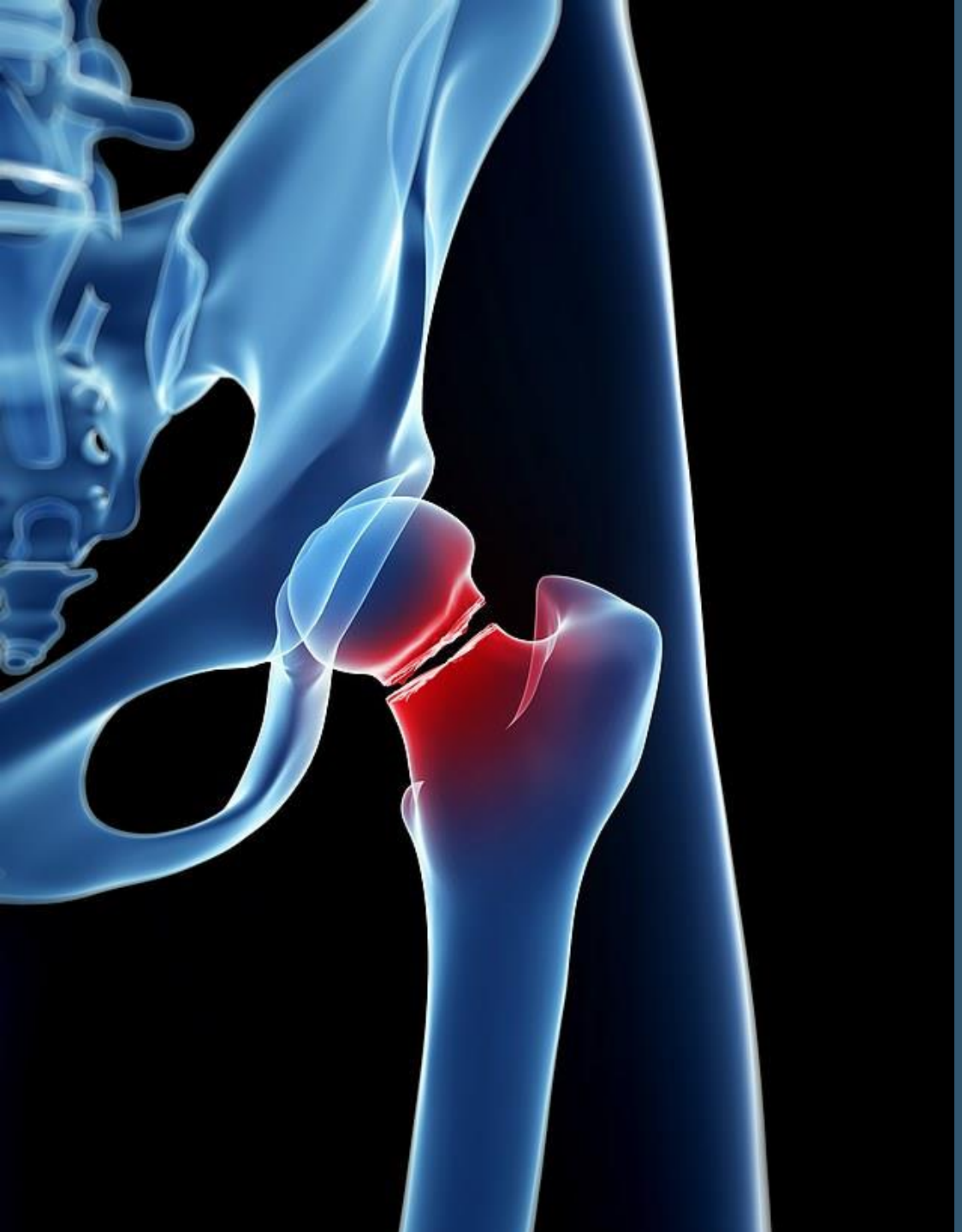

Romosozumab (Evenity®) ▼

a new treatment option for osteoporosis
in postmenopausal women
at high risk of fracture

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Gerontology and Geriatrics, KU Leuven, Belgium

BELU-P-RM-OP-2200024

▼ - this medicine is subject to additional monitoring

Conflicts of interest

I have the following potential conflicts of interest to report:

I received consultancy fees, lectures fees and/or travel fees from Alexion, Amgen, Sandoz, Takeda and UCB, unrelated to this work.

Overview

① Discovery and mechanism of action of sclerostin and Romosozumab

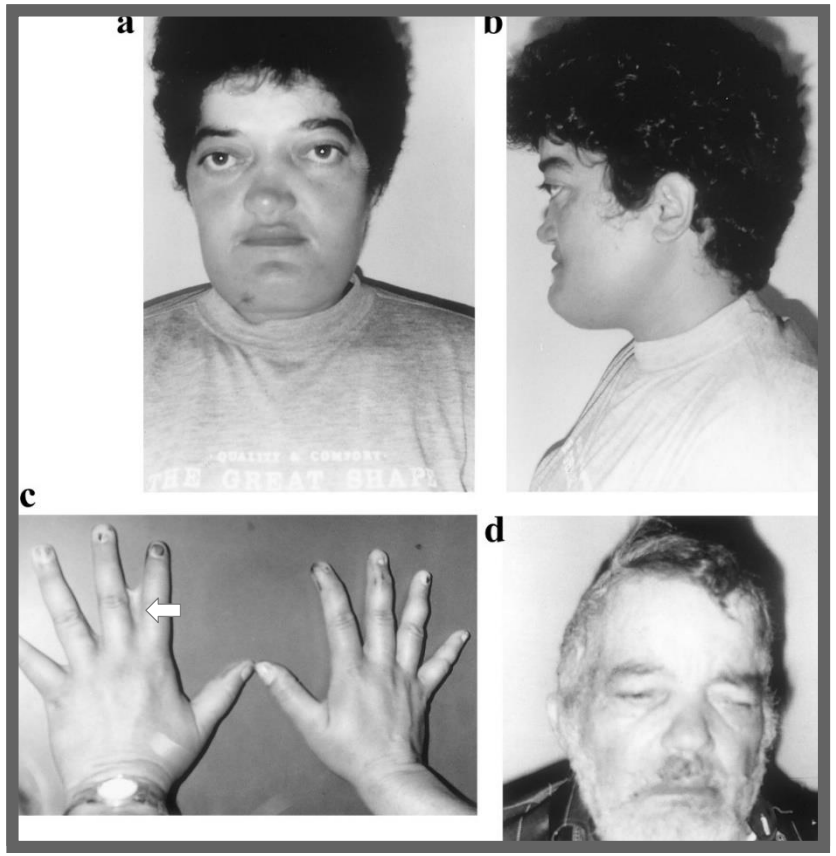
② Pivotal phase III trials with Romosozumab

③ Cardiovascular safety of Romosozumab

④ Reimbursement criteria for Romosozumab in Belgium

⑤ Conclusion

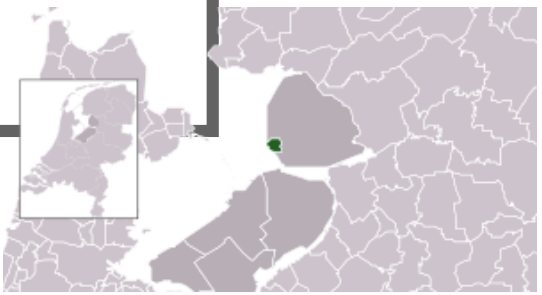
Sclerosteosis
(Truswell-Hansen disease)



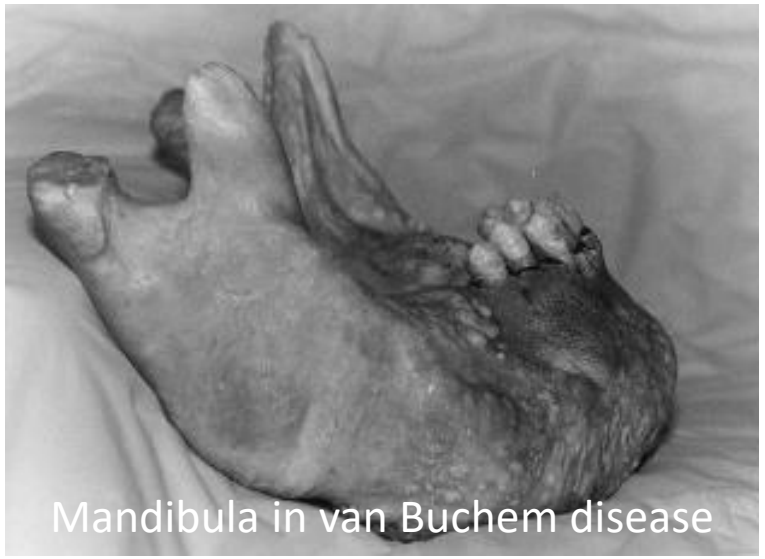
- First described in 1958
- Autosomal recessive disorder
- Most prominent in Afrikaner population in South Africa
- Progressive bone overgrowth, most pronounced in the skull and mandibule
- Increased intracranial pressure and entrapment of cranial nerves (eg. N. II, VII, VIII)
- Variable syndactyly, usually digit II and III
- Fractures have never been reported

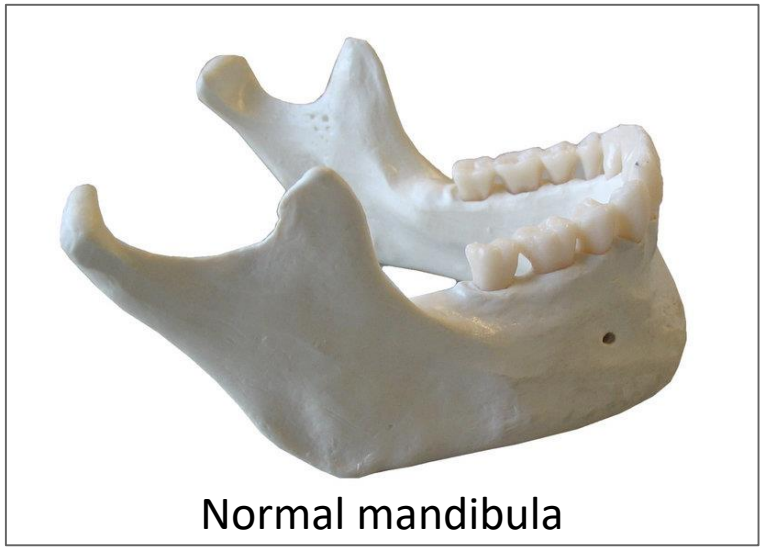
van Buchem disease
(Hyperostosis Corticalis Familaris Generalisata)

- Autosomal recessive disorder
- Described by prof. van Buchem in 1955
- Clinical features similar to sclerosteosis, but generally milder & no syndactyly
- Patients almost never fracture (very rarely after high-energetic trauma)
- Mainly in Urk (Flevoland, NL)

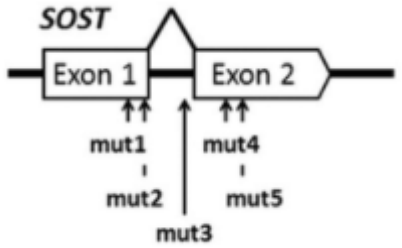


Progressive bone overgrowth due to mutation in SOST gene


Mandibula in van Buchem disease

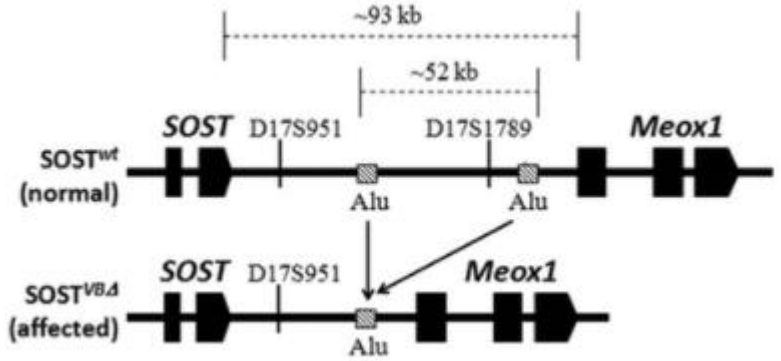

Normal mandibula

Sclerosteosis

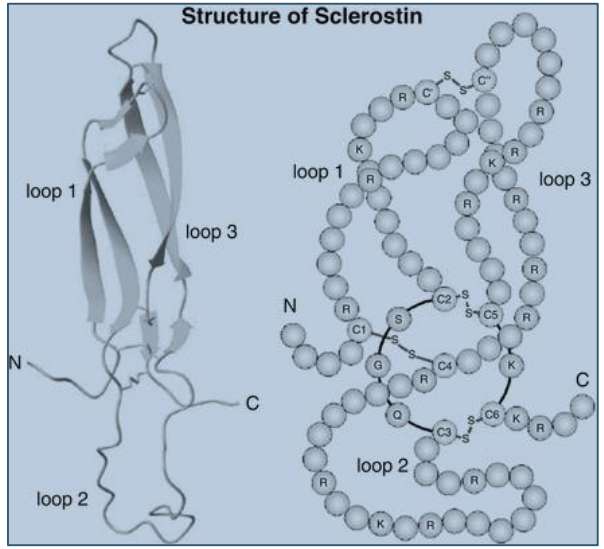


loss of function mutations in SOST gene
➔ ***no sclerostin*** *is synthesized*

Van Buchem disease

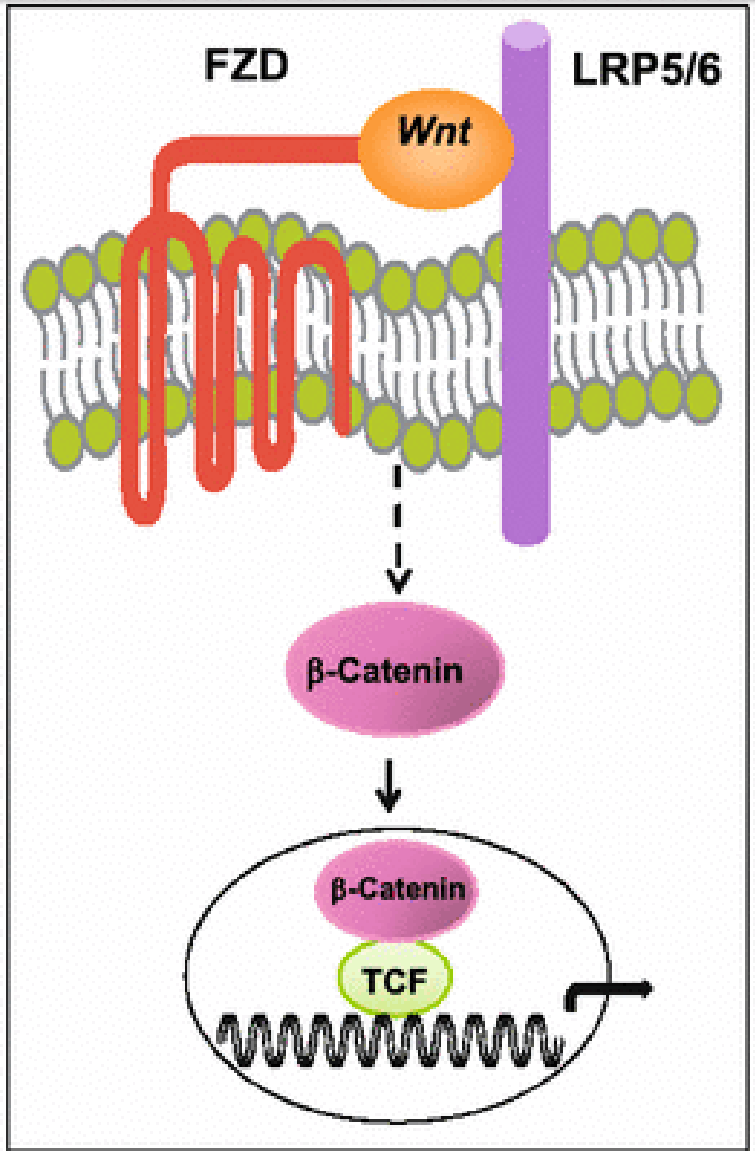


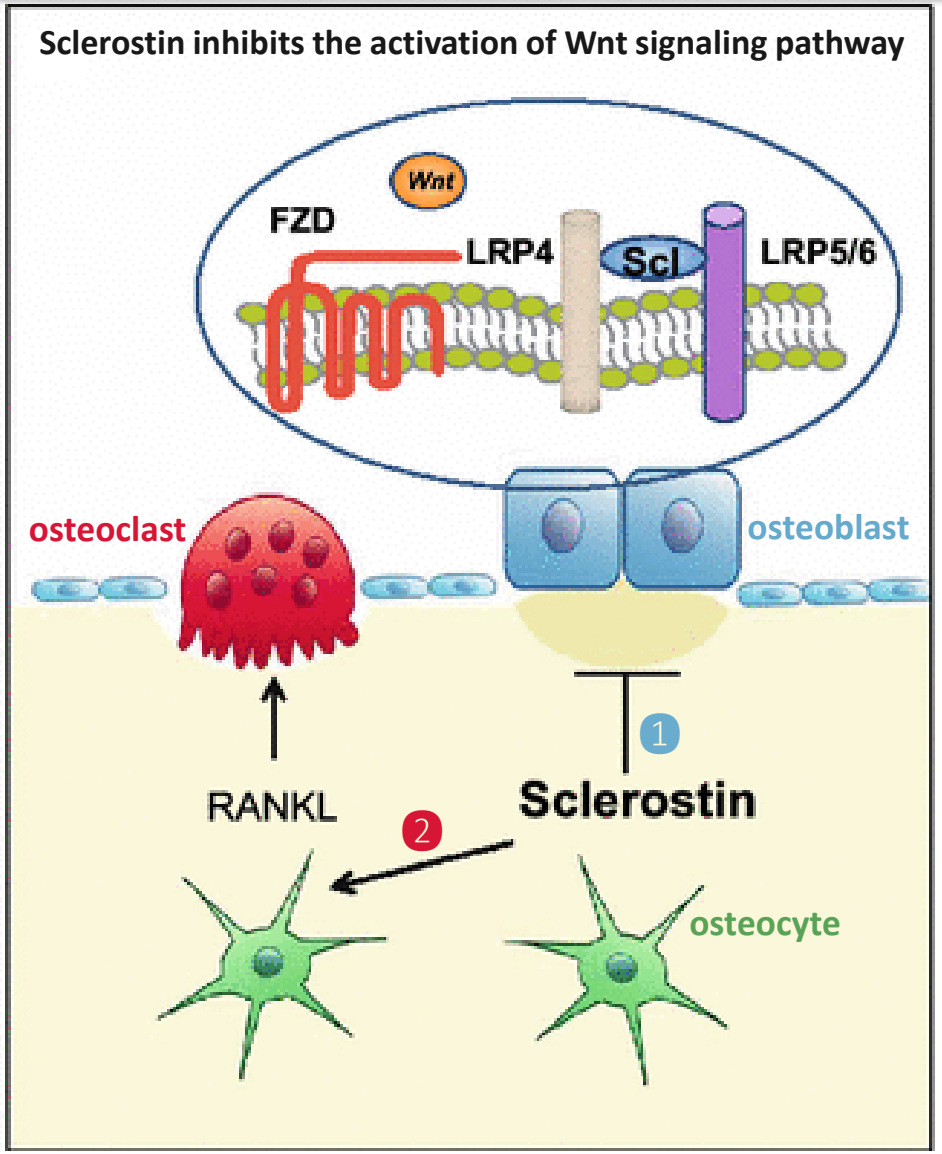
52 kb deletion downstream of SOST gene
➔ ***reduced sclerostin*** *production*



Sebastian. Bone 2017; 96: 76-84

Canonical Wnt-signaling pathway and the effect of sclerostin on bone cells

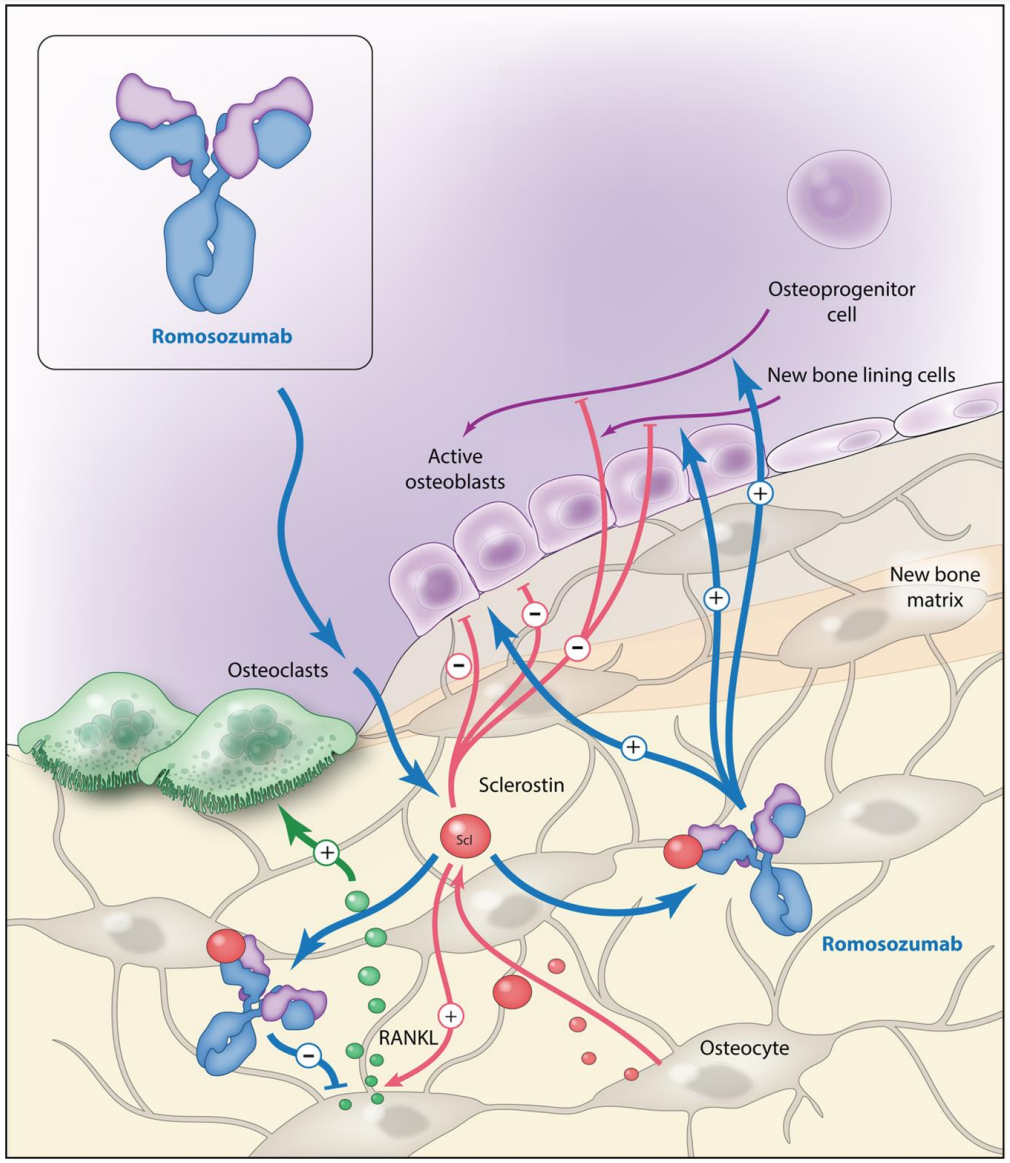




FZD = frizzled receptor

Appelman-Dijkstra. Calcif Tissue Int. 2016; 98: 370–380

Mode of action of Romosozumab



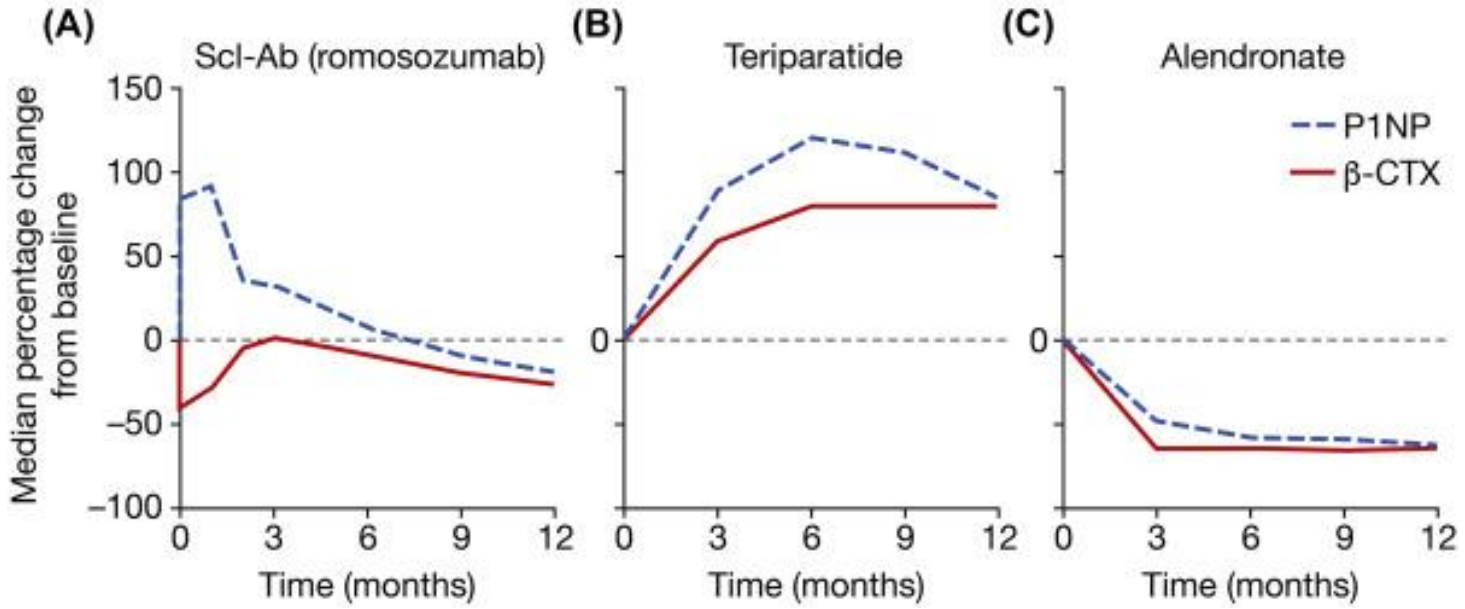
ROMOSOZUMAB

- Monoclonal antibody that binds and inhibits **SCLEROSTIN**
- Increases bone formation by
  - reactivation of bone lining cells
  - increasing bone matrix production
  - recruitment of osteoprogenitor cells
- Decreases bone resorption by
  - decreasing RANKL production

Uncoupling of bone formation and resorption

Solling. Ther Adv Musculoskel Dis 2018; 10: 105-15

Effect of osteoporosis medication on bone turnover markers



P1NP= procollagen type 1 N-propeptide (marker of bone formation)
β-CTX = C-terminal cross-linking telopeptide of collagen (marker of bone resorption)

Adapted from: McClung. N Engl J Med 2014; 370, 412-20

Overview

① Discovery and mechanism of action of sclerostin and Romosozumab

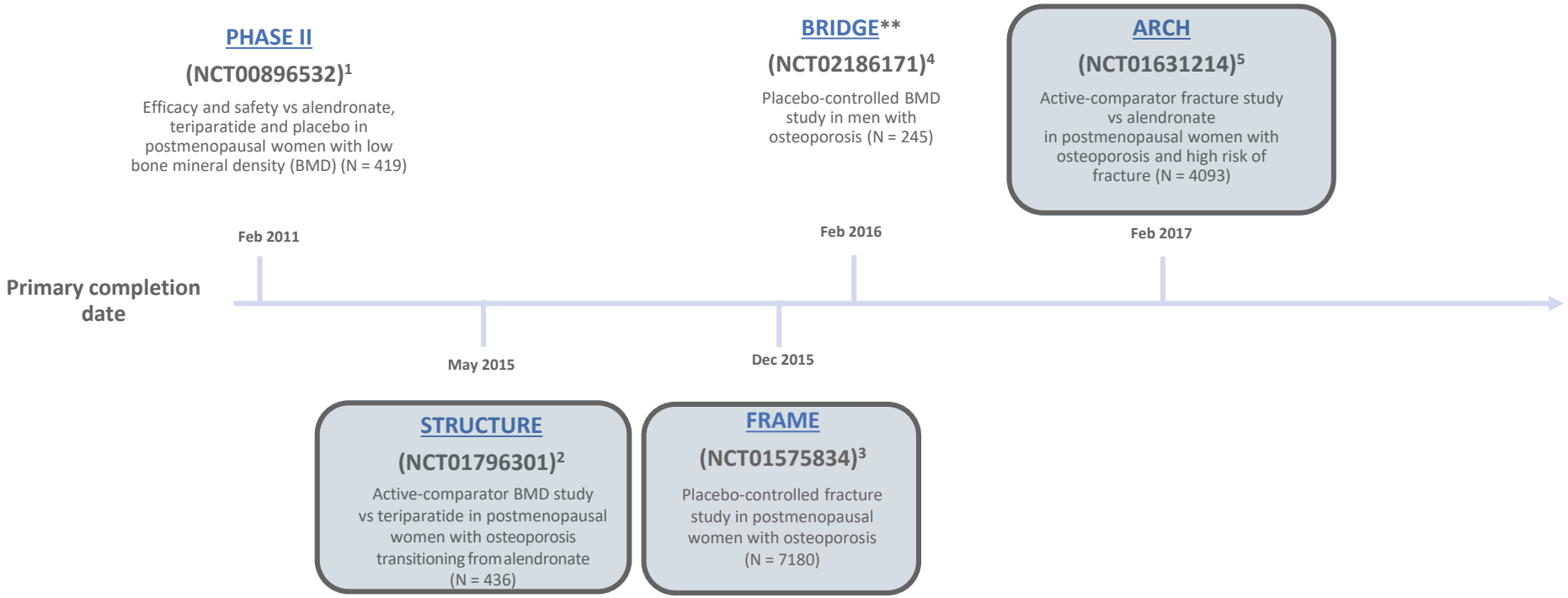
② Pivotal phase III trials with Romosozumab

③ Cardiovascular safety

④ Reimbursement criteria for Romosozumab in Belgium

⑤ Conclusion

Overview of the Romosozumab clinical program*



* Not all romosozumab clinical studies listed.

** Romosozumab is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture. Romosozumab is not approved for use in men.

1. McClung. N Engl J Med 2014;370:412–20;
2. Langdahl. Lancet 2017;390:1585–94;
3. Cosman. N Engl J Med 2016;375:1532–43;
4. Lewiecki. J Clin Endocrinol Metab 2018;103:3183–93;
5. Saag. N Engl J Med 2017;377:1417–27.

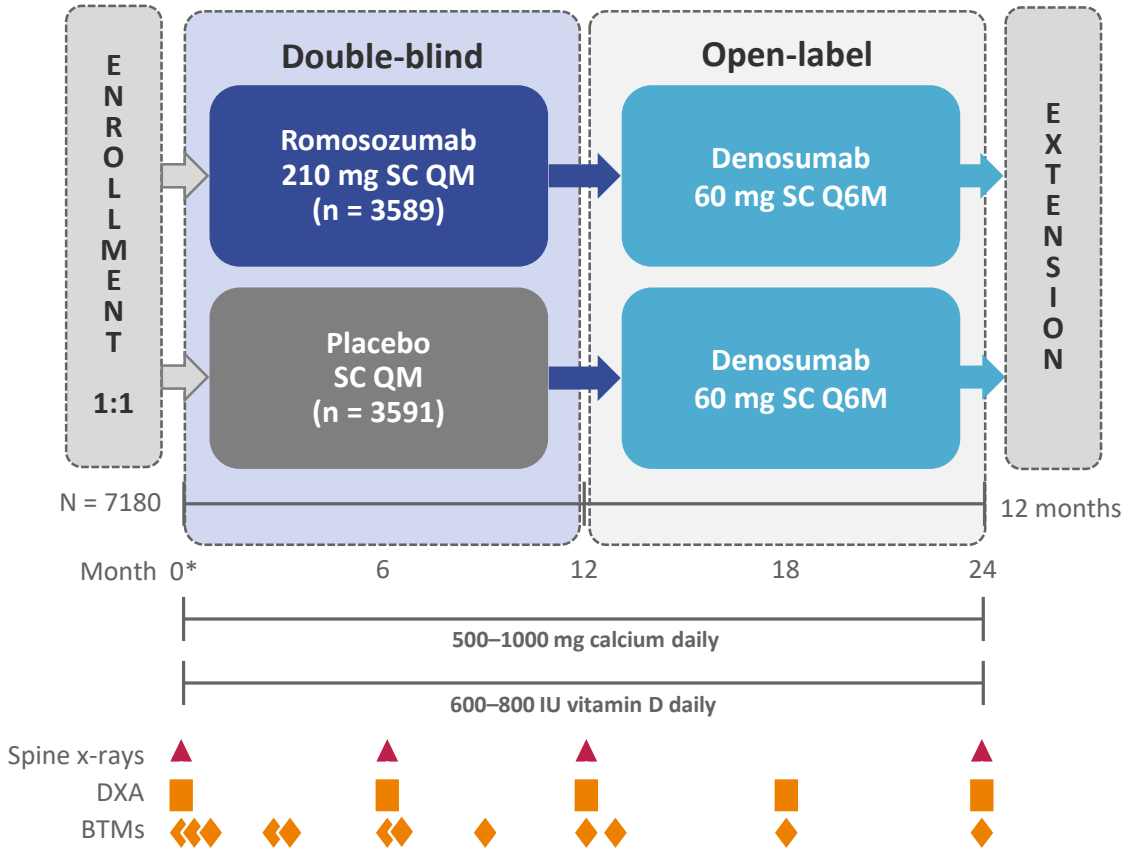
Phase III – FRAME

FRActure Study in Postmenopausal WoMen with OstEoporosis

Romosozumab vs. placebo in postmenopausal women with osteoporosis

FRAME
Study design

FRActure study in postmenopausal wo**M**en with ost**e**oporosis - Phase III, randomized, double-blind, placebo-controlled trial



Inclusion:

- Postmenopausal women aged 55 to 90 years
- BMD T-score ≤–2.5 at the total hip or femoral neck

Exclusion:

- BMD T-score ≤–3.5 at the total hip or femoral neck
- History of hip fracture, or any severe or more than 2 moderate vertebral fractures
- Recent osteoporosis therapy (washout period varied by agent)

➔ Relative low fracture risk population

Co-primary endpoints:

- Subject incidence of new vertebral fracture through 12 & 24 months

Secondary fracture endpoints:

- Subject incidence of clinical, nonvertebral and other fracture categories through 12 and 24 months

*A loading dose of 50,000–60,000 IU vitamin D was given to subjects with a baseline serum vitamin D 25(OH)D level of ≤40 ng/mL.
BMD=bone mineral density; BTM=bone turnover markers; DXA=dual-energy x-ray absorptiometry; IU = international unit; QM=once monthly; Q6M=every 6 months.

Cosman. N Engl J Med 2016; 375: 1532-43

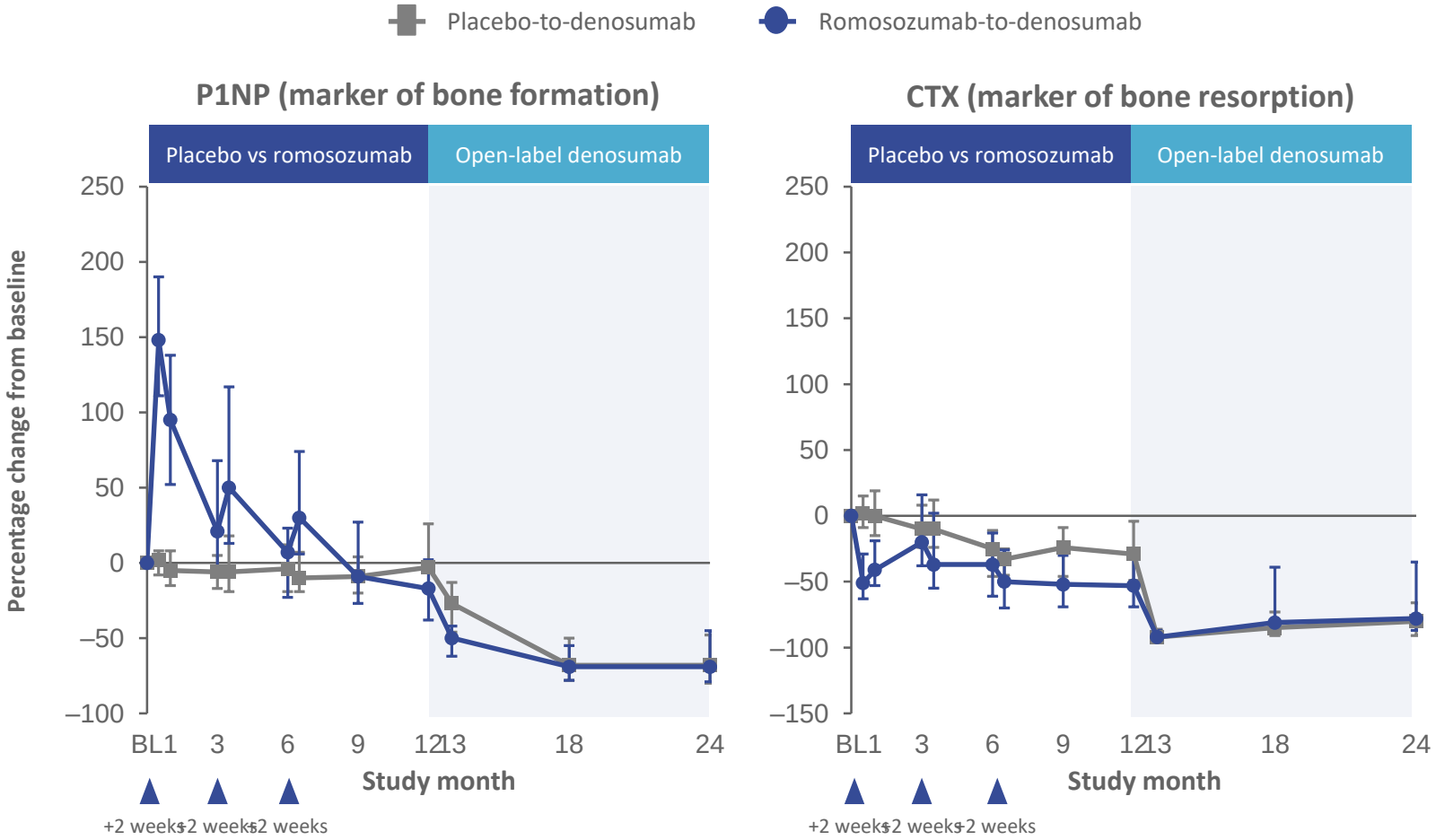
FRAME
Baseline characteristics and subject disposition

	Placebo (n = 3591)	Romosozumab (n = 3589)
Age, mean (SD), years	70.8 (6.9)	70.9 (7.0)
≥75 years, n (%)	1121 (31.2)	1119 (31.2)
Ethnicity, n (%)		
Hispanic or Latino	1416 (39.4)	1427 (39.8)
Not Hispanic or Latino	2175 (60.6)	2162 (60.2)
Lumbar spine BMD T-score, mean (SD)	–2.71 (1.04)	–2.72 (1.04)
Total hip BMD T-score, mean (SD)	–2.46 (0.47)	–2.48 (0.47)
Femoral neck BMD T-score, mean (SD)	–2.74 (0.29)	–2.76 (0.28)
Prior nonvertebral fracture on or after age 45, %	21.8%	21.7%
Prevalent vertebral fracture, %	18.0%	18.7%
Number of prevalent vertebral fractures, %		
1	13.8%	14.1%
≥ 2	4.1%	4.6%
Most severe vertebral fracture grade, %		
Mild	10.5%	10.5%
Moderate	7.3%	8.2%
Severe	0.1%	<0.1%
Completed 12-month double-blind period, n (%)	3205 (89)	3185 (89)
Completed 24-month study period, n (%)	3032 (84)	2994 (83)

Percentages based on number of subjects randomised. Vertebral fracture grade based on Genant semi-quantitative scale.
BMD = bone mineral density; SD = standard deviation.

Cosman. N Engl J Med 2016; 375: 1532-43

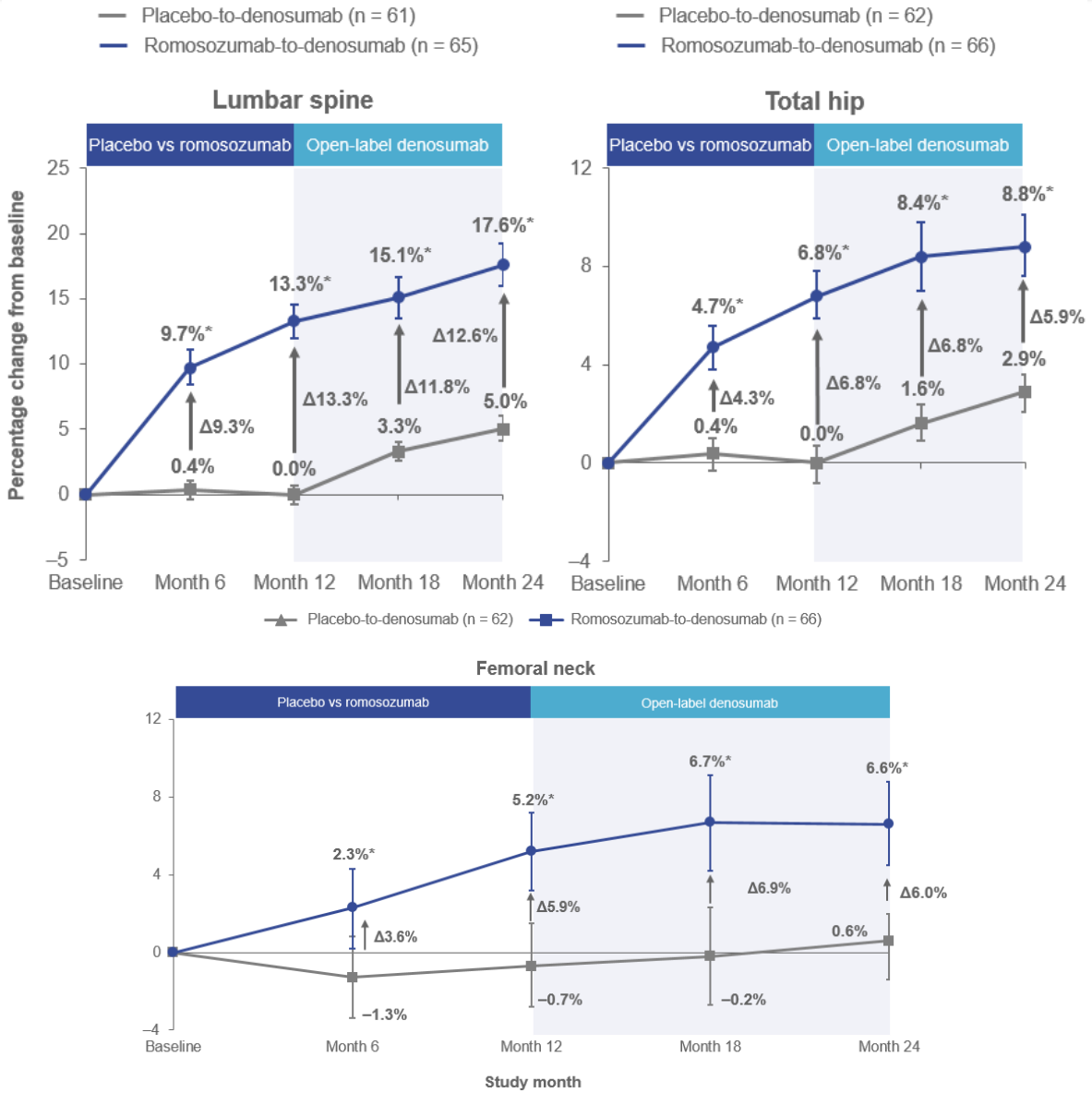
FRAME
P1NP and CTX through month 24



Data are median and interquartile range. Placebo-to-denosumab n = 62; romosozumab-to-denosumab n = 62 (P1NP), n = 61 (CTX).
BL= baseline; CTX = C-terminal telopeptide; P1NP = procollagen type 1 N-terminal propeptide.

Cosman. N Engl J Med 2016; 375: 1532-43

FRAME: lumbar spine, total hip & femoral neck BMD through month 24

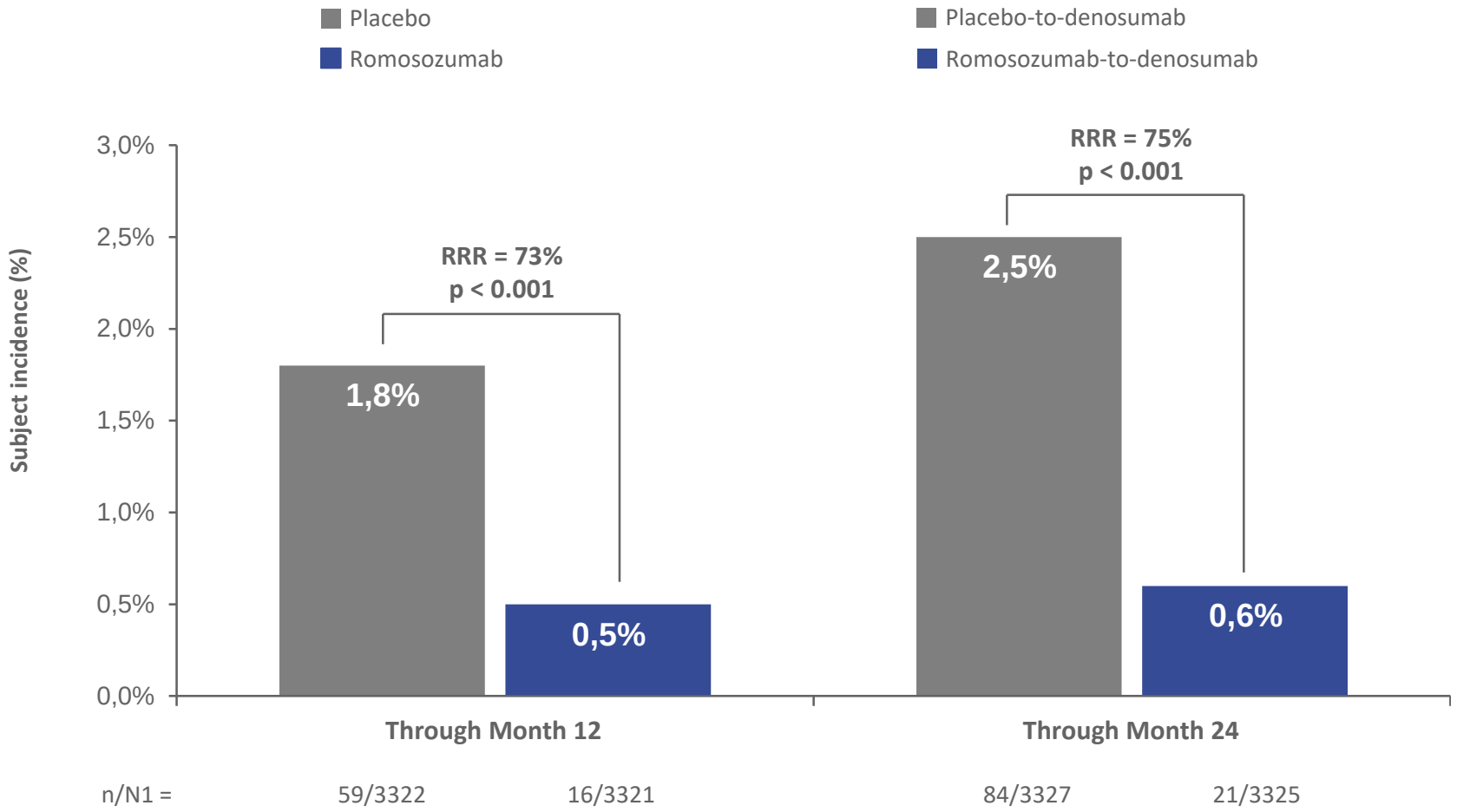


*p < 0.001 compared with placebo. Data are least square means (95% CI) adjusted for relevant baseline covariates.
BMD = bone mineral density; CI = confidence interval; Δ = difference.

Upon request this slide has been provided by UCB.

Cosman. N Engl J Med 2016; 375: 1532-43

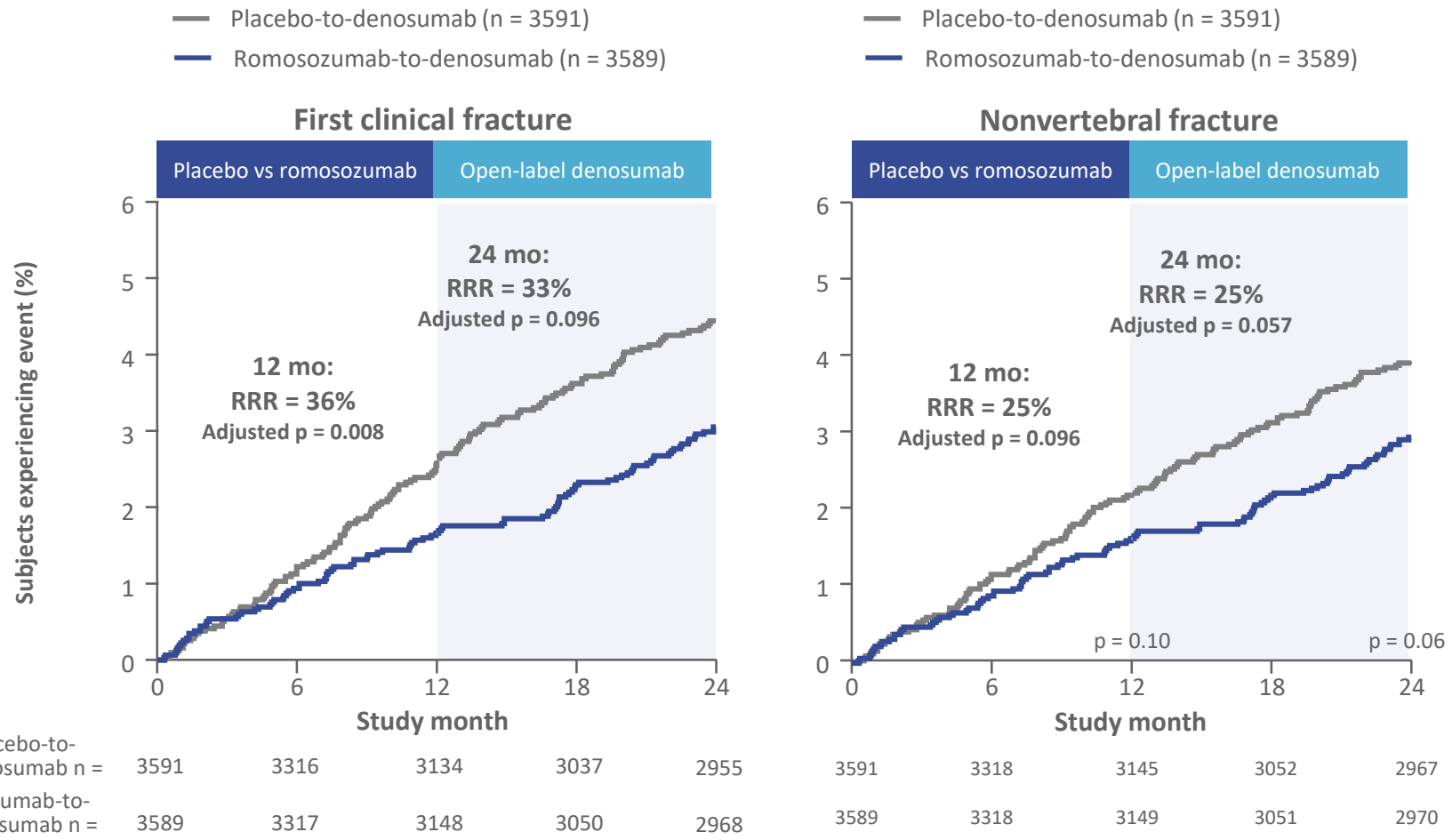
FRAME
Incidence of new vertebral fracture through month 12 and 24



n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures; p value based on logistic regression model adjusted for age (<75, ≥75) and prevalent vertebral fracture.
RRR = relative risk reduction.

Cosman. N Engl J Med 2016; 375: 1532-43

FRAME
Time to first clinical and nonvertebral fracture through month 24



Clinical fractures included all nonvertebral and symptomatic vertebral fractures. Non-vertebral fractures comprised the majority (more than 85%) of clinical fractures and excluded fractures of the skull, facial bones, metacarpals, fingers and toes, pathologic fractures and fractures associated with high trauma. n = number of subjects at risk for event at time point of interest. p value based on RRR. RRR = relative risk reduction.

Cosman. N Engl J Med 2016; 375: 1532-43

FRAME Post-hoc analysis of regional background fracture risk

Baseline demographic and clinical characteristics

Latin American population had fewer prior fractures and lower 10-year risk of fracture by FRAX relative to Rest-of-World

Characteristic	Rest-of-World‡ (n = 4096)	Latin America (n = 3084)
Age, mean (SD), years	70.3 (6.9)	71.7 (6.9)
<75 years, n (%)	2923 (71.4)	2017 (65.4)
≥75 years, n (%)	1173 (28.6)	1067 (34.6)
Ethnicity, n (%)		
Hispanic or Latino	33 (0.8)	2810 (91.1)
Not Hispanic or Latino	4063 (99.2)	274 (8.9)
T-score, mean (SD)		
Total hip	–2.4 (0.5)	–2.5 (0.5)
Femoral neck	–2.8 (0.3)	–2.8 (0.3)
Lumbar spine	–2.5 (1.0)	–3.0 (1.0)
Prevalent vertebral Fx, n (%)	802 (19.6)	515 (16.7)
Number of prevalent vertebral Fx, n (%)		
1	597 (14.6)	405 (13.1)
≥2	205 (5.0)	110 (3.6)
Most severe vertebral Fx grade,* n (%)		
Mild	461 (11.3)	295 (9.6)
Moderate/severe	341 (8.2)	220 (7.1)
Prior nonvertebral Fx at or after age 45, n (%)	1093 (26.7)	467 (15.1)
FRAX Fx risk, median (IQR)		
10-year probability of major osteoporotic Fx	14.5 (10.4–21.2)	7.3 (5.7–10.2)
10-year probability of hip Fx	5.7 (3.8–8.6)	3.0 (2.2–4.4)
25(OH)vitamin D, median (IQR), ng/mL	27.6 (23.6–33.2)	26.8 (23.4–31.3)
Serum P1NP,† median (IQR), µg/L	49.0 (33.5–64.8)	55.3 (46.5–65.1)
Serum β-CTx,† median (IQR), ng/L	481 (298–697)	570 (428–683)

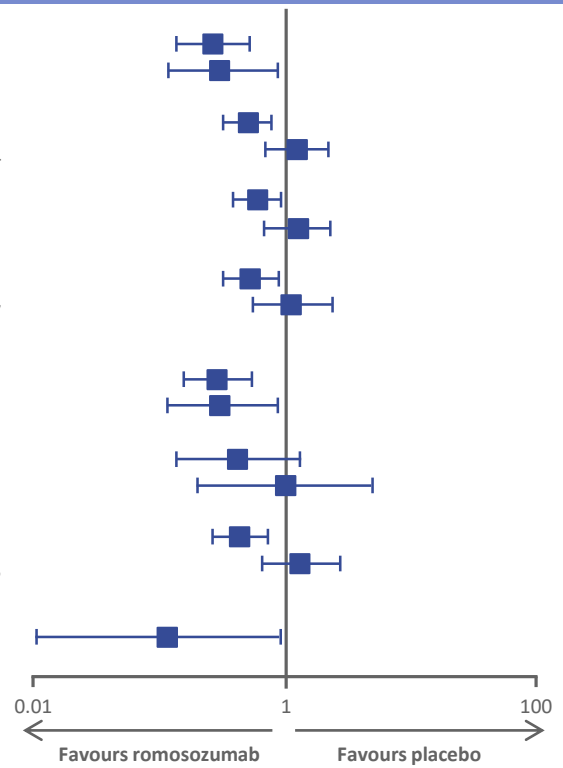
*Assessed using Genant grading scale. †Data shown are for subjects included in the bone turnover and biomarker marker substudy who had a baseline and post-baseline measurement (P1NP, n = 124; β-CTx, n = 123). ‡Rest-of-World: Central/Eastern Europe, Western Europe and Australia/New Zealand, Asia Pacific, North America.
β-CTx = β-isomer of CTx; FRAX = Fracture Risk Assessment Tool, calculated with incorporation of BMD; Fx = fracture; IQR = interquartile range.

Cosman. J Bone Miner Res 2018; 33: 1407-16

FRAME Post-hoc analysis of regional background fracture risk

Effect of 12 months Romosozumab on fracture risk in Rest-of-World Versus Latin America

	RR or HR	p value	Treatment-by-region interaction p value	Romosozumab	Placebo
New vertebral fracture*					
Rest-of-World	0.26	<0.001		11/1857 (0.6%)	43/1892 (2.3%)
Latin America	0.30	0.014	0.79	5/1464 (0.3%)	16/1430 (1.1%)
Clinical fracture					
Rest-of-World	0.48	<0.001		33/2039 (1.6%)	69/2057 (3.4%)
Latin America	1.17	0.590	0.014	25/1550 (1.6%)	21/1534 (1.4%)
Nonvertebral fracture					
Rest-of-World	0.58	0.012		32/2039 (1.6%)	56/2057 (2.7%)
Latin America	1.25	0.47	0.041	24/1550 (1.5%)	19/1534 (1.2%)
Major nonvertebral fracture†‡					
Rest-of-World	0.52	0.012		21/2039 (1.0%)	41/2057 (2.0%)
Latin America	1.12	0.75	0.087	16/1550 (1.0%)	14/1534 (0.9%)
New/worsening vertebral fracture*[a]					
Rest-of-World	0.28	<0.001		12/1857 (0.6%)	43/1892 (2.3%)
Latin America	0.30	0.014	0.90	5/1464 (0.3%)	16/1430 (1.1%)
Hip fracture					
Rest-of-World	0.41	0.12		4/2039 (0.2%)	10/2057 (0.5%)
Latin America	0.99	0.99	0.38	3/1550 (0.2%)	3/1534 (0.2%)
Major osteoporotic fracture†§					
Rest-of-World	0.42	<0.001		21/2039 (1.0%)	50/2057 (2.4%)
Latin America	1.28	0.50	0.013	17/1550 (1.1%)	13/1534 (0.8%)
Multiple new/worsening Vertebral fracture*‖					
Rest-of-World	0.11	0.012		1/1857 (< 0.1%)	9/1892 (0.5%)

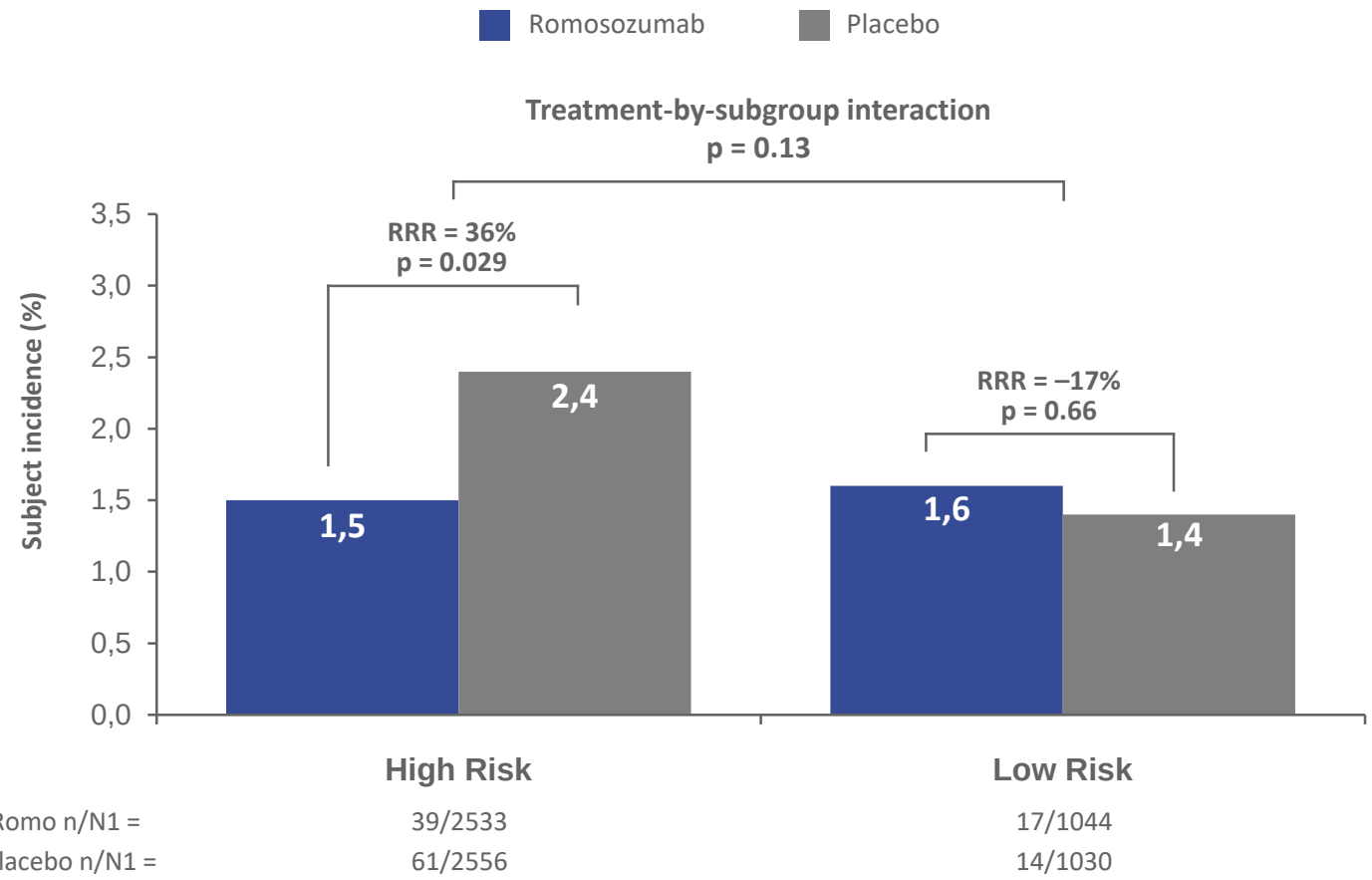


*Risk ratio was based on Mantel-Haenszel method adjusted for age and prevalent vertebral fracture stratification variables; p values were based on a logistic regression model, adjusted for age and prevalent vertebral fracture stratification variables. †HR and p values were based on a Cox proportional hazards model, adjusted for age and prevalent vertebral fracture stratification variables. ‡Major nonvertebral fracture included fractures of the pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm and hip. §Major osteoporotic fracture included clinical vertebral fractures and fractures of the hip, forearm and humerus, regardless of trauma severity. ‖No events were observed in Latin America through 12 months of the study.
Latin America: Colombia, Brazil, Argentina, Dominican Republic, Mexico. Rest-of-World: Central/Eastern Europe, Western Europe and Australia/New Zealand, Asia Pacific, North America. CI = confidence interval; HR = hazard ratio; RR = risk ratio.

Cosman. J Bone Miner Res 2018; 33: 1407-16

FRAME Post-hoc analysis of regional background fracture risk

Nonvertebral fracture efficacy in patients at high vs. low risk based on FRAX in overall study population

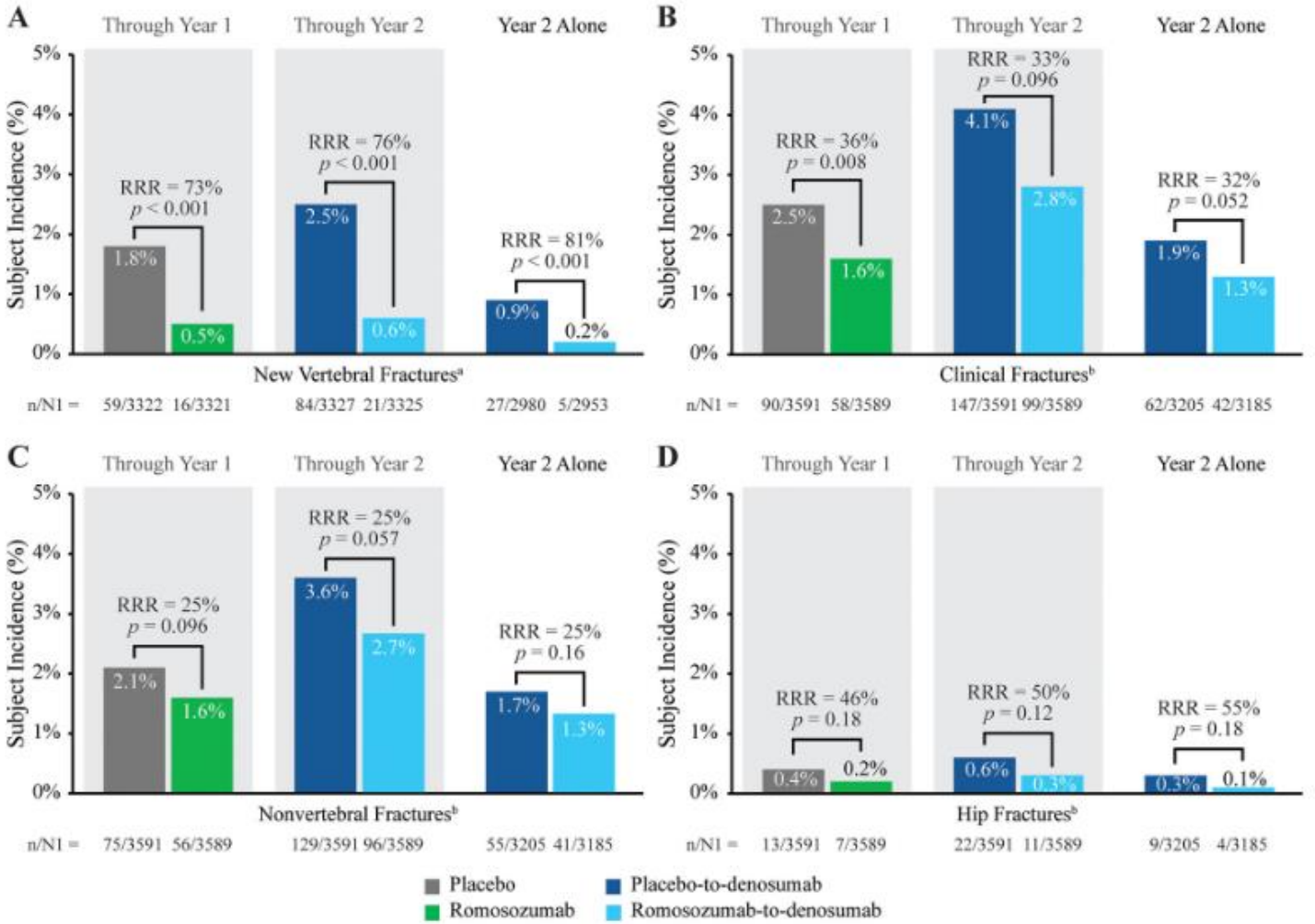


High risk defined as 10-year probability of major osteoporotic fracture ≥20% or hip fracture ≥3%

Post-hoc analysis.
High risk: 10-year probability of major osteoporotic fracture ≥20% or hip fracture ≥3%; low risk: 10-year probability of major osteoporotic fracture <20% and hip fracture <3%. HR ratio estimates based on a Cox proportional hazards model, adjusted for age and prevalent vertebral fracture stratification variables. RRR = relative risk reduction. n/N1 = number of subjects with fractures/number of subjects in the analysis set.

Cosman. J Bone Miner Res 2018; 33: 1407-16

FRAME
Fracture incidence through year 1 and 2, and year 2 alone



*Risk ratio based on Mantel–Haenszel method adjusted for age and prevalent vertebral fracture stratification variables; p values were based on a logistic regression model, adjusting for age and prevalent vertebral fracture stratification variables; missing data handled using last observation carried forward. p values through Year 1 and through Year 2 were adjusted; p values in Year 2 alone were nominal.
n/N1 = number of patients with fractures/number of patients in the analysis set; RRR = relative risk reduction.

Upon request provided by UCB.

Cosman. J Bone Miner Res 2018; 33: 1219-26

FRAME
Subject incidence of adverse events through 24 months

	Double-blind period		24-month study period	
	Romosozumab (n = 3581) n (%)	Placebo (n = 3576) n (%)	Romosozumab-to-denosumab (n = 3581) n (%)	Placebo-to-Denosumab (n = 3576) n (%)
Incidence of all adverse events during treatment†	2806 (78.4)	2850 (79.7)	3053 (85.3)	3069 (85.8)
Arthralgia	467 (13.0)	429 (12.0)	585 (16.3)	565 (15.8)
Nasopharyngitis	459 (12.8)	438 (12.2)	557 (15.6)	546 (15.3)
Back pain	375 (10.5)	378 (10.6)	463 (12.9)	516 (14.4)
Serious adverse events	344 (9.6)	312 (8.7)	565 (15.8)	540 (15.1)
Adjudicated serious cardiovascular events‡	44 (1.2)	41 (1.1)	82 (2.3)	79 (2.2)
Death	29 (0.8)	23 (0.6)	52 (1.5)	47 (1.3)
Adjudicated cardiovascular death‡	17 (0.5)	15 (0.4)	31 (0.9)	29 (0.8)
Events leading to discontinuation of trial regimen	103 (2.9)	94 (2.6)	122 (3.4)	110 (3.1)
Events leading to discontinuation of trial participation	44 (1.2)	50 (1.4)	52 (1.5)	56 (1.6)
Events of interest§				
Hypocalcaemia	1 (<0.1)	0	6 (0.2)	3 (0.1)
Hypersensitivity¶	242 (6.8)	245 (6.9)	314 (8.8)	331 (9.3)
Injection-site reaction‖	187 (5.2)	104 (2.9)	188 (5.2)	106 (3.0)
Osteonecrosis of the jaw‡	1 (<0.1)	0	2 (<0.1)	0
Atypical femoral fracture‡	1 (<0.1)	0	1 (<0.1)	0

*The population for this analysis included all the patients who underwent randomisation and received at least one dose of placebo or romosozumab in the 12-month double-blind period. At Month 12, patients made the transition to denosumab for the second year of the trial. †The events listed are the most frequent adverse events in the double-blind period that occurred in 10% or more of the patients in either group. ‡The events listed include adverse events that were adjudicated as positive by an independent adjudication committee. Cardiovascular deaths include fatal events that were adjudicated as being cardiovascular-related or undetermined (presumed to be cardiac-related). §Events of interest were those that were identified by prespecified Medical Dictionary for Regulatory Activities search strategies. ¶Seven patients in the romosozumab group had serious adverse events during the 12-month double-blind period. Events that were reported by the investigator as being related to romosozumab included dermatitis, allergic dermatitis and macular rash, all of which resolved; the drug was withdrawn or withheld in these cases. ‖The most frequent adverse events of injection-site reactions (occurring in >0.1% of the patients) in the romosozumab group during the 12-month double-blind period included injection-site pain (in 1.7% of the patients), erythema (1.5%), bruising (0.8%), pruritus (0.7%), swelling (0.4%), haemorrhage (0.4%), rash (0.3%) and haematoma (0.2%).

Cosman. N Engl J Med 2016; 375: 1532-43

Phase III – ARCH

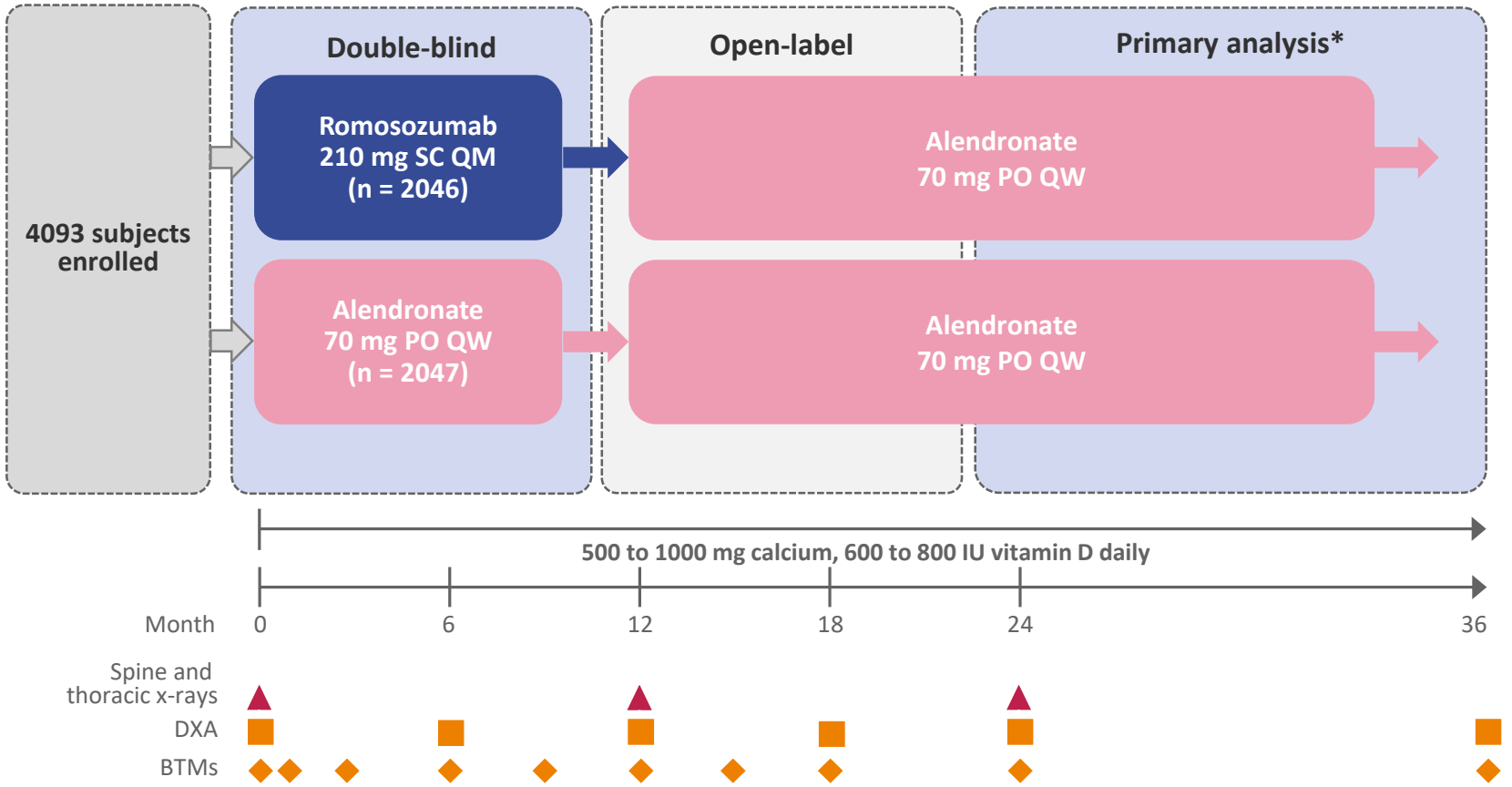
Active-controlled fracture study in postmenopausal women with osteoporosis at High risk of fracture (ARCH)

Romosozumab vs. alendronate in postmenopausal women
with osteoporosis at high risk of fracture

ARCH
Study design

Active-cont**R**olled fra**C**ture study in postmenopausal women with osteoporosis at **H**igh risk of fracture

Phase III, randomized, double-blind, active-controlled trial



***Primary analysis:** performed when clinical fracture events had been confirmed in at least 330 patients and all patients had completed month 24. Median time on study at primary analysis was **33 months** (IQR: 27–40).

BTM = bone turnover marker; DXA = dual-energy x-ray absorptiometry; IQR = interquartile range; IU = international unit; PO = orally; QM = monthly; QW = weekly; SC = subcutaneous.

Upon request provided by UCB.

Saag. N Engl J Med 2017;377:1417-27

ARCH
Key eligibility criteria

Inclusion criteria[1]

- Postmenopausal women aged 55 to 90 years
- **BMD T-score and fracture history**
  - BMD T-score ≤ –2.5 at the total hip or femoral neck, and
    - ≥ 1 moderate or severe vertebral fractures

    or
    - ≥ 2 mild vertebral fractures

OR

  - BMD T-score ≤ –2.0 at the total hip or femoral neck, and
    - ≥2 moderate or severe vertebral fractures

    or
    - hip fracture sustained 3–24 months prior to randomization

Exclusion criteria[1,2]

- Contraindications or signs of intolerance to alendronate
- Recent use of agents affecting bone metabolism

➔ high fracture risk population

Saag. N Engl J Med 2017;377:1417-27

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Demographics and clinical characteristics at baseline

Characteristic	Romosozumab (n = 2046)*	Alendronate (n = 2047)*
Age, years	74.4 ± 7.5	74.2 ± 7.5
BMD T-score		
Femoral neck	–2.89 ± 0.49	–2.90 ± 0.50
Lumbar spine	–2.94 ± 1.25	–2.99 ± 1.24
Total hip	–2.78 ± 0.68	–2.81 ± 0.67
Previous osteoporotic fracture	2022 (98.8%)	2029 (99.1%)
Prevalent vertebral fracture	1969 (96.2%)	1964 (95.9%)
Grade of most severe vertebral fracture†		
Mild	68 (3.3%)	73 (3.6%)
Moderate	532 (26.0%)	570 (27.8%)
Severe	1369 (66.9%)	1321 (64.5%)
Previous nonvertebral fracture	767 (37.5%)	770 (37.6%)
Previous hip fracture‡	175 (8.6%)	179 (8.7%)
10-year risk of major OP fracture by FRAX§	20.2 ± 10.2	20.0 ± 10.1
Body-mass index, kg/m^2	25.46 ± 4.41	25.36 ± 4.42
Median 25-hydroxyvitamin D, ng/mL (IQR)	28.4 (24.0–34.8)	27.6 (24.0–34.2)
Median serum P1NP¶, µg/L (IQR)	50.6 (37.5–64.7)	44.7 (32.7–64.4)
Median serum β-CTX¶, ng/L (IQR)	276.0 (166.0–407.0)	230.0 (137.0–388.0)

± values are means ± SD. There were no significant between-group differences at baseline. Percentages may not total 100 because of rounding.
*Number of patients who were randomly assigned to the 12-month double-blind period of the trial. †Assessed using the Genant grading scale. ‡Excludes pathologic or high-trauma hip fracture. §FRAX® is a registered trademark of Professor JA Kanis, University of Sheffield. ¶Data shown are for the 266 patients (128 in the alendronate group and 138 in the romosozumab group) who enrolled in the biomarker substudy and who had measurements of bone-turnover markers both at baseline and at one or more visits after baseline.
β-CTX = β-isomer of C-terminal telopeptide of type I collagen; FRAX= Fracture Risk Assessment Tool; IQR = interquartile range;
OP = osteoporotic; P1NP = procollagen type 1 N-terminal propeptide; SD = standard deviation.

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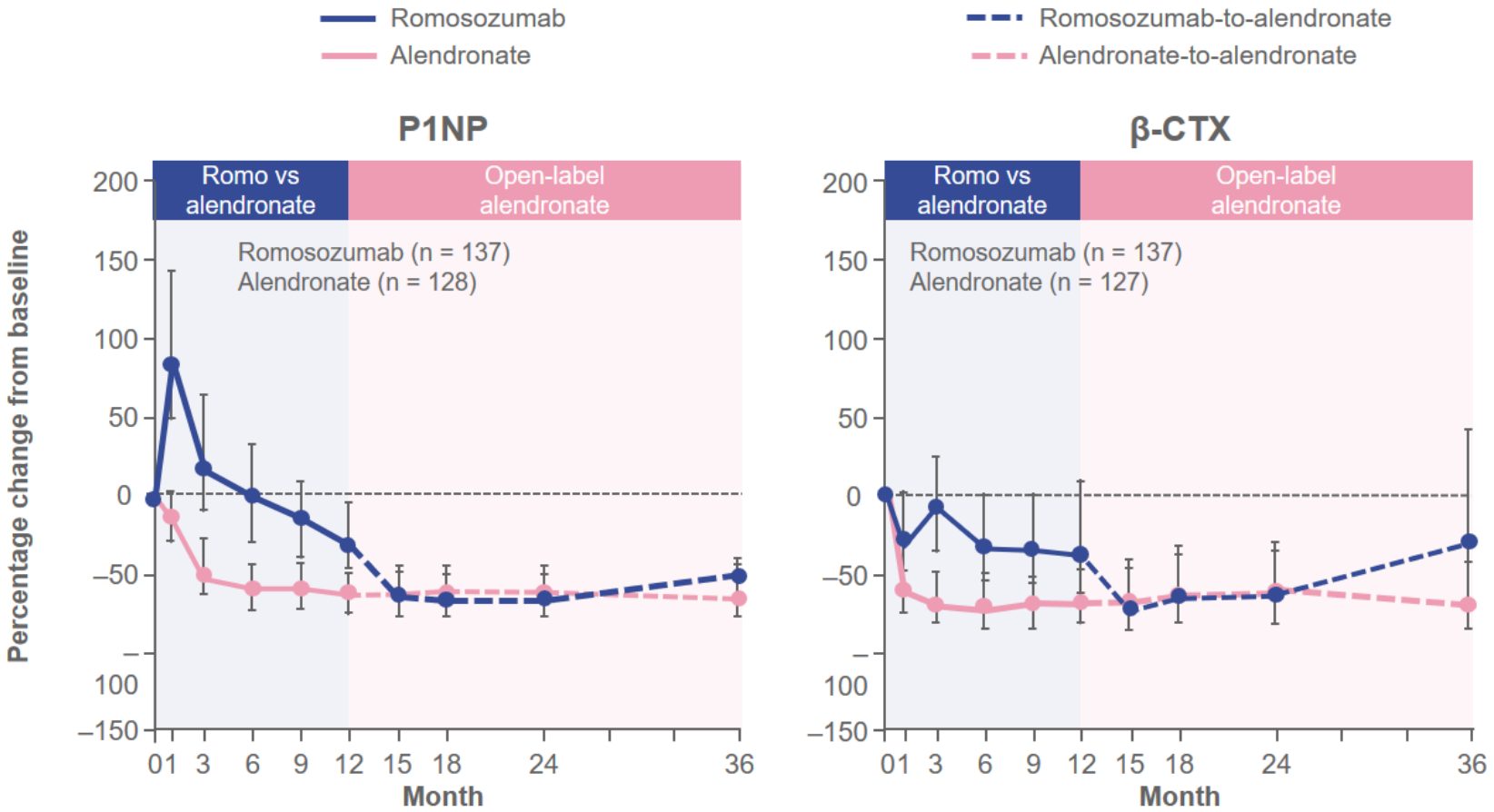
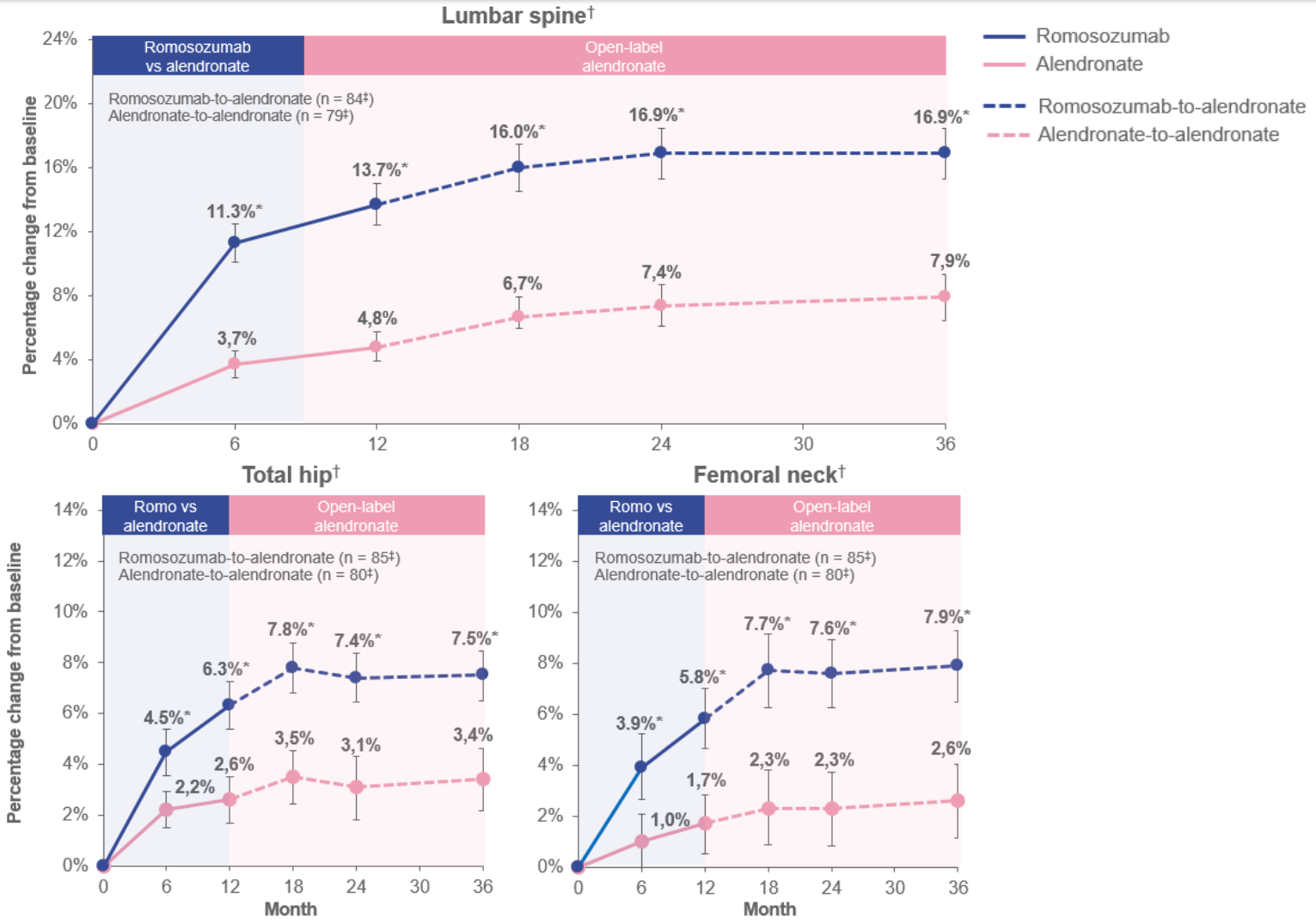
ARCH
% Change from baseline in serum P1NP and CTX levels through month 36



The substudy population was representative of the overall trial population.
$p < 0.001$ for the comparisons at Months 1, 3, 6, 9 and 12. Bars indicate interquartile ranges for the levels of P1NP and β-CTX.
β-CTX = β-isomer of C-terminal telopeptide of type I collagen; P1NP = procollagen type 1 N-terminal propeptide.

Saag. N Engl J Med 2017;377:1417-27

ARCH
% Change from baseline in LS, TH and FN BMD through Month 36

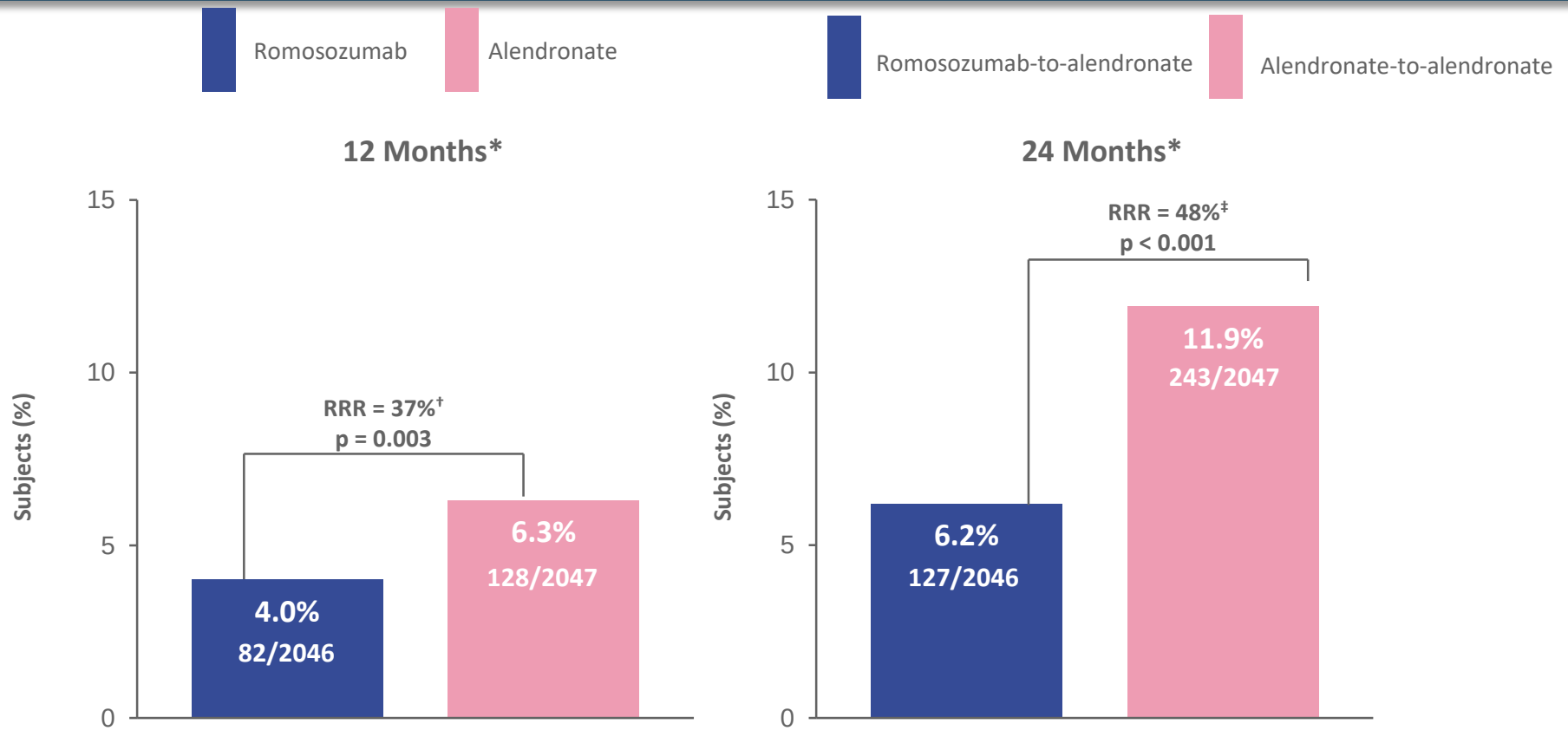


Data are least squares means (95% CI). The substudy population was representative of the overall study (data not shown).
*Nominal $p < 0.001$ (not-adjusted for multiplicity).
†ANCOVA model using LOCF adjusted for treatment, presence of severe vertebral fracture at baseline, baseline BMD value, machine type and baseline BMD value-by-machine type interaction.
‡Number of subjects with values at baseline and at least one post-baseline visit at Month 6 or Month 18.
ANCOVA = analysis of covariance; LOCF = last observation carried forward.

Upon request provided by UCB.

Saag. N Engl J Med 2017;377:1417-27

ARCH
Incidence of new vertebral fracture through month 12 and 24



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.

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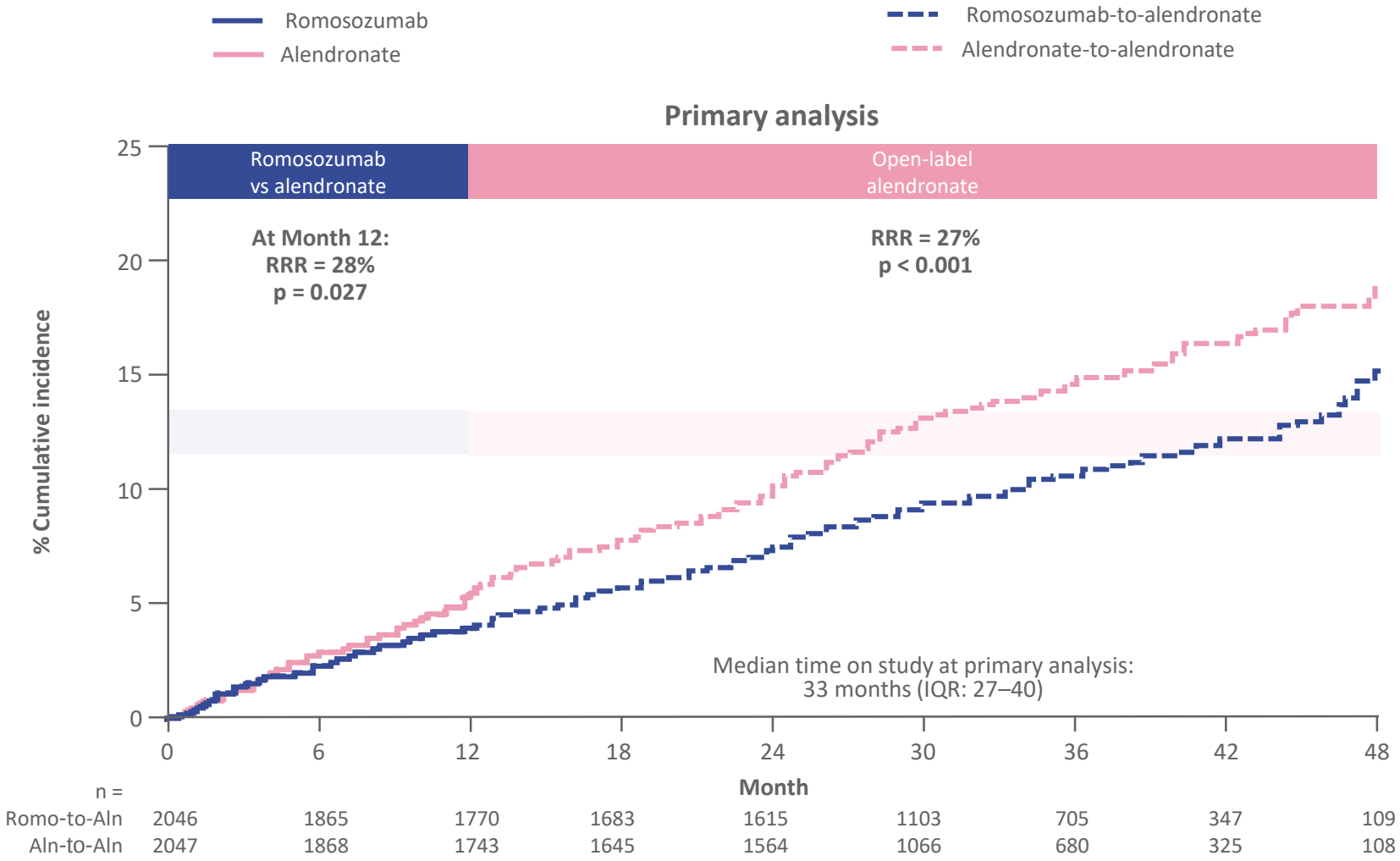
ARCH
Incidence of clinical fracture at primary analysis



n = number of subjects at risk for event at time point of interest.
ALN = alendronate; IQR = interquartile range; Romo = romosozumab; RRR = relative risk reduction.

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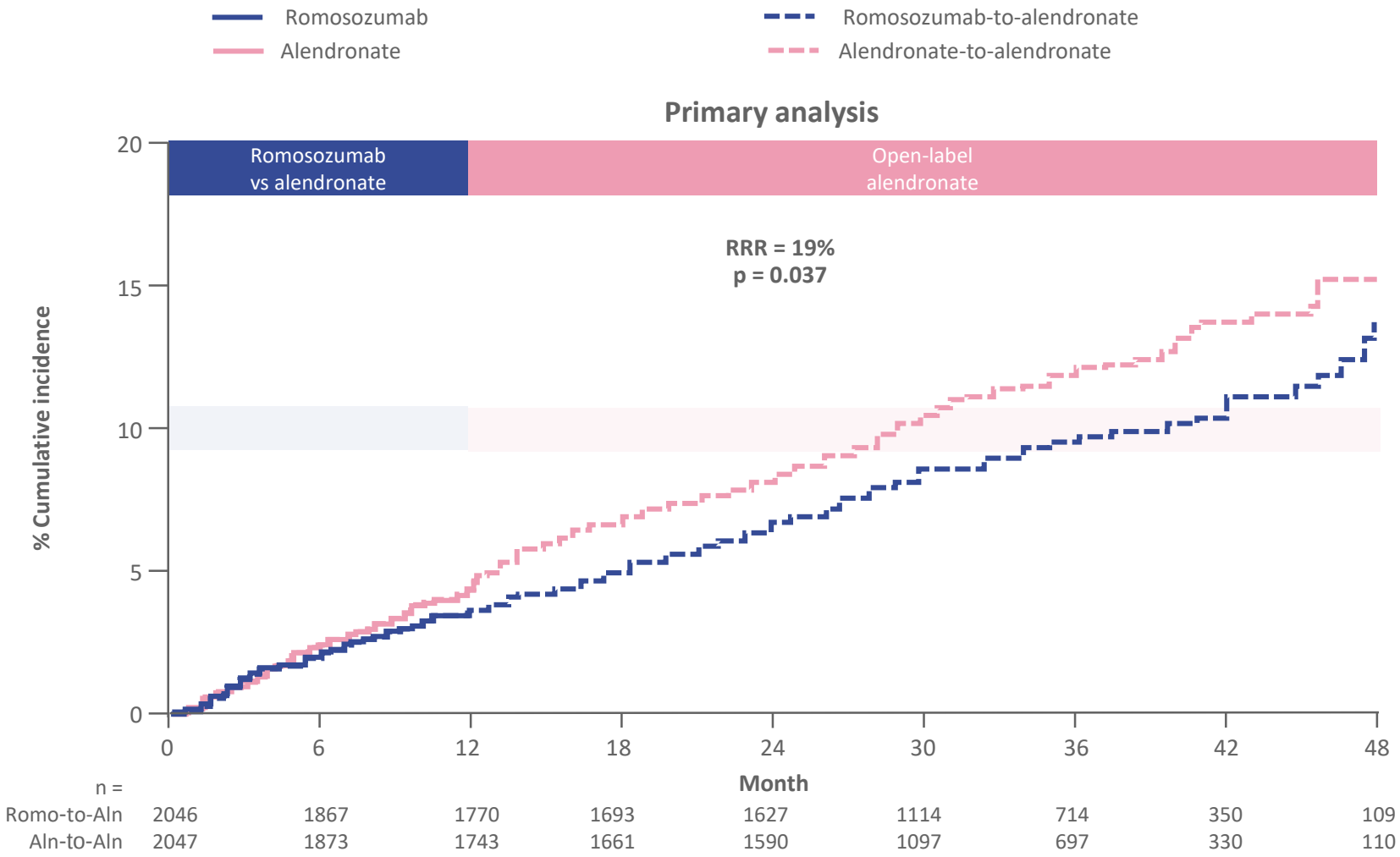
ARCH
Incidence of nonvertebral fractures at primary analysis



Non-vertebral fractures = Secondary endpoint. n = number of subjects at risk for event at time point of interest.
ALN = alendronate; Romo = romosozumab; RRR = relative risk reduction.

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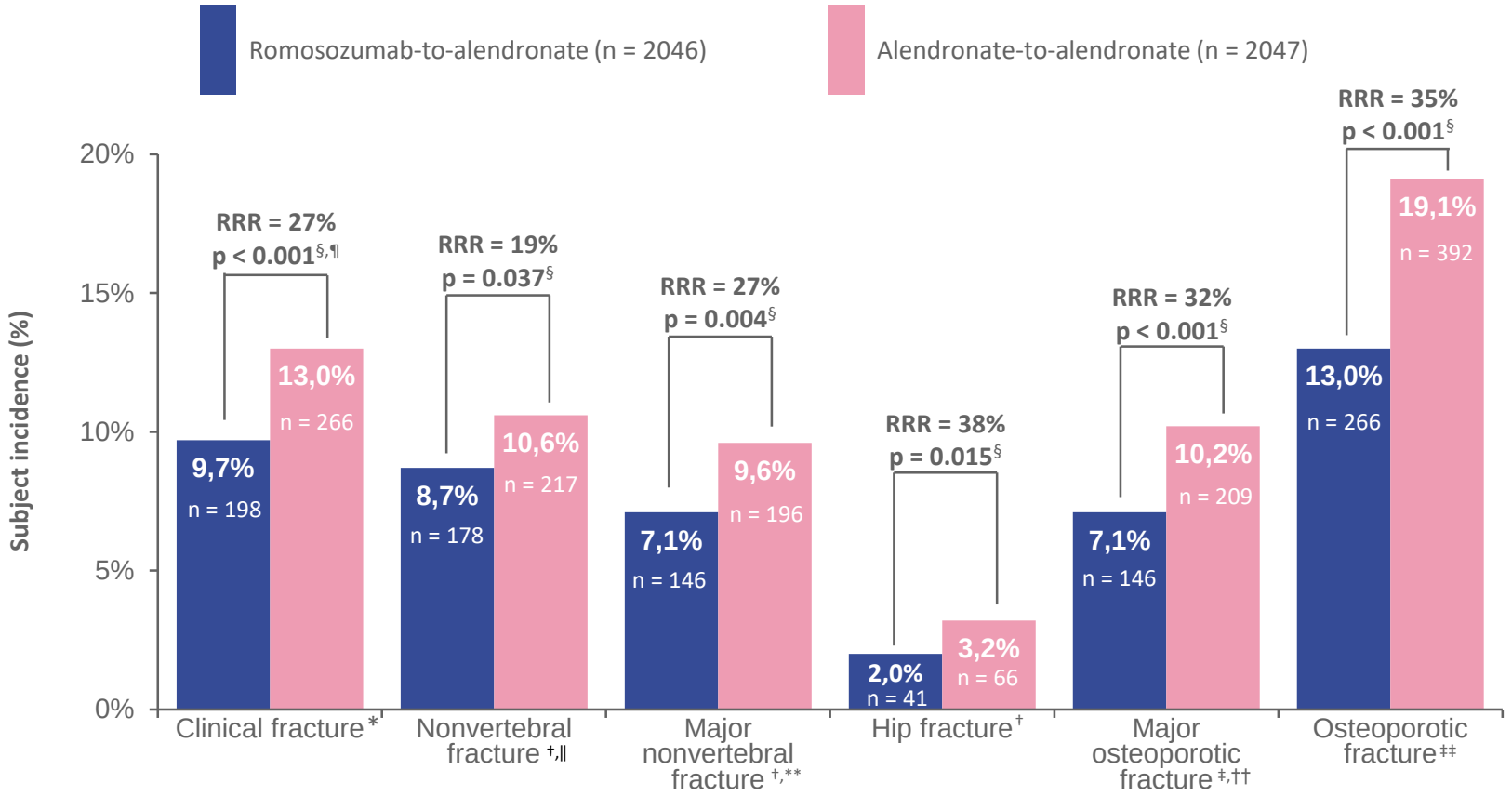
ARCH
Other fracture endpoints at primary analysis



*Primary endpoint. †Secondary endpoint. ‡Exploratory endpoint. §Risk ratios and p-values based on a Cox proportional hazards model adjusting for age strata, baseline total hip BMD T-score and presence of severe vertebral fracture at baseline. ¶The nominal p-value for new vertebral fracture at month 24 using the logistic regression model was < 0.001 for clinical fracture at primary analysis using the Cox proportional hazards model described above. The larger of the two p-values is less than 0.05, thus both endpoints were statistically significant using the Hochberg procedure and the statistical testing continued to the secondary endpoints in the testing sequence described previously. ‖Nonvertebral fractures excluded fractures of the skull, facial bones, metacarpals, fingers and toes. Pathologic or high trauma fractures were also excluded. **Major nonvertebral fracture included fractures of the pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm and hip. ††Major osteoporotic fracture include fractures of the hip, forearm and humerus that are not associated with a pathologic fracture regardless of trauma severity, and clinical vertebral fractures. ‡‡Osteoporotic fractures include any osteoporotic nonvertebral fractures that are not associated with high trauma severity or pathologic fractures and new or worsening vertebral fractures regardless of trauma severity or pathologic fractures.

Note: All fracture types, including nonvertebral fractures, excluded severe trauma (except major osteoporotic fractures) or pathologic fractures. Severe trauma was defined as a fall from higher than the height of a stool, chair, first rung on a ladder or equivalent (> 20 inches), or severe trauma other than a fall per investigator judgment.
RRR = relative risk reduction

Saag. N Engl J Med 2017;377:1417-27

ARCH: adverse events, events of interest and 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)
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%)
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%)
Cardiovascular 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 revascularization	0	2 (<0.1%)	2 (<0.1%)	5 (0.2%)
Death of all causes	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.

Upon request provided by UCB.

Saag. N Engl J Med 2017;377:1417-27

Phase III – STRUCTURE

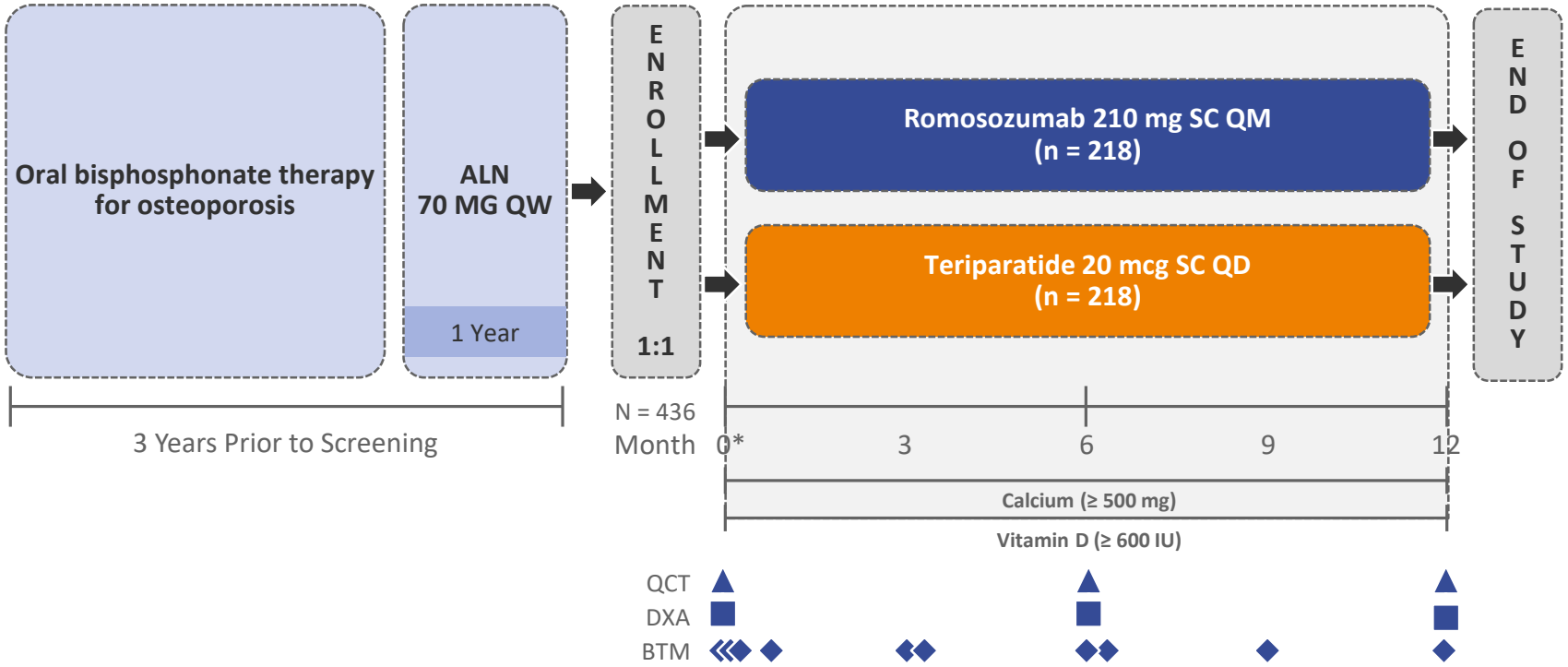
STudy evaluating effect of RomosozUmab Compared with Teriparatide in postmenopaUsal women with osteoporosis at high risk for fracture pReviously treated with bisphosphonatE therapy

Romosozumab vs. teriparatide in postmenopausal women with osteoporosis at high risk of fracture previously treated with bisphosphonate therapy

Phase III, randomized, open-label, active-controlled trial

STRUCTURE
Study design

Inclusion criteria	• Postmenopausal women age 55 to 90 years • BMD T-score ≤ –2.5 at the total hip, femoral neck, or lumbar spine • History of nonvertebral fracture after age 50 or vertebral fracture • Oral bisphosphonate for ≥3 years
Exclusion criteria	• Recent use of agents that affect bone metabolism • History of metabolic or bone disease except osteoporosis



*A loading dose of 50,000–60,000 IU vitamin D was given to subjects in the romo group with a baseline serum vitamin D 25(OH)D level between 50-100 nmol/L
ALN = alendronate; BTM = bone turnover marker; DXA = dual-energy x-ray absorptiometry; IU = international unit; QCT = quantitative computed tomography; QD = daily; QM = once a month; QW = once a week; SC = subcutaneous.

Upon request provided by UCB.

Langdahl. Lancet 2017;390:1585-94

STRUCTURE
Baseline characteristics

	Teriparatide (n = 218)	Romosozumab (n = 218)
Age (years)	71.2 (7.7)	71.8 (7.4)
Race		
American Indian or Alaska native	1 (< 1%)	4 (2%)
Asian	2 (1%)	0
Multiple	1 (<1%)	0
White	196 (90%)	191 (88%)
Other	18 (8%)	23 (11%)
Alendronate in the year before screening	216 (99%)	218 (100%)
Oral BP use in the 3 years before screening	218 (100%)	218 (100%)
Duration of previous alendronate use (years)	5.8 (3.1)	5.5 (3.2)
Duration of previous BP use (years)	6.2 (2.9)	6.2 (2.9)
Alendronate use in the 3 years before the study	202 (93%)	192 (88%)
Previous fracture	217 (<100%)	218 (100%)
BMD T-score		
Total hip	–2.21 (0.72)	–2.27 (0.75)
Femoral neck	–2.43 (0.66)	–2.49 (0.67)
Lumbar spine	–2.87 (1.04)	–2.83 (1.10)
Total hip cortical vBMD by QCT (mg/cm^3)	475.8 (57.5)	472.8 (64.3)
Total hip integral vBMD by QCT (mg/cm^3)	194.5 (34.4)	194.9 (38.9)
Hip strength under fall loading conditions (N)	2,923 (506)	2,892 (494)
Serum CTX (pmol/L)*	1012 (732–1,378)	982 (654–1,348)
Serum P1NP (µmol/L)†	0.33 (0.27–0.44)	0.33 (0.24–0.45)

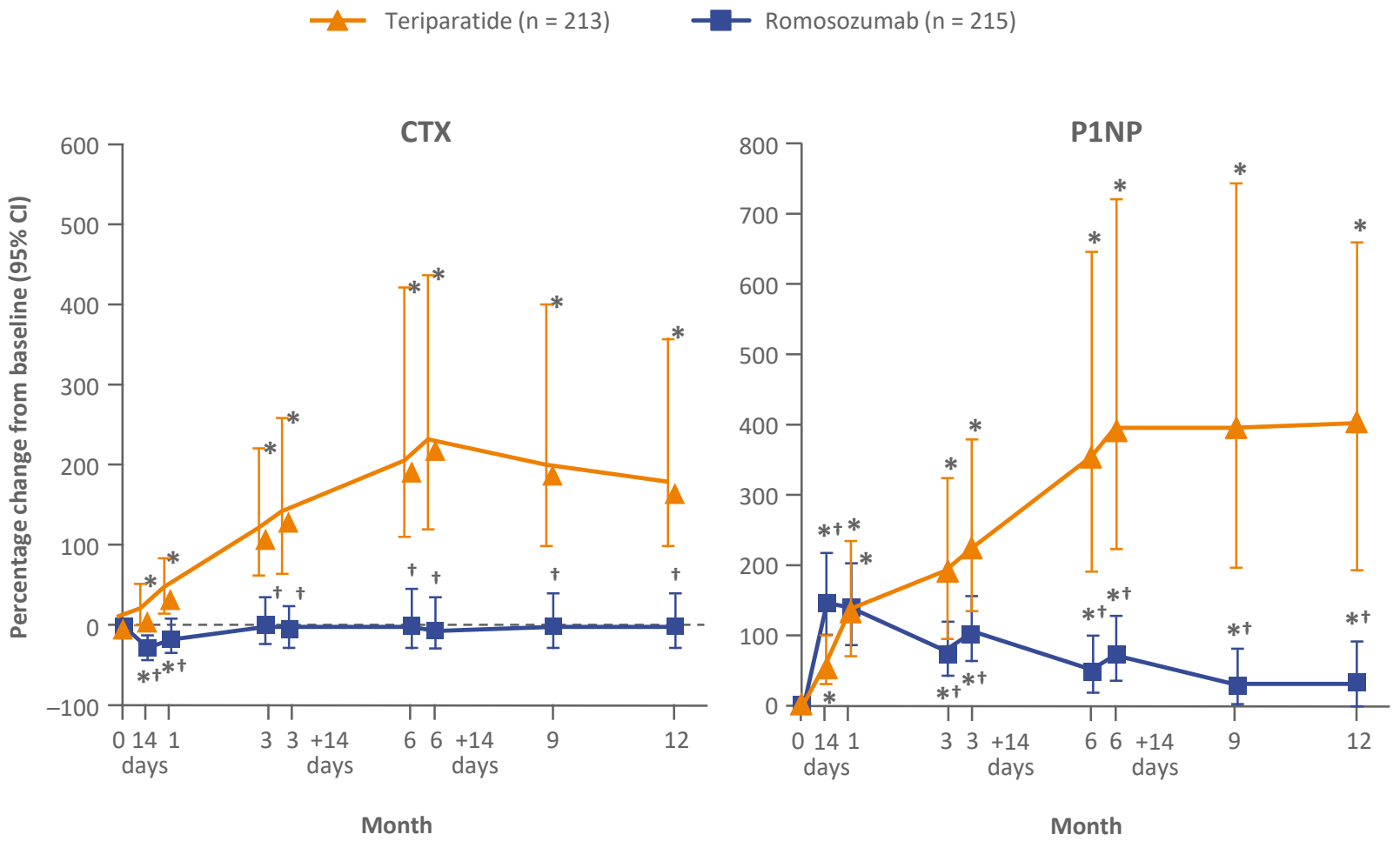
Data are mean (SD), n (%), or median (IQR).
*Premenopausal reference range for serum CTX 861–3,875 pmol/L. †Premenopausal reference range for serum P1NP 0.23–0.82 µmol/L.
BP = bisphosphonate; CTX = C-telopeptide of type 1 collagen; IQR = interquartile range; P1NP = procollagen type 1 N-terminal propeptide.

Upon request provided by UCB.

Langdahl. Lancet 2017;390:1585-94

STRUCTURE

Median % change from baseline in serum P1NP and CTX over 12 months

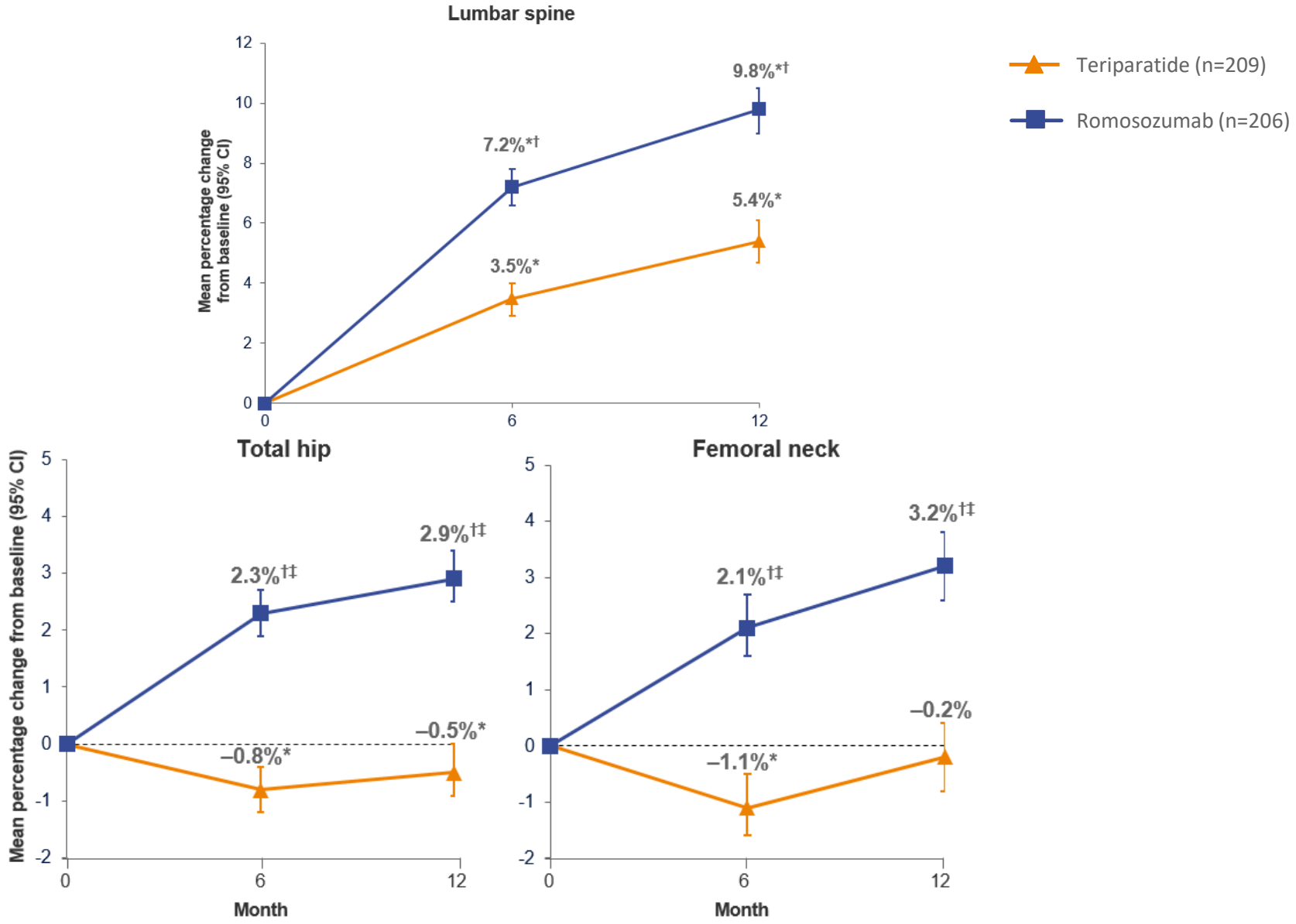


Data are median (IQR). *p < 0.0001 vs baseline. †p < 0.0001 vs teriparatide.
CTX = serum C-telopeptide of type 1 collagen; IQR = interquartile range; P1NP = serum procollagen type 1 N-terminal propeptide.

Langdahl. Lancet 2017;390:1585-94

STRUCTURE

Percentage change in LS, TH and FN aBMD by DXA at months 6 and 12



Data are least-squares means and 95% CI. *p < 0.0001 versus baseline. †p < 0.0001 versus teriparatide

Upon request provided by UCB.

Langdahl. Lancet 2017;390:1585-94

STRUCTURE
Subject incidence of adverse events through 12 months

	Teriparatide (n = 214)	Romosozumab (n = 218)
All adverse events	148 (69%)	164 (75%)
Serious adverse events	23 (11%)	17 (8%)
Adverse events		
Arthralgia*	13 (6%)	22 (10%)
Hypercalcaemia*	22 (10%)	2 (<1%)
Hypocalcaemia†	0	3 (1%)
Injection-site reaction‡	6 (3%)	17 (8%)
Nasopharyngitis*	22 (10%)	28 (13%)
Leading to discontinuation of investigational product§	12 (6%)	6 (3%)
Death¶	1 (< 1%)	1 (<1%)

Data are number of patients (%). Denominator is number of patients who received at least one dose of investigational product.
*Events reported as 10% or higher in either treatment group.
†Includes events reported as hypocalcaemia and decreased blood calcium concentration.
‡Reported as different types of injection-site reactions with the most frequent as injection-site pain in the romosozumab group. §Adverse events leading to study discontinuation in each treatment group were single event types with no particular pattern. ¶There were two deaths during the trial, unrelated to investigational product; one participant with leukaemia in the romosozumab group had a haemorrhage and one participant in the teriparatide group had a gastrointestinal haemorrhage.

Langdahl. Lancet 2017;390:1585-94

Overview

① Discovery and mechanism of action of sclerostin and Romosozumab

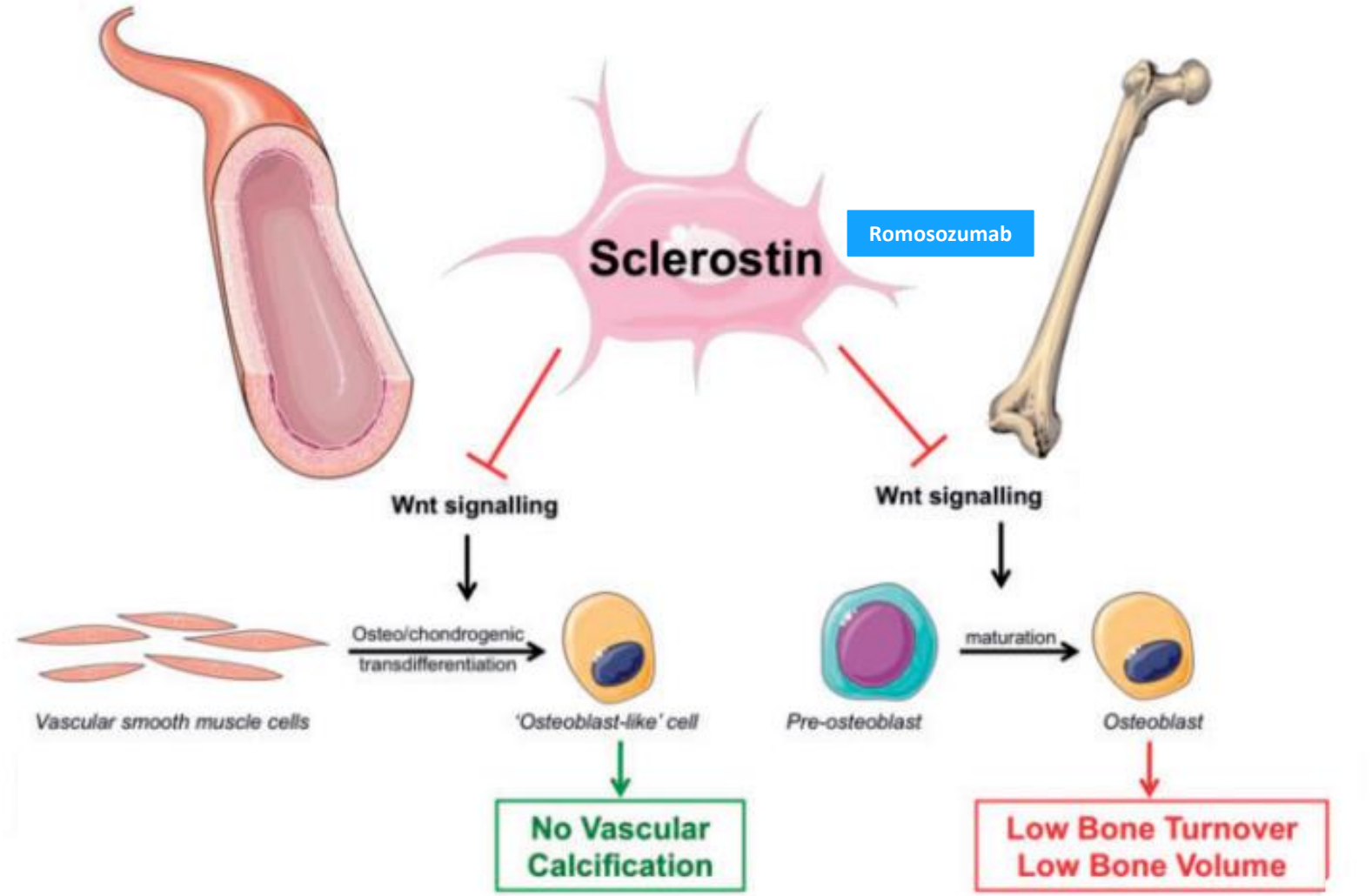
② Pivotal phase III trials with Romosozumab

③ Cardiovascular safety of Romosozumab

④ Reimbursement criteria for Romosozumab in Belgium

⑤ Conclusion

Sclerostin may function as negative regulator of vascular calcification



Adapted from: Brandenburg. Nephrol Dial Transplant; 2019 34: 408–414

FRAME
Subject incidence of adverse events through 24 months

No imbalance in adjudicated cardiovascular adverse events

	Double-blind period		24-month study period	
	Romosozumab (n = 3581) n (%)	Placebo (n = 3576) n (%)	Romosozumab-to-denosumab (n = 3581) n (%)	Placebo-to-Denosumab (n = 3576) n (%)
Incidence of all adverse events during treatment†	2806 (78.4)	2850 (79.7)	3053 (85.3)	3069 (85.8)
Arthralgia	467 (13.0)	429 (12.0)	585 (16.3)	565 (15.8)
Nasopharyngitis	459 (12.8)	438 (12.2)	557 (15.6)	546 (15.3)
Back pain	375 (10.5)	378 (10.6)	463 (12.9)	516 (14.4)
Serious adverse events	344 (9.6)	312 (8.7)	565 (15.8)	540 (15.1)
Adjudicated serious cardiovascular events‡	44 (1.2)	41 (1.1)	82 (2.3)	79 (2.2)
Death	29 (0.8)	23 (0.6)	52 (1.5)	47 (1.3)
Adjudicated cardiovascular death‡	17 (0.5)	15 (0.4)	31 (0.9)	29 (0.8)
Events leading to discontinuation of trial regimen	103 (2.9)	94 (2.6)	122 (3.4)	110 (3.1)
Events leading to discontinuation of trial participation	44 (1.2)	50 (1.4)	52 (1.5)	56 (1.6)
Events of interest§				
Hypocalcaemia	1 (<0.1)	0	6 (0.2)	3 (0.1)
Hypersensitivity¶	242 (6.8)	245 (6.9)	314 (8.8)	331 (9.3)
Injection-site reaction‖	187 (5.2)	104 (2.9)	188 (5.2)	106 (3.0)
Osteonecrosis of the jaw‡	1 (<0.1)	0	2 (<0.1)	0
Atypical femoral fracture‡	1 (<0.1)	0	1 (<0.1)	0

*The population for this analysis included all the patients who underwent randomisation and received at least one dose of placebo or romosozumab in the 12-month double-blind period. At Month 12, patients made the transition to denosumab for the second year of the trial. †The events listed are the most frequent adverse events in the double-blind period that occurred in 10% or more of the patients in either group. ‡The events listed include adverse events that were adjudicated as positive by an independent adjudication committee. Cardiovascular deaths include fatal events that were adjudicated as being cardiovascular-related or undetermined (presumed to be cardiac-related). §Events of interest were those that were identified by prespecified Medical Dictionary for Regulatory Activities search strategies. ¶Seven patients in the romosozumab group had serious adverse events during the 12-month double-blind period. Events that were reported by the investigator as being related to romosozumab included dermatitis, allergic dermatitis and macular rash, all of which resolved; the drug was withdrawn or withheld in these cases. ‖The most frequent adverse events of injection-site reactions (occurring in >0.1% of the patients) in the romosozumab group during the 12-month double-blind period included injection-site pain (in 1.7% of the patients), erythema (1.5%), bruising (0.8%), pruritus (0.7%), swelling (0.4%), haemorrhage (0.4%), rash (0.3%) and haematoma (0.2%).

Cosman. N Engl J Med 2016; 375: 1532-43

STRUCTURE
Subject incidence of adverse events through 12 months

Cardiovascular adverse events were not adjudicated

	Teriparatide (n = 214)	Romosozumab (n = 218)
All adverse events	148 (69%)	164 (75%)
Serious adverse events	23 (11%)	17 (8%)
Adverse events		
Arthralgia*	13 (6%)	22 (10%)
Hypercalcaemia*	22 (10%)	2 (<1%)
Hypocalcaemia†	0	3 (1%)
Injection-site reaction‡	6 (3%)	17 (8%)
Nasopharyngitis*	22 (10%)	28 (13%)
Leading to discontinuation of investigational product§	12 (6%)	6 (3%)
Death¶	1 (< 1%)	1 (<1%)

Data are number of patients (%). Denominator is number of patients who received at least one dose of investigational product.
*Events reported as 10% or higher in either treatment group.
†Includes events reported as hypocalcaemia and decreased blood calcium concentration.
‡Reported as different types of injection-site reactions with the most frequent as injection-site pain in the romosozumab group. §Adverse events leading to study discontinuation in each treatment group were single event types with no particular pattern. ¶There were two deaths during the trial, unrelated to investigational product; one participant with leukaemia in the romosozumab group had a haemorrhage and one participant in the teriparatide group had a gastrointestinal haemorrhage.

Langdahl. Lancet 2017;390:1585-94

ARCH: adverse events, events of interest and 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)
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%)
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%)
Cardiovascular 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 revascularization	0	2 (<0.1%)	2 (<0.1%)	5 (0.2%)
Death of all causes	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.

Upon request provided by UCB.

Saag. N Engl J Med 2017;377:1417-27

Cardiovascular safety of Romosozumab
Meta-analysis of FRAME & ARCH

FRAME (Romo-to-Dmab ⇔ Placebo-to-Dmab) (postmenopausal women, mean age 70.9 y)				ARCH (Romo-to-ALN ⇔ ALN-to-ALN) (postmenopausal women, mean age 74.4 y)			FRAME & ARCH Meta-analysis	BRIDGE* (men)	
	Romo; n (%)	**Pbo; n (%)**	**HR**	**Romo; n (%)**	**ALN; n (%)**	**HR**	**HR**	**Romo; n (%)**	**Pbo; n (%)**
Safety analysis	3581	3576		2040	2014			163	81
MACE**	30 (0.8)	29 (0.8)	1.03 (0.62–1.72)	41 (2.0)	22 (1.1)	**1.87 (1.11–3.14)**	1.39 (0.97–2.00)	6 (3.7)	2 (2.5)
CV deaths	17 (0.5)	15 (0.4)	1.13 (0.56–2.26)	17 (0.8)	12 (0.6)	1.42 (0.68–2.97)		2 (1.2)	1 (1.2)
Myocardial infarction	9 (0.3)	8 (0.2)	1.12 (0.43–2.91)	16 (0.8)	5 (0.2)	**3.21 (1.18–8.77**)			
Stroke	8 (0.2)	10 (0.3)	0.80 (0.32–2.02)	13 (0.6)	7 (0.3)	1.86 (0.74–4.67)			
Any CV SAE	46 (1.3)	46 (1.3)	1.00 (0.66–1.50)	50 (2.5)	38 (1.9)	1.32 (0.87–2.01)	1.14 (0.85–1.53)	8 (4.9)	2 (2.5)
Cardiac ischemic event	16 (0.4)	16 (0.4)	1.00 (0.50–2.00)	16 (0.8)	6 (0.3)	**2.68 (1.50–6.84)**		3 (1.8)	0 (0.0)
Heart failure	7 (0.2)	5 (0.1)	1.40 (0.44–4.40)	4 (0.2)	8 (0.4)	0.50 (0.15–1.66)		1 (0.6)	0 (0.0)
Non-coronary revascularization	1 (<0.01)	2 (<0.01)	0.50 (0.05–5.49)	3 (0.1)	5 (0.2)	0.60 (0.14–2.52)			
Cerebrovascular event	10 (0.3)	11 (0.3)	0.91 (0.39–2.14)	16 (0.8)	7 (0.3)	**2.30 (0.94–5.58)**		3 (1.8)	1 (1.2)

**Romosozumab is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture. Romosozumab is not approved for use in men.*

**MACE (major adverse cardiovascular event) = MI, stroke and cardiovascular or unexplained death

Langdahl. J Clin Metab Endocrinol 2021; 106: 1845-53

ARCH
Comparison of baseline CV risk factors

	Overall study population		Patients with positively adjudicated serious CV AE in the double-blind period	
	Romosozumab (n = 2040)	Alendronate (n = 2014)	Romosozumab (n = 50)	Alendronate (n = 38)
Age (years), mean ± SD	74.4 ± 7.5	74.2 ± 7.5	76.3 ± 7.3	76.3 ± 7.7
Age ≥75 years	1070 (52.5%)	1049 (52.1%)	33 (66.0%)	22 (57.9%)
CV risk score,* median (Q1, Q3)	4 (2, 7)	4 (2, 7)	6.5 (3, 10)	7 (3, 10)
Any history of CV risk factor	1625 (79.7%)	1607 (79.8%)	48 (96.0%)	35 (92.1%)
History of CV disease	1497 (73.4%)	1456 (72.3%)	46 (92.0%)	34 (89.5%)
History of CNS vascular disorder	147 (7.2%)	183 (9.1%)	7 (14.0%)	6 (15.8%)
History of hypercholesterolemia	708 (34.7%)	674 (33.5%)	25 (50.0%)	14 (36.8%)
History of hypertension	1248 (61.2%)	1227 (60.9%)	42 (84.0%)	32 (84.2%)
History of diabetes	664 (32.5%)	658 (32.7%)	24 (48.0%)	18 (47.4%)
Current/former smoker	533 (26.1%)	591 (29.3%)	20 (40.0%)	12 (31.6%)
eGFR 30–<60 mL/min/1.73 m²	508 (24.9%)	476 (23.6%)	17 (34.0%)	12 (31.6%)
eGFR 60–<90 mL/min/1.73 m²	1257 (61.6%)	1189 (59.0%)	27 (54.0%)	22 (57.9%)
Patients with CV-related baseline medications	1229 (60.2%)	1212 (60.2%)	39 (78.0%)	30 (78.9%)
Anti-platelet therapy	471 (23.1%)	455 (22.6%)	16 (32.0%)	11 (28.9%)
Aspirin	437 (21.4%)	421 (20.9%)	15 (30.0%)	11 (28.9%)
Statins	495 (24.3%)	474 (23.5%)	17 (34.0%)	10 (26.3%)
Beta blockers	509 (25.0%)	473 (23.5%)	22 (44.0%)	17 (44.7%)
ACE inhibitors	528 (25.9%)	489 (24.3%)	20 (40.0%)	15 (39.5%)
Angiotensin II receptor antagonists	347 (17.0%)	374 (18.6%)	12 (24.0%)	9 (23.7%)
Anti-coagulants	563 (27.6%)	537 (26.7%)	23 (46.0%)	17 (44.7%)

Data are n (%) unless otherwise noted.
*Modified after Samelson EJ, *et al.*[2] The score was determined as follows: ischaemic heart disease or central nervous system haemorrhages and cerebrovascular conditions (4 points), diabetes mellitus (3 points), age ≥70 years (2 points), age 65 to 69 years (1 point), current/former smoker (1 point), hypertension (1 point) and hyperlipidaemia (1 point); if positive for all three criteria: Smoking, hypertension and hyperlipidaemia, 1 extra point was added (i.e. total of 4 points).
CNS = central nervous system; CV = cardiovascular; eGFR = estimated glomerular filtration rate; Q1 = 25th percentile; Q3 = 75th percentile; SAE = serious adverse event; SD = standard deviation.

Saag. N Engl J Med 2017;377:1417-27

Cardiovascular safety of Romosozumab

- Er geldt een **contra-indicatie voor het gebruik van romosozumab** bij patiënten die **eerder een myocardinfarct of beroerte** hebben gehad.

- Wanneer u bepaalt of romosozumab bij een individuele patiënt kan worden gebruikt, moet u rekening houden met het risico dat zij loopt op fracturen in het komende jaar en haar cardiovasculaire risico, op basis van risicofactoren (bijv. vastgestelde cardiovasculaire aandoening, hypertensie, hyperlipidemie, diabetes mellitus, roken, ernstige nierfunctiestoornis, leeftijd). **Romosozumab mag uitsluitend worden gebruikt als de voorschrijver en de patiënt het erover eens zijn dat de voordelen opwegen tegen de risico's.**

- Als een patiënt een **myocardinfarct of een beroerte krijgt tijdens de behandeling**, moet de behandeling met **romosozumab worden stopgezet.**

- Le romosozumab est **contre-indiqué** chez les patients présentant des **antécédents d'infarctus du myocarde (IDM) ou d'accident vasculaire cérébral** (AVC).

- L'évaluation de la pertinence d'un traitement par romosozumab doit tenir compte du risque de fracture encouru par le patient concerné au cours de l'année à venir et de son risque cardiovasculaire, déterminé à partir de plusieurs facteurs de risque (par exemple, présence d'une maladie cardiovasculaire établie, hypertension, hyperlipidémie, diabète, tabagisme, insuffisance rénale sévère, âge). **Le romosozumab doit uniquement être utilisé si le prescripteur et le patient conviennent que le rapport bénéfice/risque est favorable.**

- Si un patient présente un **infarctus du myocarde (IDM) ou un accident vasculaire cérébral (AVC) pendant le traitement**, le **romosozumab doit être arrêté**.

Evenity, SmPC

Overview

① Discovery and mechanism of action of sclerostin and Romosozumab

② Pivotal phase III trials with Romosozumab

③ Cardiovascular safety of Romosozumab

④ Reimbursement criteria for Romosozumab in Belgium

⑤ Conclusion

II - Elementen te bevestigen door een arts-specialist in de reumatologie, fysiotherapie of inwendige geneeskunde:

Ik ondergetekende, dokter in de geneeskunde, erkend specialist in de reumatologie, in fysiotherapie of inwendige geneeskunde, verklaar dat de hierboven vermelde menopauzale rechthebbende, lijdt aan ernstige osteoporose en tegelijk voldoet aan alle volgende voorwaarden :

1. een recente majeure osteoporotische fractuur vertoont (zoals gedefinieerd door de Belgian Bone Club 2020 guidelines (Maturitas 139 (2020) 69–89)), zijnde :

   ☐ een fractuur van het bekken, de heup, de femur of de humerus, of bij personen > of = 75 jaar ook van de radius of de ulna, die plaats had tijdens de 24 maanden vóór de aanvraag tot vergoeding, aangetoond door een radiologisch onderzoek

   of

   ☐ een wervelfractuur gedefinieerd door een vermindering van minstens 25 % en van minstens 4 mm in absolute waarde, van de hoogte van de voor- of de achterrand of van het centrum van de beschouwde wervel, die plaats had tijdens de 24 maanden vóór de aanvraag tot vergoeding, aangetoond door een radiologisch onderzoek

EN

2.

   ☐ een T-score, berekend ten opzichte van een vrouwelijke referentiepopulatie van<-2,5 ter hoogte van de lumbale wervelzuil (L1-L4 of L2-L4) of van de heup(volledige zone of zone van de hals) bij een onderzoek uitgevoerd met radiologische absorptiometrie met dubbele energie uitgevoerd maximum 6 maanden vóór de aanvraag tot vergoeding,

   of,

   ☐ een antecedent (eventueel ouder dan 24 maanden vóór aanvraag tot vergoeding) vertoont van een wervelfractuur gedefinieerd door een vermindering van minstens 25 % en van minstens 4 mm in absolute waarde, van de hoogte van de voor- of de achterrand of van het centrum van de beschouwde wervel, aangetoond door een radiologisch onderzoek. Deze antecedente wervelfractuur dient een andere wervelfractuur te betreffen dan de wervelfractuur bedoeld in het bovenstaande criterium 1.

Ik voeg bij de huidige aanvraag het(de) protocol(len) van de radiologie als ook het verslag van absorptiometrie.

Op basis van deze elementen, verzoek ik de adviserend arts de vergoeding van de farmaceutische specialiteit op basis van romosozumab 210 mg per maand voor een éénmalige periode van 12 maanden maximum, wat overeenkomt met maximum 12 verpakkingen van 2 voorgevulde spuiten of pennen van 105 mg, toe te staan.

II – Eléments à attester par un médecin spécialiste en rhumatologie, en physiothérapie ou en médecine interne:

Je soussigné, docteur en médecine, spécialiste reconnu en rhumatologie, en physiothérapie ou en médecine interne, certifie que le bénéficiaire ménopausé mentionné ci-dessus souffre d'une ostéoporose sévère et remplit simultanément toutes les conditions suivantes:

1. un antécédent récent de fracture ostéoporotique majeure (selon les critères défini par les Belgian Bone Club 2020 guidelines (Maturitas 139 (2020) 69–89), c.à.d. :

   ☐ une fracture du bassin, de la hanche, du fémur ou de l'humérus, aussi du radius ou de l'ulna chez des personnes > ou = 75 ans, qui a eu lieu au cours des 24 mois précédant la demande de remboursement, démontré par un examen radiologique

   ou

   ☐ une fracture vertébrale définie par une réduction d'au moins 25 %, et d'au moins 4 mm en valeur absolue, de la hauteur du bord antérieur ou postérieur ou du centre des vertèbres considérées, qui a eu lieu au cours des 24 mois précédant la demande de remboursement, démontré par un examen radiologique

ET

2.

   ☐ Un T-score calculé par rapport à une population de référence féminine < -2.5 au niveau de la colonne lombaire (L1-L4 ou L2-L4) ou de la hanche (zone totale ou zone propre du col) lors d'un examen réalisé par la technique d'absorptiométrie radiologique à double énergie effectué au maximum 6 mois avant la demande de remboursement,

   ou

   ☐ un antécédent (éventuellement plus que 24 mois avant la demande de remboursement) de fracture vertébrale définie par une réduction d'au moins 25 %, et d'au moins 4 mm en valeur absolue, de la hauteur du bord antérieur ou postérieur ou du centre des vertèbres considérées, démontré par un examen radiologique. Cette fracture vertébrale antérieure doit être une fracture vertébrale différente de celle de la fracture vertébrale visée dans le critère 1. ci-dessus.

Je joins au présent formulaire le(s) protocole(s) de la radiographie et de l'absorption radiologique à double énergie.

Sur base de ces éléments, je demande au médecin-conseil le remboursement de la spécialité pharmaceutique à base de romosozumab à 210 mg par mois pour une période unique de 12 mois maximum, ce qui porte le nombre total à 12 conditionnements maximum de 2 seringues ou stylos préremplis de 105 mg.

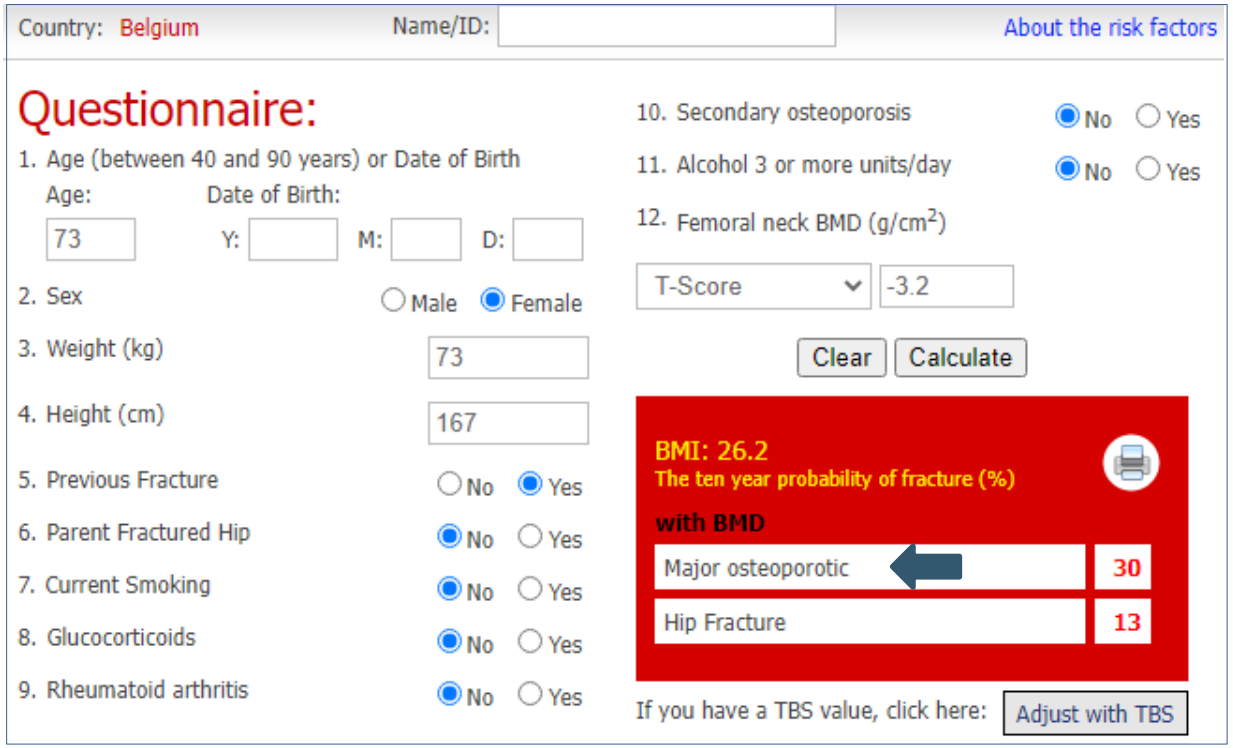
Definition of major osteoporotic fracture (MOF)

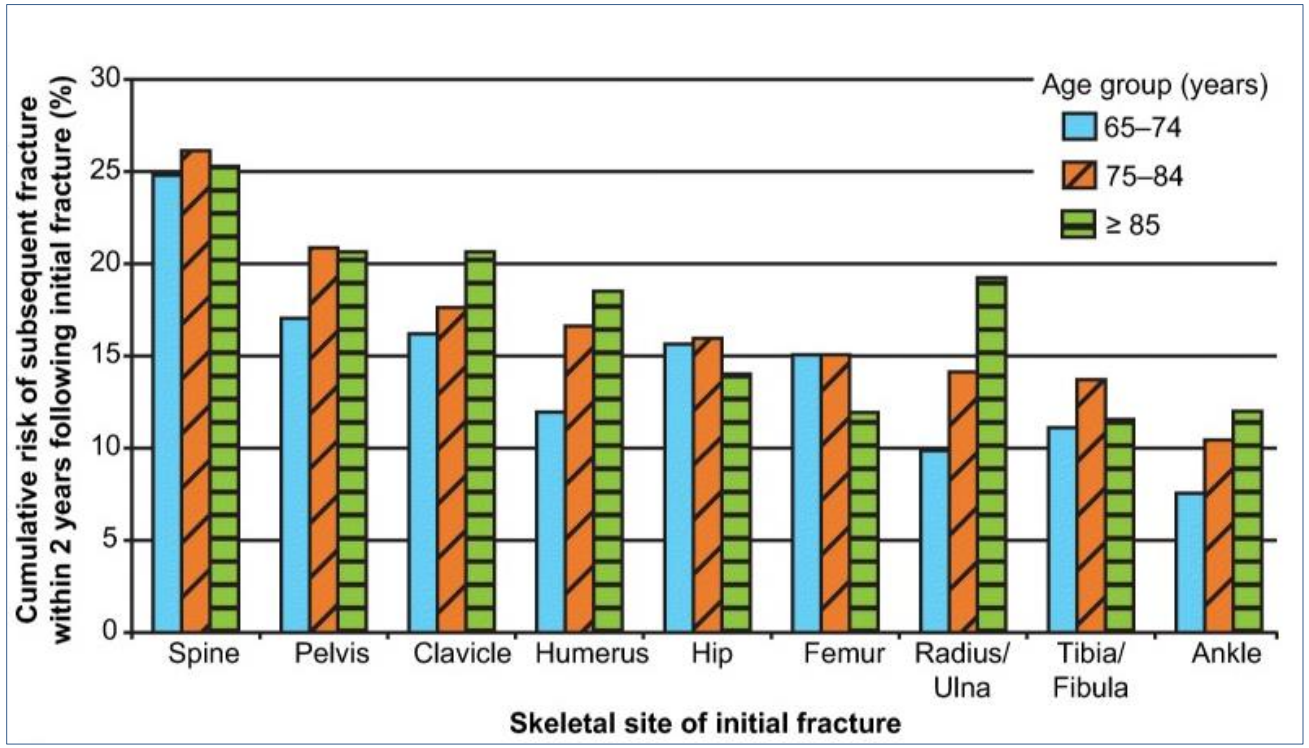
FRAX® Fracture Risk Assessment Tool

hip, clinical spine
proximal humerus
distal forearm

2020 BBC guidelines

hip, vertebral
humerus, pelvis, femur
forearm (if ≥ 75 years old)

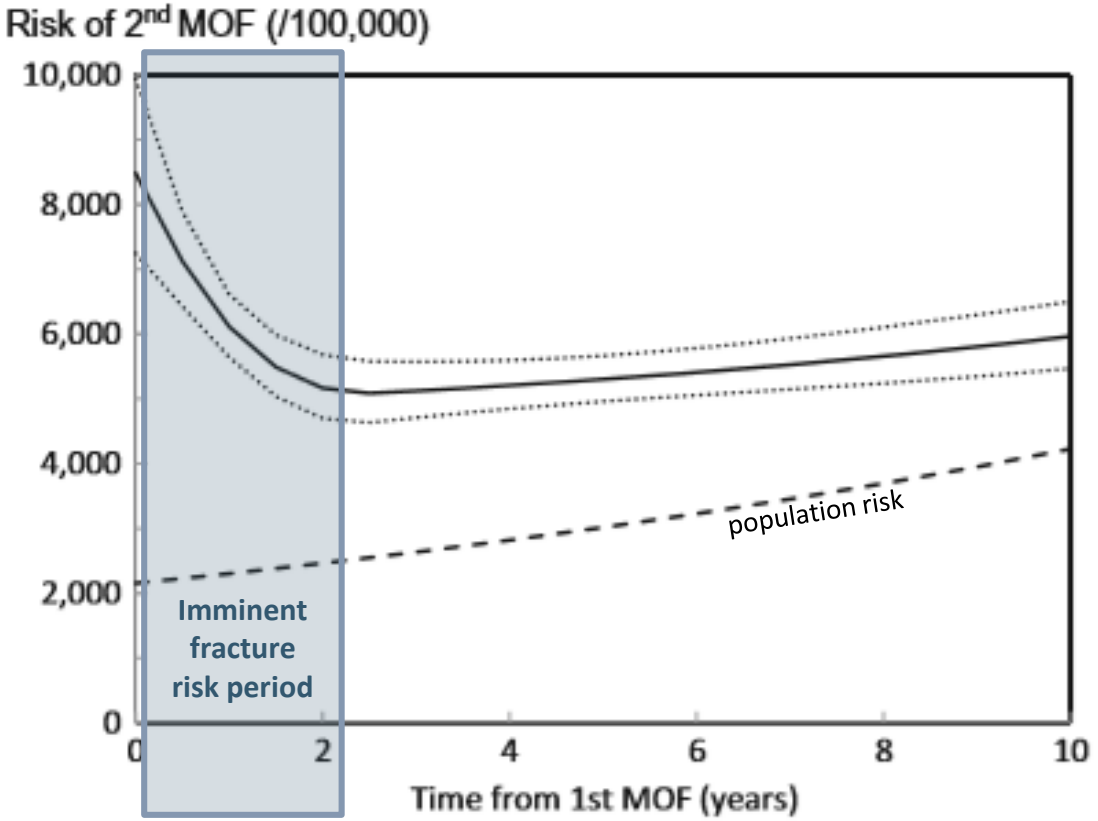




Kanis. Osteoporos Int 2008; 19: 385-97; Sanchez-Rodriguez. Maturitas 2020; 139: 69-89; Balasubramanian. Osteopor Int 2019; 30:79-92

Risk of a recent osteoporotic fracture

Imminent fracture risk



- Population based cohort N=18.872 ♀ & ♂
- Followed for 510.265 person years
  - N=5039: ≥ 1 MOF
  - N=1919: second MOF

Risk of second MOF:

- 1 year after first MOF:
  2.7 (2.4-3.0)x higher than the population risk
- 10 years after first MOF:
  1.4 (1.2-1.6)x higher than the population risk

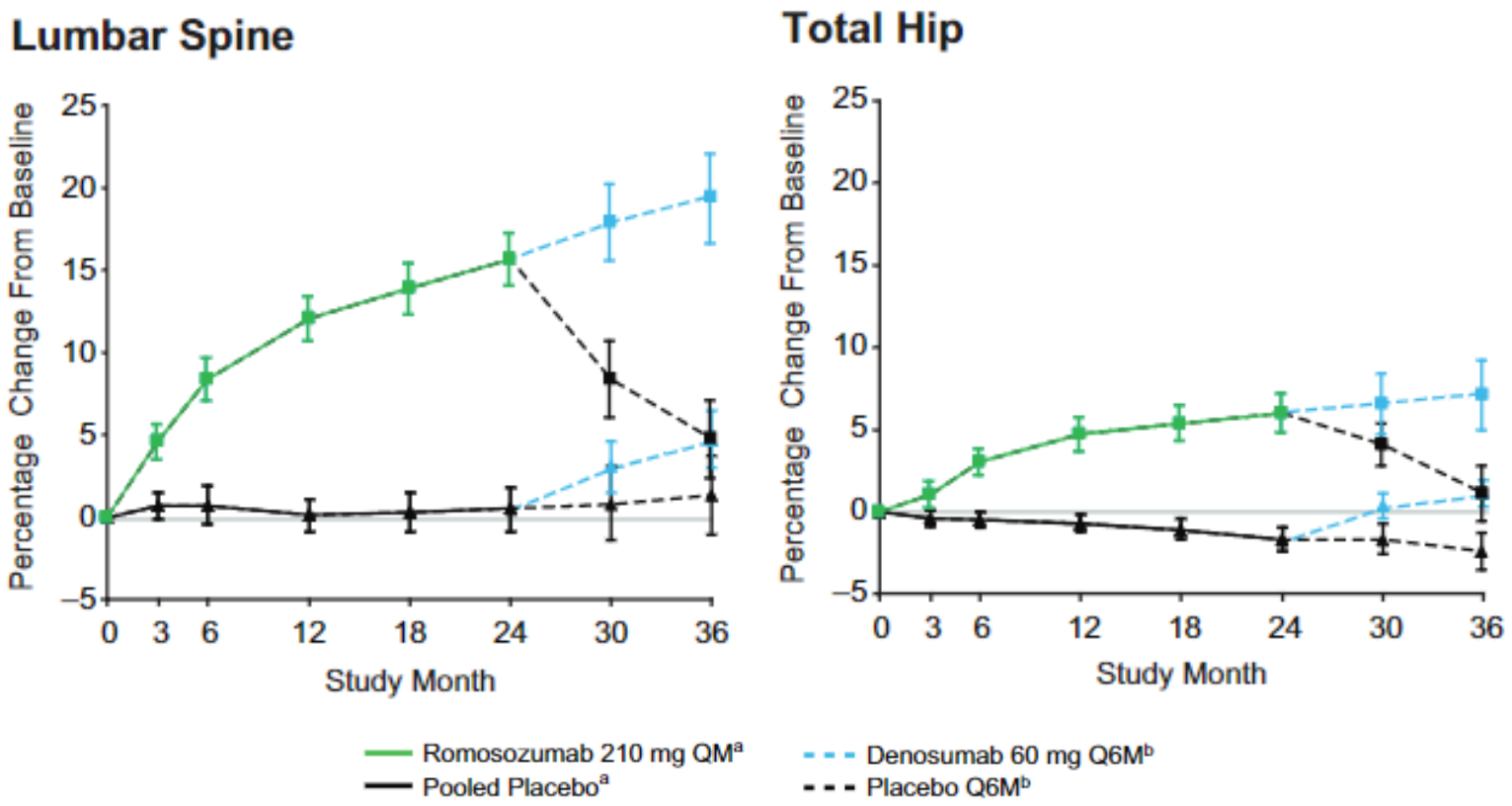
Time dependency of re-fracture after index fracture
Dashed line is risk of first MOF in whole population for a ♀ 75 years at baseline

MOF= major osteoporotic fracture

Johansson. Osteoporos Int 2017; 28: 775-80

Need for follow-on treatment after discontinuation of Romosozumab

After discontinuation of Romosozumab, BMD returns to pretreatment levels with placebo



Phase 2 RCT in women aged 55 to 85 years
T-score ≤ –2.0 at LS, total hip or FN and ≥ –3.5 at each of these sites

McClung. J Bone Miner Res 2018; 33: 1397-1406

Overview

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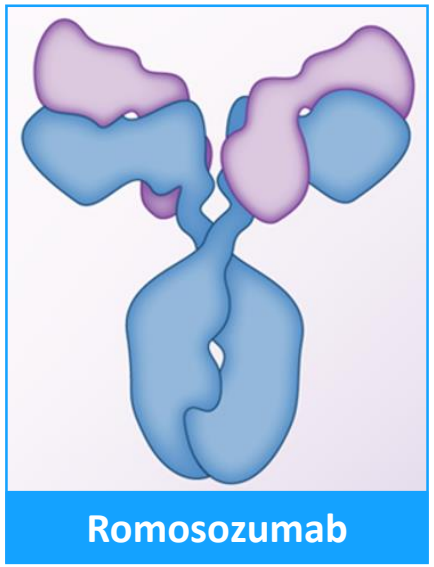
⑤ Conclusion

Romosozumab (Evenity®) ▼



- Monoclonal antibody that uncouples bone formation and resorption
- Quickly and strongly increases BMD and decreases fracture risk
- Superior to Alendronate in treatment-naive (ARCH) and Teriparatide in pre-treated (STRUCTURE) patients

▼ - this medicine is subject to additional monitoring

Summary of anabolic treatment in Belgium

	Romosozumab	Teriparatide
Indication	Treatment of severe osteoporosis in postmenopausal women at high risk of fracture	• Treatment of osteoporosis in postmenopausal women and men at increased risk of fracture • Treatment of osteoporosis associated with sustained systemic GC use in women and men at increased risk for fracture
Contraindication	• Hypocalcaemia • History of myocardial infarction or stroke	• Pre-existing hypercalcaemia • Severe renal impairment • Metabolic bone diseases (incl. hyperparathyroidism and Paget's disease of bone) other than primary osteoporosis or GIOP • Unexplained elevations of alkaline phosphatase • Prior external beam or implant radiation R/ to the skeleton • Skeletal malignancies or bone metastases
Posology	210 mg 1x per month SC	20 µg 1x per day SC
Duration	12 months	9 months + 9 months (when ↗ T-score after 9 months)
First line	Yes	No
Second line	Yes: after previous R/ with bisphosphonates, Dmab or SERM	Yes: after previous R/ with bisphopshonate or SERM for ≥ 12 months
Reimbursement criteria	1. MOF (defined by 2020 BBC guidelines) within last 24 months 2. T-score ≤ -2.5 or a moderate VFx	1. 2 moderate VFx (1 while on-treatment with BP or SERM) 2. T-score ≤ -2.5
Follow-on treatment	Bisphosphonates or denosumab	Bisphosphonates or denosumab
Allowed physicians	Rheumatology, physiotherapy, internal medicine (incl. geriatrician)	Rheumatology, physiotherapy, internal medicine (incl. geriatrician)