

Effects of 24 Months of Treatment With Romosozumab Followed by 12 Months of Denosumab or Placebo in Postmenopausal Women With Low Bone Mineral Density: A Randomized, Double-Blind, Phase 2, Parallel Group Study

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ABSTRACT

Over 12 months, romosozumab increased bone formation and decreased bone resorption, resulting in increased bone mineral density (BMD) in postmenopausal women with low BMD (NCT00896532). Herein, we report the study extension evaluating 24 months of treatment with romosozumab, discontinuation of romosozumab, alendronate followed by romosozumab, and romosozumab followed by denosumab. Postmenopausal women aged 55 to 85 years with a lumbar spine (LS), total hip (TH), or femoral neck T-score ≤ -2.0 and ≥ -3.5 were enrolled and randomly assigned to placebo, one of five romosozumab regimens (70 mg, 140 mg, 210 mg monthly [QM]; 140 mg Q3M; 210 mg Q3M) for 24 months, or open-label alendronate for 12 months followed by romosozumab 140 mg QM for 12 months. Eligible participants were then rerandomized 1:1 within original treatment groups to placebo or denosumab 60 mg Q6M for an additional 12 months. Percentage change from baseline in BMD and bone turnover markers (BTMs) at months 24 and 36 and safety were evaluated. Of 364 participants initially randomized to romosozumab, placebo, or alendronate, 315 completed 24 months of treatment and 248 completed the extension. Romosozumab markedly increased LS and TH BMD through month 24, with largest gains observed with romosozumab 210 mg QM (LS = 15.1%; TH = 5.4%). Women receiving romosozumab who transitioned to denosumab continued to accrue BMD, whereas BMD returned toward pretreatment levels with placebo. With romosozumab 210 mg QM, bone formation marker P1NP initially increased after treatment initiation and gradually decreased to below baseline by month 12, remaining below baseline through month 24; bone resorption marker β -CTX rapidly decreased after treatment, remaining below baseline through month 24. Transition to denosumab further decreased both BTMs, whereas after transition to placebo, P1NP returned to baseline and β -CTX increased above baseline. Adverse events were balanced between treatment groups through month 36. These data suggest that treatment effects of romosozumab are reversible upon discontinuation and further augmented by denosumab. © 2018 The Authors *Journal of Bone and Mineral Research* published by Wiley Periodicals, Inc.

KEY WORDS: ROMOSOZUMAB; DENOSUMAB; BONE MINERAL DENSITY; POSTMENOPAUSAL OSTEOPOROSIS

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Introduction

Osteoporosis is a disorder of low bone mass and impaired bone strength resulting in an increased risk of fracture.⁽¹⁾ Sclerostin is an osteocyte-derived inhibitor of bone formation and stimulator of bone resorption.⁽²⁾ In animal models, inhibition of sclerostin improves bone structure and increases or normalizes bone mass and bone strength.^(3–5)

Romosozumab is a humanized anti-sclerostin antibody that stimulates bone formation and decreases bone resorption.⁽⁶⁾ The first 12 months of this phase 2 study in postmenopausal women with low bone mass evaluated the efficacy and safety of different romosozumab doses (70 mg, 140 mg, and 210 mg) administered by subcutaneous (s.c.) injection at 1- or 3-month intervals to identify the optimal romosozumab regimen.⁽⁷⁾ The higher doses of romosozumab (140 mg or 210 mg) administered monthly (QM) produced greater increases in bone mineral density (BMD) than treatment with the other romosozumab regimens, and by month 6, 210 mg romosozumab QM increased lumbar spine BMD greater than alendronate or teriparatide.⁽⁷⁾ In postmenopausal women with osteoporosis, romosozumab 210 mg QM for 12 months reduced the risk of new vertebral and clinical fractures.⁽⁸⁾ In another study in postmenopausal women with a fragility fracture,⁽⁹⁾ romosozumab 210 mg QM versus alendronate 70 mg weekly (QW) for 12 months followed by open-label alendronate 70 mg QW in both treatment arms reduced the risk of new vertebral fracture at month 24 and clinical, nonvertebral, and hip fractures at the time of the primary analysis.

This report describes the results of the continuation of the phase 2 study in which patients received romosozumab or alendronate/romosozumab for 24 months followed by 12 months of placebo or denosumab (Fig. 1). We evaluated the effects of romosozumab treatment up to 24 months

(focusing on the 210 mg QM dose that was evaluated in the phase 3 studies^(8,9)), the discontinuation of romosozumab, and switching between therapies (24 months of romosozumab followed by 12 months of denosumab or placebo and 12 months of alendronate followed by 12 months of romosozumab, followed by 12 months of denosumab or placebo). Thus, this study investigates the effects of several possible treatment sequences on surrogate endpoints and gives information about their consequences.

Materials and Methods

Study design

In this phase 2, international, multicenter, randomized, placebo-controlled, parallel group study, ambulatory postmenopausal women, aged 55 to 85 years with low bone mass (T -score ≤ -2.0 at the lumbar spine, total hip, or femoral neck and ≥ -3.5 at each of the three sites) and who were not at high risk for fracture were enrolled. Key exclusion criteria have been described⁽⁷⁾ and are provided in Supplemental Methods.

As previously published,⁽⁷⁾ we enrolled 419 women at 28 study centers in Argentina, Austria, Belgium, Canada, Denmark, Spain, and the United States. A total of 364 of the women were randomly assigned to one of five dosing regimens of s.c. romosozumab (70 mg, 140 mg, or 210 mg QM, or 140 mg or 210 mg every 3 months [Q3M]) or to one of two open-label comparators (70 mg of oral alendronate QW or 20 μ g of s.c. teriparatide daily) (Fig. 1).⁽⁷⁾ The remaining 52 women were randomly assigned to a group that received placebo injections QM or Q3M.

The randomization was performed by means of an interactive voice-response system according to a schedule prepared by the

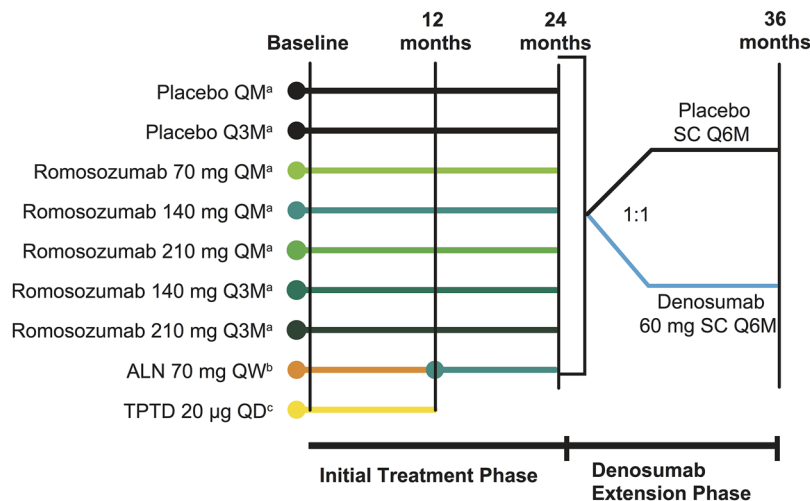


Fig. 1. Study schema. Administration of placebo and the various romosozumab doses was blinded, whereas alendronate and teriparatide were administered in an open-label fashion. All participants were instructed to take calcium (≥ 1 g) and vitamin D (≥ 800 IU) daily. Primary outcome measure was the percent change from baseline at month 12 in BMD at the lumbar spine for individual romosozumab groups and pooled placebo arms.⁽⁷⁾ ^aParticipants randomized to the placebo and romosozumab arms continued with their assigned treatment for an additional 12 months. ^bParticipants initially randomized to receive open-label alendronate started receiving romosozumab 140 mg QM at month 12. ^cParticipants initially randomized to receive teriparatide stopped the study at month 12 and were not included in the present analysis. ALN = alendronate; QM = every month; Q3M = every 3 months; Q6M = every 6 months; QW = every week; QD = every day; SC = subcutaneous; TPTD = teriparatide.

sponsor before initiation of the study. In the romosozumab and placebo groups, participants, study-site investigators, and study personnel were not aware of the study drug (romosozumab or placebo) and dose but were aware of the dosing schedule (QM or Q3M). Placebo groups received doses at the same frequency as the counterpart romosozumab groups.

Upon completion of the first 12 months, women in the romosozumab and placebo groups continued their assigned treatment for an additional 12 months (Fig. 1). Women in the alendronate group were transitioned to receive romosozumab 140 mg s.c. QM for an additional 12 months, and women in the teriparatide group ended study participation.

At the end of 24 months, eligible consenting participants were rerandomized (1:1) within their original treatment group to double-blind treatment with placebo or denosumab 60 mg (Amgen Inc., Thousand Oaks, CA, USA) every 6 months (Q6M) for 12 months (Fig. 1). Study participants were eligible for the extension if they had no contraindications for denosumab treatment, including hypocalcemia or hypersensitivity to denosumab; had not sustained a clinical vertebral fracture or fragility fracture of the wrist, humerus, hip, or pelvis; and did not have a decrease in BMD of $\geq 7.0\%$ from baseline during the initial 24-month treatment phase of the study. Throughout the study, all women were instructed to take calcium (≥ 1 g) and vitamin D (≥ 800 IU) daily.

The study protocol was approved by the ethics committee or institutional review board for each center, and the study was conducted in accordance with International Conference on Harmonization guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki. All participants provided written informed consent. This trial is registered at ClinicalTrials.gov, number NCT00896532.

Study procedures

BMD was measured at the lumbar spine and proximal femur by means of dual-energy X-ray absorptiometry at baseline, month 3, and every 6 months thereafter, and at the 1/3 radius at baseline and annually. BioClinica (Princeton, NJ, USA, previously known as Synarc) analyzed the scans and provided quality control of the scanners and the individual scans.

Blood was collected for serum chemistry, hematology, and determination of bone turnover marker levels. Levels of the bone-formation marker P1NP and the bone-resorption marker β -CTX were determined as previously described for the first 12 months⁽⁷⁾ and then at months 12 (+1 day), 13, 14, 15, 18, 21, 24, 27, 30, and 36. Serum levels of anti-romosozumab antibodies were assessed at baseline and months 15, 18, 21, 24, and 27. Samples were tested for romosozumab neutralizing activity in vitro as described.⁽⁷⁾

Adverse events were collected as observed by the investigator or reported by subjects.

Study outcomes

The primary endpoint was the percentage change from baseline in BMD at the lumbar spine after 12 months of treatment. Results for all enrolled participants through month 12 have been reported by McClung and colleagues.⁽⁷⁾ This report describes BMD, bone turnover markers, and safety results with up to 24 months of romosozumab therapy and after transition to denosumab or placebo for 12 months. The responses to the romosozumab 210 mg QM dose will be emphasized because this dose has been evaluated in phase 3 studies.^(8,9)

Statistical analysis

Participants initially randomized to all arms except to the teriparatide arm were included in the month 24 analysis. All participants in the two placebo dose groups (QM and Q3M) were pooled as one group for comparison to the other treatment groups. Details of statistical methods used for the first 24 months of this study are described in McClung and colleagues⁽⁷⁾ and are provided in Supplemental Methods.

Participants rerandomized at month 24 were included in the month 36 analysis, and all endpoints are summarized descriptively. Analysis of the percentage change from baseline in BMD and bone turnover markers included all participants who had undergone randomization, had a baseline value, and had a month 24 value and at least one subsequent measurement. Percentage changes in BMD from baseline to month 36 are presented with means and 95% confidence intervals (CIs), and percentage changes in BMD from month 24 to months 30 and 36 are presented with means and standard deviation. Percentage changes in P1NP and β -CTX from baseline or month 24 to months 27, 30, and 36 are presented with medians and interquartile ranges.

Safety analysis included all participants who underwent randomization and received at least one dose of a study drug during the first 12 months of the study and received at least one dose of blinded denosumab or placebo from months 24 to 36. Safety endpoints included the incidence and severity of adverse events; changes from baseline in vital signs, laboratory values, and electrocardiographic variables; and the incidence of the formation of anti-romosozumab antibodies.

Results

Participant disposition

A total of 419 women were enrolled into the study. Participants initially randomized to receive teriparatide stopped the study at month 12 and were not included in the present analysis. Participant disposition through month 36 is shown in Fig. 2. Of the 364 participants initially randomized (excluding the teriparatide arm), 315 (87%) completed the first 24 months and 49 (13%) withdrew from the study before completing the month 24 visit. The most common reasons for study discontinuation were consent withdrawn (22 [6%] participants) and adverse event (19 [5%] participants). Forty-eight of the 52 women in the romosozumab 210 mg QM group completed the 24-month study.

A total of 260 of the 315 participants who completed the first 24 months of the study were eligible and consented to be randomized in the denosumab extension phase (131, placebo; 129, denosumab) (Fig. 2). Of these, 248 (95%) completed the extension phase (Fig. 2). Of the 12 participants who discontinued study during the extension phase ($n = 8$, placebo; $n = 4$, denosumab), 2 did so because of an adverse event (both in the placebo group). Of the 48 women in the romosozumab 210 mg QM group who completed 24 months, 8 chose not to take part in the third study year. The remainder were randomized to receive placebo ($n = 20$) or denosumab ($n = 20$) during the denosumab extension.

Baseline demographics

Baseline demographic and key characteristics for participants in the first 24 months of the study were balanced across the randomized arms (Supplemental Table S1). Among all participants, the mean age was 67 years, 87.4% of participants were white, and the mean baseline BMD *T*-scores at the lumbar spine,

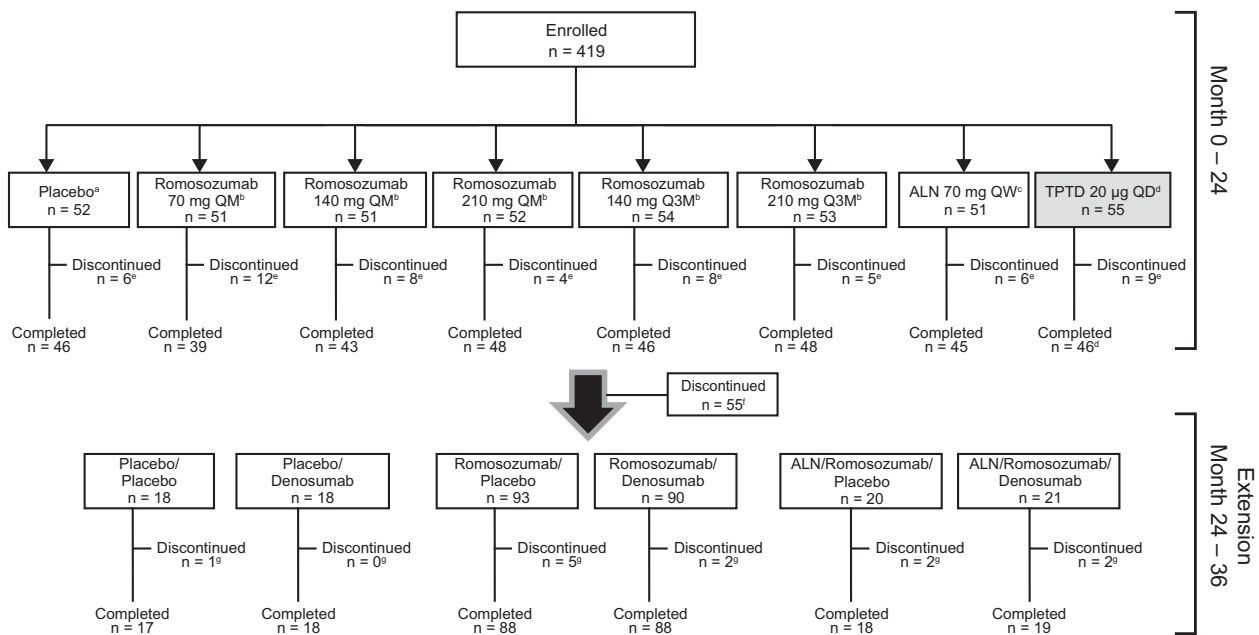


Fig. 2. Disposition of initially randomized participants during the first 24 months of the study and disposition of participants rerandomized at month 24. Participants were randomized 1:1:1:1:1:1:1:1 to the first 24 months of treatment. Administration of placebo and the various romosozumab doses was blinded, whereas alendronate and teriparatide were administered in an open-label fashion. At month 24, participants were rerandomized (1:1) within treatment group to placebo or denosumab (60 mg s.c. Q6M) for 12 months. ^aAt month 12, participants initially randomized to receive placebo continued to receive placebo up to month 24. ^bAt month 12, participants initially randomized to receive a specific dose and schedule of romosozumab continued to receive their assigned treatment up to month 24. ^cAt month 12, participants initially randomized to receive open-label alendronate were transitioned to receive romosozumab 140 mg QM treatment for 12 months, up to month 24. ^dParticipants initially randomized to receive teriparatide (gray box) stopped the study at month 12 and were not included in the present analysis. ^eCumulative number of participants who discontinued the study during the first 24 months. ^fParticipants were either ineligible for randomization or did not provide consent. ^gNumber of participants who discontinued the study between month 24 and month 36. ALN = alendronate; QM = every month; Q3M = every 3 months; QW = every week; QD = every day; SC = subcutaneous; TPTD = teriparatide.

total hip, femoral neck, and 1/3 radius were -2.29 , -1.56 , -1.95 , and -2.01 , respectively. Baseline demographic and key characteristics for participants who entered the 12-month denosumab extension were also balanced across the placebo and denosumab arms (Table 1).

Efficacy

BMD

At month 24, the largest gains in BMD from baseline were observed with romosozumab 210 mg QM. At the lumbar spine, BMD increased by 11.3% at month 12 and by 15.1% at month 24; at the total hip and femoral neck, BMD increased by 4.1% and 3.7% at month 12, and by 5.4% and 5.2% at month 24, respectively (all $p \leq 0.01$ versus placebo) (Fig. 3A, C, Supplemental Fig. S1A, and Supplemental Tables S2–4). Significant gains in BMD from baseline at the lumbar spine, total hip, and femoral neck were also observed at month 24 with the other romosozumab treatment groups (all $p \leq 0.01$ versus placebo) (Supplemental Tables S2–4). In the group switching from alendronate to romosozumab 140 mg QM, BMD at the lumbar spine, total hip, and femoral neck increased from baseline by 4.0%, 1.9%, and 1.3%, respectively, at month 12, and by 9.0%, 2.6%, and 2.6% at month 24 (Fig. 3B, D, Supplemental Fig. S1B, Supplemental

Tables S2–4). BMD at the 1/3 radius at month 24 remained comparable to placebo in all treatment groups and had decreased modestly compared with the original baseline (romosozumab 210 mg QM, -1.3% ; placebo, -1.4%) (Fig. 3E, F, Supplemental Table S5).

Participants who had received romosozumab 210 mg QM for 24 months and transitioned to denosumab during the extension continued to accrue BMD between month 24 and month 36, with additional mean gains of 2.6% at the lumbar spine, 1.9% at the total hip, and 1.4% at the femoral neck, as well as 0.4% at the 1/3 radius (Fig. 3A, C, E, Supplemental Fig. S1A, Supplemental Table S6). Over the full 36 months of therapy, the average increases in BMD were 19.4% at the lumbar spine and 7.1% at the total hip. For all romosozumab doses combined, transition to denosumab for 12 months also resulted in additional mean BMD gains at the lumbar spine (3.6%), total hip (2.2%), femoral neck (1.5%), and 1/3 radius (0.9%) from months 24 to 36 (Supplemental Table S6). Similar results were observed with denosumab therapy in the alendronate/romosozumab group (Fig. 3B, D, and F, Supplemental Fig. S1B, Supplemental Table S6), except that no gains were observed at the 1/3 radius. In contrast, BMD in the total hip decreased by 5.4%, returning to the pretreatment level, and lumbar spine BMD decreased by 9.3% but remained above baseline in participants who received placebo for 12 months after stopping romosozumab 210 mg QM.

Table 1. Baseline Demographic and Clinical Characteristics of Participants Rerandomized at Month 24

Initially randomized	Placebo ^a		Romosozumab ^a		Alendronate/romosozumab ^{a,b}		All ^a	
	Placebo ^c (N = 18)	Denosumab 60 mg Q6M ^c (N = 18)	Placebo ^c (N = 93)	Denosumab 60 mg Q6M ^c (N = 90)	Placebo ^c (N = 20)	Denosumab 60 mg Q6M ^c (N = 21)	Pooled placebo ^c (N = 131)	Denosumab 60 mg Q6M ^c (N = 129)
Rerandomized								
Age, mean years (SD)	69.3 (7.4)	64.2 (4.1)	66.2 (6.5)	66.8 (6.5)	66.6 (5.6)	67.0 (6.3)	66.7 (6.5)	66.5 (6.2)
White	17 (94.4)	14 (77.8)	79 (84.9)	76 (84.4)	19 (95.0)	18 (85.7)	115 (87.8)	108 (83.7)
BMD T-score, mean (SD)								
Lumbar spine	-2.27 (0.65)	-2.22 (0.58)	-2.35 (0.66)	-2.29 (0.74)	-1.82 (0.62)	-2.37 (0.54)	-2.25 (0.67)	-2.29 (0.69)
Total hip	-1.36 (0.62)	-1.15 (0.62)	-1.51 (0.61)	-1.68 (0.61)	-1.54 (0.62)	-1.49 (0.72)	-1.49 (0.61)	-1.57 (0.65)
Femoral neck	-1.72 (0.65)	-1.66 (0.50)	-1.94 (0.53)	-2.05 (0.55)	-1.88 (0.53)	-1.84 (0.69)	-1.90 (0.55)	-1.96 (0.58)
1/3 radius	-1.81 (1.00)	-1.71 (0.90)	-1.95 (1.00)	-2.09 (0.98)	-2.06 (0.76)	-2.09 (1.20)	-1.95 (0.96)	-2.03 (1.01)
Fracture history, n (%)								
Yes	7 (38.9)	6 (33.3)	23 (24.7)	27 (30.0)	7 (35.0)	8 (38.1)	37 (28.2)	41 (31.8)
Serum P1NP (µg/L), median (IQR)	38 (34, 45)	52 (46, 59)	52 (41, 64)	50 (38, 61)	45 (39, 55)	52 (42, 58)	49 (39, 62)	51 (40, 61)
Serum β-CTX (ng/L), median (IQR)	384 (312, 573)	504 (378, 673)	518 (396, 688)	536 (381, 661)	423 (328, 561)	558 (429, 616)	486 (362, 649)	535 (388, 651)

Q6M = every 6 months; BMD = bone mineral density; IQR = interquartile range; QM = every month.

N = number of participants randomized into the denosumab extension phase of the study.

^aRandomized treatment group up to month 24.

^bParticipants initially randomized to receive alendronate started receiving romosozumab 140 mg QM at month 12.

^cRandomized treatment group for the extension phase.

Bone turnover markers

In participants who received romosozumab 210 mg QM, rapid increases in the bone formation marker P1NP were observed after the initial dose (Fig. 4A). This increase was transitory. Values gradually decreased and were below baseline by month 12 and remained below baseline through month 24 (Fig. 4A, Supplemental Table S7). While most marker measurements were obtained predose, the one postdose measurement at 12 months + 1 week showed a small, transitory increase in P1NP compared with the predose measurement 1 week earlier (Supplemental Table S7).

Levels of the bone resorption marker β-CTX rapidly decreased from baseline in participants receiving romosozumab 210 mg QM after the first dose and remained below baseline through month 24 (Fig. 4B). Generally, similar responses were noted in the other treatment groups (Supplemental Table S8). For all doses of romosozumab evaluated, a transitory decrease in β-CTX was observed 1 week after the month 12 dose.

In participants treated with alendronate, P1NP and β-CTX were reduced from baseline in the first year (Fig. 4C, D, Supplemental Tables S7 and S8). Both markers increased after transition to romosozumab 140 mg QM but remained below baseline through month 24 (Fig. 4C, D, Supplemental Tables S7 and S8).

From months 24 to 36, both P1NP and β-CTX levels decreased in participants who transitioned from romosozumab 210 mg QM to denosumab. In participants who transitioned to placebo, P1NP levels gradually returned to pretreatment levels (Fig. 4A, Supplemental Table S9). β-CTX levels initially increased rapidly and substantially above baseline after romosozumab

discontinuation and remained above baseline at month 36 (Fig. 4B, Supplemental Table S10). Similar results were observed in the other romosozumab treatment groups (Supplemental Tables S9 and S10).

When participants treated with alendronate followed by romosozumab 140 mg QM transitioned to denosumab, both P1NP and β-CTX levels decreased and remained low through month 36 (Fig. 4C, D, Supplemental Tables S9 and S10). In participants who transitioned to placebo, both P1NP and β-CTX levels increased slowly toward baseline but remained below baseline through month 36 (Fig. 4C, D, Supplemental Tables S9 and S10).

Safety

In the first 24 months of the study, the subject incidences of adverse events and serious adverse events in the placebo group, the romosozumab 210 mg QM group, and the combined romosozumab groups were similar (Table 2). Serious adverse events reported in more than 1 participant in the combined romosozumab treatment groups were osteoarthritis, pneumonia, appendicitis, and breast cancer. Cardiovascular serious adverse events were investigator reported and collected using standard safety reporting procedures. Serious adverse events falling under cardiac, vascular, or nervous system disorders through month 24, and at month 36, were comparable between the treatment groups.

One fatal adverse event in the placebo group and 1 in the romosozumab (70 mg QM) group occurred in the first 12 months.⁽⁷⁾ No additional fatal adverse events occurred through month 24. Two subjects experienced fragility fractures, one each in the placebo group and the romosozumab 210 mg QM group (Table 2).

— Romosozumab 210 mg QM^a — Alendronate 70 mg QW^a - - - Denosumab 60 mg Q6M^b
— Pooled Placebo^a — Romosozumab 140 mg QM^a - - - Placebo Q6M^b

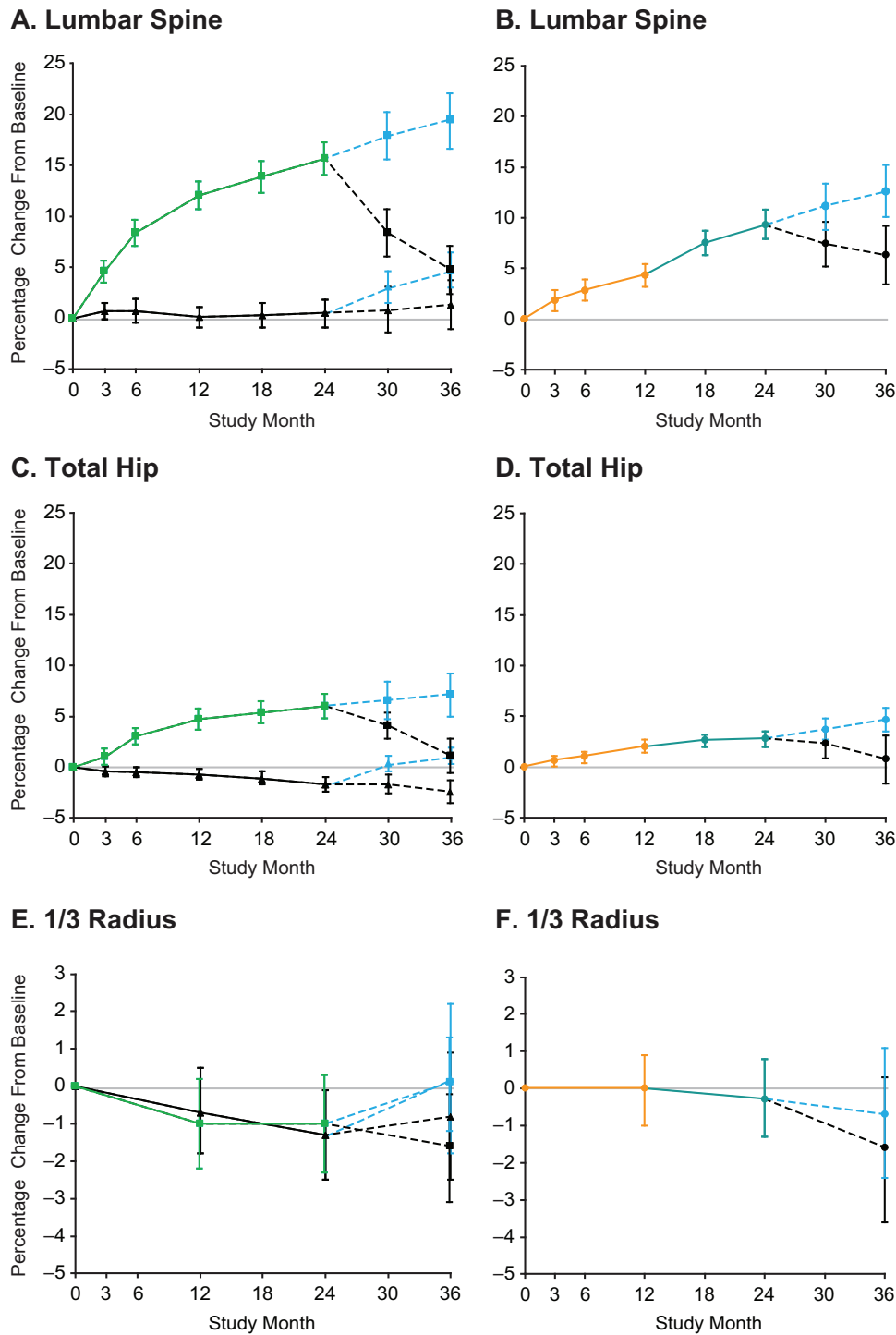


Fig. 3. Percentage change from baseline in BMD at the lumbar spine (A, B), total hip (C, D), and 1/3 radius (E, F) through month 36. Results include only participants who had received romosozumab 210 mg QM ($n = 40$) for 24 months and were then rerandomized (1:1) to receive denosumab 60 mg Q6M ($n = 20$) or placebo Q6M ($n = 20$) for another 12 months; participants who had received placebo (pooled) ($n = 36$) for 24 months and were rerandomized (1:1) to receive denosumab 60 mg Q6M ($n = 18$) or placebo Q6M ($n = 18$) for another 12 months; or participants who received alendronate for 12 months followed by romosozumab 140 mg monthly for 12 months ($n = 41$) and were rerandomized (1:1) to receive denosumab 60 mg Q6M ($n = 21$) or placebo ($n = 20$) for an additional 12 months. Data are means and bars indicate 95% CIs. ^aRandomized treatment group up to month 24. ^bRerandomized treatment group at month 24. QM = every month; Q6M = every 6 months.

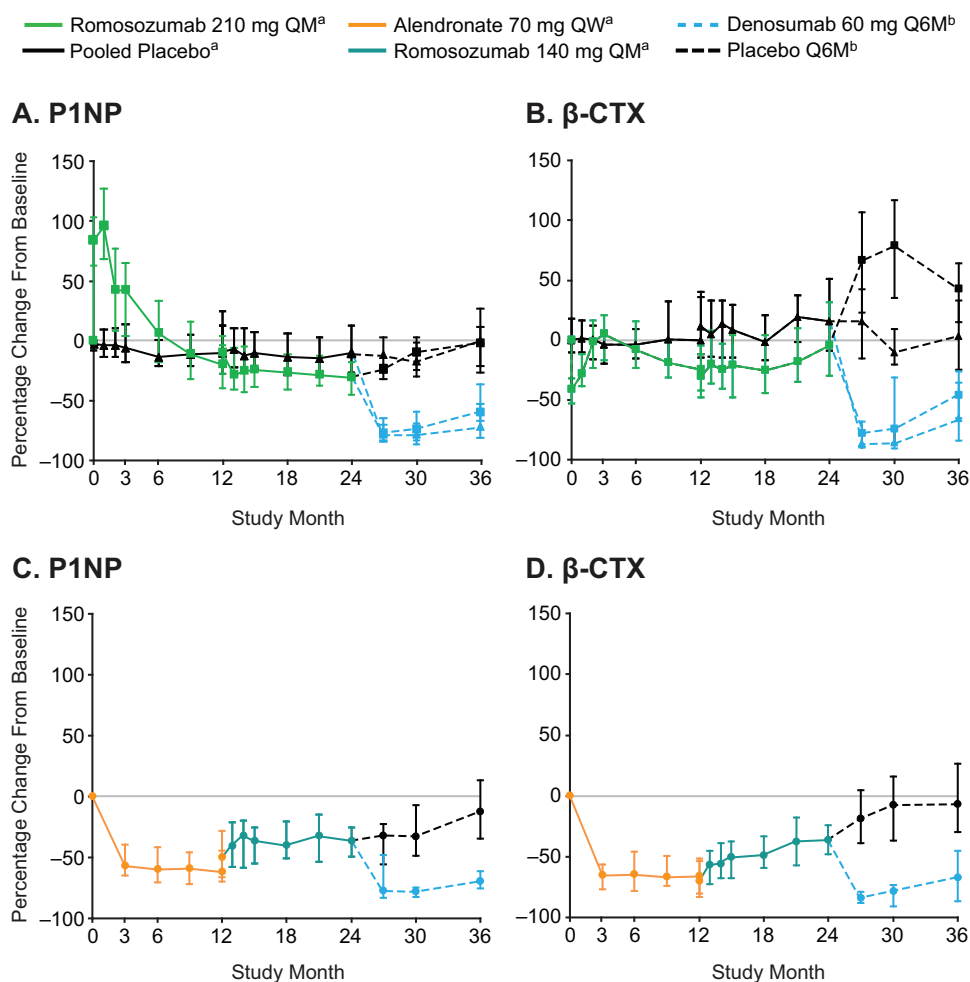


Fig. 4. Percentage change from baseline in bone turnover markers through month 36. Results include only participants who had received romosozumab 210 mg QM ($n = 40$) for 24 months and were then rerandomized (1:1) to receive denosumab 60 mg Q6M ($n = 20$) or placebo Q6M ($n = 20$) for another 12 months; participants who had received placebo (pooled) ($n = 36$) for 24 months and were rerandomized (1:1) to receive denosumab 60 mg Q6M ($n = 18$) or placebo Q6M ($n = 18$) for another 12 months; or participants who received alendronate for 12 months followed by romosozumab 140 mg monthly for 12 months ($n = 41$) and either denosumab 60 mg Q6M ($n = 21$) or placebo ($n = 20$) for an additional 12 months. Data shown are median changes in the bone-formation marker serum P1NP (A, C) and the bone-resorption marker serum β -CTX (B, D). Bars indicate interquartile ranges. ^aRandomized treatment group up to month 24. ^bRerandomized treatment group at month 24. QM = every month; Q6M = every 6 months.

Adverse events potentially associated with injection site reactions were observed more frequently with romosozumab than with placebo (4.0% in the placebo group versus 5.9% in the romosozumab 210 mg QM group, and 15.3% in the combined romosozumab groups through month 24). These were reported as mild, did not lead to study drug discontinuation or study withdrawal, and were generally nonrecurring with continued administration of romosozumab (subject incidence of injection site reactions from month 12 to month 24: 0% in the placebo group, 0% in the romosozumab 210 mg QM group, and 3.5% in the combined romosozumab groups).

Through month 24 of treatment with romosozumab, binding antibodies were identified in all the romosozumab groups (14.3% to 32.1%; 15.7% in the romosozumab 210 mg QM group), including the alendronate 70 mg QW/romosozumab 140 mg QM group (23.5%), with no apparent dose-related trend. Of these, antibodies with in vitro neutralizing activity were reported in 3 (5.8%) participants in the romosozumab 140 mg Q3M group,

4 (7.5%) in the romosozumab 210 mg Q3M group, and 1 (2.0%) in the romosozumab 210 mg QM group. As previously described, development of binding or neutralizing anti-romosozumab antibodies appeared to have no effect on the incidence of adverse events, pharmacokinetics, or pharmacodynamics.⁽⁷⁾

Adverse events reported during the extension with denosumab are shown in Table 3. The numbers of participants reporting adverse events and serious adverse events were similar across all groups that transitioned either to placebo or denosumab. None of the serious adverse events led to discontinuation from the study or investigational product in either treatment group. No deaths occurred during year 3 of the study.

The subject incidence of fragility fractures from months 24 to 36 was 5 (3.9%) in the placebo group and 4 (3.2%) in the denosumab group (Table 3). No vertebral fractures were reported during months 24 to 36 in participants who transitioned from romosozumab to placebo. Two participants

Table 2. Adverse Events With 24 Months of Romosozumab Therapy

	Treatment group		
	Placebo N = 50 n (%)	Romosozumab 210 mg QM N = 51 n (%)	Romosozumab All doses ^a N = 255 n (%)
Any adverse event ^b	48 (96.0)	48 (94.1)	245 (96.1)
Serious adverse event	9 (18.0)	6 (11.8)	36 (14.1)
Leading to study discontinuation	0 (0)	0 (0)	5 (2.0)
Death	1 (2.0)	0 (0)	1 (0.4)
Injection site reactions ^c	2 (4.0)	3 (5.9)	39 (15.3)
Fragility fractures ^{d,e}	1 (2.0)	1 (2.0)	1 (0.4)

QM = every month.

N = number of participants who received ≥ 1 dose of investigational product.

^aIncludes only participants who received romosozumab in the first 12 months and continued to receive romosozumab up to 24 months.

^bThe Medical Dictionary for Regulatory Activities v15.0 was used to code and report adverse events.

^cAdverse events potentially associated with injection site reactions included any of the following events occurring at the injection site: pain, hematoma, erythema, reaction, discomfort, hemorrhage, or rash.

^dDefined as all adverse events of fractures excluding locations in the skull, face, hand, foot, tooth, and excluding pathological fractures and fractures associated with severe trauma or a fall from higher than the height of a stool, chair, first rung on a ladder, or equivalent (>20 inches).

^eOne subject in the placebo group had a radius fracture event and one subject in the romosozumab 210 mg QM group had a radius fracture and an ulna fracture on the same day.

who transitioned from romosozumab to denosumab had reports of vertebral fractures; neither had received romosozumab 210 mg QM in the first 2 years. No atypical fractures were reported in any of the groups.

At month 36, the incidence of antibodies binding to romosozumab was 25.1% (45/179) in participants who had received romosozumab for the first 24 months; of these, 3.4% (6/179) were positive for romosozumab neutralizing antibodies. In the group of participants who had received romosozumab 210 mg QM, 7 (17.5%) and 1 (2.5%) had binding and neutralizing antibodies, respectively. For participants who had received

alendronate for the first 12 months and transitioned to romosozumab from months 12 to 24, the incidence of romosozumab binding antibodies was 18.4% (7/38), and none developed romosozumab neutralizing antibodies.

Discussion

In this extension of the phase 2 study, we explored four important questions related to treatment with romosozumab: 1) the efficacy and safety of 24 months of treatment with romosozumab, which is twice as long as the 12-month treatment regimen evaluated in the phase 3 program; 2) the response to romosozumab in patients who had taken alendronate for 12 months; 3) the effects of discontinuing therapy on BMD and bone turnover markers; and 4) the effect of a follow-on treatment with denosumab after 2 years of romosozumab.

Continuing romosozumab treatment for a second year resulted in further increases in BMD at the lumbar spine and proximal femur. However, the BMD increments during the second year of romosozumab treatment were smaller than those observed during the first year, consistent with the bone turnover marker results indicating reductions in indices of bone formation and bone resorption during the second year of romosozumab therapy. Thus, although there was incremental benefit in the second year of treatment without new safety signals, the greatest benefit of romosozumab was achieved in the first year of treatment in this phase 2 study. Based in part on these observations, the phase 3 studies with romosozumab were designed to evaluate the effect of therapy for 12 months followed by anti-remodeling agents. In the recent report of the FRAME study by Cosman and colleagues,⁽⁸⁾ the risk of vertebral fracture was reduced by 73% after 12 months of romosozumab treatment compared with placebo, and by 75% with 12 months of follow-on treatment with denosumab compared with the group that received placebo for 12 months followed by denosumab for 12 months. Similarly, in the ARCH study,⁽⁹⁾ romosozumab for 12 months followed by alendronate reduced the risk of new vertebral fracture over 24 months (48%) and that

Table 3. Adverse Events Starting in the Extension Phase (Month 24 to Month 36) Following Romosozumab Discontinuation and Transition to Placebo or Denosumab

	Treatment group	
	Placebo N = 127 n (%)	Denosumab 60 mg Q6M N = 125 n (%)
Any adverse event ^a	96 (75.6)	99 (79.2)
Serious adverse event	7 (5.5)	8 (6.4)
Leading to study discontinuation	2 (1.6)	0 (0)
Death	0 (0)	0 (0)
Injection site reaction ^b	0 (0)	1 (0.8)
Fragility fractures ^c	5 (3.9)	4 (3.2)

Q6M = every 6 months.

N = number of participants who received ≥ 1 dose of investigational product.

^aThe Medical Dictionary for Regulatory Activities v15.1 was used to code and report adverse events.

^bAdverse events potentially associated with injection site reactions included any of the following events occurring at the injection site: pain, hematoma, erythema, reaction, discomfort, hemorrhage, or rash.

^cDefined as all adverse events of fractures excluding locations in the skull, face, hand, foot, tooth, and excluding pathological fractures and fractures associated with severe trauma or a fall from higher than the height of a stool, chair, first rung on a ladder, or equivalent (>20 inches).

of clinical (27%), nonvertebral (19%), and hip fractures (38%) at the time of the primary analysis versus alendronate alone. The risk reductions in new vertebral (37%) and clinical fractures (28%), compared with alendronate, were already significant after 12 months.

Unlike the large increases in BMD at the lumbar spine and total hip, BMD at the 1/3 radius site was not affected by romosozumab therapy, whereas the small decrease observed in the placebo group was somewhat attenuated by alendronate. The clinical significance of these observations is unclear because, as stated above, romosozumab followed by alendronate was significantly more effective in reducing the risk of nonvertebral and hip fractures than was therapy with alendronate alone.⁽⁹⁾

The response to romosozumab 140 mg QM in patients previously treated with alendronate is of interest because many patients who might be candidates for romosozumab will have already received bisphosphonate therapy. The additional gains in BMD observed in this group during the second year of the study (5% at the lumbar spine and 0.7% at the total hip) were only slightly less than observed in treatment-naïve women who had received that dose of romosozumab during year 1 of the study (5.5% and 1.3% in the lumbar spine and total hip, respectively).⁽⁷⁾ This is consistent with data from a recently published study⁽¹⁰⁾ where 12 months of treatment with romosozumab 210 mg QM, evaluated in phase 3 studies, was compared with treatment with teriparatide 20 µg daily in participants transitioning from oral bisphosphonate and showed greater increases in bone mass and bone strength (by finite element analysis) than treatment with teriparatide.

In subjects who were treated with romosozumab for 24 months followed by denosumab for 12 months, markers of bone remodeling decreased promptly and additional gains in BMD at both the hip and spine were observed. The average BMD increases from baseline of 19.4% at the lumbar spine and 7.1% at the total hip with 2 years of romosozumab 210 mg QM followed by 12 months of denosumab 60 mg Q6M were similar to the responses achieved with 6 to 8 years of denosumab therapy.⁽¹¹⁾ Although direct comparisons cannot be made, these increases also compare favorably with increases of approximately 15% at the lumbar spine and 6% at the total hip in patients who received teriparatide alone or in combination with denosumab for 2 years followed by denosumab in the third year.⁽¹²⁾

As expected from the clinical pharmacology of romosozumab, the inhibitory effects on markers of bone remodeling resolved quickly upon discontinuation of therapy. P1NP, a marker of bone formation, returned to the level observed in placebo-treated patients, whereas β-CTX, a marker of bone resorption, increased above pretreatment levels before returning toward baseline. BMD at the lumbar spine and total hip declined toward baseline after discontinuation. Similar responses were observed upon discontinuation of romosozumab, a different humanized anti-sclerostin antibody, after 12 months of treatment.⁽¹³⁾ These data are also similar to the rebound in bone turnover and rapid decrease in BMD upon discontinuing non-bisphosphonate anti-remodeling agents such as estrogen, denosumab, and odanacatib, changes that are associated with rapid loss of vertebral fracture protection.^(14–18) Such results highlight the need for a follow-on treatment with an anti-remodeling agent after discontinuation of romosozumab to maintain or possibly enhance the benefits of the treatment, as was observed in the subjects randomized to denosumab after stopping romosozumab.

Other than mild injection site reactions, no important safety issues related to therapy were identified in patients who received 24 months of romosozumab or during the follow-on year of denosumab therapy. This is similar to the safety profile noted in the much larger group of patients who received 12 months of romosozumab 210 mg QM followed by 12 months of denosumab therapy in the FRAME study.⁽⁸⁾ Although romosozumab-binding antibodies were detected, this occurred predominately during the first 12 months of therapy and was not associated with measurable impairments of clinical response or with adverse effects.

The major strength of our study is that it provides safety and efficacy data on treatment with romosozumab in women with osteoporosis for up to 2 years and clinically relevant patterns of sequential therapy with romosozumab and anti-remodeling agents. However, the findings from this study should be considered in the context of several limitations, including the small sample sizes in the individual dosing groups, short follow-up periods, use of surrogate outcomes (percentage changes in BMD and bone turnover markers) for efficacy evaluation, and absence of a current best practice comparator group such as 3 years of a potent antiresorptive agent. In addition, the comparator group treated with alendronate/romosozumab was exposed to a lower dose of romosozumab (140 mg QM) than the group treated with romosozumab 210 mg QM for 2 years. Therefore, this study does not address the question of how the sequence of a bisphosphonate followed by the recommended dose of romosozumab 210 mg QM compares with the use of an equivalent dose of romosozumab only. However, in a recently published study, patients were transitioned from bisphosphonate treatment to either romosozumab 210 mg QM or teriparatide 20 µg once daily.⁽¹⁰⁾ The BMD increases at the spine and the hip were greater with romosozumab than with teriparatide⁽¹⁰⁾ but were smaller than those observed with romosozumab 210 mg QM in treatment-naïve populations.^(7–9)

In summary, treatment with romosozumab in postmenopausal women with low bone mass led to substantial and continued increases in BMD over 2 years. The effects on BMD were further augmented by follow-on therapy with denosumab. Like other non-bisphosphonate drugs for osteoporosis, effectiveness wanes within 1 year after discontinuing therapy, suggesting that following romosozumab with an anti-remodeling drug is important to maintain the skeletal response. Romosozumab was well tolerated over a 2-year period, and no safety issues were noted upon transitioning to denosumab. These results support the use of romosozumab as a therapy for postmenopausal women with osteoporosis.

Disclosures

MRM: research grants (Amgen), advisory board (Amgen, Radius Health), consulting fees or honorarium (Amgen), payment for lectures and/or speakers bureau (Radius Health), support for travel/accommodations (Amgen, Radius Health), and provisions of writing assistance, medicines, equipment, or administrative support (Amgen). JM, SB, and AG: employees and stock/stock options (Amgen). JPB: research grants (Amgen, Eli Lilly), advisory boards (Amgen, Eli Lilly, Merck), consulting fees or honorarium (Amgen, Eli Lilly, Merck), expert testimony (Pfizer), payment for lectures and/or speakers bureau (Amgen, Eli Lilly), payment for development of educational presentations (Amgen). AD-P: research grants (Amgen), stock/stock options (Active Life

Scientific), consulting fees or honorarium (Amgen, Eli Lilly, UCB Pharma, Radius Health, Mereo), payment for lectures and/or speakers bureau (Amgen, Eli Lilly). HR: no conflicts to disclose. JC: former employee and stock/stock options (UCB Pharma), current employee (Baxalta, a division of Shire). PM: employee and stock/stock options (UCB Pharma). MAB: consulting fees or honorarium and payment for lectures and/or speakers bureau (Amgen). SG: consulting fees or honorarium (Amgen, UCB Pharma), payment for lectures and/or speakers bureau (Amgen), support for travel/accommodations (Amgen, Willpharma), board membership (Belgian Bone Club). HGB: research grants (Amgen), consulting fees or honorarium (Amgen, Merck, Shire, Radius Health), payment for lectures and/or speakers bureau (Amgen, Shire, Radius Health), support for travel/accommodations (Amgen), payment for development of educational materials (Vindico). JRZ: research grants (Amgen).

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