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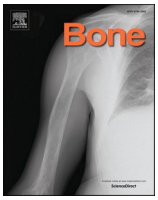

Romosozumab reduces incidence of new vertebral fractures across severity grades among postmenopausal women with osteoporosis

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ABSTRACT

Vertebral fractures (VFs) are the most common type of osteoporotic fracture, and their prevalence and severity are key risk factors for future fragility fractures. Here, we assess the treatment effect of romosozumab on the incidence of new on-study VFs according to Genant severity grades (mild, moderate, and severe). Data are reported from two phase 3 clinical studies for patients who received romosozumab versus placebo through 12 months, followed by denosumab through 24 months (FRAME: NCT01575834), and for patients who received romosozumab through 12 months, followed by alendronate through 24 months, versus alendronate only through 24 months (ARCH: NCT01631214). The treatment effect of romosozumab is reported for all included patients, and for patients with prevalent and severe baseline VFs. The incidence of new moderate-or-severe VFs was reduced through 12 months for patients treated with romosozumab versus placebo (FRAME; 0.25% versus 1.42%, respectively; $p < 0.001$) or alendronate (ARCH; 2.78% versus 4.00%, respectively; $p = 0.042$). Furthermore, the treatment effect of romosozumab on the incidence of new VFs across moderate and severe severity grades was independent of baseline VF prevalence or severity; through 12 months, consistent reductions in new moderate-or-severe VFs were observed regardless of prevalent (FRAME; $p = 0.18$) or severe (ARCH; $p = 0.52$) VFs at baseline. Reductions in the incidence of new moderate and severe VFs were sustained through 24 months, after transition from romosozumab to denosumab or alendronate, independent of baseline VF prevalence or severity; no significant interactions were observed between the incidence of new moderate-or-severe VFs and the presence of prevalent (FRAME; $p = 0.81$) or severe (ARCH; $p = 0.99$) VFs at baseline. With increasing recommendations for initial treatment with bone-forming agents for postmenopausal women with osteoporosis, these analyses will help to inform treatment decisions for patients at very high risk of VF.

1. Introduction

Osteoporosis carries an increased risk of fracture and is associated with increased morbidity and mortality [1]. Vertebral fractures (VFs) are one of the most common postmenopausal osteoporotic fractures and are the hallmark of a patient with clinical osteoporosis [2–4]. Despite this, it is estimated that only one third of VFs receive medical attention [5–7].

VF prevalence and severity, in combination with a low bone mineral density (BMD), are key predictors and risk factors for future fracture in patients with osteoporosis [2,8–11]. Moreover, even asymptomatic VFs can be a harbinger for high risk of future osteoporotic fractures [12,13]. The presence of at least one VF substantially increases the risk of future additional fracture both within one year and through to two years [2,8],

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and the imminent risk following sentinel fragility fractures reflects the importance of rapid treatment and intervention after a fracture [14]. Visual grading of VFs, observed on a lateral radiograph of the spine, has become the standard methodology for assessments of fracture severity (mild, moderate, or severe) [15–17]. Fracture severity has been associated with increased morbidity and mortality; the higher the severity, the greater the morbidity and subsequent fracture risk [9]. Accordingly, an improved understanding of VF treatment efficacy, across the spectrum of new and existing VF severities, is highly relevant to clinical practice.

For patients at greatest risk of future fracture, who frequently have sustained a considerable loss of bone structure, available evidence and recent guidelines are increasingly supportive of initial treatment with a bone-forming agent [18–20]. Bone-forming agents that rapidly reduce fracture risk, particularly in the first year after fracture, could substantially improve clinical outcomes [21]. Romosozumab is a humanized monoclonal antibody that inhibits the activity of the osteocyte protein sclerostin, thereby exerting a dual effect to stimulate bone formation while inhibiting bone resorption [22–24]. Owing to its anti-fracture efficacy, recent treatment guidelines recommend romosozumab as a first-line treatment for postmenopausal women at imminent or very high fracture risk [18–20].

Previously, in FRAME (Fracture Study in Postmenopausal Women with Osteoporosis), romosozumab resulted in a rapid and significant reduction in the incidence of morphometric and clinical VFs over 12 months of treatment versus placebo [22,25]. Furthermore, in ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk), the risk of new VFs was significantly reduced for patients who received romosozumab for 12 months compared with patients who received alendronate [26]. In both FRAME and ARCH, initial treatment with romosozumab led to greater gains in BMD versus treatment with placebo or alendronate. The effect of romosozumab on the reduction of fracture risk and BMD was sustained up to three years, after transition from romosozumab to either denosumab or alendronate [22,26,27].

Here, we report post hoc analyses which extend on efficacy data previously reported from the FRAME and ARCH clinical studies [22,26]. The aims of these analyses were to 1) assess the treatment effect of romosozumab on the incidence of new VFs, according to Genant severity grades (mild, moderate, and severe), and 2) assess this treatment effect on the incidence of new mild, moderate, severe, and moderate-or-severe VFs among patients with prevalent or severe baseline VFs. We compare the effect of romosozumab versus placebo, and romosozumab versus alendronate through 12 months, and after transition to subsequent antiresorptive treatment through 24 months.

2. Methods

2.1. Study design

These post hoc analyses were based on data from the FRAME (NCT01575834) and ARCH (NCT01631214) phase 3, randomized, international, double-blinded clinical trials (Fig. 1) [22,26]. Briefly, patients in FRAME were randomized 1:1 to receive either romosozumab or placebo for 12 months. After 12 months, all patients entered an open-label period and received denosumab for a further 24 months (including a 1-year extension study). In ARCH, patients were randomized 1:1 to receive either romosozumab or alendronate for 12 months, after which, patients in both groups entered an open-label period and received alendronate for the remainder of the study. On entering the open-label periods, blinding to the initial treatment was maintained in both studies.

Lateral radiographs of the spine were assessed for the presence of VFs and graded using the Genant severity grading system. Radiographs were processed and analyzed at a central imaging vendor (BioClinica) as previously described [22,26]; assessors remained blinded to treatment in both studies. The analyses reported here include assessments performed at baseline, and every 12 months thereafter, in the FRAME and ARCH clinical trials (Fig. 1). In ARCH, the primary analysis was performed at 24 months and X-rays were not collected for all patients through 36 months. Therefore, here we report data through 24 months only.

2.2. Patients

All patients included in the FRAME and ARCH clinical studies were ambulatory postmenopausal women aged 55–90. Patients were included in FRAME if they met the following criteria: BMD T-score at total hip or femoral neck of ≤ -2.5 and ≥ -3.5; no hip fracture; no severe and no

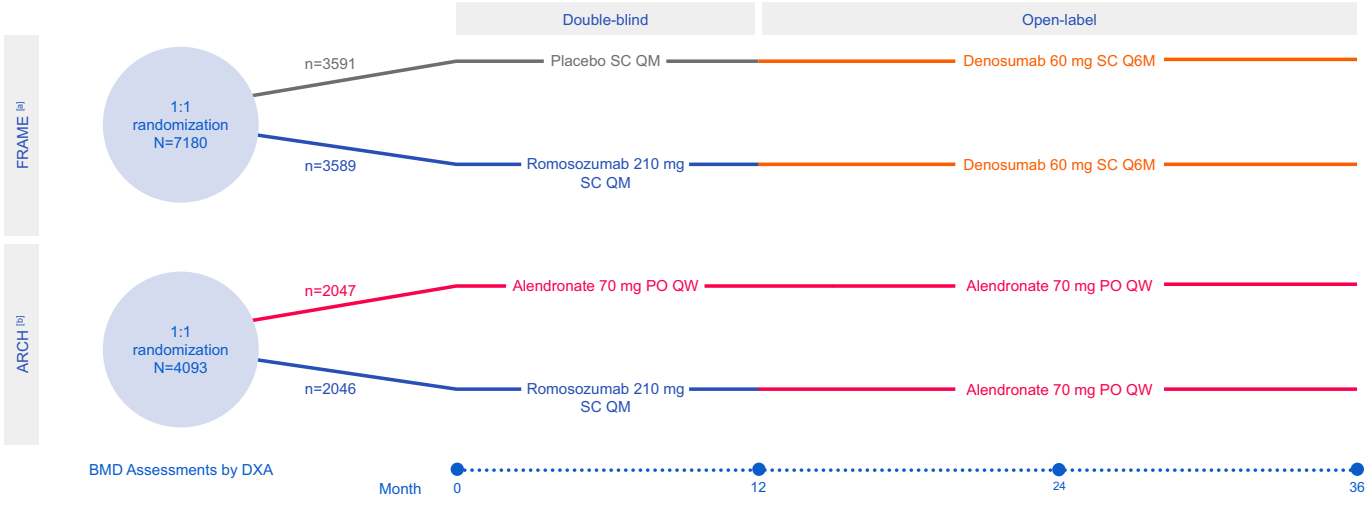

Fig. 1. FRAME and ARCH study designs
[a] Patients enrolled in FRAME were postmenopausal women aged 55–90 with a TH or FN BMD T-score −2.5 to −3.5; patients with a BMD T-score ≤ −3.5 at the TH or FN, prior hip fracture or any severe or > 2 moderate VFs were excluded; [b] Patients enrolled in ARCH were postmenopausal women aged 55–90 with a BMD T-score at TH or FN ≤ −2.5 and either: ≥ 1 moderate/severe VFs or ≥ 2 mild VFs; or a BMD T-score of ≤ − 2.0 at TH or FN and either ≥ 2 moderate/severe VFs or a fracture of the proximal femur that occurred within 3–24 months before randomization; patients with a contraindication to alendronate were excluded. BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; FN: femoral neck; PO: orally; QM: monthly; Q6M: every six months; QW: weekly; SC: subcutaneous; TH: total hip; VFs: vertebral fracture. (For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this chapter.)

more than 2 moderate VFs. Patients were included in ARCH if they met the following criteria: BMD T-score at total hip or femoral neck ≤ −2.5 and either ≥ 1 moderate or severe VFs, or ≥ 2 mild VFs; or BMD T-score of ≤ −2.0 at total hip or femoral neck, and either ≥ 2 moderate or severe VFs, or a fracture of the proximal femur that occurred within 3 to 24 months before randomization. Patients with exposure to treatments affecting bone metabolism were excluded from FRAME and ARCH, including intravenous bisphosphonate treatment within 5 years before randomization or more than 3 years cumulative oral bisphosphonate use (full exclusion criteria have been previously described) [22,26].

All patients with a baseline spinal X-ray and at least one post-baseline evaluation of VFs at or before 24 months from the FRAME and ARCH trials were included in these analyses.

2.3. Statistical analysis

In these post hoc analyses, data are reported for the percentage of patients with a new VF through 12 and 24 months. New vertebral fractures were evaluated at scheduled visits and were defined as those which occurred on-study, in a normal vertebra at baseline. Patients with one or more VF during the trials are reported; however, refracture or further degradation of a previously fractured vertebra was not evaluated in these analyses. If more than one new VF was present at a scheduled visit, the severity grade was determined by the most severe grade of new VF.

Treatment effects through 12 months and 24 months were analyzed separately and are reported with odds ratios (ORs) and 95% confidence intervals (CIs). To assess the treatment effect on new mild, new moderate, or new severe VFs, a multinomial logistic regression model with categorical outcomes (new severe VFs, new moderate VFs, new mild VFs, or no new VFs) was applied. To assess the treatment effect on new moderate-or-severe VFs, a multinomial logistic regression model with categorical outcomes (new mild VFs, new moderate-or-severe VFs, or no new VFs) was applied. To assess the treatment effect on all new VFs, a binary logistic regression model was used. New VF results were adjusted for age strata and presence of prevalent VFs at baseline in FRAME, and adjusted for age strata, baseline total hip BMD T-score, and presence of severe VFs at baseline in ARCH.

To assess whether treatment effects differed according to prevalent or severe VFs at baseline, the treatment-by-subgroup interaction effects (presence of any VFs in FRAME and presence of severe VFs in ARCH) were added to the main statistical model and analyzed.

Missing outcomes were imputed by the last observation carried forward (LOCF) method. Patients with missing or unreadable baseline spine radiographs were excluded from the analyses.

3. Results

3.1. Patient disposition and baseline characteristics

Across the FRAME and ARCH clinical studies, a total of 11,273 patients were randomized; in FRAME, 7180 patients were enrolled to receive either romosozumab ($n = 3589$) or placebo ($n = 3591$) [22]; in ARCH, 4093 patients were enrolled to receive either romosozumab ($n = 2046$) or alendronate ($n = 2047$) [26].

Demographics and baseline disease characteristics, summarized in Table 1, for patients in FRAME and ARCH have previously been published in detail [22,26]. The mean age of patients in FRAME was 70.9 years compared to 74.3 years in ARCH. Due to the defined inclusion criteria for each study, patients in ARCH had more severe osteoporosis and a higher risk of fracture than patients in FRAME; patients in FRAME had a mean lumbar spine BMD T-score of −2.72 and patients in ARCH had a mean score of −2.96 at baseline. Prevalent VFs also differed due to the nature of each study and the inclusion criteria, allowing for an evaluation of efficacy across a wide range of baseline VF prevalence and severities; the prevalence of severe VFs was higher in ARCH than in FRAME (65.7% versus <0.1%) (Table 1).

Table 1
Baseline demographics and characteristics.

Patient characteristics	FRAME		ARCH	
	Romo/Dmab ($N = 3589$)	Placebo/Dmab ($N = 3591$)	Romo/ALN ($N = 2046$)	ALN ($N = 2047$)
Age, years, mean ± SD	70.9 ± 7.0	70.8 ± 6.9	74.4 ± 7.5	74.2 ± 7.5
BMI, kg/m^2, mean ± SD	24.7 ± 4.3	24.7 ± 4.4	25.5 ± 4.4	25.4 ± 4.4
Lumbar spine BMD T-score, mean ± SD	−2.72 ± 1.04	−2.71 ± 1.04	−2.94 ± 1.25	−2.99 ± 1.24
Total hip BMD T-score, mean ± SD	−2.48 ± 0.47	−2.46 ± 0.47	−2.78 ± 0.68	−2.81 ± 0.67
Femoral neck BMD T-score, mean ± SD	−2.76 ± 0.28	−2.74 ± 0.29	−2.89 ± 0.49	−2.90 ± 0.50
FRAX score,[a] mean ± SD	13.4 ± 8.8	13.4 ± 8.5	20.2 ± 10.2	20.0 ± 10.1
Prevalent VFs, n (%)				
Yes	672 (18.7)	645 (18.0)	1969 (96.2)	1964 (95.9)
No	2795 (77.9)	2839 (79.1)	69 (3.4)	80 (3.9)
Not readable/missing	122 (3.4)	107 (3.0)	8 (0.4)	3 (0.1)
Most severe baseline fracture grade,[b] n (%)				
Normal	2795 (77.9)	2839 (79.1)	69 (3.4)	80 (3.9)
Mild	378 (10.5)	378 (10.5)	68 (3.3)	73 (3.6)
Moderate	293 (8.2)	263 (7.3)	532 (26.0)	570 (27.8)
Severe	1 (<0.1)	4 (0.1)	1369 (66.9)	1321 (64.5)
Not readable/missing[c]	122 (3.4)	107 (3.0)	8 (0.4)	3 (0.1)

Baseline characteristics are reported for all patients randomized in the FRAME and ARCH clinical studies.
[a] 10-year probability of major osteoporotic fracture calculated with BMD using the FRAX version 3.9 (www.shef.ac.uk/frax/).
[b] Most severe fracture grade was assessed with the Genant semi-quantitative grading scale.
[c] Not readable was defined as at least one vertebra with a missing Genant grade between T4 and L4, and all remaining vertebrae with a Genant grade of 0.
ALN: alendronate; BMI: body mass index; BMD: bone mineral density; Dmab; denosumab; FRAX: Fracture Risk Assessment Tool; Romo: romosozumab; SD: standard deviation; VFs: vertebral fractures.

The majority of patients enrolled in FRAME and ARCH had not received a prior treatment for osteoporosis; 6.8% of patients in FRAME and 9.0% of patients in ARCH had previously received an osteoporosis medication, the majority of which were oral bisphosphonates (4.9% of patients in FRAME and 6.2% of patients in ARCH had received an oral bisphosphonate treatment).

Safety of romosozumab through 24 and 36 months in the FRAME and ARCH clinical studies, respectively, has been published previously [22,26].

3.2. Romosozumab treatment effect on new mild, moderate, severe, and moderate-or-severe VFs through 12 months

Overall, the percentage of patients with a new VF (mild, moderate, or severe) was significantly reduced through 12 months with romosozumab versus placebo (0.47% versus 1.79%; OR 0.25 [95% CI: 0.14–0.45]; $p < 0.001$) and versus alendronate (3.26% versus 5.00%; OR 0.63 [95% CI: 0.44–0.89]; $p = 0.009$) (Fig. 2A).

Reductions in new VFs were observed with romosozumab across VF severity grades. Through 12 months, romosozumab-treated patients experienced significantly fewer new moderate (0.09% versus 0.90%; OR 0.10 [95% CI: 0.03–0.33]; $p < 0.001$), or new severe VFs (0.16% versus

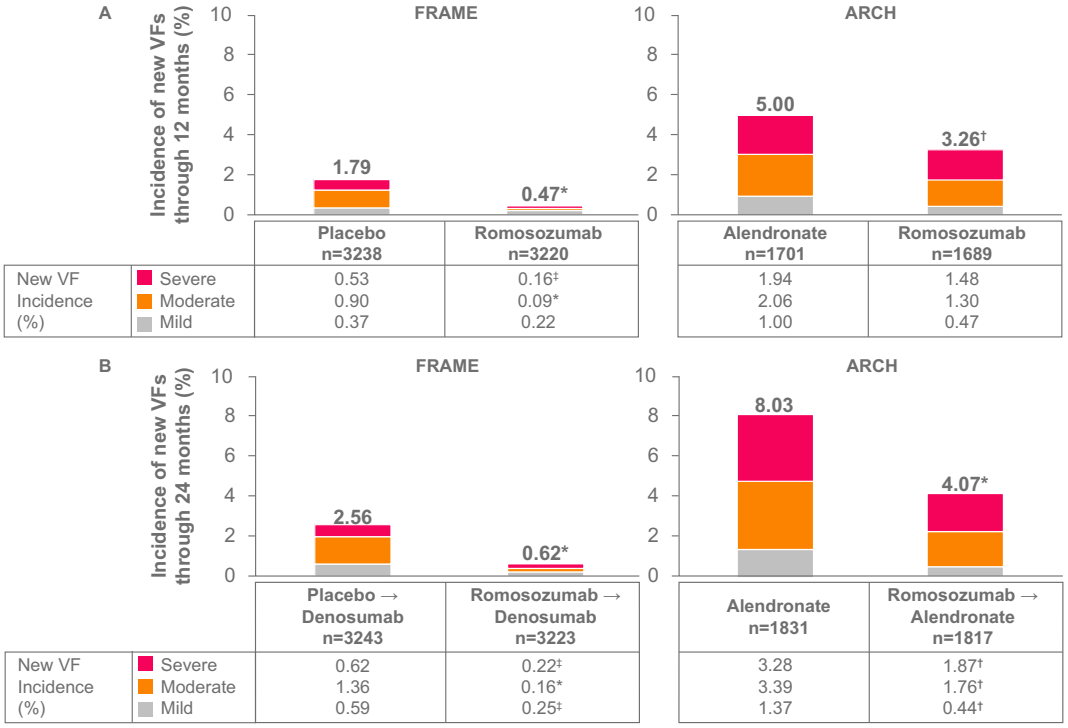

Fig. 2. Percentage of patients with a new vertebral fracture across severity grades through 12 and 24 months
Incidences of new VFs (mild, moderate, and severe) are reported through 12 months (Panel A) and 24 months (Panel B) for FRAME and ARCH. In FRAME, patients received romosozumab or placebo for 12 months, before transitioning to denosumab through 24 months. In ARCH, patients received either romosozumab or alendronate for 12 months, and alendronate from 12 months through 24 months. *p* values were based on the Wald test; $^{*}p < 0.001$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.05$ romosozumab versus comparator treatment. Missing values were imputed by carrying forward the last non-missing post-baseline value prior to the missing value (LOCF). LOCF: last observation carried forward; n: number of patients in the primary efficacy analysis set for VFs; VFs: vertebral fractures. (For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this chapter.)

0.53%; OR 0.29 [95% CI: 0.11–0.78]; $p = 0.014$) (Fig. 2A). Numerically fewer romosozumab-treated versus placebo-treated patients experienced a new mild VF, however differences did not achieve statistical significance (0.22% versus 0.37%; OR 0.58 [95% CI 0.23–1.48]; $p = 0.26$). For patients treated with romosozumab versus alendronate, although differences in incidence of VF did not achieve statistical significance, numerically fewer romosozumab-treated versus alendronate-treated patients experienced a new mild (0.47% versus 1.00% OR 0.46 [95% CI: 0.20–1.06); $p = 0.068$), new moderate (1.30% versus 2.06%; OR 0.62 [95% CI: 0.36–1.06]; $p = 0.083$), or new severe VF (1.48% versus 1.94%; OR 0.73 [95% CI: 0.43–1.24]; $p = 0.24$) (Fig. 2A).

The risk of new moderate-or-severe VFs was significantly reduced in patients receiving romosozumab versus placebo (0.25% versus 1.42%; OR 0.17 [95% CI 0.08–0.36]; $p < 0.001$) or alendronate (2.78% versus 4.00%; OR 0.67 [95% CI: 0.46–0.99]; $p = 0.042$).

Furthermore, romosozumab reduced the risk of both new moderate and new severe VFs with similar efficacy; no significant difference was observed for the reduction in the incidence of a new on-study severe VF versus a new on-study moderate VF through 12 months for patients in FRAME ($p = 0.19$) and ARCH ($p = 0.67$).

3.3. Treatment effect of romosozumab followed by denosumab or alendronate on the risk of new mild, moderate, severe, and moderate-or-severe VFs through 24 months

Reductions in the risk of new VFs across severity grades were sustained with romosozumab through 24 months after transition to denosumab (0.62% versus 2.56%; OR 0.23 [95% CI: 0.14–0.38]; $p < 0.001$) or alendronate (4.07% versus 8.03%; OR 0.48 [95% CI: 0.36–0.64]; $p < 0.001$) (Fig. 2B).

Patients who transitioned from romosozumab to denosumab versus placebo to denosumab experienced fewer new mild (0.25% versus 0.59%; OR 0.41 [95% CI 0.18–0.95]; $p = 0.037$), new moderate (0.16% versus 1.36%; OR 0.11 [95% CI: 0.04–0.28]; $p < 0.001$), or new severe VFs (0.22% versus 0.62%; OR 0.34 [95% CI: 0.14–0.81]; $p = 0.014$) (Fig. 2B). Similarly, patients who transitioned from romosozumab to alendronate versus patients who remained on alendronate experienced fewer new mild (0.44% versus 1.37%; OR 0.30 [95% CI 0.14–0.67]; $p = 0.003$), new moderate (1.76% versus 3.39%; OR 0.50 [95% CI: 0.32–0.77]; $p = 0.002$), or new severe VFs (1.87% versus 3.28%; OR 0.53 [95% CI: 0.35–0.81]; $p = 0.004$) (Fig. 2B).

Furthermore, the incidence of new moderate-or-severe VFs was significantly reduced for patients who initially received romosozumab, compared with patients who initially received placebo (0.37% versus 1.97%; OR 0.18 [95% CI: 0.10–0.34]; $p < 0.001$) or alendronate (3.63% versus 6.66%; OR 0.51 [95% CI: 0.38–0.70]; $p < 0.001$).

Following transition from romosozumab to an antiresorptive agent, the incidence of new moderate and new severe VFs was reduced with similar efficacy; no significant difference between the reduction in incidence of a new on-study severe or a new on-study moderate VF was observed in FRAME ($p = 0.08$) or ARCH ($p = 0.83$).

3.4. Treatment effect of romosozumab on the risk of new VFs in patients with prevalent or severe baseline VFs

Through 12 months and 24 months, the treatment effect of romosozumab for the reduction of new VFs across all grades was independent of the presence of prevalent baseline VFs; no significant interactions were observed between the romosozumab treatment effect and prevalent baseline VFs (Table 2). Additionally, the treatment effect of romosozumab on the reduction of new moderate, severe, and moderate-or-severe VFs was independent of the presence of severe baseline VFs

Table 2
Treatment effect on the risk of new vertebral fractures across severity grades and the interaction between romosozumab treatment effect and prevalent baseline vertebral fractures in FRAME.

	Treatment effect[a]		*p* values for interaction between treatment effect and prevalent VFs at baseline[b]	
	Romosozumab through 12 months OR (95% CI)	Romosozumab/denosumab through 24 months OR (95% CI)	Through 12 months	Through 24 months
All new VFs[c]	0.25 (0.14, 0.45); $p < 0.001$	0.23 (0.14, 0.38); $p < 0.001$	$p = 0.20$	$p = 0.56$
New mild VFs	0.58 (0.23, 1.48); $p = 0.26$	0.41 (0.18, 0.95); $p = 0.037$	$p = 0.97$	$p = 0.25$
New moderate VFs	0.10 (0.03, 0.33); $p < 0.001$	0.11 (0.04, 0.28); $p < 0.001$	$p = 0.33$	$p = 0.98$
New severe VFs	0.29 (0.11, 0.78); $p = 0.014$	0.34 (0.14, 0.81); $p = 0.014$	$p = 0.37$	$p = 0.60$
New moderate-or-severe VFs	0.17 (0.08, 0.36); $p < 0.001$	0.18 (0.10, 0.34); $p < 0.001$	$p = 0.18$	$p = 0.81$

[a] Odds ratios were based on binary (for all new VFs versus no new VFs) or multinomial (for new mild, new moderate, new severe, and new moderate-or-severe VFs versus no new VFs) logistic regression models adjusted for treatment, age strata, and presence of prevalent VFs at baseline.
[b] Interaction *p* values (treatment-by-presence of prevalent VF at baseline) were calculated based on the binary/multinomial logistic regression model adjusted for treatment, age strata, presence of prevalent vertebral fracture at baseline, and treatment by presence of prevalent vertebral fracture at baseline interaction and were based on the Wald test.
[c] Mild, moderate, or severe. CI: confidence interval; OR: odds ratio; VFs: vertebral fractures.

through both 12 months and 24 months (Table 3).

Among patients enrolled in FRAME with prevalent VFs at baseline, numerically fewer patients treated with romosozumab versus placebo experienced a new moderate, or severe VF after 12 months (Fig. 3A). Furthermore, through 12 months, patients enrolled in ARCH with severe VFs at baseline experienced numerically fewer new VFs across severity grades with romosozumab versus alendronate (Fig. 3A). Due to the low number of patients enrolled in ARCH with no VFs or a mild VF at baseline, data were inconclusive for these sub-populations. Through 24 months, the treatment effect of romosozumab continued among patients enrolled in FRAME for the reduction of VFs across new VF severity grades after patients transitioned to denosumab (Fig. 3B). Similarly, the treatment effect also continued through 24 months for patients enrolled in ARCH with moderate or severe baseline VFs who transitioned from romosozumab to alendronate.

4. Discussion

Antiresorptive agents have been used as a first-line treatment option for patients with osteoporosis, independent of disease severity [28]. Recent evidence from head-to-head trials versus bisphosphonates has demonstrated superior reductions in fracture risk with bone-forming agents [26,29]. Accordingly, new guidelines recommend initial treatment with a bone-forming agent for patients at imminent or very high risk of fracture [18–20,30].

For patients with osteoporosis, the development of a VF is indicative of poor bone quality and strength [31]. Whilst any VF implies increased risk, the degree of vertebral deformity (i.e., the fracture severity grade) is also an important indicator of further risk; the greater the VF severity, the higher the risk and morbidity [4,9,31,32]. Accordingly, understanding the efficacy of a therapeutic agent across a range of fracture grades is important to tailor individualized treatment. The data reported here further characterize the previously reported efficacy of romosozumab for the reduction of VF risk [22,26], and support that for postmenopausal women at very high fracture risk, romosozumab treatment for 1 year, followed by an antiresorptive agent, provides sustained reductions across VF severity grades, in particular the moderate and severe grades, in patients with and without VFs at baseline.

Through 12 months, fewer VFs were observed with romosozumab versus placebo or alendronate in postmenopausal women with osteoporosis across moderate and severe VF severity grades. The beneficial effect of romosozumab continued after transitioning to an antiresorptive agent and reductions in the incidence of new VFs were sustained through 24 months of treatment, after transition from romosozumab to denosumab or alendronate at 12 months, compared with patients who had received placebo followed by denosumab, or alendronate throughout.

Although it is well understood that the presence of VFs increases the risk of subsequent fracture, few studies have reported details of the efficacy of treatments in reducing risk of subsequent VFs [9,11,33]. Furthermore, few studies take into account the severity of baseline fracture(s) [9]. To our knowledge, no studies have evaluated treatment effects across severity grades (mild, moderate, or severe) of new VFs.

Here, we utilized an interaction testing model to test the treatment effect of romosozumab on new VFs for patients with prevalent baseline VFs in FRAME, and severe baseline VFs in ARCH. Our analyses

Table 3
Treatment effect on the risk of new vertebral fractures across severity grades and the interaction between romosozumab treatment effect and severe baseline vertebral fractures in ARCH.

	Treatment effect[a]		*p* values for interaction between treatment effect and severe VFs at baseline[b]	
	Romosozumab through 12 months OR (95% CI)	Romosozumab/alendronate through 24 months OR (95% CI)	Through 12 months	Through 24 months
All new VFs[c]	0.63 (0.44, 0.89); $p = 0.009$	0.48 (0.36, 0.64); $p < 0.001$	$p = 0.93$	$p = 0.54$
New mild VFs	0.46 (0.20, 1.06); $p = 0.068$	0.30 (0.14, 0.67); $p = 0.003$	$p = 0.12$	$p = 0.09$
New moderate VFs	0.62 (0.36, 1.06); $p = 0.083$	0.50 (0.32, 0.77); $p = 0.002$	$p = 0.36$	$p = 0.87$
New severe VFs	0.73 (0.43, 1.24); $p = 0.24$	0.53 (0.35, 0.81); $p = 0.004$	$p = 0.87$	$p = 0.80$
New moderate-or-severe VFs	0.67 (0.46, 0.99); $p = 0.042$	0.51 (0.38, 0.70); $p < 0.001$	$p = 0.52$	$p = 0.99$

[a] Odds ratios were based on binary (for all new VFs versus no new VFs) or multinomial (for new mild, new moderate, new severe, and new moderate-or-severe VFs versus no new VFs) logistic regression models adjusted for treatment, age strata, baseline total hip BMD T-score, and presence of severe VFs at baseline.
[b] Interaction *p* values (treatment-by-presence of severe VF at baseline) were calculated based on the binary/multinomial logistic regression model adjusted for treatment, age strata, baseline total hip BMD T-score, presence of severe vertebral fracture at baseline, and treatment-by-presence of severe vertebral fracture at baseline interaction and were based on the Wald test.
[c] Mild, moderate, or severe. BMD: bone mineral density; CI: confidence interval; OR: odds ratio; VFs: vertebral fractures.

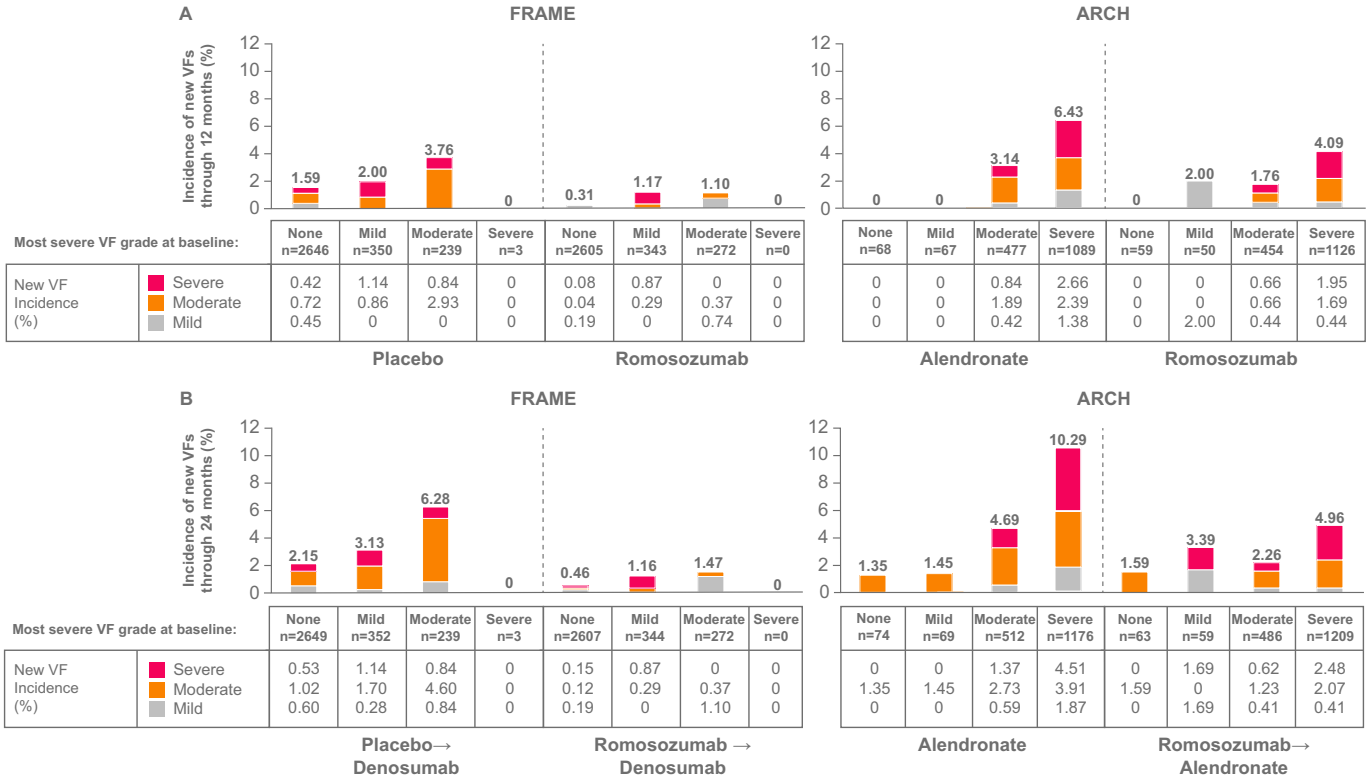

Fig. 3. Incidence of new vertebral fractures across severity grades through 12 and 24 months by most severe vertebral fracture grade at baseline
Incidences of new VFs (mild, moderate, and severe) through 12 months (Panel A) and 24 months (Panel B) in the FRAME and ARCH studies are reported by most severe (Genant semi-quantitative grade) at baseline (none, mild, moderate, or severe). In the FRAME study, patients received romosozumab or placebo for 12 months, before transitioning to denosumab through 24 months. In ARCH, patients received either romosozumab or alendronate for 12 months, and then alendronate from 12 months through 24 months. Missing values were imputed by carrying forward the last non-missing post-baseline value prior to the missing value (LOCF). LOCF: last observation carried forward; n: number of patients in the primary efficacy analysis set for VFs; VFs: vertebral fractures. (For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this chapter.)

demonstrate the efficacy of romosozumab for the reduction of fracture risk across all new VF severity grades for patients with prevalent baseline VFs, and across new moderate and new severe VF grades for patients with severe VFs at baseline. In particular, the reduction in fracture risk extends to the clinically relevant moderate-to-severe fracture grade. The results presented here with romosozumab further support the use of bone-forming agents as a first-line treatment strategy for patients at high risk of experiencing a VF, e.g. those with prevalent VFs, regardless of severity [18–20,34].

Despite its post hoc nature, this study has multiple strengths including a comparison of romosozumab against placebo and an active comparator, alendronate. In addition, this study considers the severity rather than just the prevalence of baseline VFs, and the grading of VFs was performed blinded to treatment by a qualified expert vendor following a strict methodology. However, a limitation of this study is that the analyses reported here do not incorporate other indicators of high fracture risk, such as recency of VFs. Although the analyses were not powered to detect differences between the treatment effect on clinical (symptomatic) and asymptomatic VFs of different severities, previous analyses of data from the FRAME trial identified that the incidence of clinical VF with romosozumab was very low [25]. Finally, given that only a small percentage of patients had received prior bisphosphonate therapy before enrolling in FRAME or ARCH, these data cannot be extrapolated beyond patients who receive romosozumab as a first-line treatment.

5. Conclusions

In summary, romosozumab treatment administered over a 12-month period, is associated with marked reductions in VF grades, in particular the moderate and severe fracture grades, versus both placebo and alendronate. This effect was sustained after transition to either of the antiresorptive agents, alendronate or denosumab. Moreover, the effect of romosozumab was independent of baseline VF prevalence or severity. Importantly, these data will allow clinicians to make informed treatment decisions for postmenopausal women with and without prevalent osteoporotic VFs who are at high risk for fracture.

Data sharing

Underlying data from this manuscript may be requested by qualified researchers six months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized IPD and redacted study documents which may include: raw datasets, analysis-ready datasets, study protocol, blank case report form, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password protected portal.

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CRediT authorship contribution statement

Substantial contributions to study conception and design: **PG, RF, MO, TT, PM, FJ, BL, ZW, MR, CL**; substantial contributions to analysis and interpretation of the data: **PG, RF, MO, TT, PM, FJ, BL, ZW, MR, CL**; drafting the article or revising it critically for important intellectual content: **PG, RF, MO, TT, PM, FJ, BL, ZW, MR, CL**; final approval of the version of the article to be published: **PG, RF, MO, TT, PM, FJ, BL, ZW, MR, CL**.

Disclosures

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Consent for publication

All the results presented in this article are in aggregate form, and no personally identifiable information was used for this study.

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