SUPPLEMENTARY MATERIAL

Osteoporosis International

Romosozumab in Patients who Experienced an On-Study Fracture: Post Hoc Analyses of the FRAME and ARCH Phase 3 Trials

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SUPPLEMENTARY MATERIAL 1:

Safety outcomes in patients with an on-study fracture

Nonvertebral fracture subgroup

In the nonvertebral fracture subgroup, during the 12-month double-blind period, the overall incidence of TEAEs was similar in patients who received romosozumab (FRAME: 57.1%; ARCH: 54.3%) and those who received placebo (FRAME: 64.5%) or alendronate (ARCH: 48.4%; **Supplementary Table 2**). Incidence of serious TEAEs, both by Month 12 and end of study, was generally similar between patients initially treated with romosozumab and comparator. The proportion of patients who required surgery for their fracture was similar between romosozumab and comparator groups in both trials. There were no fracture-related complications (i.e., nonunion, malunion, delayed healing, chronic pain, osteomyelitis), nor incidences of hypocalcemia, reported in the nonvertebral fracture subgroup of patients who received romosozumab followed by denosumab through 36 months in FRAME, or romosozumab followed by alendronate through end of study in ARCH (**Supplementary Table 2**).

Vertebral fracture subgroup

In the vertebral fracture subgroup, the overall incidence of TEAEs by Month 12 was similar between patients who received romosozumab (FRAME: 82.4%; ARCH: 76.1%) and placebo (FRAME: 93.2%) or alendronate (ARCH: 83.0%; **Supplementary Table 3**). Incidence of serious TEAEs by Month 12 was similar in romosozumab and comparator groups within each study. Between Month 12 and end of study, serious TEAEs occurred less frequently in the group that initially received romosozumab versus placebo in FRAME, however, the incidence of serious TEAEs during the open-label period was similar between groups in ARCH. No fracture-related complications, nor incidences of hypocalcemia, were reported (**Supplementary Table 3**).

Supplementary Table 1. Timing of fracture relative to administration of study treatment in nonvertebral fracture subgroup

	FRAME		ARCH	
	Romo (N=56)	**PBO (N=76)**	**Romo (N=70)**	**ALN[a] (N=95)**
Timing of first nonvertebral fracture occurrence, following randomization				
Mean (SD), days	169.8 (111.2)	179.2 (104.0)	151.3 (101.7)	184.3 (113.8)
Median, days	167.0	176.5	152.0	170.0
Range, days	8–372	2–366	1–357	2–374
Number of treatment doses received prior to fracture				
Mean (SD)	5.8 (3.6)	6.1 (3.5)	5.1[b] (3.4)	6.3 (3.6)
Number of doses missed prior to fracture, n (%)[c]				
0	50 (89.3)	-	66 (94.3)	-
1	4 (7.1)	-	2 (2.9)	-
2	2 (3.6)	-	0 (0.0)	-
3	0 (0.0)	-	1 (1.4)	-
Timing of treatment dose prior to fracture				
n	56	76	69[b]	95
Mean (SD), days	19.6 (14.4)	23.6 (24.4)	22.6 (18.6)	19.6 (13.6)
Median, days	18.0	21.0	20.0	19.0
Range, days	1–94	1–148	1–131	1–89
Timing of treatment dose after fracture				
n	48[d]	-	60[e]	-
Mean (SD), days	21.0 (26.6)	-	22.5 (34.4)	-
Median, days	15.0	-	14.0	-
Range, days	0–159	-	0–197	-
Number of doses received after fracture by end of double-blind period				
n	48[d]	66[f]	60[e]	77[g]
Mean (SD), doses	6.1 (3.4)	5.7 (3.3)	6.1 (3.2)	5.8 (3.2)
Median, doses	6.5	6.0	6.0	6.0
Range, doses	1–11	1–11	1–11	1–11

[a] Doses of romosozumab-matched subcutaneous placebo injection are considered. [b] One patient's first nonvertebral fracture was on the same date as the first romosozumab dose. [c] Percentage based on number of patients with on-study nonvertebral fracture by Month 12 (N). [d] One patient discontinued romosozumab before first nonvertebral fracture, one patient discontinued romosozumab after first nonvertebral fracture, and six patients completed the planned romosozumab doses. [e] Seven patients discontinued romosozumab before first nonvertebral fracture, one patient discontinued romosozumab after first nonvertebral fracture and two patients completed the planned romosozumab doses. [f] One patient discontinued placebo before first nonvertebral fracture, two patients discontinued after first nonvertebral fracture, and seven patients completed the planned placebo doses. [g] Three patients discontinued romosozumab-matched placebo before first nonvertebral fracture, one patient discontinued after first nonvertebral fracture, and 14 patients completed the planned treatment doses. ALN: alendronate; PBO: placebo; Romo: romosozumab; SD: standard deviation.

Supplementary Table 2. Safety outcomes in patients in the nonvertebral fracture subgroup

	FRAME		ARCH	
	Romo/ Dmab (N=56)	**PBO/ Dmab (N=76)**	**Romo/ ALN (N=70)**	**ALN/ ALN (N=95)**
TEAE summary				
Overall TEAEs by Month 12, n[a] (%)	32 (57.1)	49 (64.5)	38 (54.3)	46 (48.4)
Serious TEAEs by Month 12, n[a] (%)	2 (3.6)	7 (9.2)	8 (11.4)	9 (9.5)
Overall TEAEs between Month 12 and end of study, n[b] (%)	41 (73.2)	56 (73.7)	50 (71.4)	69 (72.6)
Serious TEAEs between Month 12 and end of study, n[b] (%)	10 (17.9)	21 (27.6)	17 (24.3)	28 (29.5)
Fracture-related TEAEs				
Nonunion, malunion, delayed healing, chronic pain, osteomyelitis by end of study, n[a,b] (%)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.1)
Fracture-related surgeries				
Patients requiring surgery related to first nonvertebral fracture by Month 12, n (%)	9 (16.1)	12 (15.8)	23 (32.9)	28 (29.5)
Hypocalcemia[c]				
Patients who have hypocalcemia by end of study, n[b] (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

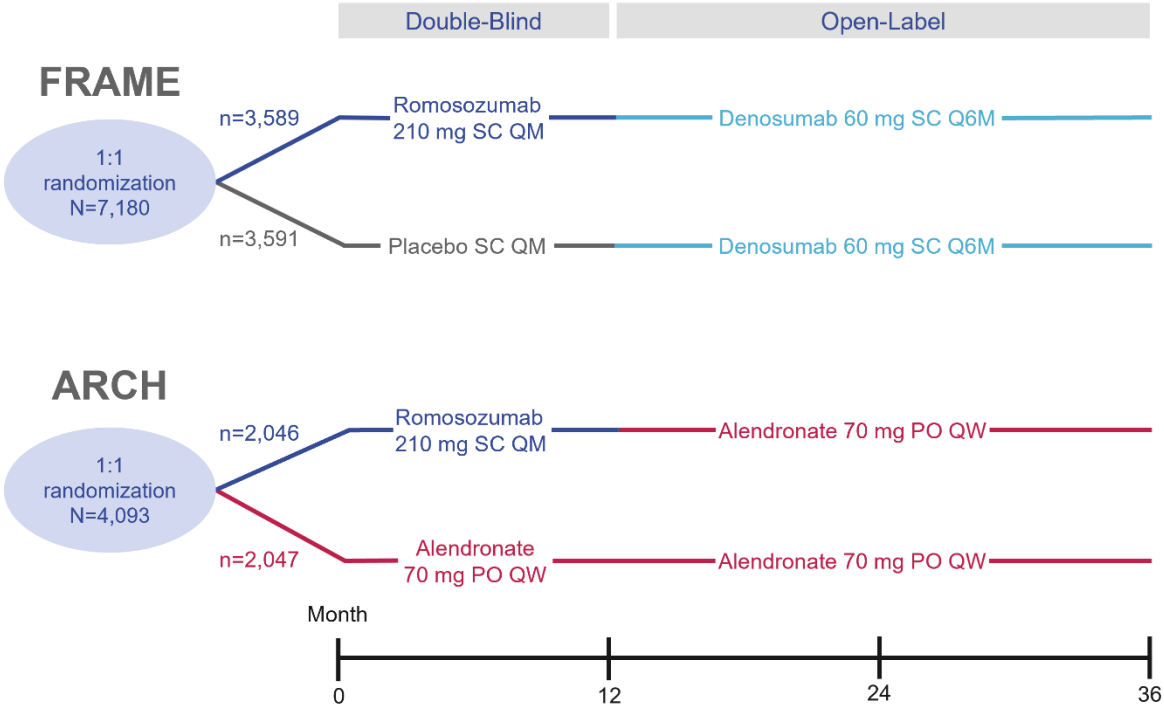
In FRAME, all patients receiving placebo or romosozumab switched to denosumab at Month 12; in ARCH all patients receiving alendronate or romosozumab switched to alendronate at Month 12. N = Number of patients who experienced a nonvertebral fracture by Month 12 and received at least one dose of investigational product; n = number of patients who experienced event. [a] Excludes any TEAEs that occurred before first nonvertebral fracture. [b] Data reported through Month 36 in FRAME or end of study in ARCH. [c] Hypocalcemia includes only TEAEs as a result of pre-defined MedDRA search strategies.
ALN: alendronate; Dmab: denosumab; MedDRA: Medical Dictionary for Regulatory Activities; PBO: placebo; Romo: romosozumab;
TEAE: treatment-emergent adverse event.

Supplementary Table 3. Safety outcomes in patients in the vertebral fracture subgroup

	FRAME		ARCH	
	Romo/ Dmab (N=17)	**PBO/ Dmab (N=59)**	**Romo/ ALN (N=67)**	**ALN/ ALN (N=100)**
TEAE summary				
Overall TEAEs by Month 12, n[a] (%)	14 (82.4)	55 (93.2)	51 (76.1)	83 (83.0)
Serious TEAEs by Month 12, n[a] (%)	3 (17.6)	6 (10.2)	14 (20.9)	21 (21.0)
Overall TEAEs between Month 12 and end of study, n[a,b] (%)	10 (58.8)	42 (71.2)	49 (73.1)	83 (83.0)
Serious TEAEs between Month 12 and end of study, n[a,b] (%)	0 (0.0)	13 (22.0)	19 (28.4)	32 (32.0)
Fracture-related TEAEs				
Nonunion, malunion, delayed healing, chronic pain, osteomyelitis during Month 12 and end of study,[b] n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypocalcemia[c]				
Patients who have hypocalcemia by end of study,[b] n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

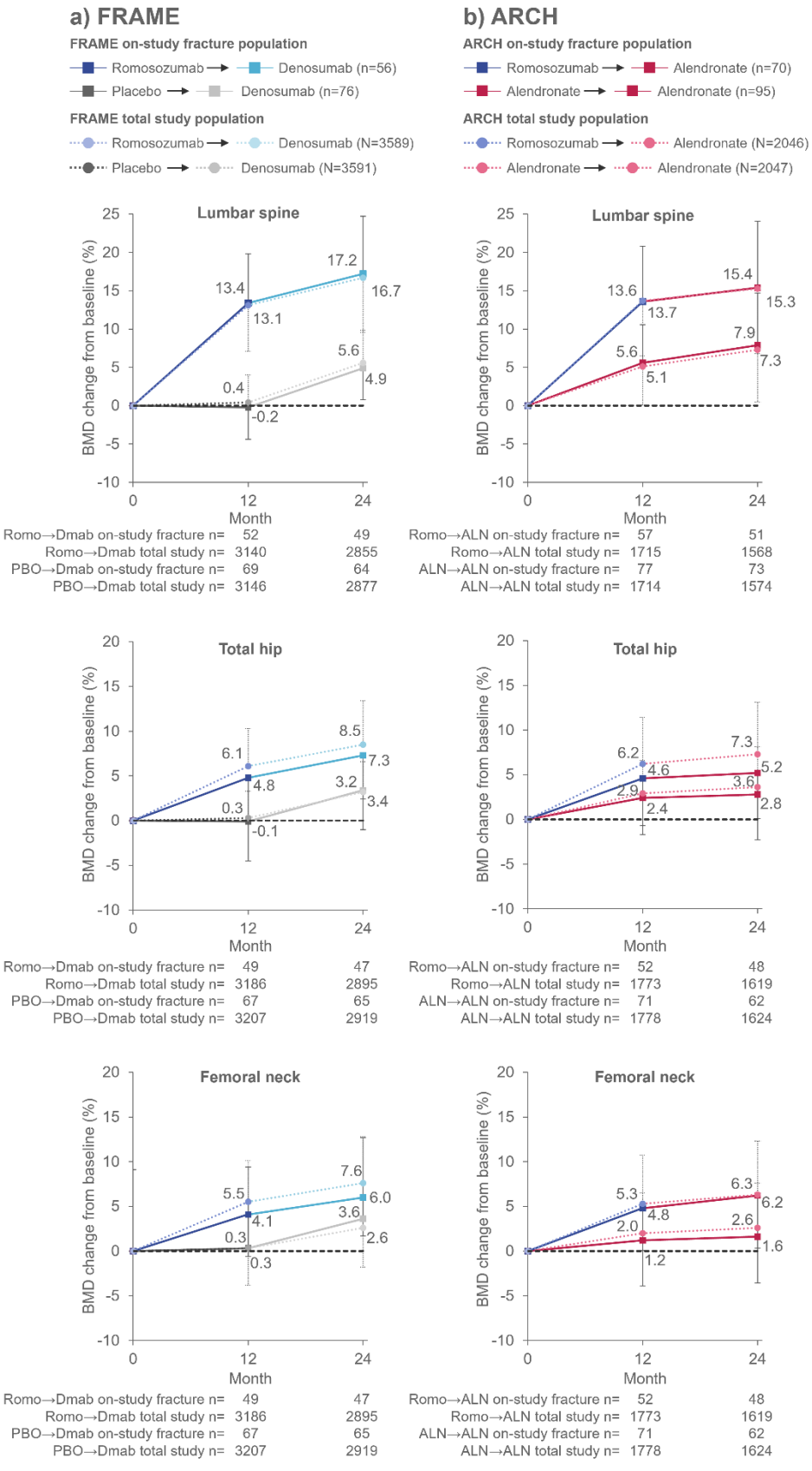
In FRAME, all patients receiving placebo or romosozumab switched to denosumab at Month 12; in ARCH all patients receiving alendronate or romosozumab switched to alendronate at Month 12. N = Number of patients who experienced a new or worsening vertebral fracture by Month 12 and received at least one dose of investigational product; n = number of patients who experienced the event. Missing new or worsening vertebral fracture status were imputed by carrying forward the last non-missing post-baseline value prior to the missing value. [a] Includes all TEAEs that occurred by Month 12 or end of study, respectively. [b] Data reported through Month 36 in FRAME or end of study in ARCH. [c] Hypocalcemia includes only treatment-emergent adverse events as a result of pre-defined MedDRA search strategies. ALN: alendronate; Dmab: denosumab; MedDRA: Medical Dictionary for Regulatory Activities; PBO: placebo; Romo: romosozumab; TEAE: treatment-emergent adverse event.

Supplementary Fig 1. FRAME and ARCH trial designs



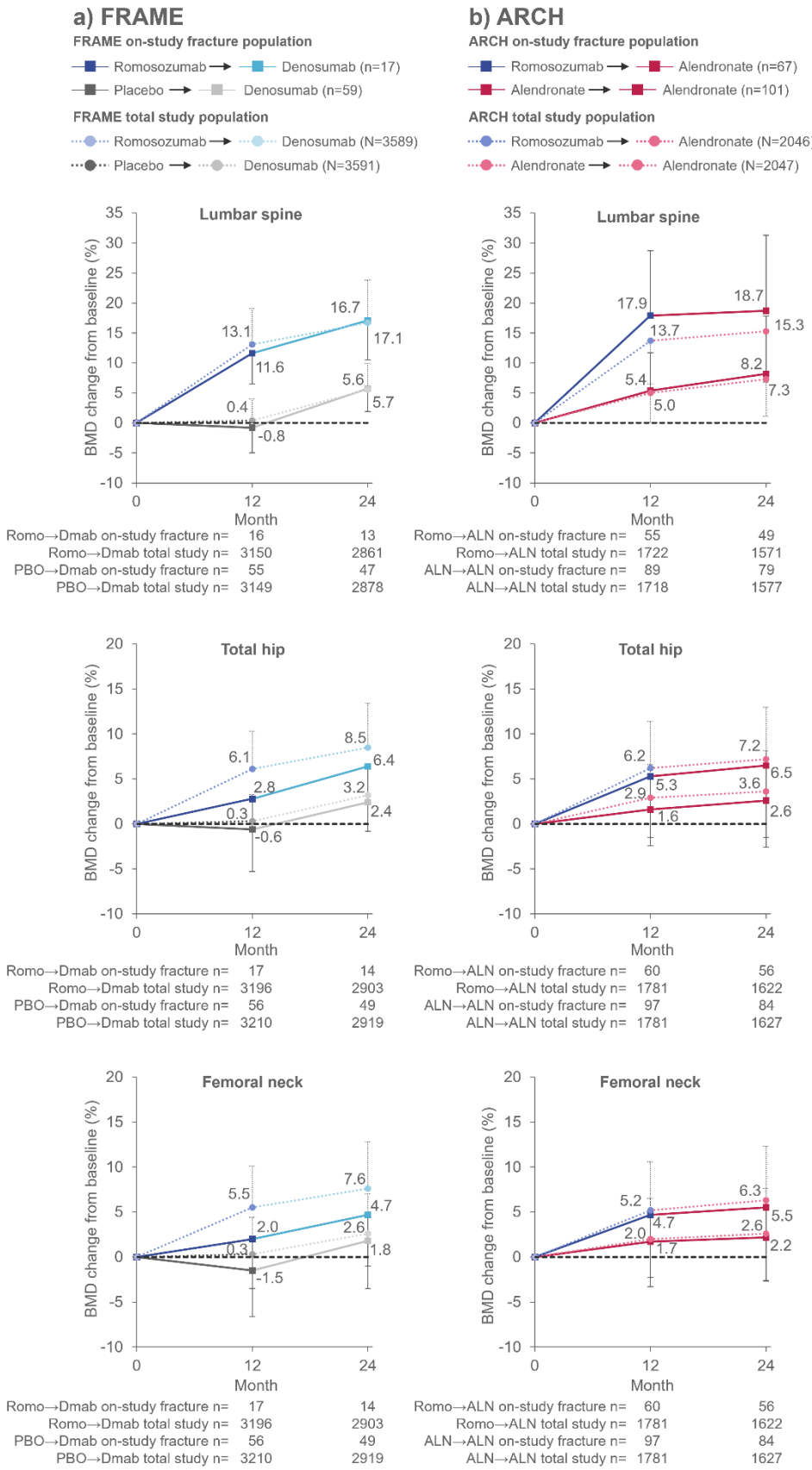
FRAME included a 24-month study period (Month 0 to 24) and a 12-month extension (Month 24 to 36). PO: orally; QM: monthly; Q6M: every six months; QW: weekly; SC: subcutaneous.

Supplementary Fig 2. BMD mean percentage change from baseline in nonvertebral fracture subgroups and total populations in (a) FRAME and (b) ARCH (observed data)



Data presented as mean (+ or – SD) BMD change from baseline (%). 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. The nonvertebral fracture subgroups comprise all randomized patients who sustained a nonvertebral fracture by Month 12. ALN: alendronate; BMD: bone mineral density. Dmab: denosumab; PBO: placebo; Romo: romosozumab; SD: standard deviation.

Supplementary Fig 3. BMD mean percentage change from baseline in vertebral fracture subgroups and total populations in (a) FRAME and (b) ARCH (observed data)



Data presented as mean (+ or – SD) BMD change from baseline (%). 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. The vertebral fracture subgroups comprise all randomized patients who sustained either a clinical, or a new or worsening radiographic, vertebral fracture by Month 12. ALN: alendronate; BMD: bone mineral density. Dmab: denosumab; PBO: placebo; Romo: romosozumab; SD: standard deviation.