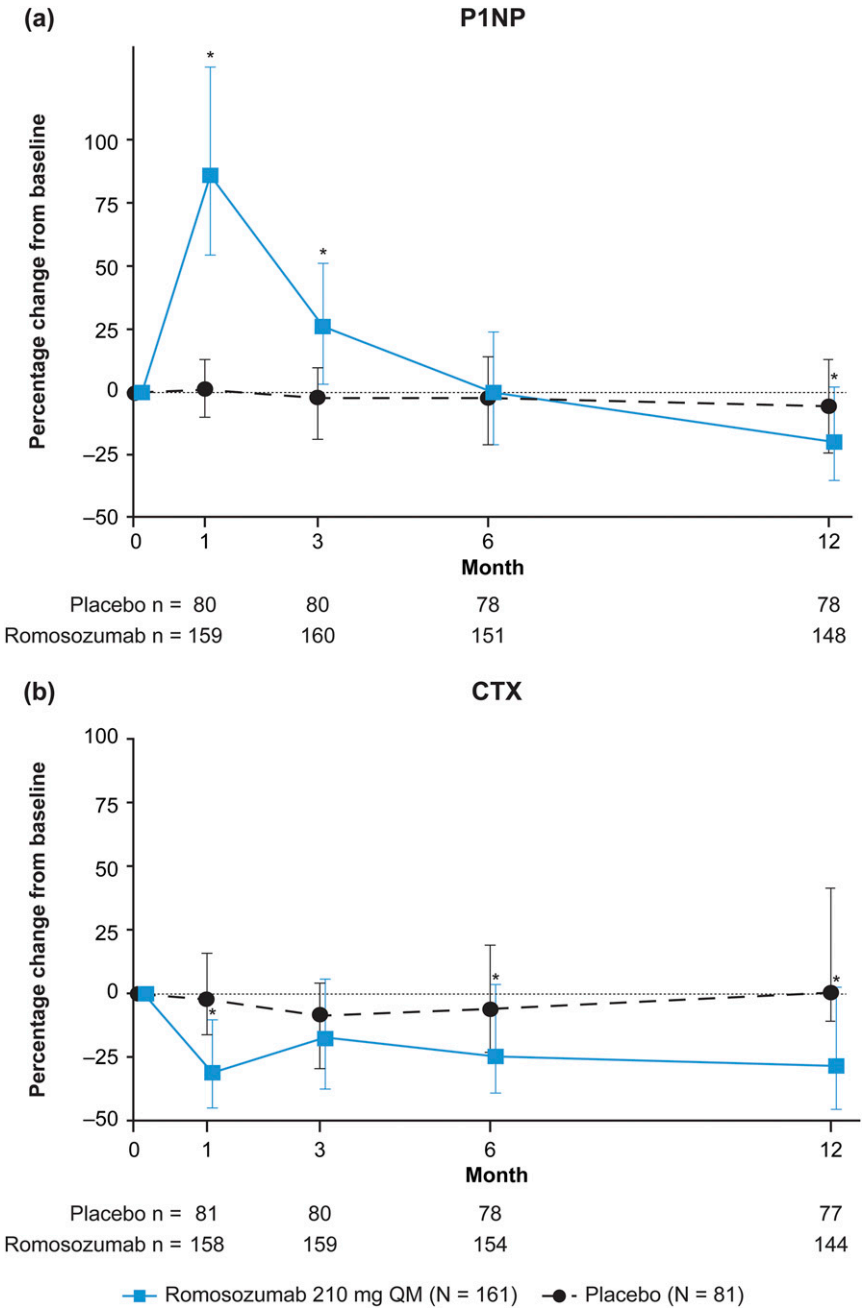

Figure 4. Percentage change from baseline in BTMs stratified by visit. Percentage change from baseline in (a) serum P1NP and (b) serum CTX levels stratified by visit. Data presented as median and interquartile range. $*P < 0.001$ vs placebo. N, all randomized subjects with a baseline and at least one postbaseline measurement; n, number of subjects with values at baseline and at the time point of interest.

studies of men, most outcome measures have included BMD and BTMs as surrogates for fracture efficacy, with no fracture endpoints, especially hip and nonvertebral fractures (17). Previous studies of men have included treatment with the bisphosphonates alendronate, risedronate, and zoledronic acid; denosumab; and teriparatide. All therapies have been shown to increase the BMD (18–25). Studies showing a reduction in vertebral fractures with alendronate, risedronate, zoledronic acid, denosumab, and teriparatide have been more limited and were not powered or designed to demonstrate antifracture efficacy, in particular for nonvertebral and hip fractures (19, 21, 24, 25).

In contrast to other approved agents for the treatment of male osteoporosis, teriparatide is an anabolic agent that has been shown to promote bone formation. Previous studies have demonstrated that teriparatide treatment increases bone remodeling, with increases in bone formation markers preceding increases in bone resorption markers, indicating a transient increase in modeling-based formation (10, 23, 26). Teriparatide treatment also results in substantial increases in BMD at the LS and FN compared with placebo (10, 23). In a substudy of a phase II clinical trial of postmenopausal women with a low bone mass, romosozumab 210 mg QM for 12 months resulted in significantly greater increases in both vertebral and femoral strength compared with teriparatide 20 μg daily (27). Finite element analyses of quantitative computed tomography scans at the spine and hip have shown that increases in bone strength at the spine can be attributed to increases in both cortical and trabecular compartments for both romosozumab and teriparatide treatment. However, increases in bone strength at the hip were attributed to both cortical and trabecular compartments for romosozumab compared with nonsubstantial changes in cortical and trabecular compartments for teriparatide (27). These data were further confirmed in a phase III trial of postmenopausal women transitioning from oral bisphosphonates to romosozumab 210 QM or teriparatide 20 μg daily (28). Similar to studies of other osteoporosis agents, a paucity of studies has described the effect of teriparatide on fractures in men. The prescribing information for teriparatide noted the occurrence of dose- and time-dependent risk of osteosarcoma in rats exposed to teriparatide (29, 30). However, this has not been observed in clinical trials or postmarketing studies (31, 32).

The rapid onset of treatment effect with romosozumab might provide protection to patients during the early stages of treatment. Subjects receiving romosozumab had attained a significantly greater BMD gain from baseline

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Table 2. Summary of Subject Incidence of Treatment-Emergent Adverse Events Through Month 12

Adverse event, n (%)	Romosozumab 210 mg QM (N = 163)	Placebo (N = 81)
Any adverse event	123 (75.5)	65 (80.2)
Serious adverse event	21 (12.9)	10 (12.3)
Adjudicated cardiovascular serious adverse event[a]	8[b] (4.9)	2 (2.5)
Cardiac ischemic event	3 (1.8)	0 (0.0)
Cerebrovascular event	3 (1.8)	1 (1.2)
Death[c,d]	2[e] (1.2)	1 (1.2)
Heart failure	1 (0.6)	0 (0.0)
Death	1 (0.6)	1 (1.2)
Leading to discontinuation of investigational product	5 (3.1)	1 (1.2)
Events of interest		
Hypocalcemia	0 (0.0)	0 (0.0)
Hypersensitivity	8 (4.9)	4 (4.9)
Injection-site reaction[f]	9 (5.5)	3 (3.7)
Malignancy	3 (1.8)	2 (2.5)
Hyperostosis	0 (0.0)	0 (0.0)
Osteoarthritis	8 (4.9)	4 (4.9)
Atypical femoral fracture[a]	0 (0.0)	0 (0.0)
Osteonecrosis of the jaw[a]	0 (0.0)	0 (0.0)
Incident fracture[g]	3 (1.8)	2 (2.5)
Subject incidence of anti-romosozumab antibody formation		
Binding antibodies	28 (17.2)	NA
Neutralizing antibodies	1 (0.6)	NA

Abbreviations: NA, not applicable; N, number of subjects who received one or more dose of investigational product; n, number of subjects with one or more event.

[a]Only included events adjudicated as positive by the independent adjudication committee.

[b]One subject presented with two cardiovascular serious adverse events.

[c]Adjudicated cardiovascular death events included fatal events adjudicated as cardiovascular-related or undetermined.

[d]Positively adjudicated cardiovascular deaths were due to cardiorespiratory arrest (romosozumab), sudden death (placebo), and unknown cause [romosozumab; occurred during the first y of the study and was reported during the follow-up period (mos 12 to 15)].

[e]One additional subject with a positively adjudicated cardiovascular serious adverse event experienced a fatal cardiovascular event (unknown cause) during the primary analysis period (through mo 12), which was reported after the primary analysis snapshot.

[f]Most reactions were reported as mild in severity.

[g]Incident fractures included vertebral and nonvertebral fractures—upper limb, rib, lumbar vertebral, thoracic vertebral, and humerus fractures.

by month 6 at the LS, TH, and FN and a statistically significant increase in P1NP and reduction in CTX by month 1 compared with subjects receiving placebo. The rapid onset of treatment benefits in this patient population has become increasingly important, because the risk of fracture increases after the occurrence of a fracture, especially the imminent risk within 1 year of the previous fracture (33–35).

In the bone biopsy specimens collected at month 12, all samples evaluable for histologic examination showed normal lamellar bone and normal mineralization. At month 12, the parameters of bone resorption had decreased and those of bone formation were unchanged in the romosozumab group compared with the placebo group. These results are consistent with the BTM results observed at month 12 (Fig. 4).

The BMD and BTM results in the present trial were consistent with those in postmenopausal women in FRAME. FRAME demonstrated that romosozumab treatment in women results in improvements in BMD, changes in BTMs, and reductions in vertebral and clinical fractures (13). The increases in BMD and changes in BTMs observed were similar to those observed in the present study (BRIDGE). In addition, the populations in BRIDGE and FRAME had a similar risk of fracture using the 10-year probability of major osteoporotic fracture by FRAX (Supplemental Fig. 2). Romosozumab also had a similar pharmacodynamic effect in men and women, as shown by the similar patterns of, timing of, and quantitative changes in the BTMs. Based on the observed BMD gains and similar fracture risk in this bridging study, the fracture reduction benefit observed in FRAME can be extrapolated to male patients with osteoporosis. This suggests that romosozumab treatment could also reduce fractures in men with osteoporosis, although a romosozumab antifracture study has not been performed in men, similar to what has been reported in previous bridging studies for alendronate and denosumab (21, 36, 37). Although the subjects in BRIDGE and FRAME had slightly different osteoporosis severity, based on the baseline minimum T-score, the subgroup analyses in BRIDGE have indicated that romosozumab is effective across a broad range of osteoporosis severity as assessed by the baseline BMD T-scores (Fig. 3). The pharmacokinetic analysis results were also similar in men and women through 12 months of treatment with romosozumab 210 mg QM, with exposure reaching a steady state at 3 months for both men and women.

Conclusions

In BRIDGE, treatment with romosozumab 210 mg subcutaneously QM increased the spine and hip BMD compared with placebo at months 6 and 12 and was well tolerated in men with osteoporosis. Romosozumab, which has a dual effect of increasing bone formation and decreasing bone resorption, appears to be a new and promising bone-forming treatment for men with osteoporosis. This dual effect is a unique aspect of romosozumab that has not been observed with any other agent approved for the treatment of osteoporosis.

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Author Contributions: E.M.L., L.C., and S.H. take responsibility for the data and accuracy of the analyses. E.M.L., T.B., S.G., K.L., P.D.M., and A.M. were involved in patient data collection and data acquisition. L.C. was involved in statistical analyses. All authors were involved in the analysis and interpretation of the data, drafting and revising the report and approving the final version, and had access to all the study data.

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Disclosure Summary: E.M.L. is employed by the New Mexico Clinical Research & Osteoporosis Center; has previously consulted for and received honoraria from Amgen Inc., Lilly, Radius, and Merck; has received grant support from Amgen Inc. and Lilly; and has served as a member of NOR and ISCD. T.B. is employed by the Medical University of Lublin and Lubelskie Centrum Diagnostyczne. S.G. is employed by Ghent University Hospital; has previously consulted for Amgen Inc. and UCB Pharma; has received grant support from Amgen Inc. and Novartis; and has received honoraria and served on a speaker's bureau for Amgen Inc.; and has served as a member of an advisory committee for UCB Pharma. P.D. Meisner is employed by and has received long-term incentives from UCB Pharma. P.D. Miller has previously consulted for, served as a member of an advisory committee, and received research grants from Amgen Inc. and Eli Lilly and Co; has served as a member of an advisory committee and received research grants from Shire Pharmaceuticals and Radius Health; and has consulted for and received research grants from Alexion, Regeneron, and Merck and Co. A.M. has previously consulted for Amgen Astellas Pharma KK. J.M. is employed by and has received stock from Amgen Inc. L.C. is employed by and has received stock from Amgen Inc. and serves on the board of directors for the Society for Clinical Trials. S.H. is employed by and has received shares from Amgen Inc. The remaining author has nothing to disclose.

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