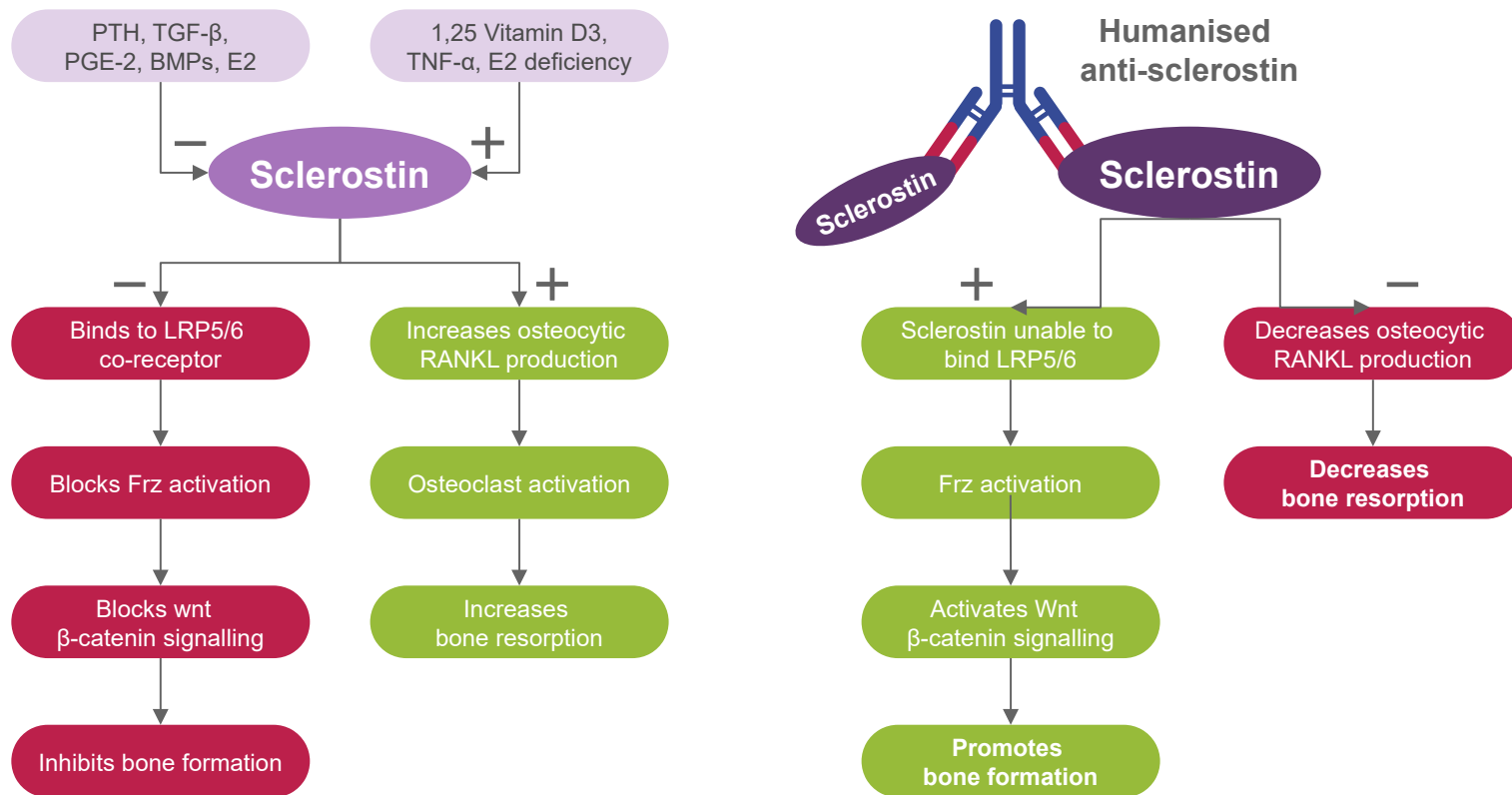# ROMOSOZUMAB

Nicola Napoli, MD PhD

Trattare Osteoporosi =

Ridurre la mortalità e la morbilità
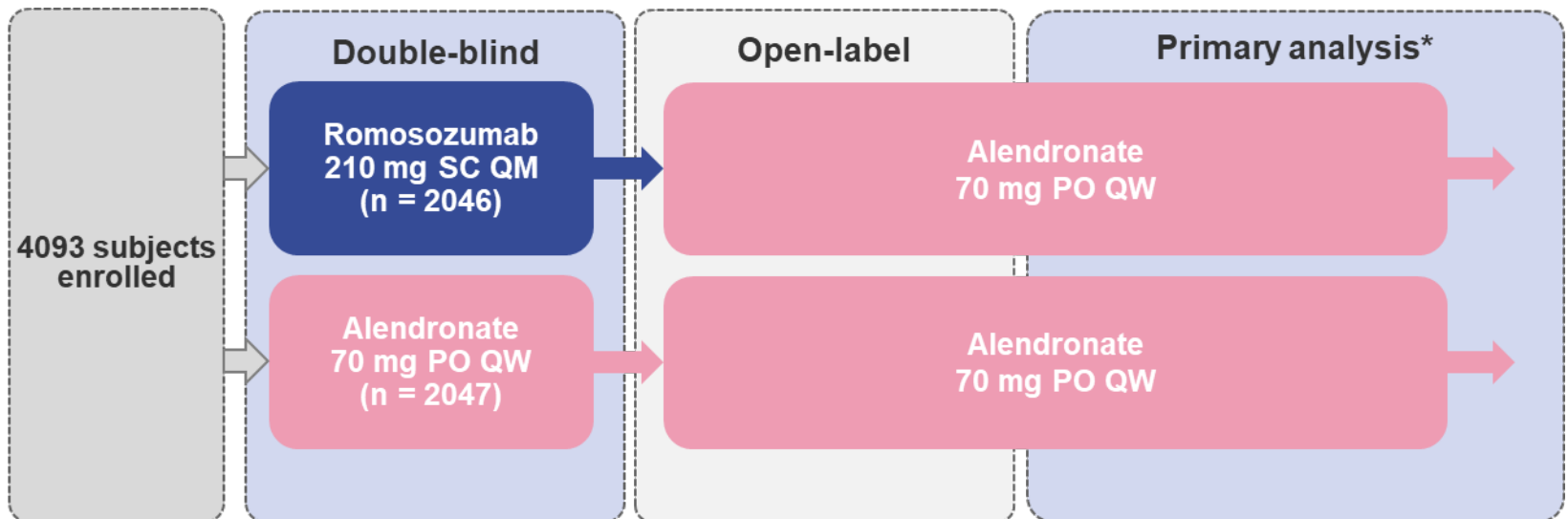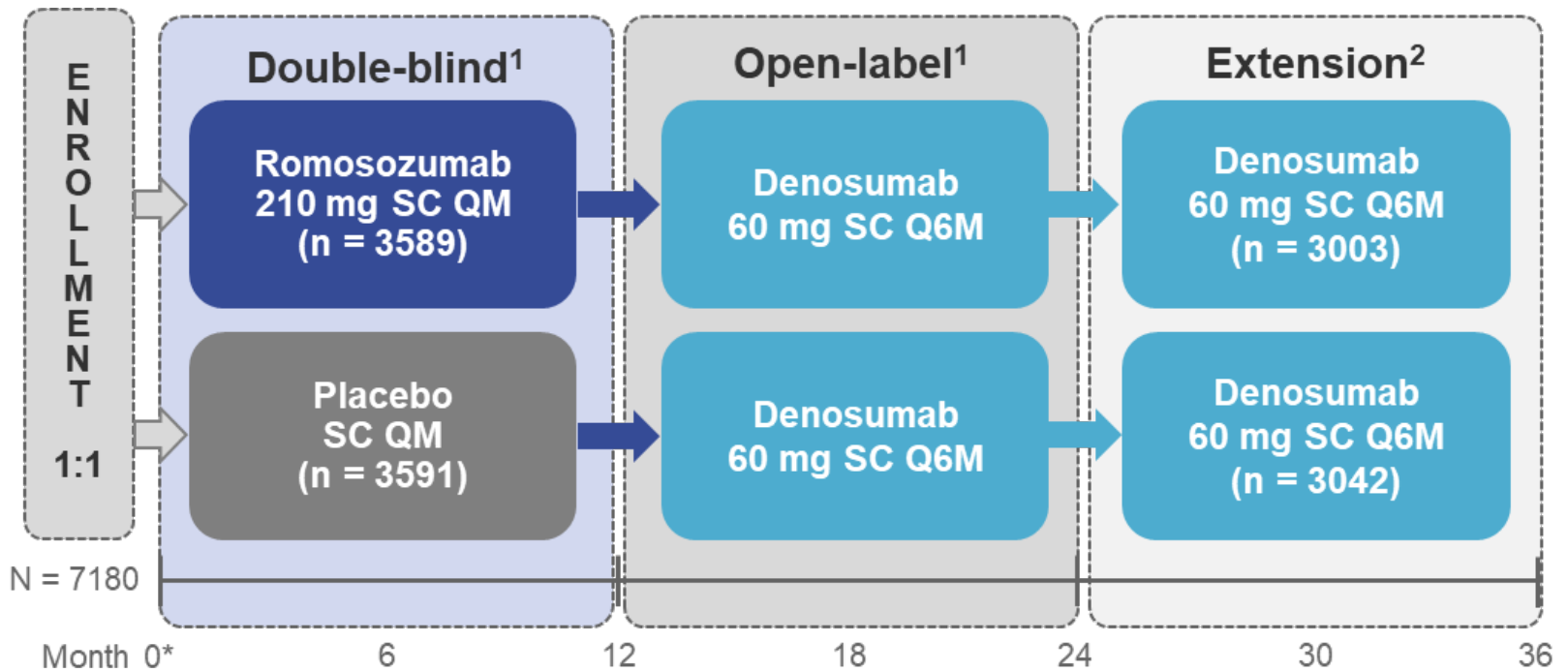
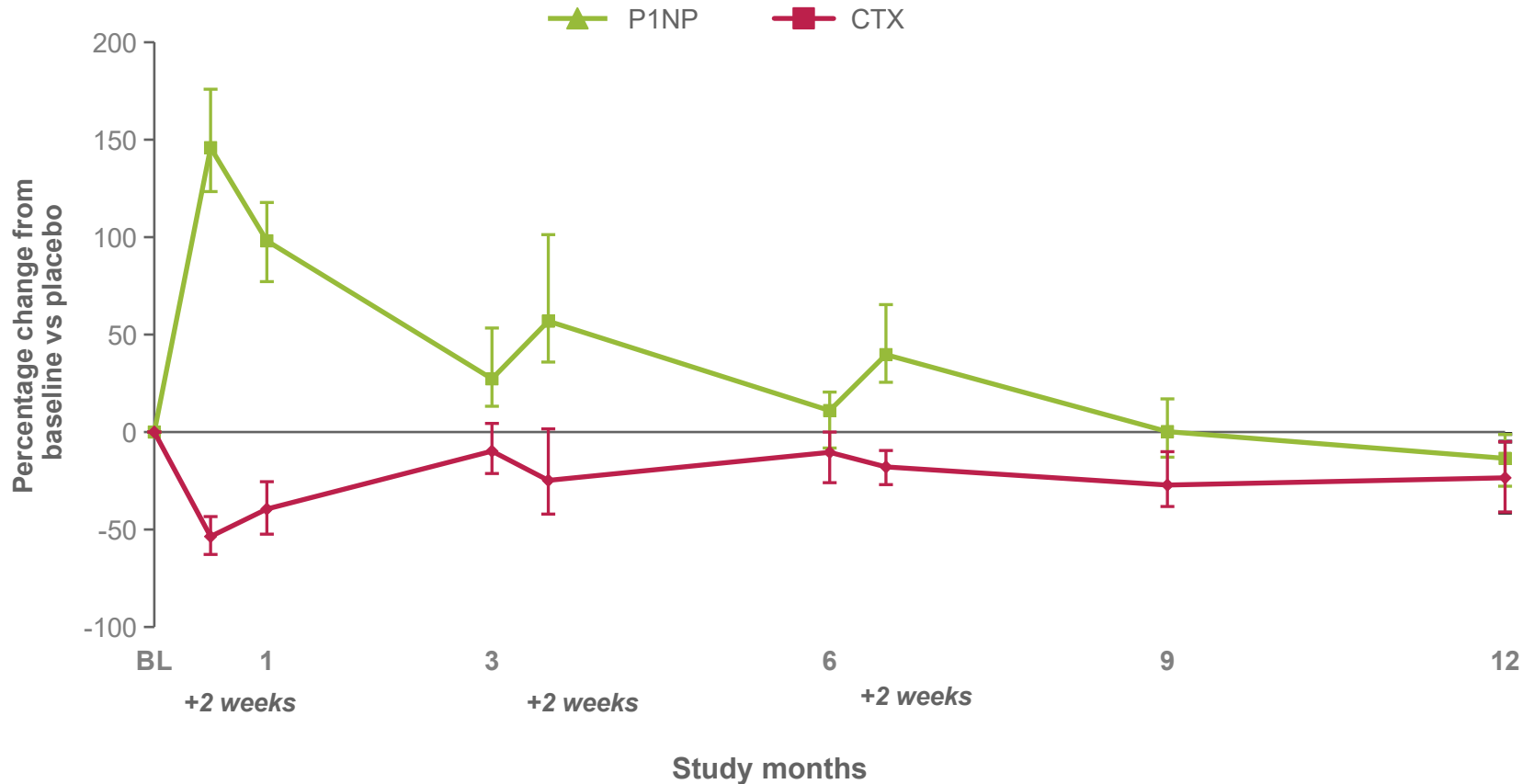# Romosozumab Exerts a Dual Effect on Bone Increasing Bone Formation and Decreasing Bone Resorption

PTH, TGF-β, PGE-2, BMPs, E2

1,25 Vitamin D3, TNF-α, E2 deficiency

− **Sclerostin** +

Humanised anti-sclerostin

Sclerostin **Sclerostin**

− | Binds to LRP5/6 co-receptor | + | Increases osteocytic RANKL production | + | Sclerostin unable to bind LRP5/6 | − | Decreases osteocytic RANKL production

Blocks Frz activation → **Osteoclast activation** → **Frz activation** → **Decreases bone resorption**

Blocks wnt β-catenin signalling → **Increases bone resorption** → **Activates Wnt β-catenin signalling**

Inhibits bone formation → **Promotes bone formation**

IT-N-RM-OP-2100011

Top diagram:

ENROLLMENT 1:1

N = 7180

Double-blind[1]
- Romosozumab 210 mg SC QM (n = 3589)
- Placebo SC QM (n = 3591)

Open-label[1]
- Denosumab 60 mg SC Q6M
- Denosumab 60 mg SC Q6M

Extension[2]
- Denosumab 60 mg SC Q6M (n = 3003)
- Denosumab 60 mg SC Q6M (n = 3042)

Month 0*   6   12   18   24   30   36

Bottom diagram:

4093 subjects enrolled

Double-blind
- Romosozumab 210 mg SC QM (n = 2046)
- Alendronate 70 mg PO QW (n = 2047)

Open-label
- Alendronate 70 mg PO QW
- Alendronate 70 mg PO QW

Primary analysis*

Dual Effect with Romosozumab?

Data from the FRAME study in 7180 postmenopausal women with osteoporosis. Patients received romosozumab 210 mg or placebo once monthly for 12 months followed by open-label denosumab 60 mg every 6 months for 12 months. Coprimary endpoints were the cumulative incidences of new vertebral fracture at 12 months and at 24 months. Serum concentrations of P1NP and CTX were measured in a substudy of 129 patients.[1] P1NP: romosozumab, n = 62; placebo, n = 62;
CTX: romosozumab, n = 61; placebo, n = 62. Data presented as bootstrapped median treatment difference and 95% CI.
BL = baseline; CI = confidence interval; CTX = C-terminal telopeptide of type 1 collagen; P1NP = procollagen type 1 N-terminal propeptide.
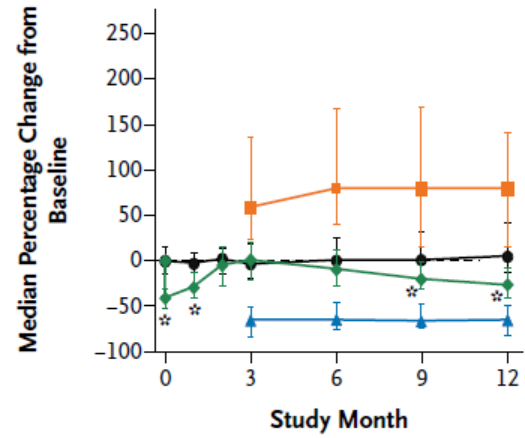Adapted from: 1. Cosman F, *et al. N Engl J Med* 2016;375:1532–43.

IT-N-RM-OP-2100011

Placebo — Alendronate — Teriparatide — 210 mg of Romosozumab monthly
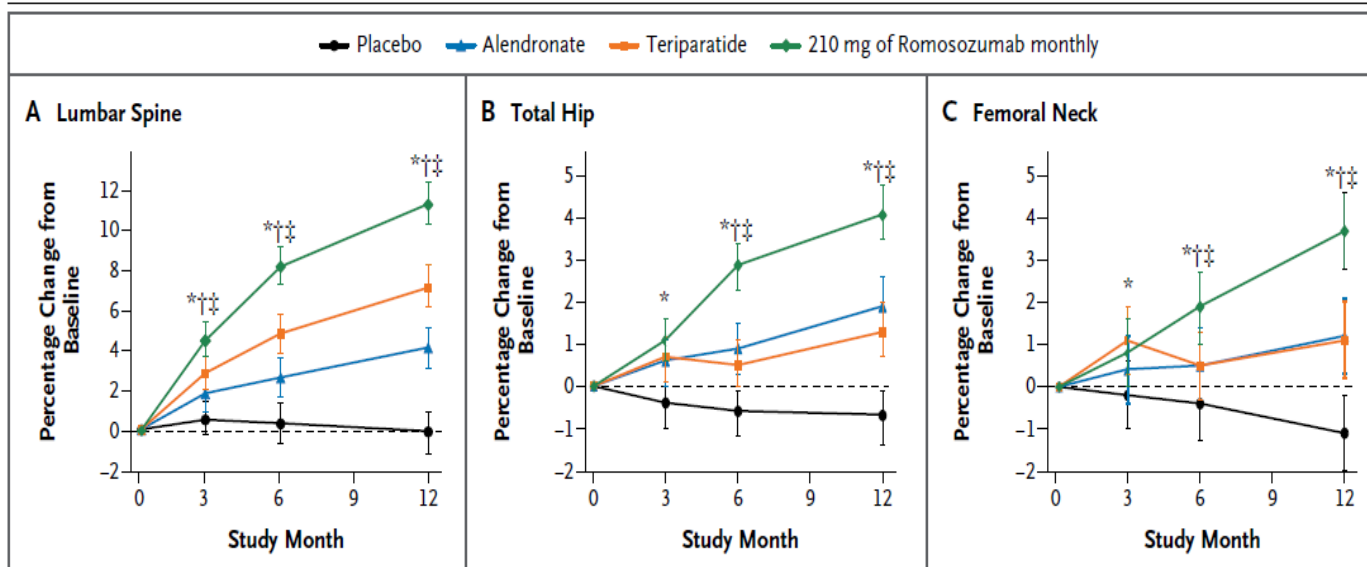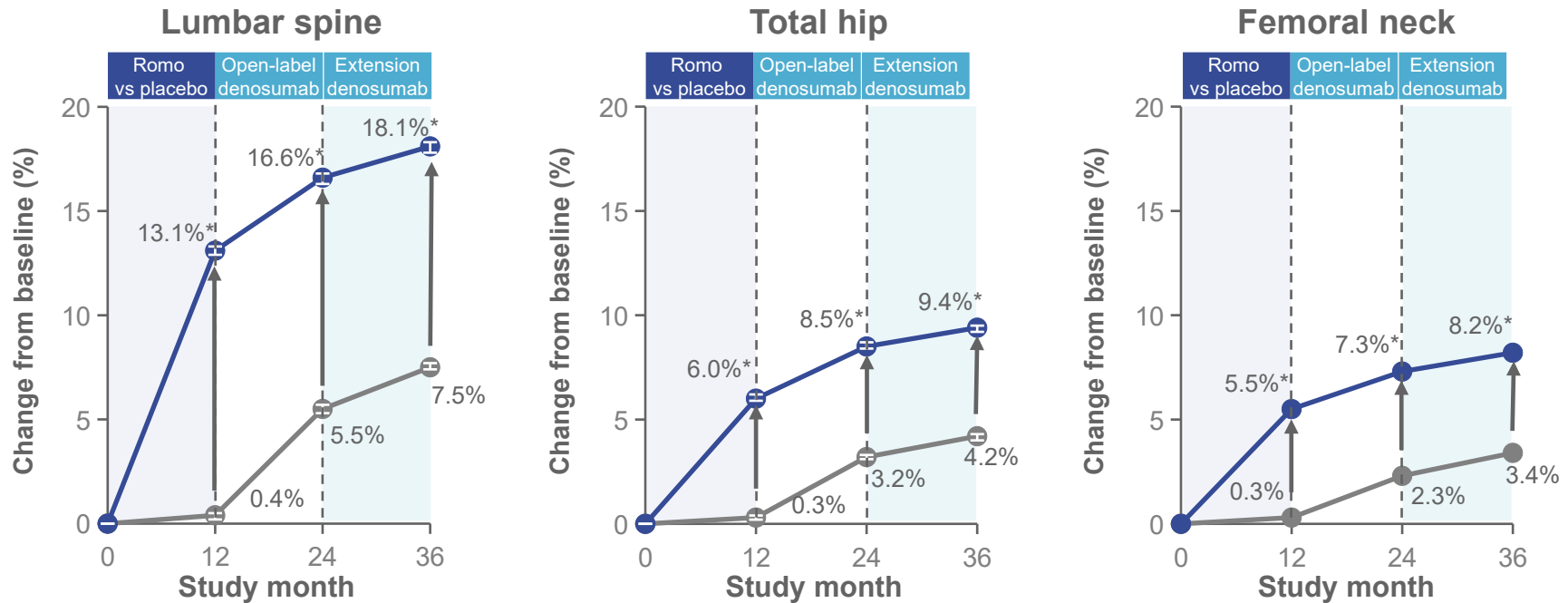
A P1NP
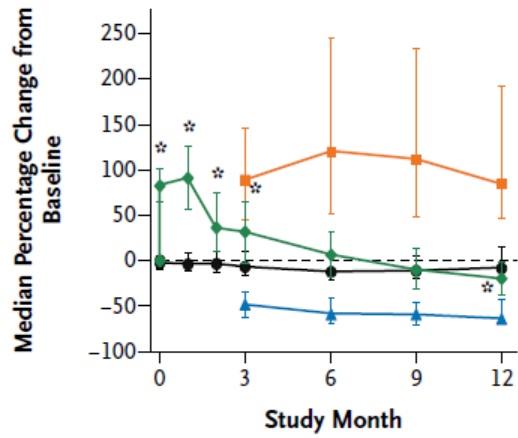
B β-CTX

ORIGINAL ARTICLE

Romosozumab in Postmenopausal Women with Low Bone Mineral Density

FRAME: Lumbar Spine, Total Hip and Femoral Neck BMD Through Month 36

━●━ Romosozumab-to-denosumab (lumbar spine, n = 3169; total hip, femoral neck, n = 3237)
━●━ Placebo-to-denosumab (lumbar spine, n = 3176; total hip, femoral neck, n = 3256)

Lumbar spine

| Romo vs placebo | Open-label denosumab | Extension denosumab |

- 13.1%* (at month 12)
- 16.6%* (at month 24)
- 18.1%* (at month 36)
- 0.4% (at month 12)
- 5.5% (at month 24)
- 7.5% (at month 36)

Y-axis: Change from baseline (%), 0 to 20
X-axis: Study month, 0 to 36

Total hip

| Romo vs placebo | Open-label denosumab | Extension denosumab |

- 6.0%* (at month 12)
- 8.5%* (at month 24)
- 9.4%* (at month 36)
- 0.3% (at month 12)
- 3.2% (at month 24)
- 4.2% (at month 36)

Y-axis: Change from baseline (%), 0 to 20
X-axis: Study month, 0 to 36

Femoral neck

| Romo vs placebo | Open-label denosumab | Extension denosumab |

- 5.5%* (at month 12)
- 7.3%* (at month 24)
- 8.2%* (at month 36)
- 0.3% (at month 12)
- 2.3% (at month 24)
- 3.4% (at month 36)

Y-axis: Change from baseline (%), 0 to 20
X-axis: Study month, 0 to 36

Least squares mean percentage change from baseline in BMD and p values were based on ANCOVA model adjusting for treatment, age and prevalent vertebral fracture stratification variables, baseline value, machine type and baseline value-by-machine type interaction, without multiplicity adjustment. Missing values were imputed by the last-observation-carried-forward method, and a sensitivity analysis with the use of a repeated measures model showed similar results.
*Nominal p < 0.001.
BMD = bone mineral density; n = number of subjects with a baseline and at least one post-baseline BMD assessment.
Adapted from: Lewiecki EM, *et al. J Bone Miner Res* 2019;34:419–28.

IT-N-RM-OP-2100011

FRAME: New Vertebral Fracture Incidence Through Month 12, 24 and 36
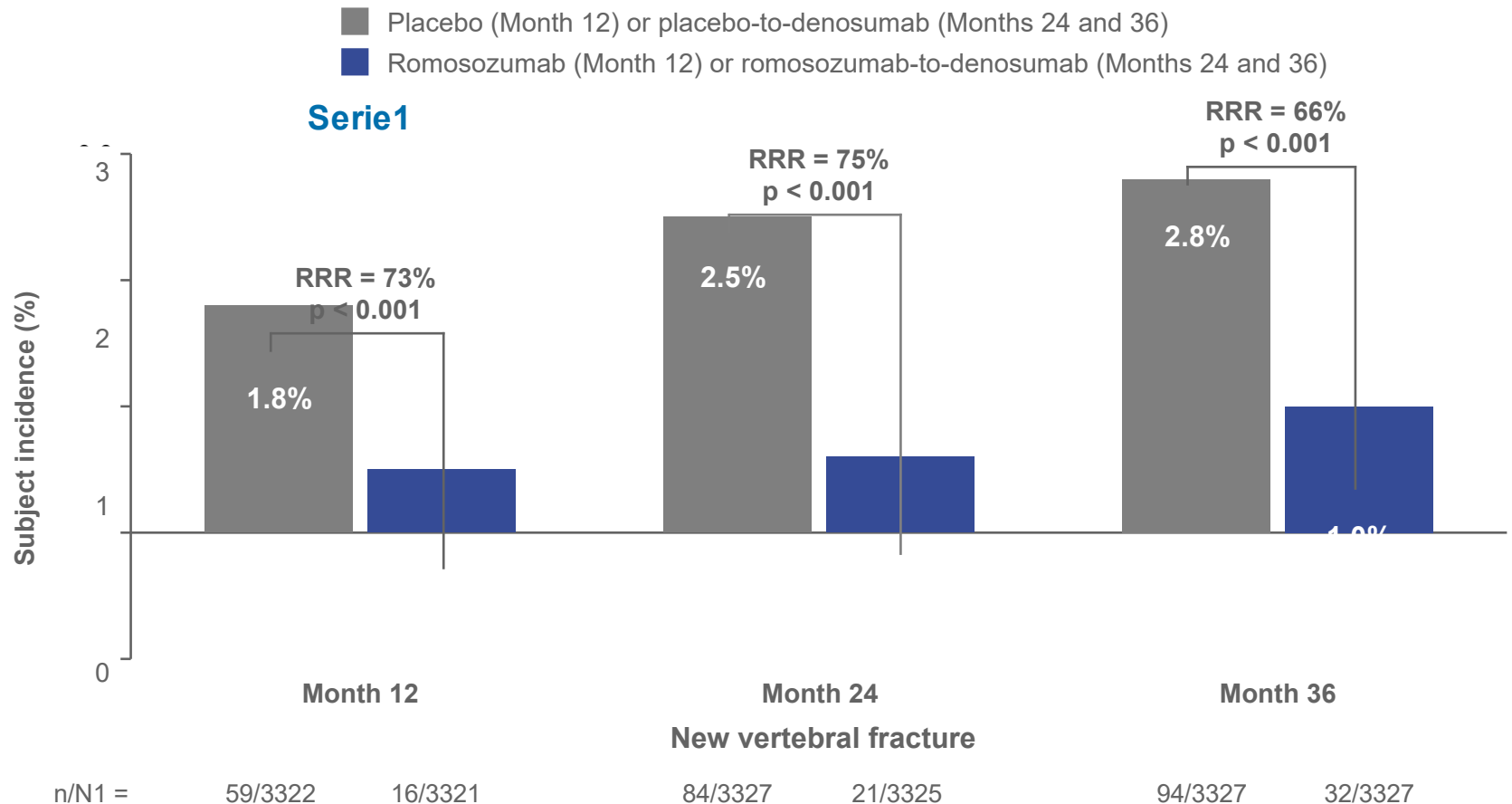
The RRR was assessed among subjects in the romosozumab group as compared with those in the placebo group at 12 months (end of the double-blind period) and at 24 and 36 months (by which time subjects in both groups had received open-label denosumab for 12 and 24 months, respectively) based on the Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables. p values were based on a logistic regression model adjusted for age and prevalent vertebral fracture stratification variables. p values for 12-month and 24-month periods are adjusted values based on a sequential testing procedure and nominal for 36 months, without multiplicity adjustment. Data displayed for 12-month and 24-month periods are as reported for the primary analysis.
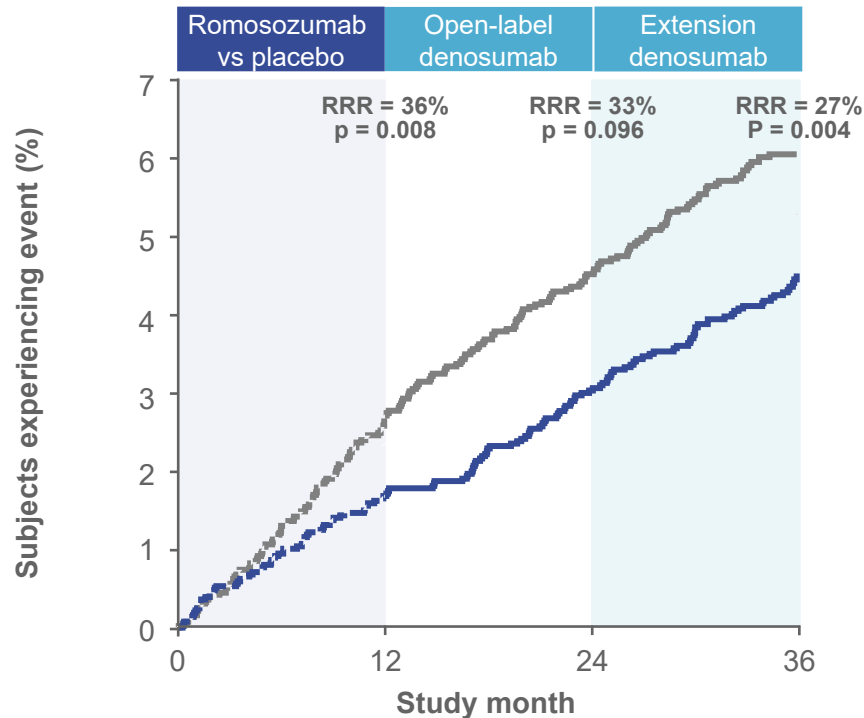n = number of subjects with fractures; N1 = number of subjects in the analysis set; RRR = relative risk reduction.
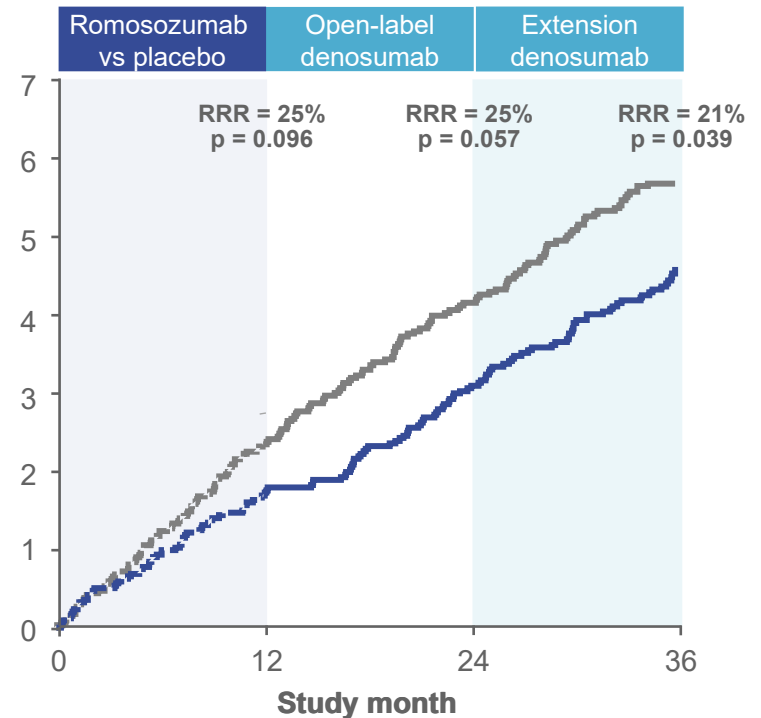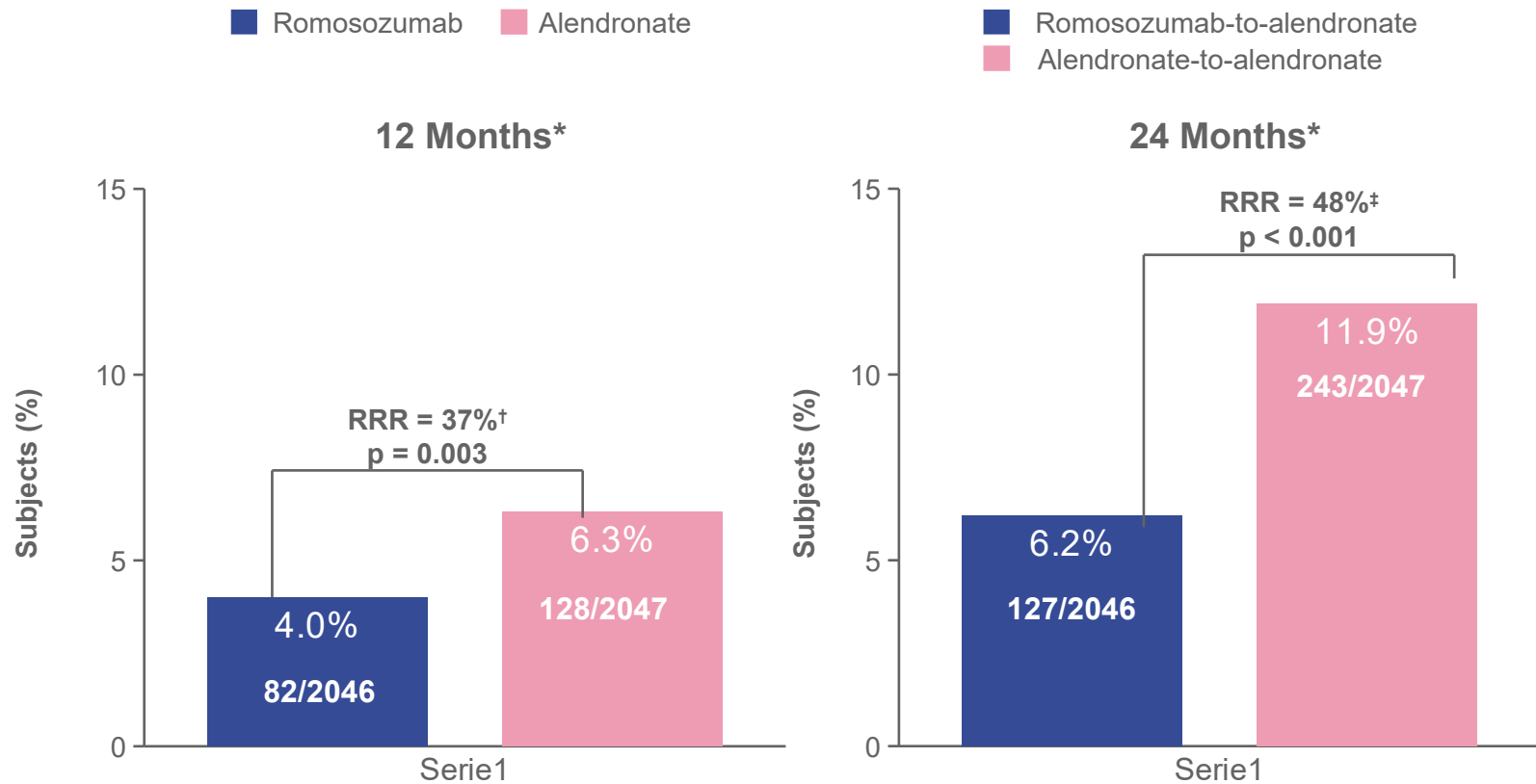Adapted from: Lewiecki EM, *et al. J Bone Miner Res* 2019;34:419–28.

IT-N-RM-OP-2100011

FRAME: Time to First Clinical and Nonvertebral Fracture Through Month 36

— Romosozumab (n = 3589)   — Placebo (n = 3591)

Clinical fractures

Romosozumab vs placebo	Open-label denosumab	Extension denosumab

RRR = 36%
p = 0.008

RRR = 33%
p = 0.096

RRR = 27%
P = 0.004

Subjects experiencing event (%)

Study month

Nonvertebral fractures

Romosozumab vs placebo	Open-label denosumab	Extension denosumab

RRR = 25%
p = 0.096

RRR = 25%
p = 0.057

RRR = 21%
p = 0.039

Study month

Romo/DMAb N1 =	3589	3148	2957	2737	3589	3149	2959	2738
Pbo/DMAb N1 =	3591	3132	2941	2738	3591	3144	2956	2750

p values for 12-month and 24-month periods are adjusted values based on a sequential testing procedure and nominal for Month 36. Data displayed for 12-month and 24-month periods are as reported for the primary analysis.
DMAb = denosumab; N1 = number of subjects at risk at the specified time point; Pbo = placebo; Romo = romosozumab; RRR = relative risk reduction.
Adapted from: Lewiecki EM, *et al. J Bone Miner Res* 2019;34:419–28.

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ARCH: Incidence of New Vertebral Fracture Through Month 24

■ Romosozumab ■ Alendronate

■ Romosozumab-to-alendronate
■ Alendronate-to-alendronate

12 Months*

24 Months*

RRR = 37%[†]
p = 0.003

RRR = 48%[‡]
p < 0.001

12 Months chart — Subjects (%):
- Romosozumab: 4.0% (82/2046)
- Alendronate: 6.3% (128/2047)

24 Months chart — Subjects (%):
- Romosozumab-to-alendronate: 6.2% (127/2046)
- Alendronate-to-alendronate: 11.9% (243/2047)

n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures.
*Missing fracture status was imputed by multiple imputation for patients without observed fracture at an earlier time point. n and % are based on the average across five imputed datasets.
[†]RRR at 12 months by LOCF: 36% (nominal p = 0.008): Romosozumab: 3.2% (55/1696) vs alendronate: 5.0% (85/1703).
[‡]RRR at 24 months by LOCF: 50% (nominal p < 0.001): Romosozumab-to-alendronate: 4.1% (74/1825) vs alendronate-to-alendronate: 8.0% (147/1843).
LOCF = last observation carried forward; RRR = relative risk reduction.
Adapted from: Saag KG, *et al. N Engl J Med* 2017;377:1417–27.

IT-N-RM-OP-2100011

ARCH: Other Fracture Endpoints at Primary Analysis

■ Romosozumab-to-alendronate (n = 2046)   ■ Alendronate-to-alendronate (n = 2047)

Subject incidence (%)

- RRR = 27% p < 0.001[§,¶] — Clinical frac... *
  - 9,7% n = 198
  - 13,0% n = 266
- RRR = 19% p = 0.037[§] — Nonvertebral ... [†,‖]
  - 8,7% n = 178
  - 10,6% n = 217
- RRR = 27% p = 0.004[§] — Major nonverteb... [†,**]
  - 7,1% n = 146
  - 9,6% n = 196
- RRR = 38% p = 0.015[§] — Hip fracture [†]
  - 2,0%
  - 3,2%
- RRR = 32% p < 0.001[§] — Major osteoporo... [‡,††]
  - 7,1% n = 146
  - 10,2% n = 209
- RRR = 35% p < 0.001[§] — osteoporotic ... [‡‡]
  - 13,0% n = 266
  - 19,1% n = 392

ARCH: Adverse Events and Events of Interest

Event	Month 12: Double-blind period		Primary Analysis: Double-blind and open-label period*	
	Romosozumab (n = 2040)	Alendronate (n = 2014)	Romosozumab-to-alendronate (n = 2040)	Alendronate-to-alendronate (n = 2014)
Adverse event during treatment	1544 (75.7%)	1584 (78.6%)	1766 (86.6%)	1784 (88.6%)
Back pain[†]	186 (9.1%)	228 (11.3%)	329 (16.1%)	393 (19.5%)
Nasopharyngitis[†]	213 (10.4%)	218 (10.8%)	363 (17.8%)	373 (18.5%)
Event leading to discontinuation of trial regimen	70 (3.4%)	64 (3.2%)	133 (6.5%)	146 (7.2%)
Event leading to discontinuation of trial participation	30 (1.5%)	27 (1.3%)	47 (2.3%)	43 (2.1%)
Event of interest[‡]				
Osteoarthritis[§]	138 (6.8%)	146 (7.2%)	247 (12.1%)	268 (13.3%)
Hypersensitivity	122 (6.0%)	118 (5.9%)	205 (10.0%)	185 (9.2%)
Injection-site reaction[¶]	90 (4.4%)	53 (2.6%)	90 (4.4%)	53 (2.6%)
Cancer	31 (1.5%)	28 (1.4%)	84 (4.1%)	85 (4.2%)
Hyperostosis[‖]	2 (<0.1%)	12 (0.6%)	23 (1.1%)	27 (1.3%)
Hypocalcaemia	1 (<0.1%)	1 (<0.1%)	4 (0.2%)	1 (<0.1%)
Atypical femoral fracture**	0	0	2 (<0.1%)	4 (0.2%)
Osteonecrosis of the jaw**	0	0	1 (<0.1%)	1 (<0.1%)

*Incidence rates at the time of the primary analysis were cumulative and included all events in the double-blind and open-label period (to February 27 2017) in patients who received at least one dose of open-label alendronate.
[†]Shown are events that occurred in 10% or more of the patients in either group during the double-blind period.
[‡]Events of interest were those that were identified by prespecified Medical Dictionary for Regulatory Activities search strategies.
[§]Prespecified events were osteoarthritis, spinal osteoarthritis, exostosis, arthritis, polyarthritis, arthropathy, monoarthritis and interspinous osteoarthritis.
[¶]The most frequent adverse events of injection-site reactions (occurring in > 0.1% of the patients) in the romosozumab group during the double-blind period included injection-site pain (1.6% of patients), erythema (1.3%), pruritus (0.8%), hemorrhage (0.5%), rash (0.4%) and swelling (0.3%).
[‖]Prespecified events were exostosis (mostly reported as heel spurs), lumbar spinal stenosis, spinal column stenosis, cervical spinal stenosis, enostosis, extraskeletal ossification and vertebral foraminal stenosis.
**Potential cases of osteonecrosis of the jaw and atypical femoral fracture were adjudicated by independent committees.
Adapted from: Saag KG, et al. N Engl J Med 2017;377:1417–27.

IT-N-RM-OP-2100011

ARCH: Serious Adverse Events

Event	Month 12: Double-blind period		Primary analysis: Double-blind and open-label period*	
	Romosozumab (n = 2040)	Alendronate (n = 2014)	Romosozumab to alendronate (n = 2040)	Alendronate to alendronate (n = 2014)
Serious adverse event	262 (12.8%)	278 (13.8%)	586 (28.7%)	605 (30.0%)
Adjudicated serious cardiovascular (CV) event[†]	50 (2.5%)	38 (1.9%)	133 (6.5%)	122 (6.1%)
Cardiac ischaemic event	16 (0.8%)	6 (0.3%)	30 (1.5%)	20 (1.0%)
Cerebrovascular event	16 (0.8%)	7 (0.3%)	45 (2.2%)	27 (1.3%)
Heart failure	4 (0.2%)	8 (0.4%)	12 (0.6%)	23 (1.1%)
Death	17 (0.8%)	12 (0.6%)	58 (2.8%)	55 (2.7%)
Noncoronary revascularisation	3 (0.1%)	5 (0.2%)	6 (0.3%)	10 (0.5%)
Peripheral vascular ischaemic event not requiring revascularisation	0	2 (<0.1%)	2 (<0.1%)	5 (0.2%)
Death	30 (1.5%)	21 (1.0%)[‡]	90 (4.4%)	90 (4.5%)[‡]

*Incidence rates at the time of the primary analysis were cumulative and included all events in the double-blind and open-label period (to February 27 2017) in patients who received at least one dose of open-label alendronate.
[†]Serious CV adverse events were adjudicated by the Duke Clinical Research Institute. CV deaths include fatal events that were adjudicated as being CV-related or undetermined (and, therefore, possibly CV-related).
[‡]One patient had a non-treatment-related serious adverse event of pneumonia that was incorrectly flagged as death in the primary analysis snapshot and was not included in the analysis of fatal events.
Adapted from: Saag KG, *et al. N Engl J Med* 2017;377:1417–27.

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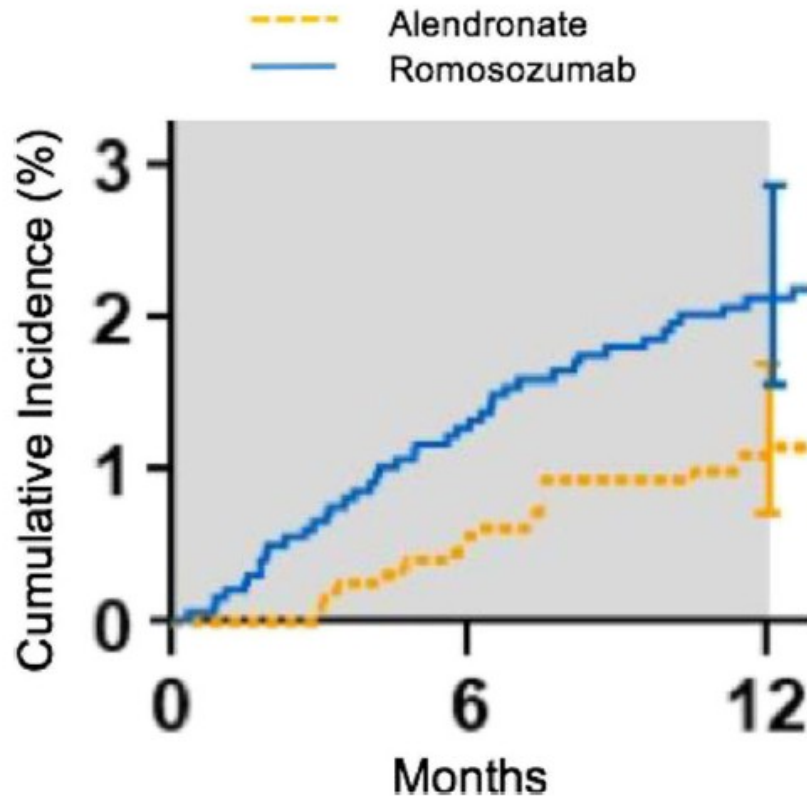
The pattern of CVD events in ARCH would indicate that alendronate provided a potent immediate but transient reduction in CVD events during the first 3 months, with fewer events than in the romosozumab for the remainder of the 12 months
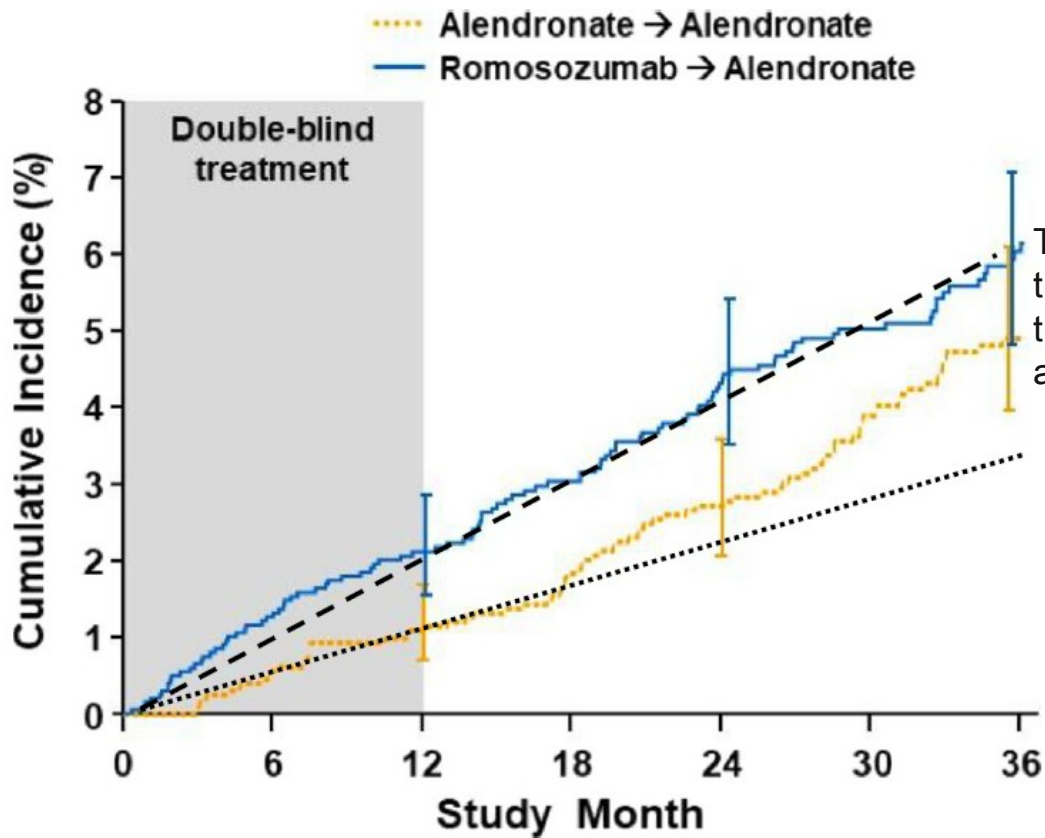
The rate of CVD events increases steadily thereafter roughly in parallel, or converging on the rates in the group receiving alendronate after romosozumab

When participants in the romosozumab group Were switched to alendronate, the rate of CV events did not change

Interpretation of Cardiovascular Safety

<u>Summary</u>
- No excess events in Romo vs. placebo in FRAME 2016 trial
- Slight increase in ischemic and cerebrovascular events in Romo vs. ALN in ARCH 2017 trial (decrease in heart failure). None were statistically significant.

<u>Potential Explanations</u>
1. Random Difference
2. ALN (comparator to Romo) *decreases* cardiovascular events, especially cerebrovascular
   - Evidence varies in individual ALN studies or meta-analyses
3. Romo increases (slightly) cardiovascular event risk

<u>Interpretation by Regulators</u>
- FDA: after initial review, asked for more information on cardiovascular. Approved 2019, but with black box warning*
- European: exclude treatment in patients with previous cardiovascular events

*may increase the risk of heart attack, stroke and cardiovascular death and should not be used in patients who have had a heart attack or stroke within the previous year or very high risk.

FRAME: Quantitative Bone Histomorphometry – Effects at 2 Months Versus Baseline
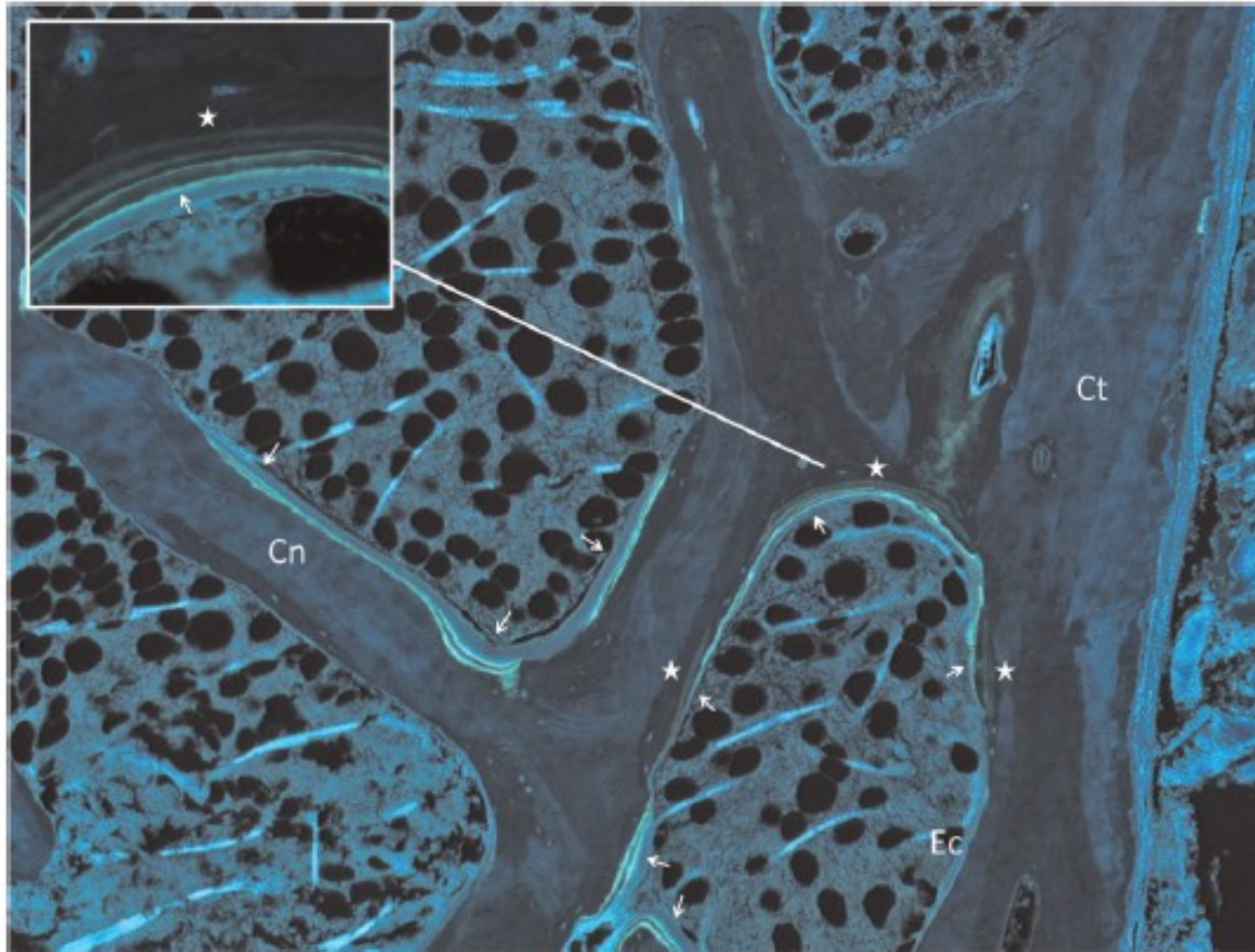
Effects of romosozumab on bone formation after 2 months. Unstained section of iliac bone biopsy after a quadruple fluorochrome labelling (star: Demeclocycline labels at baseline; arrow: Tetracycline labels at Month 2).
Cn = cancellous, Ct = cortical, Ec = endocortical. Original magnification: ×50; box magnification: ×200.
Chavassieux P, et al. J Bone Miner Res 2019;34:1597–608.

Romosozumab - histomorphometry

	Month 2			Month 12		
	Placebo $N = 14$	Romosozumab 210 mg QM $N = 15$	p value[a]	Placebo $N = 31$	Romosozumab 210 mg QM $N = 39$	p value[a]
Cancellous bone						
Cn-W.Th	31.7[b]	31.6	0.91	29.5	31.8	0.014
μm	(30.4, 33.9)	(30.7, 33.6)		(27.8, 32.3)	(30.8, 34.1)	
Cn-OS/BS	7.2	14.2	0.058	7.8	4.4	0.16
%	(1.7, 15.5)	(9.4, 24.3)		(3.7, 15.4)	(2.8, 9.0)	
Cn-OV/BV	1.3	3.0	0.007	1.7	0.8	0.016
%	(0.2, 1.9)	(1.4, 5.4)		(0.8, 4.5)	(0.4, 1.7)	
Cn-O.Th	8.6	9.7	0.029	9.9	9.7	0.57
μm	(6.9, 9.5)	(9.0, 12.6)		(8.5, 12.5)	(8.6, 11.0)	
Cn-MAR[c]	0.65	0.57	0.097	0.54	0.48	0.015
μm/day	(0.54, 0.70)	(0.50, 0.59)		(0.50, 0.61)	(0.36, 0.55)	
Cn-MAR[d]	0.65	0.57	0.097	0.55	0.49	0.047
μm/day	(0.54, 0.70)	(0.50, 0.59)		(0.50, 0.61)	(0.41, 0.58)	
Cn-MS/BS	2.3	5.6	0.002	3.0	0.6	0.004
%	(0.7, 3.1)	(3.7, 8.4)		(0.9, 5.4)	(0.0, 2.2)	
Cn-BFR/BS[c]	5.175	12.075	0.004	6.755	1.577	0.014
μm³/μm²/year	(2.919, 7.165)	(7.319, 16.132)		(2.691, 13.213)	(0.928, 6.452)	
Cn-BFR/BS[d]	5.175	12.075	0.004	6.923	3.395	0.046
μm³/μm²/year	(2.919, 7.165)	(7.319, 16.132)		(2.736, 13.213)	(1.310, 7.332)	
Cn-BFR/BV	11.0	23.1	0.005	13.3	3.3	0.001
%/year	(6.6, 14.8)	(14.2, 31.5)		(4.4, 26.2)	(1.6, 8.9)	
Cn-Aj.AR	0.19	0.18	0.76	0.20	0.09	0.043
μm/day	(0.08, 1.07)	(0.14, 0.36)		(0.13, 0.26)	(0.06, 0.29)	
Cn-Ac.f	0.18	0.38	0.003	0.24	0.05	0.006
/year	(0.10, 0.21)	(0.23, 0.49)		(0.09, 0.46)	(0.03, 0.18)	
Cn-FP	166.5	176.4	0.76	150.0	369.8	0.018
days	(29.7, 379.2)	(84.2, 232.3)		(109.8, 228.7)	(130.3, 524.9)	
Cn-Mlt	48.5	62.7	0.62	56.3	101.3	0.038
days	(6.3, 115.7)	(26.7, 76.2)		(37.2, 90.4)	(44.6, 149.2)	

Chavassieux P et al. J Bone Miner Res 2019 34(9) 1597-1608

FRAME: Bone Resorption Parameters After 2 and 12 Months of Romosozumab

	Month 2			Month 12		
	Placebo n = 14	Romosozumab 210 mg QM n = 15	Paired p value*	Placebo n = 31	Romosozumab 210 mg QM n = 39	Paired p value*
Cancellous bone						
Cn-ES/BS, %	3.4 (1.9, 4.5)	1.8 (0.9, 3.2)	0.022	2.9 (2.0, 4.5)	1.1 (0.5, 1.7)	<0.001
Cn-Oc.S/BS, %	0.1 (0.04, 0.2)	0.0 (0.0, 0.1)	0.032	0.1 (0.0, 0.3)	0.0 (0.0, 0.03)	0.001
Cn-Oc.N/BS, /100 mm	2.4 (1.0, 5.6)	0.0 (0.0, 2.4)	0.024	2.0 (0.0, 6.5)	0.0 (0.0, 1.4)	<0.001
Endocortical bone						
Ec-ES/BS, %	6.3 (3.3, 7.7)	1.6 (0.6, 3.5)	0.003	4.1 (3.0, 6.5)	0.5 (0.2, 1.2)	<0.001
Ec-Oc.S/BS, %	0.2 (0.0, 0.3)	0.0 (0.0, 0.1)	0.12	0.0[†] (0.0, 0.4)	0.0[†] (0.0, 0.0)	<0.001
Ec-Oc.N/BS, /100 mm	4.4 (0.0, 7.7)	0.0 (0.0, 4.8)	0.14	0.0[‡] (0.0, 8.4)	0.0[‡] (0.0, 0.0)	0.001

Values are median (quartile 1 and quartile 3) unless otherwise specified.
*Wilcoxon rank sum test. [†]Mean ± SD: 0.3 ± 0.7 in placebo, 0.03 ± 0.09 in romosozumab. [‡]Mean ± SD: 8.1 ± 16.2 in placebo, 1.0 ± 2.9 in romosozumab.
Cn = cancellous; Ec = endocortical; ES/BS = eroded surface per unit of bone surface; Oc.N/BS = osteoclast number per unit of bone surface;
Oc.S/BS = osteoclast surface per unit of bone surface; QM = monthly.
Chavassieux P, *et al. J Bone Miner Res* 2019;34:1597–608.

IT-N-RM-OP-2100011

Romosozumab - histomorphometry

After 2 months
Referent to total bone surface

Eriksen EF et al. JBMR 2022 37(1) 36-40
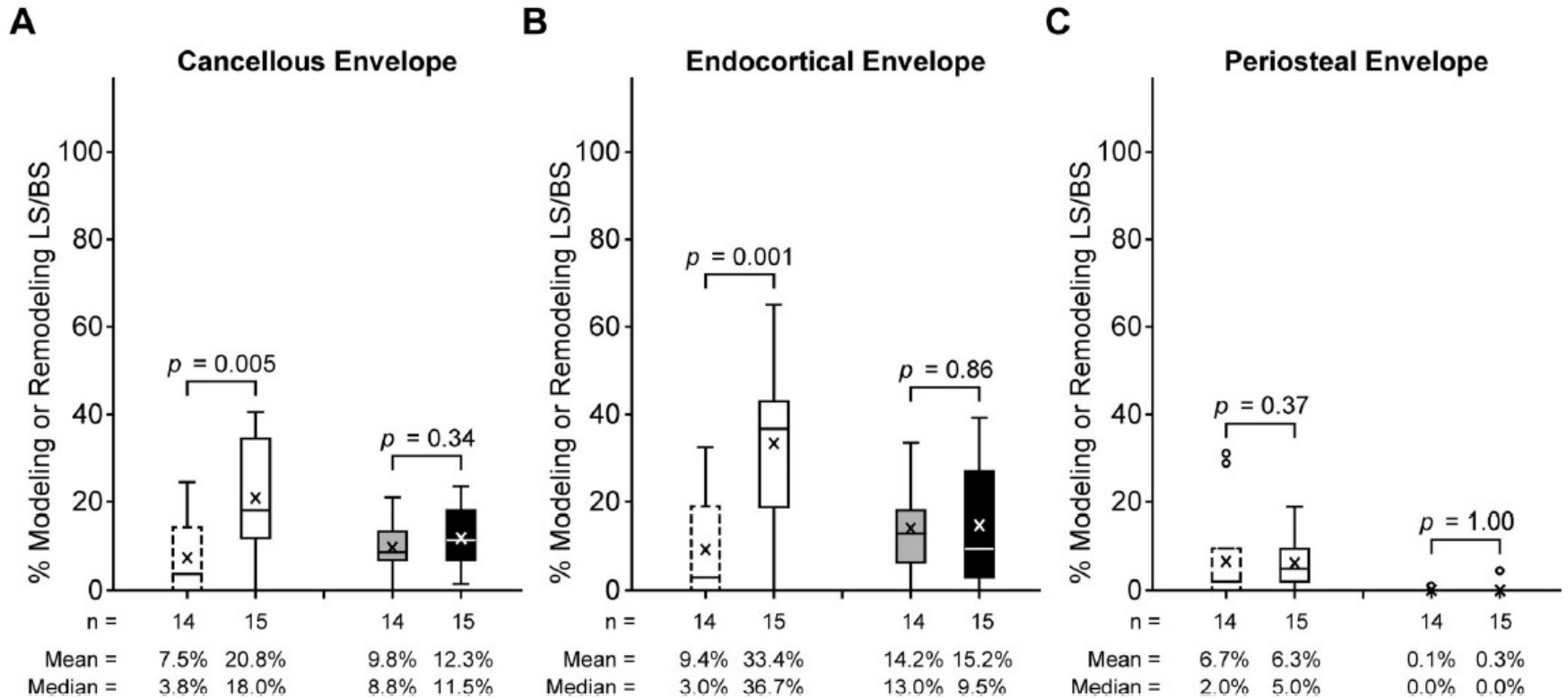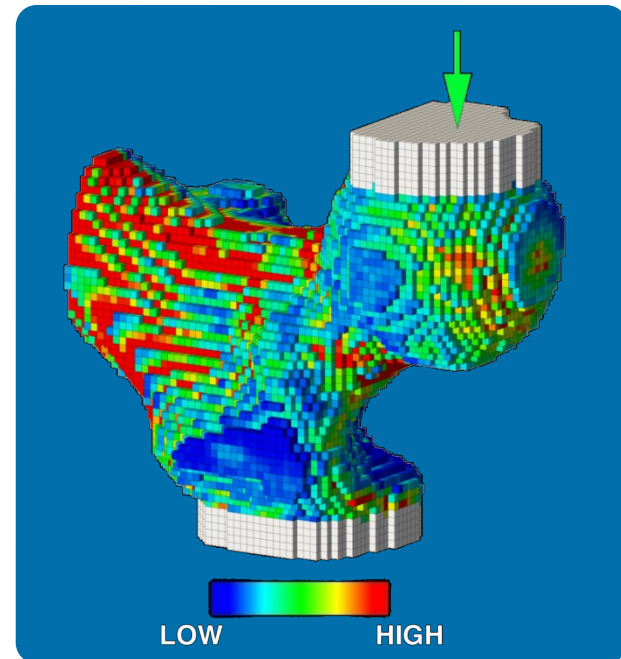
STRUCTURE: QCT MIAF [Volume of Interest (VOI)] and QCT FEA

■ "Cortical" VOI (threshold)　　■ Subcortical VOI (data not presented)　　■ Trabecular VOI (peeled)
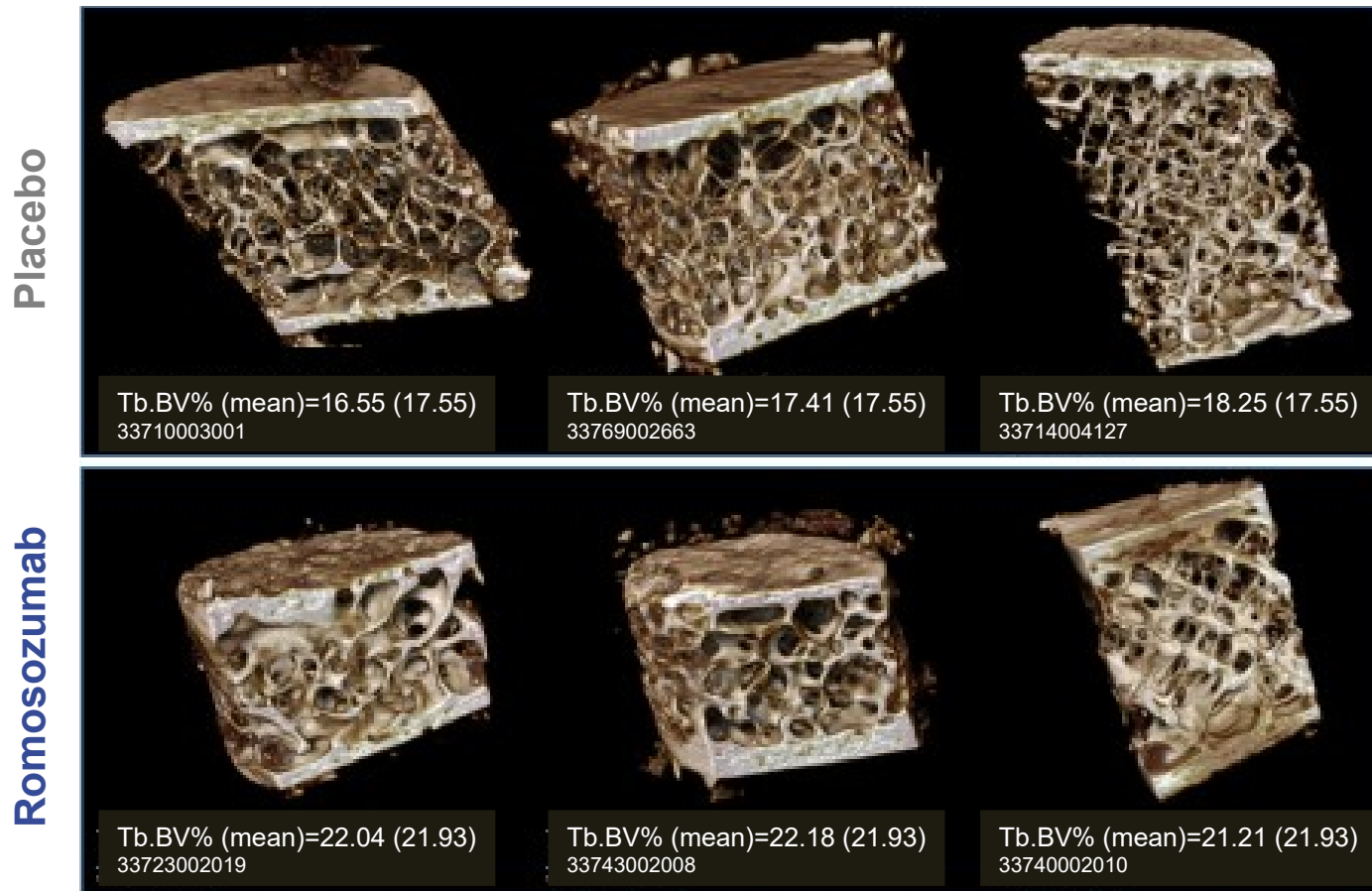

QCT MIAF
Volumetric measurement

Integral VOI
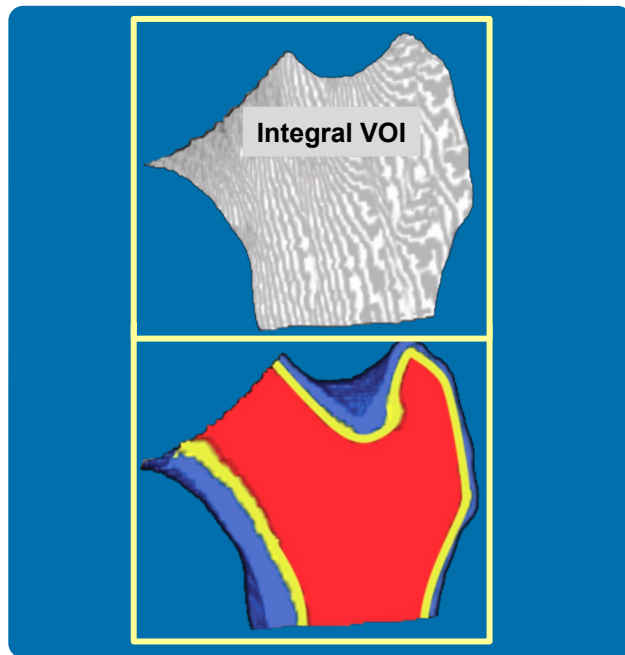
Total hip BMD/BMC

QCT FEA
Biomechanical strength

LOW　　HIGH

Total hip strength in lateral fall
Incorporates geometry and BMD (material properties) to estimate strength

FRAME: Effects of Romosozumab at Month 12 on Bone Mass and Microarchitecture Assessed by µCT

Images are selected from subjects who had Tb.BV% values close to the group mean.
µCT = micro computed tomography; Tb.BV = trabecular bone volume.
1. Chavassieux P, *et al*. *J Bone Miner Res* 2019;34:1597–608; 2. Roux J-P, *et al*. Poster presented at ASBMR 2017, 8–11 Nov, Denver, Colorado US. (#MO0664)

Imminent fracture risk

a. One-year hip fracture model for IFx cohort
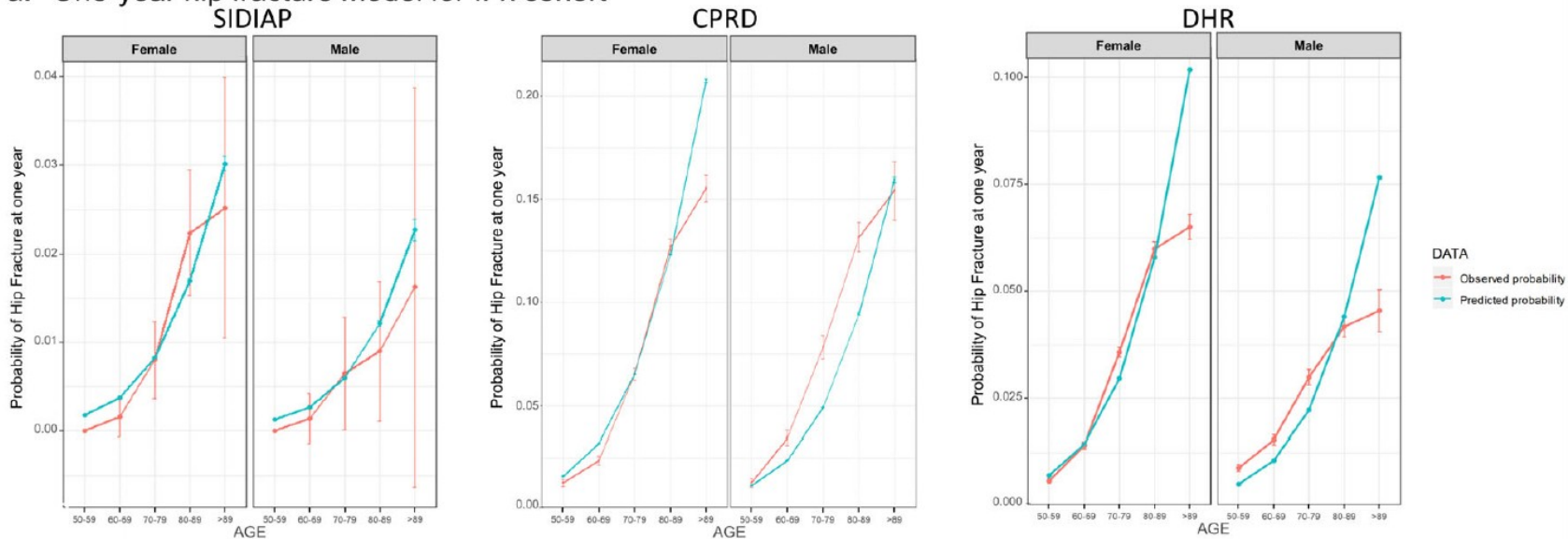
c. Two-year hip fracture model for IFx cohort
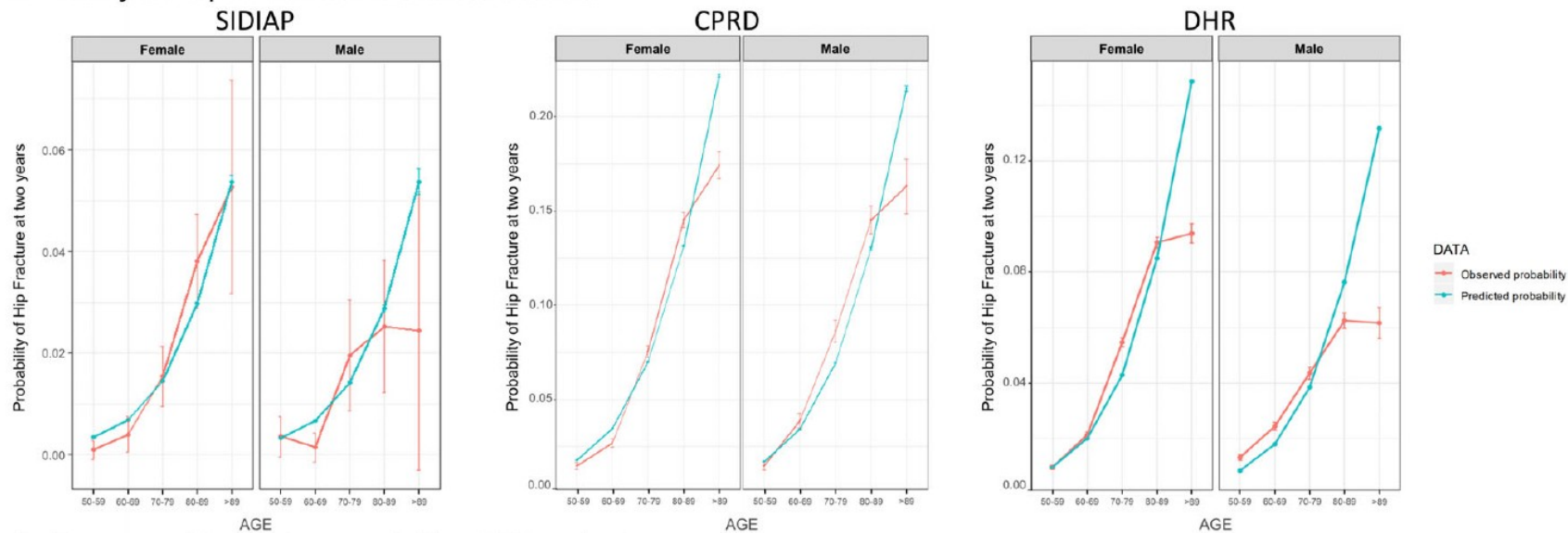
Risk factors for imminent fracture risk

Prior fracture timing
Prior fracture location (mostly vertebral fractures)
FallsFrailty and comorbidities

- advanced age
- poor health status (Charlson comorbidity index score ≥ 1)
- CNS diseases
- Alzheimer's disease
- MMSE < 23
- wheelchair, mobility impairment or low walking speed

Glucocorticoid initiation
Medications

- narcotics and sedatives (including benzodiazepines)
- antidepressants (except tricyclics)
- anti-Parkinson medications

Female gender
Hip BMD T score *
* Only for non-vertebral and hip fractures

Conclusions

- Treatment with romosozumab for 12 months was superior to alendronate alone with respect to the risks of a new vertebral, clinical, nonvertebral, and hip fracture

- Inhibition of sclerostin with romosozumab, increasing bone modeling and reducing bone resorption, causes rapid and large increase in bone mass without increasing remodeling space

- these actions likely contribute to the observed rapid reductions in fracture risk reported in the FRAME and ARCH clinical trials of romosozumab and underscore the clinical <u>relevance of increasing bone formation while reducing bone resorption</u>, a unique dual effect resulting from romosozumab

- These unique features make romosozuab an ideal treatment in patients with imminent / high risk of fracture

OTHER 33%

VERTEBRAL 27%

2 MILLION
FRACTURES
PER YEAR

WRIST 19%

HIP 15%

PELVIC
6%
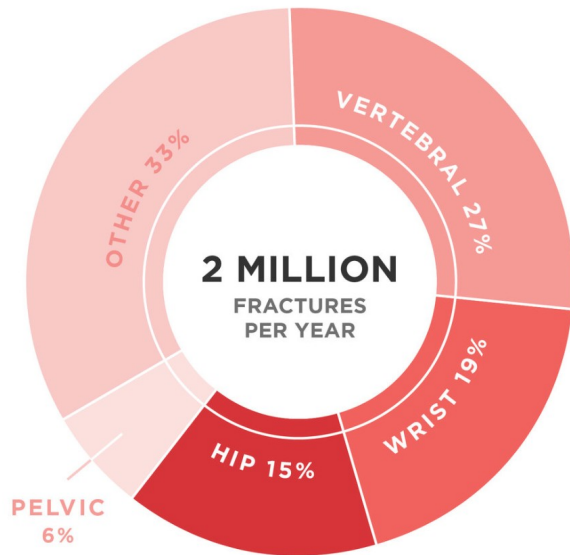
**Osteoporotic Fractures by Type,
per year[1]**

100%

50%

0%

23%

96%

OSTEOPOROSIS MEDICATION
AFTER HIP FRACTURE[2]

BETA BLOCKERS
AFTER HEART ATTACK[3]
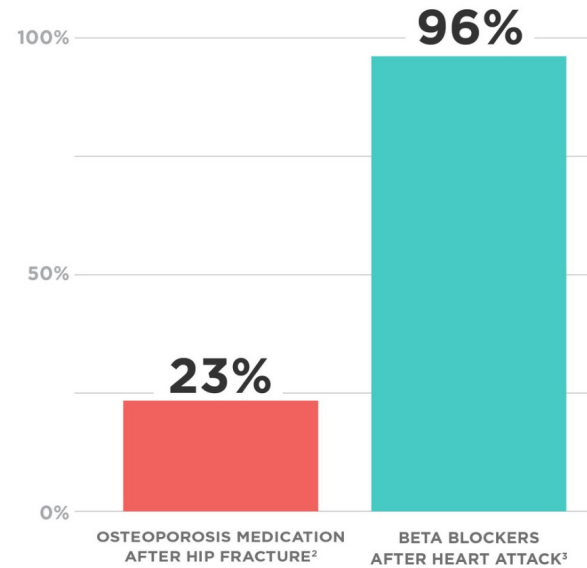
**Only 23% of Patients Receive Osteoporosis
Medication After a Hip Fracture[2]**

TAKE ACTION

Secondary Fracture Prevention: Consensus Clinical Recommendations from a Multistakeholder Coalition

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