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ORIGINAL ARTICLE

Romosozumab in patients who experienced an on-study fracture: post hoc analyses of the FRAME and ARCH phase 3 trials

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Abstract

Summary Post hoc analysis of FRAME and ARCH revealed that on-study nonvertebral and vertebral fractures by Month 12 were less common in women initially treated with romosozumab versus placebo or alendronate. Recurrent fracture risk was also lower in romosozumab-treated patients, and there were no fracture-related complications. Results support continuing romosozumab treatment post-fracture.

Purpose Post hoc analysis evaluating efficacy and safety of romosozumab, administered in the immediate post-fracture period, in the FRAME and ARCH phase 3 trials.

Methods In FRAME (NCT01575834) and ARCH (NCT01631214), postmenopausal women with osteoporosis were randomized 1:1 to romosozumab 210 mg monthly or comparator (FRAME, placebo; ARCH, alendronate 70 mg weekly) for 12 months, followed by antiresorptive therapy (FRAME, denosumab; ARCH, alendronate). In patients who experienced on-study nonvertebral or new/worsening vertebral fracture by Month 12, we report the following: fracture and treatment-emergent adverse event (TEAE) incidence through 36 months, bone mineral density changes (BMD), and romosozumab timing. Due to the sample sizes employed, meaningful statistical comparisons between treatments were not possible.

Results Incidence of on-study nonvertebral and vertebral fractures by Month 12 was numerically lower in romosozumab- versus comparator-treated patients (FRAME, 1.6% and 0.5% versus 2.1% and 1.6%; ARCH, 3.4% and 3.3% versus 4.6% and 4.9%, respectively). In those who experienced on-study nonvertebral fracture by Month 12, recurrent nonvertebral and subsequent vertebral fracture incidences were numerically lower in patients initially treated with romosozumab versus comparator (FRAME, 3.6% [2/56] and 1.8% [1/56] versus 9.2% [7/76] and 3.9% [3/76]; ARCH, 10.0% [7/70] and 5.7% [4/70] versus 12.6% [12/95] and 8.4% [8/95], respectively). Among those with on-study vertebral fracture by Month 12, recurrent vertebral and subsequent nonvertebral fracture incidences were numerically lower with romosozumab versus comparator (FRAME, 0.0% [0/17] and 0.0% [0/17] versus 11.9% [7/59] and 8.5% [5/59]; ARCH, 9.0% [6/67] and 7.5% [5/67] versus 15.0% [15/100] and 16.0% [16/100], respectively). In patients with fracture by Month 12, no fracture-related complications were reported in romosozumab-treated patients. BMD gains were numerically greater with romosozumab than comparators.

Conclusion Data suggest support for the efficacy and safety of continuing romosozumab treatment following fracture.

Trial registrations NCT01575834; NCT01631214.

Keywords Bone mineral density · Fracture risk · On-study fracture · Osteoporosis · Romosozumab

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Introduction

A previous fracture is well-documented as a strong risk factor for the occurrence of future fracture [1–4]. The risk for subsequent fracture is at its greatest immediately following a fracture [3, 5, 6]; incidence of fracture after a prior fragility fracture has been reported as 7.6% in the first year and 11.6% in the first 2 years post-fracture [7]. Indeed, it has been reported that approximately half of recurrent fractures occur within the first 2 years after a fragility fracture [3, 7]. To reduce the risk of further fractures, it is therefore important to initiate treatment promptly after fracture [8].

However, despite being at imminent fracture risk, most patients are not prescribed treatments for osteoporosis in the year following a fracture [9, 10]. The reluctance to prescribe anti-osteoporotic medications immediately following a fracture may be due to concerns that they could interfere with fracture healing [11–13]. These concerns derive in part from the theory that suppression of bone remodeling, the mechanism of action for antiresorptive treatments, could affect remodeling and repair at the fracture site [14, 15]. However, the current clinical evidence indicates that there is no apparent detrimental effect of antiresorptive agents on fracture healing [14–17]. Similarly, prior studies of anabolic agents have shown no adverse effect on fracture healing [8].

Romosozumab is a humanized monoclonal antibody that binds to and inhibits sclerostin, thereby increasing Wnt signaling and exerting a dual effect on bone, increasing bone formation while decreasing bone resorption [18–21]. In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) and Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) trials, 12 monthly doses of 210 mg subcutaneous romosozumab treatment led to a reduction in the risk of vertebral and clinical (a composite of nonvertebral and symptomatic vertebral) fractures, as compared with either placebo (FRAME) or alendronate (ARCH) [21, 22]. Furthermore, in both trials, romosozumab treatment resulted in substantially greater gains in bone mineral density (BMD) at the total hip, femoral neck, and lumbar spine, compared with comparator treatments.

In this post hoc analysis of the FRAME and ARCH phase 3 trials, we evaluate the efficacy and safety of romosozumab administration in two subgroups of patients who, during the first 12 months of either trial, sustained a nonvertebral or a new or worsening vertebral fracture (including symptomatic and radiographically detected vertebral fractures). We evaluate safety during the first year and through the maximum available follow-up antiresorptive period (up to 36 months).

Methods

Study design

The post hoc analyses reported here are based on data from the FRAME (NCT01575834) and ARCH (NCT01631214) phase 3, international, randomized, double-blinded, parallel-group trials, as reported previously [21, 22]. Informed consent was obtained from all participants in the FRAME and ARCH trials. Briefly, in both trials, patients were randomized 1:1 to receive either 210 mg monthly romosozumab subcutaneously or comparator (FRAME, placebo; ARCH, 70 mg weekly oral alendronate) for 12 months (Supplementary Fig. 1). In ARCH, patients also received matched placebo for either romosozumab or alendronate. At Month 12 in FRAME, all patients entered an open-label period and received 60 mg denosumab subcutaneously every 6 months for a year, followed by a 12-month extension study in which patients continued to receive denosumab every 6 months; therefore, end of study represents a total treatment period of 36 months. After 12 months in ARCH, all patients received open-label weekly oral alendronate (70 mg) until end of study (median total treatment period 33 months). On entering the open-label periods, blinding to the initial treatment was maintained in both studies.

Both trials enrolled postmenopausal women aged 55–90 years. Patients in FRAME had a T-score of − 2.5 to − 3.5 at the total hip or femoral neck. Patients in ARCH had at least one of the following: (i) a T-score ≤ –2.5 at the total hip or femoral neck and either ≥ 1 moderate or severe vertebral fracture, or ≥ 2 mild vertebral fractures; (ii) a T-score ≤ –2.0 at the total hip or femoral neck and either ≥ 2 moderate or severe vertebral fractures, or a fracture of the proximal femur sustained 3–24 months prior to randomization. Exclusion criteria for FRAME included a history of hip fracture and any severe or more than two moderate vertebral fractures. In ARCH, patients were excluded for an inability to take alendronate oral tablets or contraindications to alendronate. Full exclusion criteria were described previously [21, 22].

Study population

In these analyses, we evaluated the efficacy and safety of romosozumab, administered in the immediate post-fracture period, in two subgroups of women who experienced a fracture during the first 12 months of the FRAME or ARCH trials: those who sustained an on-study nonvertebral fracture, and those who sustained an on-study new or worsening vertebral fracture. Vertebral fractures were

identified via lateral radiographs of the spine, performed at Month 12, using the Genant grading scale (grades range from 0 to 3, with higher grades indicating greater severity) at the central imaging vendor (BioClinica [now Clario]). Adjudicators were blinded to treatment group. New or worsening vertebral fractures were defined as an increase of ≥ 1 grade in previously normal, or previously fractured vertebrae, respectively.

Study outcomes

In the aforementioned subgroups of patients who sustained an on-study fracture by Month 12, we report the incidence and location of fracture and the percentage change in BMD from baseline (i.e., entry to the FRAME or ARCH trial) at Months 12 and 24 at the lumbar spine, total hip, and femoral neck in patients in who received at least one dose of study treatment. In the nonvertebral fracture subgroup, we additionally report the number and timing of romosozumab or romosozumab-matched subcutaneous placebo doses prior to and after the first occurrence of nonvertebral fracture.

The incidence (%) of treatment-emergent adverse events (TEAEs) in both subgroups is reported for Months 0–12 and Months 0–end of study; data through end of study are cumulative and include TEAEs that occurred during the double-blind and open-label periods. For patients in the nonvertebral fracture subgroup, TEAEs that occurred before the first nonvertebral fracture are excluded; in the vertebral fracture subgroup, all TEAEs that occurred by Month 12 are reported.

Overall TEAEs, serious TEAEs and TEAEs of interest are reported. Serious TEAEs were defined as TEAEs which met one or more of the following criteria: fatal, life threatening, requiring in-patient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability or incapacity, or any other medically important serious event. TEAEs of interest, related to the fracture, included nonunion, malunion, delayed healing, chronic pain, and osteomyelitis. Adverse events are reported by preferred term, coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

Study procedures and analysis

Full study procedures for the FRAME and ARCH phase 3 trials have been previously reported [21, 22]. Adverse events were reported by individual trial sites. Measurements of BMD at the lumbar spine and proximal femur were performed by dual-energy X-ray absorptiometry (DXA) at baseline and every 12 months thereafter using Lunar or Hologic bone densitometers. DXA scans were processed and analyzed blinded to treatment at the central imaging vendor.

The analysis undertaken in this post hoc study was descriptive in nature and hypothesis testing was not undertaken. Descriptive statistics on continuous measurements comprise means, medians, ranges, and standard deviations (SD), while categorical data are summarized using counts and percentages. Data are standardly reported as observed data; missing new or worsening vertebral fracture status was imputed by carrying forward the last non-missing post-baseline value prior to the missing value.

Results

Patient baseline characteristics

In both FRAME and ARCH, the baseline characteristics of patients within each treatment group who experienced on-study fracture within 12 months were well balanced (Table 1) and were largely similar to their respective full treatment populations [21, 22]. However, at baseline, patients in both FRAME and ARCH who subsequently experienced vertebral fracture by Month 12, had numerically lower mean (SD) T-score at the lumbar spine (FRAME: romosozumab: − 3.16 [0.76], placebo: − 3.25 [1.00]; ARCH: romosozumab: − 3.40 [1.21], alendronate: − 3.21 [1.25]) than their respective full treatment populations (FRAME: romosozumab: − 2.72 [1.04], placebo: − 2.71 [1.04]; ARCH: romosozumab: − 2.94 [1.25], alendronate: − 2.99 [1.24]) [21, 22]. Consistent with the inclusion and exclusion criteria for each trial, patients in ARCH had higher rates and grades of prevalent vertebral fracture and a higher baseline nonvertebral fracture rate than patients in FRAME. In addition, patients in ARCH were on average older and had generally lower T-scores and higher Fracture Risk Assessment Tool (FRAX) scores.

Incidence of first on-study fracture in FRAME and ARCH

Nonvertebral fracture subgroup

The incidence of nonvertebral fracture by Month 12 was numerically lower in romosozumab-treated patients than those treated with comparator (Table 1). In FRAME, 56/3589 (1.6%) romosozumab-treated patients and 76/3591 (2.1%) patients treated with placebo experienced an on-study nonvertebral fracture by Month 12. In ARCH, 70/2046 (3.4%) romosozumab-treated patients and 95/2047 (4.6%) patients treated with alendronate experienced an on-study nonvertebral fracture by Month 12. The anatomic location of the first on-study nonvertebral fracture by Month 12 in FRAME and ARCH is shown in Table 2. In both trials, the radius was the most common nonvertebral fracture location.

Table 1 Baseline demographics and characteristics of patients with on-study fracture

	FRAME				ARCH			
	Nonvertebral fracture subgroup[a]		Vertebral fracture subgroup[b]		Nonvertebral fracture subgroup[a]		Vertebral fracture subgroup[b]	
	Romo (*N* = 56/3589 [1.6%])	PBO (*N* = 76/3591 [2.1%])	Romo (*N* = 17/3589 [0.5%])	PBO (*N* = 59/3591 [1.6%])	Romo (*N* = 70/2046 [3.4%])	ALN (*N* = 95/2047 [4.6%])	Romo (*N* = 67/2046 [3.3%])	ALN (*N* = 101/2047 [4.9%])
Age ≥ 75 years, *n* (%)	15 (26.8)	26 (34.2)	6 (35.3)	20 (33.9)	38 (54.3)	54 (56.8)	33 (49.3)	63 (62.4)
BMI, kg/m^2, mean (SD)	25.39 (4.46)	24.73 (4.27)	24.51 (3.56)	23.93 (3.81)	25.40 (4.60)	25.05 (4.64)	24.85 (4.03)	25.30 (4.59)
T-score, mean (SD)								
Lumbar spine	–2.74 (1.15)[c]	–2.68 (1.13)[d]	–3.16 (0.76)[e]	–3.25 (1.00)[f]	–2.78 (1.39)[g]	–3.11 (1.21)[h]	–3.40 (1.21)[i]	–3.21 (1.25)[j]
Total hip	–2.54 (0.51)	–2.43 (0.45)	–2.41 (0.57)	–2.54 (0.42)	–2.82 (0.66)	–2.98 (0.74)	–3.13 (0.79)	–2.96 (0.75)
Femoral neck	–2.79 (0.34)	–2.68 (0.32)	–2.76 (0.26)	–2.76 (0.31)	–2.90 (0.53)	–2.97 (0.54)	–3.08 (0.61)	–2.95 (0.61)
FRAX score (%),[k] mean (SD)								
10-year probability of MOF	14.0 (7.3)	16.4 (11.9)	17.4 (7.2)	16.0 (10.7)	20.9 (9.2)	22.0(10.3)	23.1 (12.9)	21.5 (11.0)
10-year probability of hip fracture	5.9 (3.8)	8.0 (9.3)	6.7 (2.6)	7.3 (7.1)	9.5 (5.9)	11.4 (8.3)	12.2 (11.5)	11.2 (9.4)
Prior osteoporotic fracture ≥ 45 years, *n* (%)	24 (42.9)	31 (40.8)	12 (70.6)	27 (45.8)	70 (100.0)	95 (100.0)	67 (100.0)	101 (100.0)
Prevalent vertebral fracture, *n* (%)								
Yes	16 (28.6)	16 (21.1)	8 (47.1)	16 (27.1)	67 (95.7)	94 (98.9)	67 (100.0)	101 (100.0)
No	39 (69.6)	58 (76.3)	8 (47.1)	42 (71.2)	2 (2.9)	1 (1.1)	0 (0.0)	0 (0.0)
Not readable/missing	1 (1.8)	2 (2.6)	1 (5.9)	1 (1.7)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Most severe Genant semi-quantitative grade of vertebral fracture, *n* (%)								
Mild	9 (16.1)	13 (17.1)	5 (29.4)	7 (11.9)	0 (0.0)	4 (4.2)	1 (1.5)	0 (0.0)
Moderate	7 (12.5)	3 (3.9)	3 (17.6)	9 (15.3)	17 (24.3)	24 (25.3)	12 (17.9)	21 (20.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	50 (71.4)	66 (69.5)	54 (80.6)	80 (79.2)

Baseline demographic and characteristic data are reported for all randomized patients who experienced a nonvertebral or vertebral fracture by Month 12; subheadings report: (number of randomized patients with fracture/total number of randomized population [% of total randomized population]). [a] Nonvertebral fracture subgroups comprise patients who sustained on-study nonvertebral fractures. [b] The vertebral fracture subgroups comprise patients who sustained either a clinical, or a new or worsening radiographic vertebral fracture. [c] *n* = 55. [d] *n* = 73. [e] *n* = 16. [f] *n* = 55. [g] *n* = 67. [h] *n* = 91. [i] *n* = 58. [j] *n* = 94. [k] 10-year probability of major osteoporotic fracture or hip fracture, calculated with BMD, based on FRAX version 3.9. *ALN* alendronate, *BMD* bone mineral density, *BMI* body mass index, *FRAX* Fracture Risk Assessment Tool, *MOF* major osteoporotic fracture, *PBO* placebo, *Romo* romosozumab, *SD* standard deviation

In patients who experienced nonvertebral fracture by Month 12, patients initially treated with romosozumab, then anti-resorptive therapy, had numerically lower rates of another nonvertebral fracture by end of study (up to 36 months) compared with patients initially treated with comparator (FRAME, 2/56 [3.6%] with romosozumab first then denosumab versus 7/76 [9.2%] with placebo first then denosumab; ARCH, 7/70 [10.0%] with romosozumab first then alendronate versus 12/95 [12.6%] with alendronate only; Table 2). Similarly, in patients with nonvertebral fracture by Month 12, rates of new or worsening vertebral fracture by end of study were numerically lower in those who initially received romosozumab, followed by antiresorptive therapy, compared with comparator (FRAME, 1/56 [1.8%] with romosozumab first then denosumab versus 3/76 [3.9%] with placebo first then denosumab; ARCH, 4/70 [5.7%] with

Table 2 Incidence and locations of on-study fractures

	FRAME		ARCH	
	Romo/Dmab	PBO/Dmab	Romo/ALN	ALN/ALN
Nonvertebral fracture subgroup				
Patients experiencing a first on-study nonvertebral fracture by Month 12, n[a]	56	76	70	95
Patients experiencing multiple-location first on-study nonvertebral fracture by Month 12, n[a,b]	10	11	18	29
Location of first nonvertebral fracture, n[b]				
Radius	23	27	28	37
Ulna	6	12	15	23
Femur intertrochanter	3	6	8	11
Humerus	5	2	5	11
Rib	1	7	5	10
Fibula	6	8	6	4
Femoral neck	4	6	4	8
Tibia	4	2	5	7
Metatarsal	8	4	1	1
Patella	1	4	5	0
Pubis	0	3	1	5
Ischium	0	2	1	2
Femur subtrochanteric	0	1	2	1
Sternal	1	2	0	1
Clavicle	1	1	0	1
Foot	1	0	0	2
Ilium	0	0	0	3
Femur distal	0	0	1	1
Carpal	1	0	0	0
Femur shaft	1	0	0	0
Sacrum	0	0	0	1
Patients who experienced another nonvertebral fracture by Month 12, n (%)[c]	0 (0.0)	2 (2.6)	2 (2.9)	3 (3.2)
Patients who experienced a new or worsening vertebral fracture during Month 12 to end of study, n (%)[c]	1 (1.8)	3 (3.9)	4 (5.7)	8 (8.4)
Patients who experienced a recurrent nonvertebral fracture by end of study, n (%)[c,d]	2 (3.6)	7 (9.2)	7 (10.0)	12 (12.6)
Location of another nonvertebral fracture by end of study, n[b]				
Radius	1	1	2	3
Ulna	1	1	2	1
Humerus	0	1	2	0
Patella	0	0	1	2
Rib	0	2	1	0
Femoral neck	0	0	0	2
Femur intertrochanter	0	0	0	2
Fibula	1	1	0	0
Tibia	1	1	0	0
Femur distal	0	0	0	1
Foot	0	1	0	0
Ischium	0	0	0	1
Metatarsal	0	0	1	0
Sacrum	0	0	0	1
Vertebral fracture subgroup				
Patients experiencing an on-study new or worsening vertebral fracture by Month 12, n[e,f]	17	59	67	100
Patients experiencing multiple on-study new or worsening vertebral fracture by Month 12, n[e,f]	1	9	20	21

Table 2 (continued)

	FRAME		ARCH	
	Romo/Dmab	PBO/Dmab	Romo/ALN	ALN/ALN
Clinical vertebral fracture, n[b,f]	3	21	12	20
Thoracic	0	11	8	14
Lumbar	3	10	4	6
Radiographic non-clinical vertebral fracture, n[b,f]	16	49	81	104
Thoracic	7	35	44	57
Lumbar	9	14	37	47
Patients who experienced another new or worsening vertebral fracture during Month 12 to end of study, n (%)[f,g]	0 (0.0)	7 (11.9)	6 (9.0)	15 (15.0)
Patients experiencing another nonvertebral fracture by end of study after Month 12, n (%)[f,g]	0 (0.0)	5 (8.5)	5 (7.5)	16 (16.0)

In FRAME, all patients receiving placebo or romosozumab switched to denosumab at Month 12; in ARCH, all patients receiving alendronate or romosozumab switched to alendronate at Month 12. [a] Nonvertebral fracture subgroups comprise patients who sustained on-study nonvertebral fractures and received at least one dose of investigational product. [b] First fractures that occurred at multiple locations simultaneously; the total number of individual fractures exceeds the overall incidence of fracture by location in each group. [c] Calculated as a percentage of the number of patients who experienced a nonvertebral fracture by Month 12 and received at least one dose of investigational product. [d] In FRAME, incidence of another on-study nonvertebral fracture is reported through Month 36, including events which occurred in the double-blind period and events which occurred in the open-label and extension periods for those patients who received at least one dose of denosumab; in ARCH, incidence of another on-study nonvertebral fracture is reported through end of study, including event that occurred in the double-blind period and events that occurred in the open-label period for those patients who received at least one dose of open-label alendronate. [e] The vertebral fracture subgroups comprise patients who sustained either a clinical, or a new or worsening radiographic vertebral fracture and received at least one dose of investigational product. [f] Missing new or worsening vertebral fracture status were imputed by carrying forward the last non-missing post-baseline value prior to the missing value. [g] Calculated as a percentage of the number of patients who experienced a new or worsening vertebral fracture by Month 12 and received at least one dose of investigational product. *ALN* alendronate, *Dmab* denosumab, *PBO* placebo, *Romo* romosozumab

romosozumab first then alendronate versus 8/95 [8.4%] with alendronate only; Table 2).

Overall, on-study nonvertebral fractures occurred with no specific pattern relative to the timing of the last administration of romosozumab prior to fracture. In patients who experienced on-study nonvertebral fracture by Month 12, the timing of the last dose of romosozumab or romosozumab-matched placebo prior to the incidence of fracture was similar between treatment groups in both FRAME and ARCH (Supplementary Table 1). The mean and median number of days in study prior to the fracture occurrence was also similar between romosozumab and comparator groups. In both trials, a subsequent dose of romosozumab was received approximately 3 weeks following the occurrence of nonvertebral fracture (mean [SD] number of days in FRAME, 21.0 [26.6]; ARCH, 22.5 [34.4]). Further data regarding the timing of study treatment dosing before and after the first on-study nonvertebral fracture are shown in Supplementary Table 1.

Vertebral fracture subgroup

Incidence of new or worsening vertebral fracture by Month 12 was numerically lower in patients treated with romosozumab than comparator-treated patients (Table 1). In FRAME, 17/3589 (0.5%) romosozumab-treated patients and 59/3591 (1.6%) patients treated with placebo experienced an on-study vertebral fracture by Month 12 (diagnosed by routine X-ray at Month 12 visit). In ARCH, 67/2046 (3.3%) romosozumab-treated patients and 101/2047 (4.9%) patients treated with alendronate experienced an on-study vertebral fracture by Month 12.

The total number of radiographic nonclinical vertebral fractures was numerically higher in both FRAME (romosozumab, $n = 16$; placebo, $n = 49$) and ARCH (romosozumab, $n = 81$; alendronate, $n = 104$) than the total number of clinical vertebral fractures (FRAME: romosozumab: $n = 3$; placebo: $n = 21$; ARCH: romosozumab: $n = 12$; alendronate: $n = 20$). The location of vertebral fractures by Month 12 in FRAME and ARCH is reported in Table 2; thoracic fractures, whether clinical or radiographic, were slightly more common than lumbar fractures.

In patients who experienced a vertebral fracture by month 12, the percentage who subsequently experienced another vertebral fracture by end of study was numerically lower in those who initially received romosozumab, then anti-resorptive therapy, versus comparator (FRAME: 0/17 [0.0%] with romosozumab first then denosumab, 7/59 [11.9%] with placebo first then denosumab; ARCH: 6/67 [9.0%] with romosozumab first then alendronate, 15/100 [15.0%] with alendronate only; Table 2). Similarly, the percentage who subsequently experienced a nonvertebral fracture by end of study was numerically

lower in women who initially received romosozumab, followed by antiresorptive therapy, versus comparator (FRAME: 0/17 [0.0%] with romosozumab first then denosumab, 5/59 [8.5%] with placebo first then denosumab; ARCH: 5/67 [7.5%] with romosozumab first then alendronate, 16/100 [16.0%] with alendronate only; Table 2).

Safety outcomes in patients with an on-study fracture

In both the nonvertebral and vertebral fracture subgroups of FRAME and ARCH, incidence of TEAEs, serious TEAEs, and the proportion of patients who required surgery for their fracture were generally similar between patients initially treated with romosozumab versus those initially treated with comparator (Supplementary Table 2 and Supplementary Table 3).

There were no fracture-related complications (i.e., nonunion, malunion, delayed healing, chronic pain, osteomyelitis) reported in patients initially treated with romosozumab in either fracture subgroups of FRAME and ARCH. Among patients with nonvertebral fracture by Month 12, one fracture-related complication was reported in the group of patients who initially received placebo (FRAME; chronic osteomyelitis of the right fibula, occurring by Month 12) and alendronate (ARCH; osteomyelitis of the left leg, occurring by Month 12). In the nonvertebral fracture subgroups, the proportion of patients who required surgery for their fracture was similar between romosozumab and comparator groups in both trials. Safety outcomes are expanded upon within Supplementary Material 1**,** Supplementary Table 2, and Supplementary Table 3.

BMD change from baseline in patients with an on-study fracture

Greater gains in BMD were observed with romosozumab treatment versus placebo (FRAME) or alendronate (ARCH) in both the nonvertebral and vertebral fracture subgroups (Supplementary Fig. 2 and Supplementary Fig. 3, respectively). However, irrespective of the treatment initially received, percentage change in BMD at the total hip and femoral neck was slightly lower in both the nonvertebral and vertebral fracture subgroups than in the full trial populations, which included those who did not experience on-study fractures.

Discussion

In these post hoc analyses of the FRAME and ARCH phase 3 trials, we evaluated the efficacy and safety of romosozumab in patients who experienced a nonvertebral, or a new or worsening vertebral fracture. In romosozumab-treated patients, incidence of first on-study fracture was numerically lower in the first year compared with placebo- or alendronate-treated patients. Importantly, incidence of recurrent nonvertebral and vertebral fractures after the first fracture was also numerically lower in women who initially received romosozumab versus comparator in both FRAME and ARCH. Overall, adverse events were balanced in patients with on-study fracture in both romosozumab and comparator groups; continuing romosozumab treatment in the acute post-fracture period was not associated with fracture-related complications or increased rates of post-fracture surgery. These numerical findings provide additional evidence underscoring the efficacy and safety of romosozumab administration in the acute post-fracture period.

Individuals who experience a fracture are at increased risk of future fractures [1–5]. One retrospective cohort study of postmenopausal women who had sustained a fracture reported the cumulative incidence of subsequent fracture within 1-year post fracture to be 9.8% for an initial fracture at any site and 7.2% for an initial fracture of the radius (being the most common fracture site in the present study) or ulna [23]. In older women, it has been reported that imminent fracture risk is greatest in those who initially experienced clinical vertebral fractures, with ~ 14% of these patients experiencing a subsequent fracture within 1 year; incidence of subsequent fracture was also high in those who sustained pelvic, clavicular, and humeral fractures [23]. In the current study, incidence of subsequent fracture, whether nonvertebral or vertebral, following either a nonvertebral or vertebral fracture occurring by Month 12, was numerically lower in those initially treated with romosozumab than those initially treated with comparator. Importantly, during Months 12–36, patients in both arms of FRAME or ARCH received the same open-label treatment (FRAME, denosumab; ARCH, alendronate) [21, 22]. Thus, the differences in incidence of recurrent fracture can be attributed to the difference in response during the 12 months of romosozumab treatment. These data provide support for the efficacy of romosozumab in patients who are at imminent fracture risk and suggest the importance of continuing treatment with romosozumab following a fracture.

Previous studies have provided no safety concerns for rapid initiation of an osteoporosis therapy after a fracture [24–27]. In one study of patients with tibial diaphyseal fractures, post-operative administration of romosozumab on Day 1 and Weeks 2, 6, and 12 following the fracture was not associated with delayed healing when compared with placebo [28]; similar results have also been observed in romosozumab-treated patients with intertrochanteric or femoral neck hip fractures [29]. The efficacy and safety of administration of other osteoporosis medications following a fracture have also been studied: in the FREEDOM trial,

administration of denosumab within 6 weeks following a fracture was not associated with delayed healing or nonunion of the fracture site [30]. Similarly, a recent meta-analysis of the effectiveness of parathyroid hormone analogues, such as teriparatide, found no detrimental effect on fracture healing [31]. Zoledronic acid was also studied in a population of acute hip fracture patients, among whom no detrimental impact of zoledronic acid treatment was found on fracture healing [32]. Collectively, these data suggest that there is no need to delay the administration of osteoporosis treatment in patients who have recently experienced fracture.

In both fracture subgroups, greater gains in BMD were observed in romosozumab-treated patients than placebo- (FRAME) or alendronate-treated (ARCH) patients. However, these gains were slightly lower at the total hip and femoral neck in patients with on-study fracture versus the full trial populations, which included those who did not experience on-study fractures. This could be related to reduced mobility or activity post-fracture or other inflammatory processes in the post-fracture period [33]. Indeed, acute bone loss after fracture has been described in multiple prior studies [33–35].

Limitations of the analyses undertaken in this study include the fact that the data are from clinical trials with defined patient inclusion criteria which may not fully reflect the characteristics of a real-world population. In addition, the FRAME and ARCH trials were not designed to evaluate the effects of romosozumab on fracture healing, and thus, the follow-up assessments employed may not have been sufficiently comprehensive to detect subtle differences between the romosozumab and comparator groups. Furthermore, fracture numbers were limited, and the sample size might not have been sufficient to observe an impact on fracture repair or complications. The relatively low rate of fracture events in the FRAME and ARCH trials precluded the ability to meaningfully conduct formal statistical testing; thus, results should be interpreted in the context of this limitation. Strengths of the study include the double-blind, parallel-group study design and the robustness of assessments in a clinical trial setting.

Conclusions

In conclusion, 1 year of romosozumab treatment before antiresorptive therapy not only reduced the incidence of fracture in the first 12 months, but also reduced the incidence of recurrent nonvertebral and vertebral fractures for up to 3 years. This suggests that initial romosozumab treatment was effective at reducing imminent fracture risk versus comparator, and this benefit appeared to be sustained after patients switched from romosozumab to either denosumab or alendronate. Continuing romosozumab treatment in the acute post-fracture period in patients who sustained a nonvertebral or vertebral fracture in the FRAME and ARCH phase 3 trials did not delay fracture healing or contribute to other skeletal adverse events. In addition, initial romosozumab treatment increased BMD at both hip and spine regions in patients with on-study fractures. These results, together with previously reported data which did not demonstrate adverse effects of romosozumab in the setting of tibial or proximal femoral fractures [28, 29], should help to give clinicians confidence that they can initiate romosozumab treatment promptly post-fracture and continue medication in patients who experience fracture while already receiving treatment.

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Data availability Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/clinical-trial-data-sharing-request/

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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

Conflicts of interest Joseph Lane received grants from Radius and Merck; served on the speakers' bureau for UCB Pharma. Bente Langdahl received fees and honoraria for lectures and advice from Amgen, Gedeon Richter, Gilead, and UCB Pharma; research grants for Aarhus University Hospital from Amgen Inc. and Novo Nordisk. Michael Stone received payments for lectures and Advisory Boards for UCB, Amgen, and Gedeon Richter. Andreas Kurth served as a consultant for Amgen, UCB, Eli Lilly, and Theramax; served on the speakers' bureaus for Amgen, UCB, Eli Lilly, and Theramax. Mary Oates is an employee and stockholder of Amgen. Jen Timoshanko is an employee

and shareholder of UCB Pharma. Zhenxun Wang is an employee and stockholder of Amgen. Cesar Libanati is an employee and shareholder of UCB Pharma. Felicia Cosman received institutional grants and research support from Amgen and from Radius Health; served as a consultant for Amgen, Biocon, Enterabio, Pfizer/Myovant and Radius Health; served on the speakers' bureaus for Amgen and Radius Health.

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