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G.U.I.D.A.
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Centro Congressi Unione Industriali
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G. IOLASCON

Romosozumab: potenza e rapidità d'azione nella terapia della fragilità scheletrica

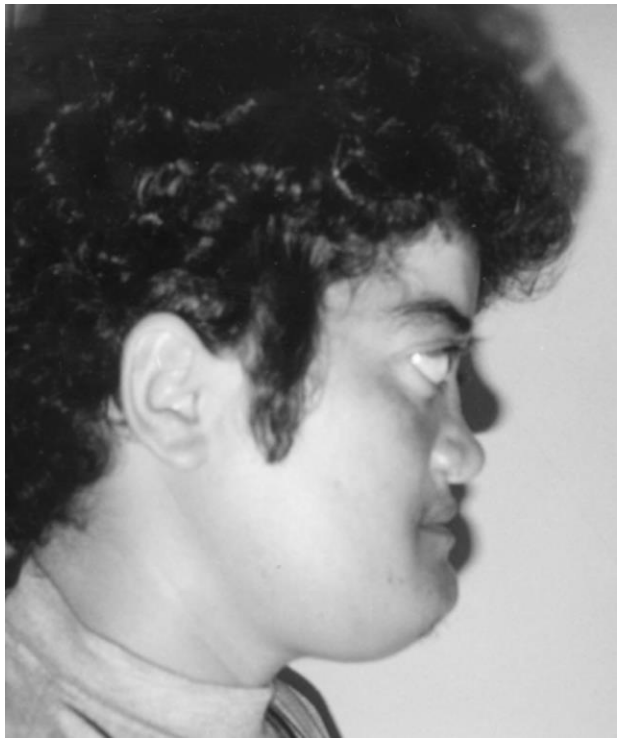
State of the art

- The past 20 years have seen marked developments in medical interventions for osteoporosis significantly reducing incidence of osteoporotic fractures
- For example, bisphosphonates decrease all fractures by 35%, non-vertebral fractures by ~25% and vertebral fractures by 50%
- Denosumab has been shown in a trial to reduce fracture rates after 10 years of treatment
- Teriaparatide significantly reduces vertebral fragility fractures risk (0.31)
- Starting with anabolic and then continuing with antiresorptive is the best treatment sequence, so it could be the preferred option in patients with a very high risk of fracture

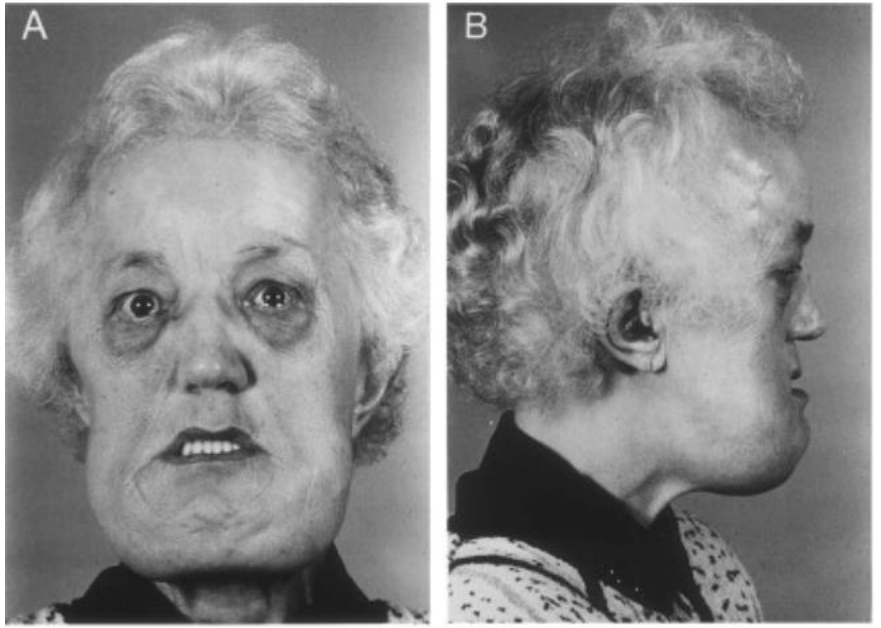
Issues

- Approved treatments (BPs,Dmab, Teriparatide) are widely available, but their use is restricted by reimbursement policies and guidelines
- Compliance and persistence to treatments are poor
- Antiresorptive therapy we can only increase bone mineral density up to a certain point; indeed, owing to a coupling between bone formation and resorption, there is no possibility of “de novo” synthesis of bone by osteoblasts
- Teriparatide increases also osteoclastic activity after a certain period; this foretells the closure of the so-called anabolic window, thus limiting further accrual of bone mass

SOST-related sclerosing bone dysplasia

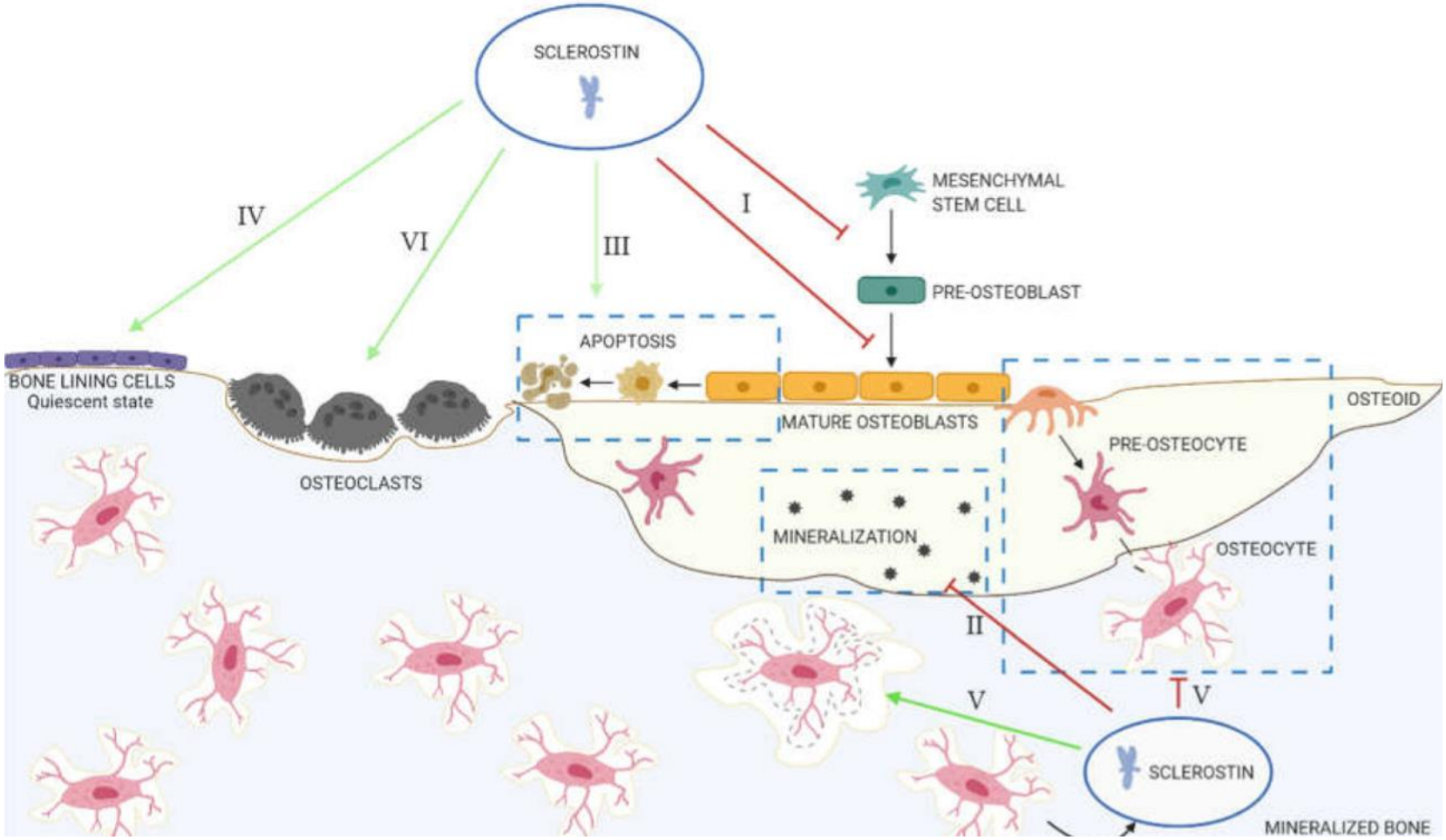


- SOST-related sclerosing bone dysplasias include Sclerosteosis and van Buchem disease, both disorders of progressive bone overgrowth due to increased bone formation
- Sclerosteosis and van Buchem disease are clinically and radiographically similar disorders that are caused by pathogenic variants in SOST but differ in severity and in type of molecular genetic variants



actions of sclerostin in the bone

- Inhibition of proliferation and differentiation of osteoprogenitor/pre-osteoblastic cells, as well as decreased activation of mature osteoblasts;
- decreased mineralization;
- increased apoptosis of the osteogenic cells;
- maintenance of bone lining cells in their quiescent state;
- regulation of osteocyte maturation and osteocytic osteolysis;
- stimulation of bone resorption.

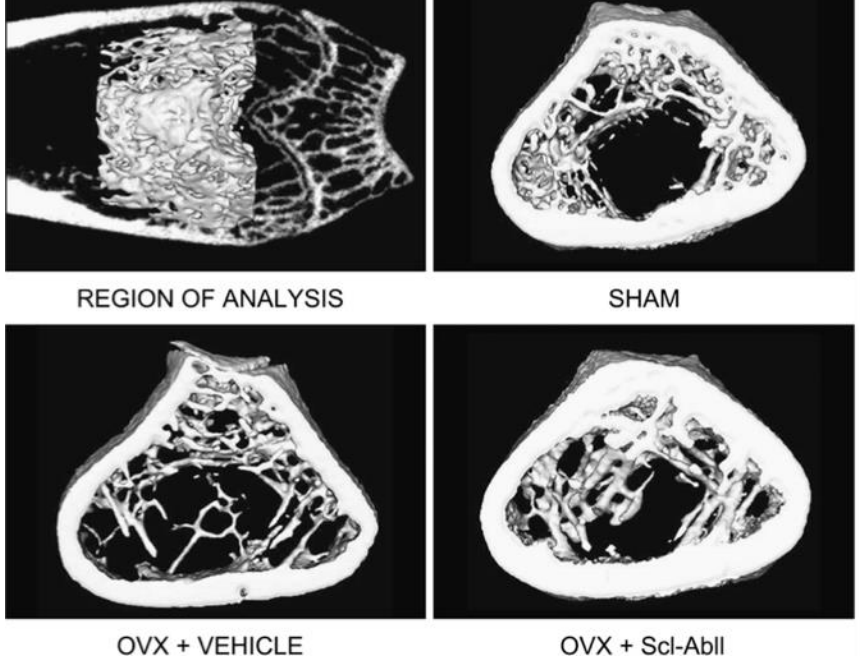


De Marè 2020

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 24, Number 4, 2009
Published online on December 1, 2008; doi: 10.1359/JBMR.081206

Sclerostin Antibody Treatment Increases Bone Formation, Bone Mass, and Bone Strength in a Rat Model of Postmenopausal Osteoporosis*

Xiaodong Li,[1,2] Michael S Ominsky,[1,2] Kelly S Warmington,[1,2] Sean Morony,[1] Jianhua Gong,[1] Jin Cao,[1] Yongming Gao,[1] Victoria Shalhoub,[1] Barbara Tipton,[3] Raj Haldankar,[3] Qing Chen,[3] Aaron Winters,[3] Tom Boone,[3] Zhaopo Geng,[1] Qing-Tian Niu,[1] Hua Zhu Ke,[1] Paul J Kostenuik,[1] W Scott Simonet,[1] David L Lacey,[1] and Chris Paszty[1]

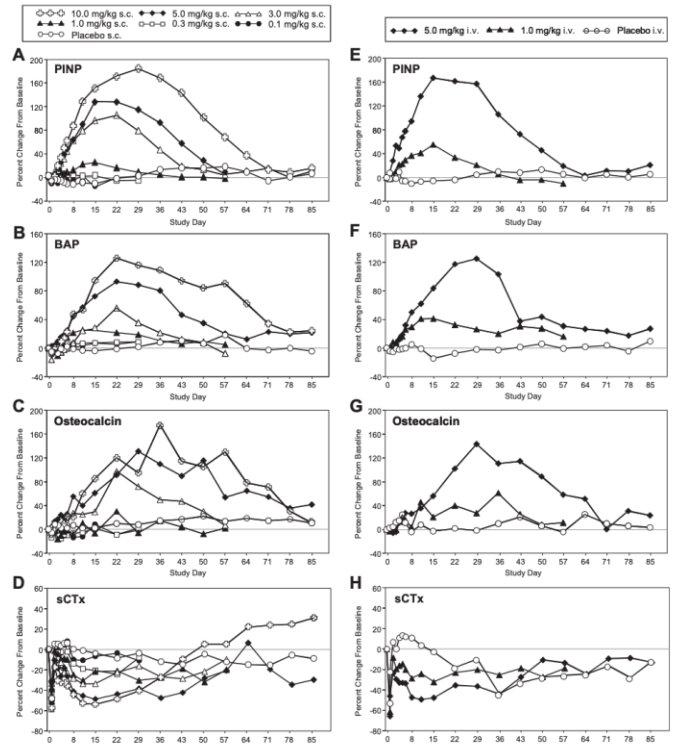


CLINICAL TRIALS

JBMR

Single-Dose, Placebo-Controlled, Randomized Study of AMG 785, a Sclerostin Monoclonal Antibody

Desmond Padhi, Graham Jang, Brian Stouch, Liang Fang, and Edward Posvar
Amgen Inc., Thousand Oaks, CA, USA

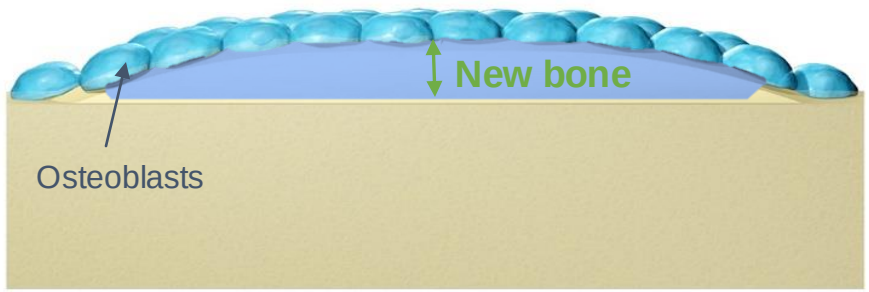


Primary effects of romosozumab and PTH receptor agonists on bone formation [1–3]

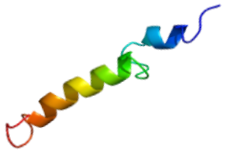
Romosozumab

Modeling-based bone formation[1–3]

- Osteoblasts build bone on nonresorbed surfaces, resulting in immediate gains in BMD
- This effect does not increase resorption space

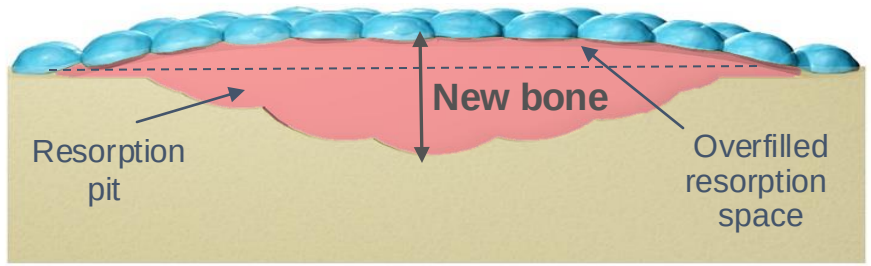


PTH receptor agonists



Remodeling-based bone formation[2,3*]

- PTH receptor agonists increase resorption space in cortical and trabecular bone by activating remodeling
- Osteoblasts must then refill resorption spaces before net BMD gains can occur by overfilling[†]

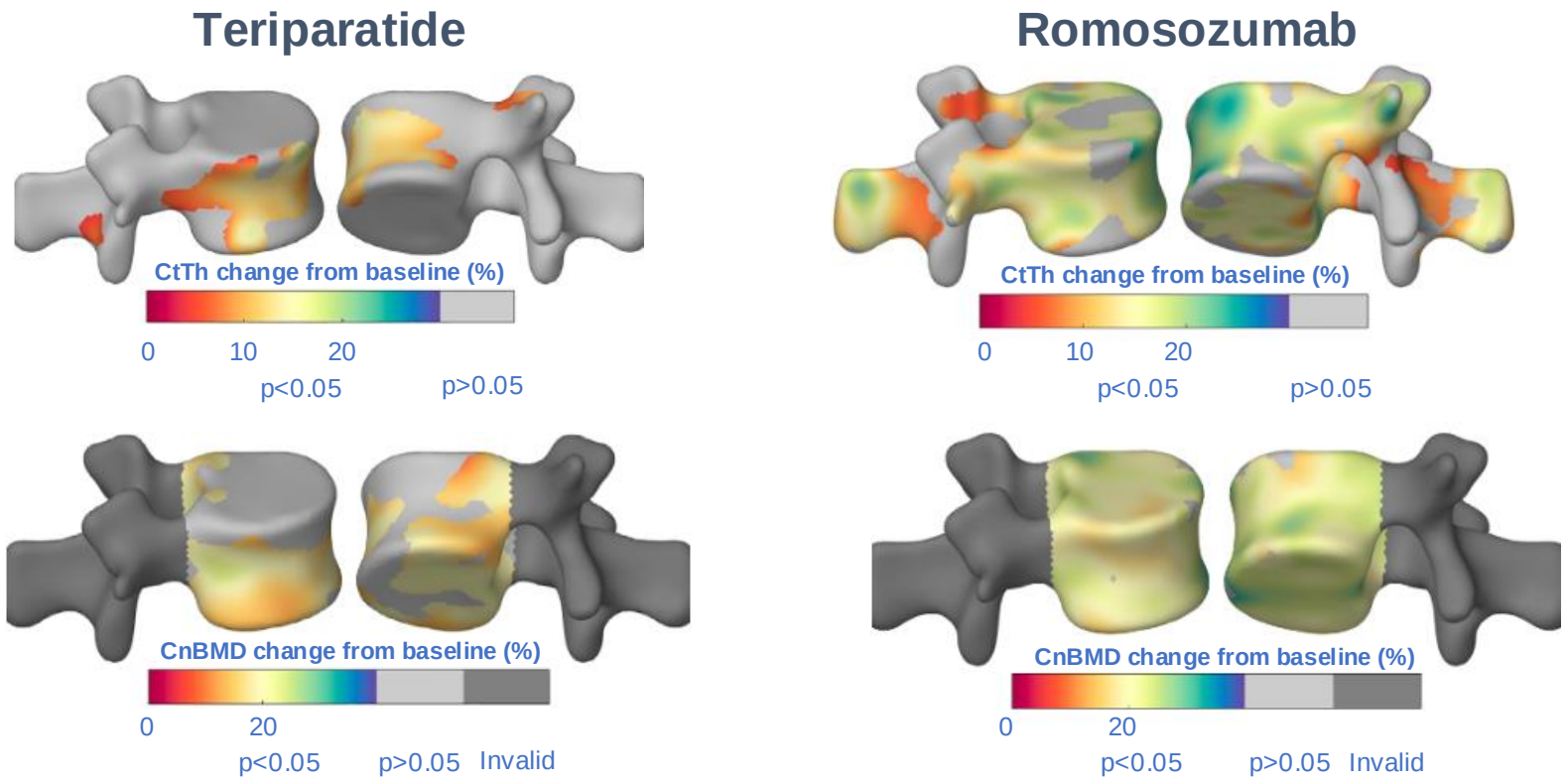


In the EU, romosozumab is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.
Please refer to your local Prescribing Information or Summary of Product Characteristics for more information.

*Requires relatively greater osteoblast output to achieve net BMD gains compared with modeling-based bone formation. [†]Bone formation occurs as long as the floor of the resorption site is intact, which is less likely in osteoporotic bone. BMD, bone mineral density; PTH, parathyroid hormone. 1. Ominsky MS, et al. Bone. 2017;96:63–75; 2. Ominsky MS, et al. Bone. 2015;81:380–391; 3. Ominsky MS, et al. J Bone Miner Res. 2014;29:1424–1430. Upper left image reproduced with permission from FDA. Background information for bone, reproductive and urologic drugs advisory committee. 16 January 2019. Biologics license application for romosozumab. https://www.fda.gov/media/121255/download. Accessed on April 2023. Upper right image reproduced with permission from BioCrick. Parathyroid hormone (1-34), bovine. https://www.biocrick.com/Parathyroid-Hormone-1-34-bovine-BCC1040.html/ Accessed on April 2023. Bottom images adapted with permission from Ke HZ, et al. Endocr Rev. 2012;33:747–783.

Romosozumab enhances vertebral bone structure in women with low bone density

Change from baseline after 12 months of treatment measured by cortical bone mapping[1]



Data were analysed from a Phase II sub-study, which enrolled patients with a low BMD (an LS, TH or FN T-score of ≤–2.0 and ≥–3.5 at each of the three sites).[2]
CnBMD, cancellous bone mineral density; CtTh, cortical thickness.

1. Poole KE, et al. J Bone Miner Res. 2022;37:256–264; 2. McClung MR, et al. N Engl J Med. 2014;370:412–420.

Overview of the Romosozumab Clinical Programme*

PHASE II

Efficacy and safety vs alendronate, teriparatide and placebo in postmenopausal women with low BMD (N = 419)

BRIDGE

Placebo-controlled BMD study in men with osteoporosis (N = 245)

ARCH

Active-comparator fracture study vs alendronate in postmenopausal women with osteoporosis and high risk of fracture (N = 4093

STRUCTURE

Active-comparator BMD study vs teriparatide in postmenopausal women with osteoporosis transitioning from alendronate (N = 436)

FRAME

Placebo-controlled fracture study in postmenopausal women with osteoporosis (N = 7180)

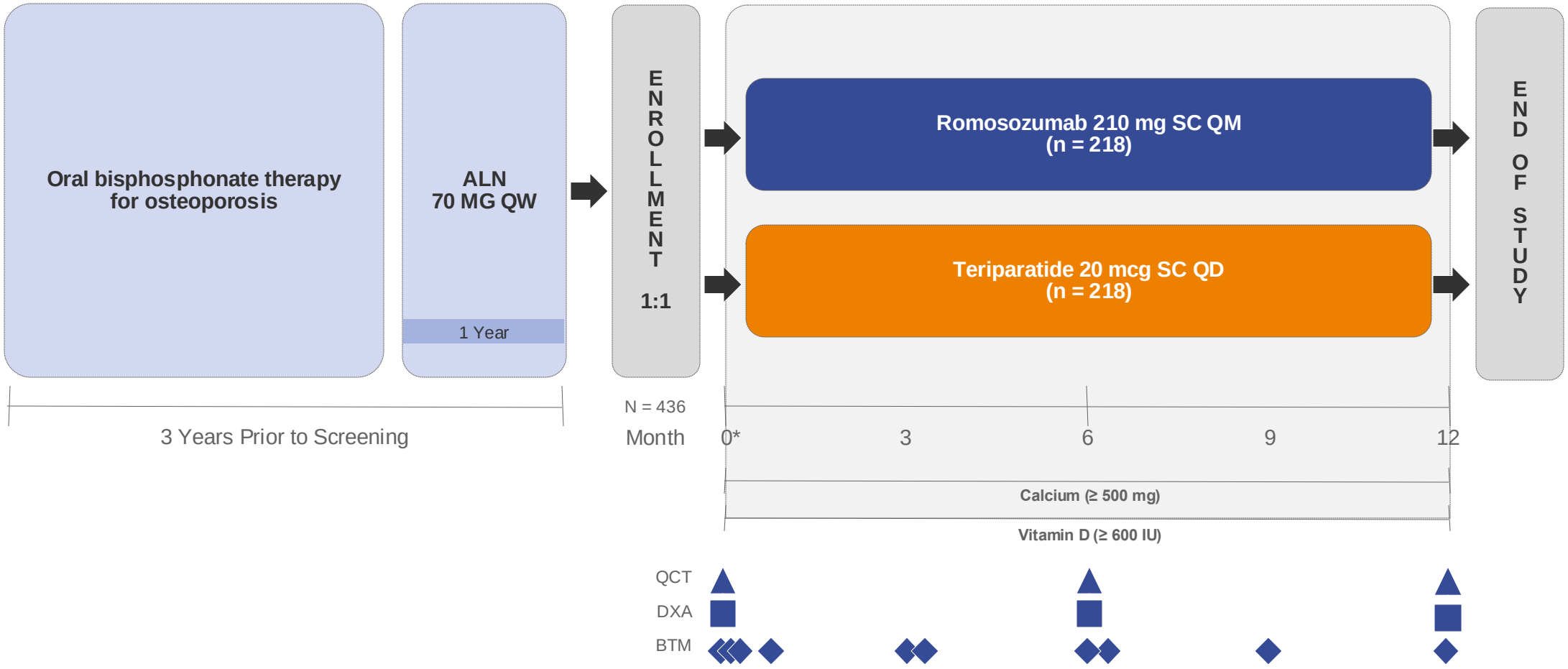
Phase III – STRUCTURE

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

- RCT to assess the effect of treatment with romosozumab 210 mg QM vs teriparatide 20 µg QD for 12 months in 436 PMO women at high risk of fracture previously transitioning from bisphosphonate therapy
- The primary endpoint was percentage change from baseline in areal BMD at the total hip through 12 months
- A post-hoc analysis assessed the relationship between P1NP and BMD in bisphosphonate-treated patients who subsequently received romosozumab or teriparatide

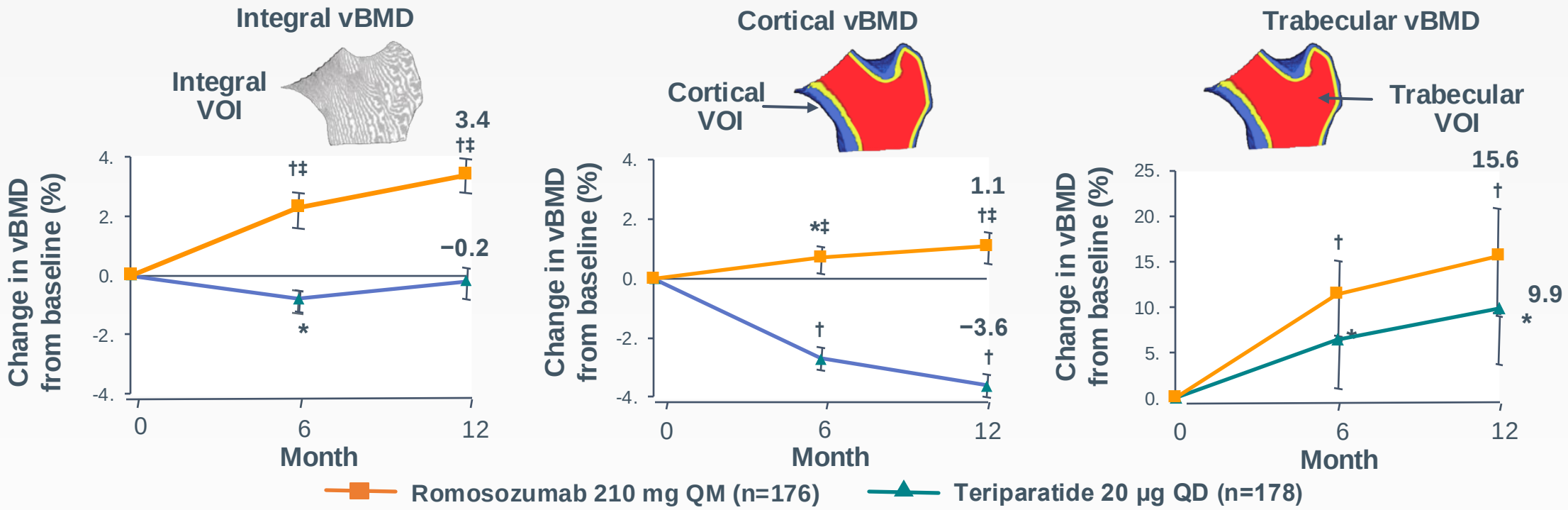
STRUCTURE Phase III Study Design

STudy evaluating effect of **R**omosoz**U**mab **C**ompared with **T**eriparatide in postmenopa**U**sal women with osteoporosis at high risk for fracture p**R**eviously treated with bisphosphonat**E** therapy



STRUCTURE: BMD gains were significantly higher with 12 months of romosozumab vs teriparatide

Change in vBMD at the hip by QCT with romosozumab or teriparatide in postmenopausal women transitioning from bisphosphonate treatment



Images adapted with permission from: Genant HK, et al. Bone. 2013;56:482–488. Graphs adapted with permission from Langdahl BL, et al. Lancet. 2017;390:1585–1594.

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

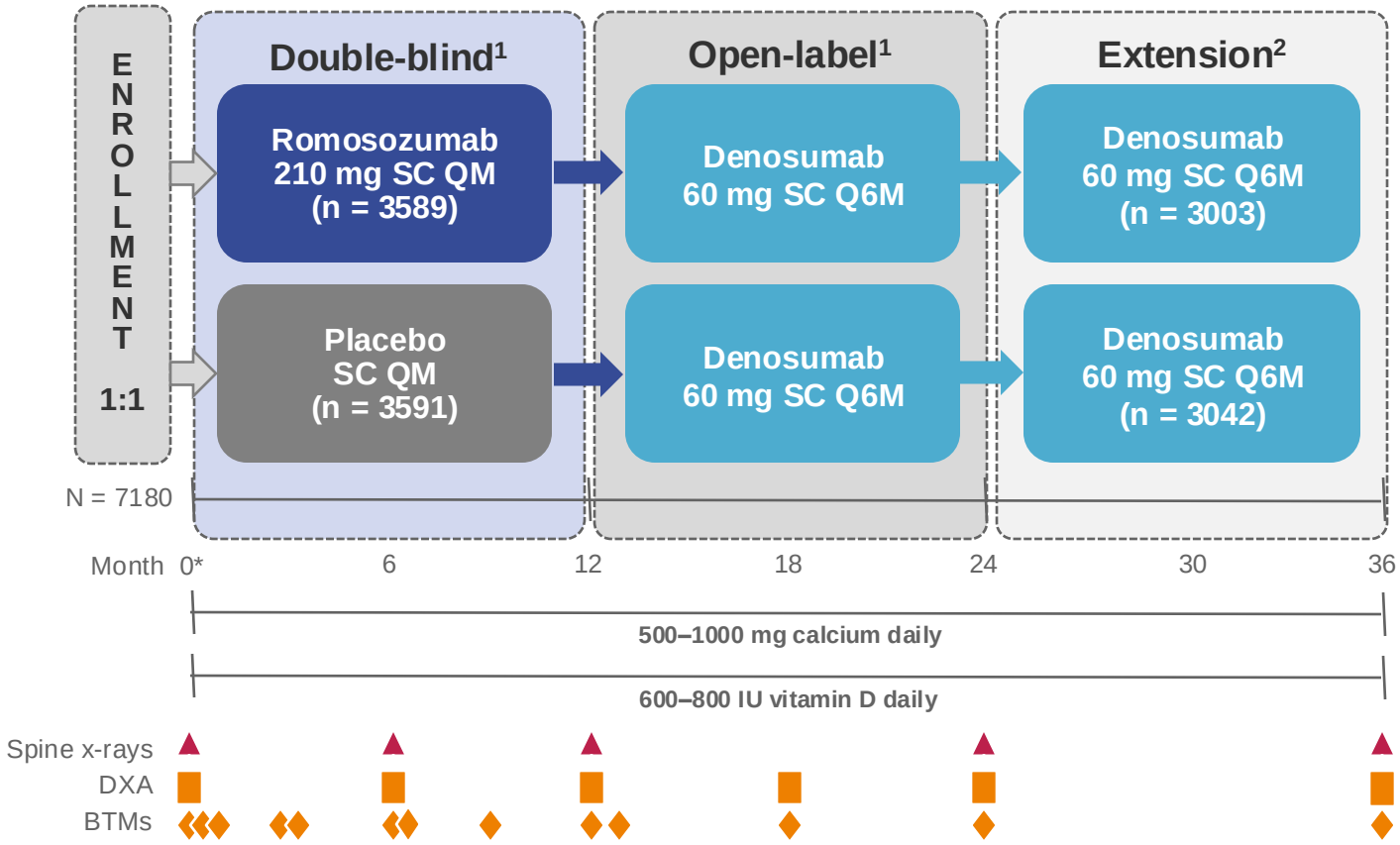
__FRA__cture Study in Postmenopausal Wo__M__en with Ost__E__oporosis (FRAME)

F Cosman, DB Crittenden, JD Adachi, N Binkley, E Czerwinski, S Ferrari, LC Hofbauer, E Lau, EM Lewiecki, A Miyauchi, CAF Zerbini, CE Milmont, L Chen, J Maddox, PD Meisner, C Libanati, A Grauer

N Engl J Med 2016;375:1532–43.

FRAME Phase III Study Design

FRActure study in postmenopausal wo**M**en with ost**E**oporosis



Inclusion[1]

- Postmenopausal women age 55–90 years
- BMD T-score –2.5 to –3.5 at TH or FN

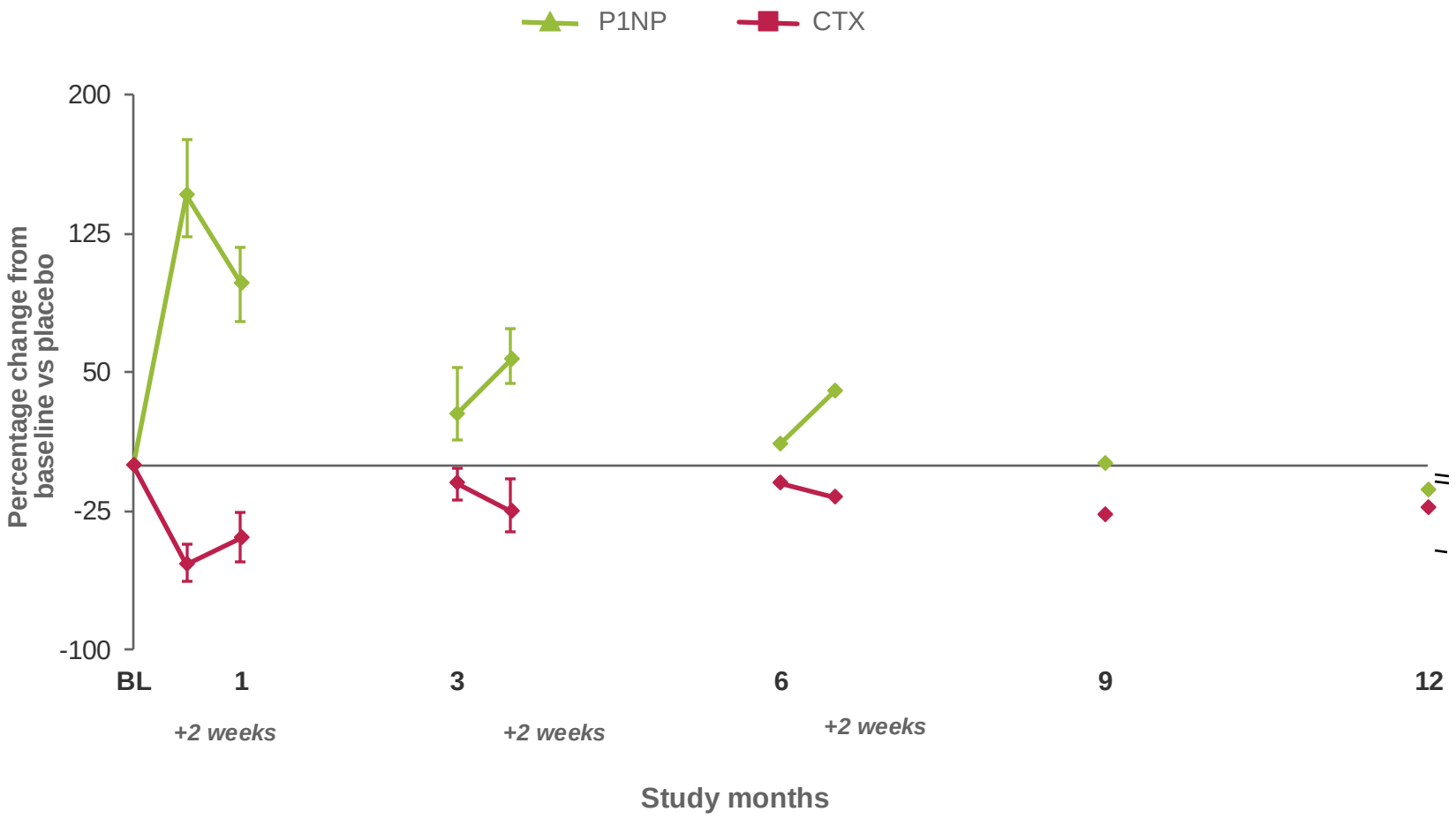
Exclusion[1]

- BMD T-score <–3.5 at TH or FN
- History of hip fracture, or any severe or >2 moderate VFx
- Recent OP therapy (washout period varied by agent)

Co-primary endpoints[1]

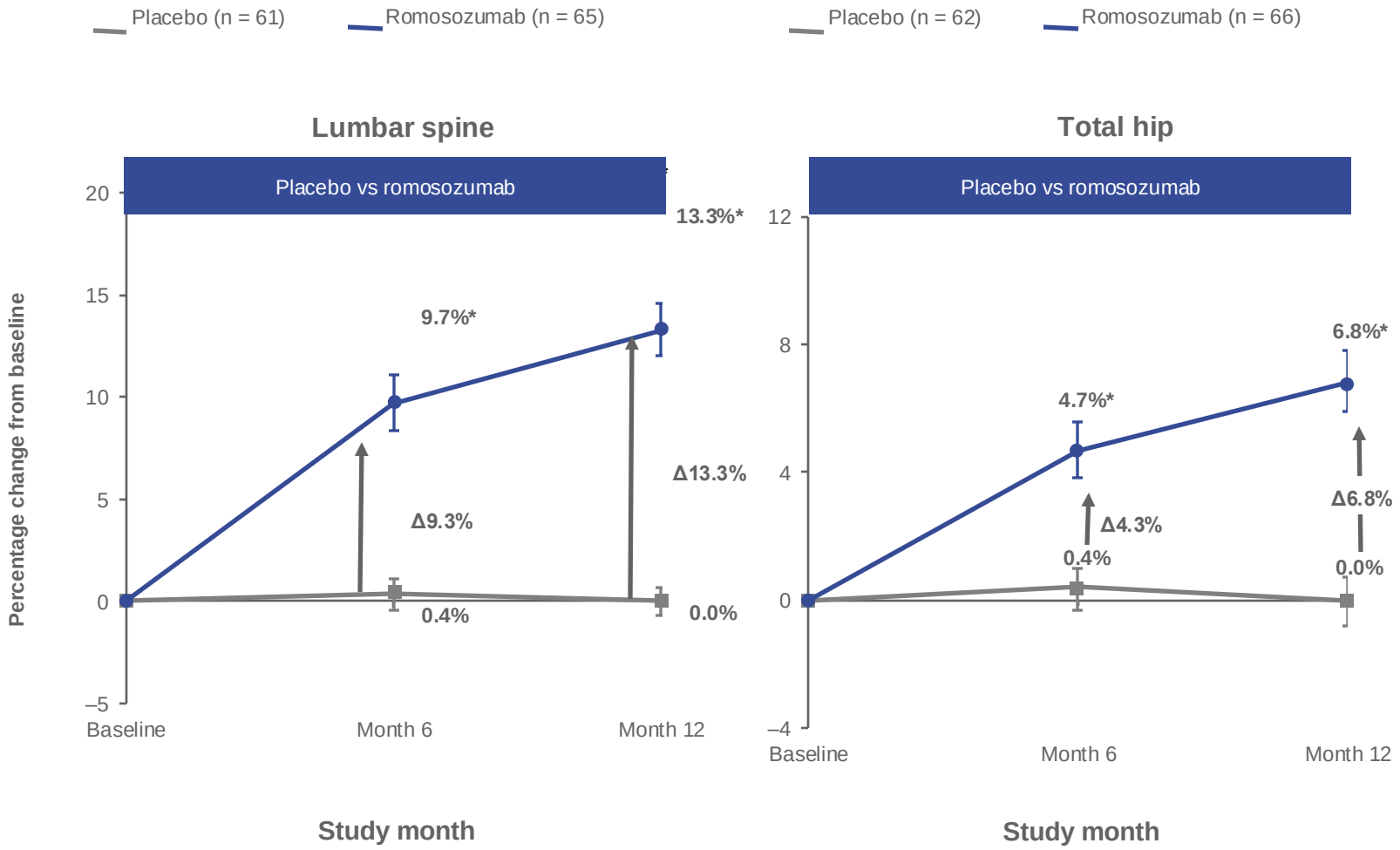
- Subject incidence of new VFx through 12 and 24 months

FRAME: Percentage Change in Serum P1NP and CTX Relative to Placebo Through Month 12



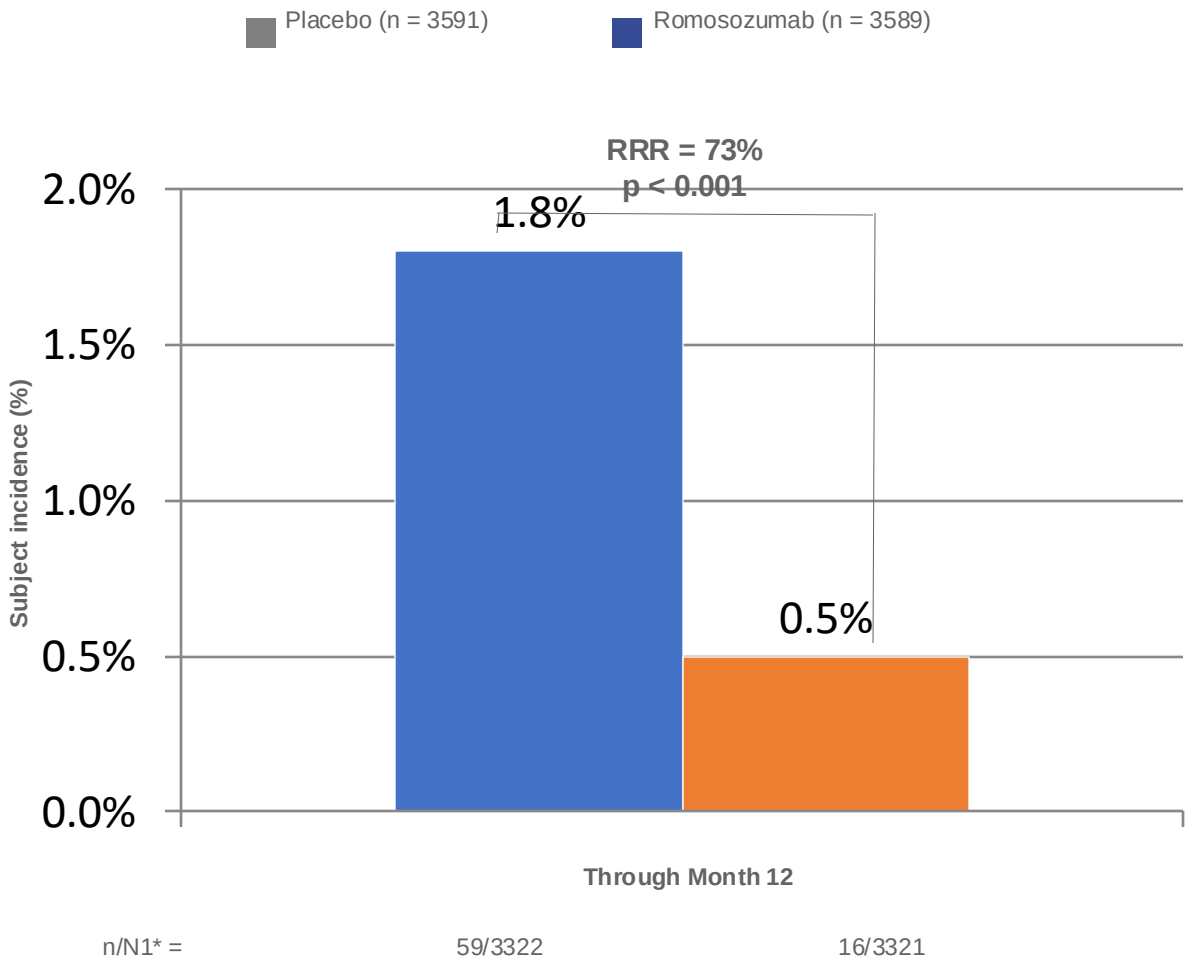
P1NP, romosozumab n = 62, placebo n = 62; CTX, romosozumab n = 61, placebo n = 62. Data presented as bootstrapped median treatment difference and 95% CI.
BL = baseline; CI = confidence interval; CTX = C-terminal telopeptide of type 1 collagen; P1NP = procollagen type 1 N-terminal propeptide.
Adapted from: Cosman F, *et al. N Engl J Med* 2016;375:1532–43.

FRAME
Lumbar Spine and Total Hip BMD
Through Month 12

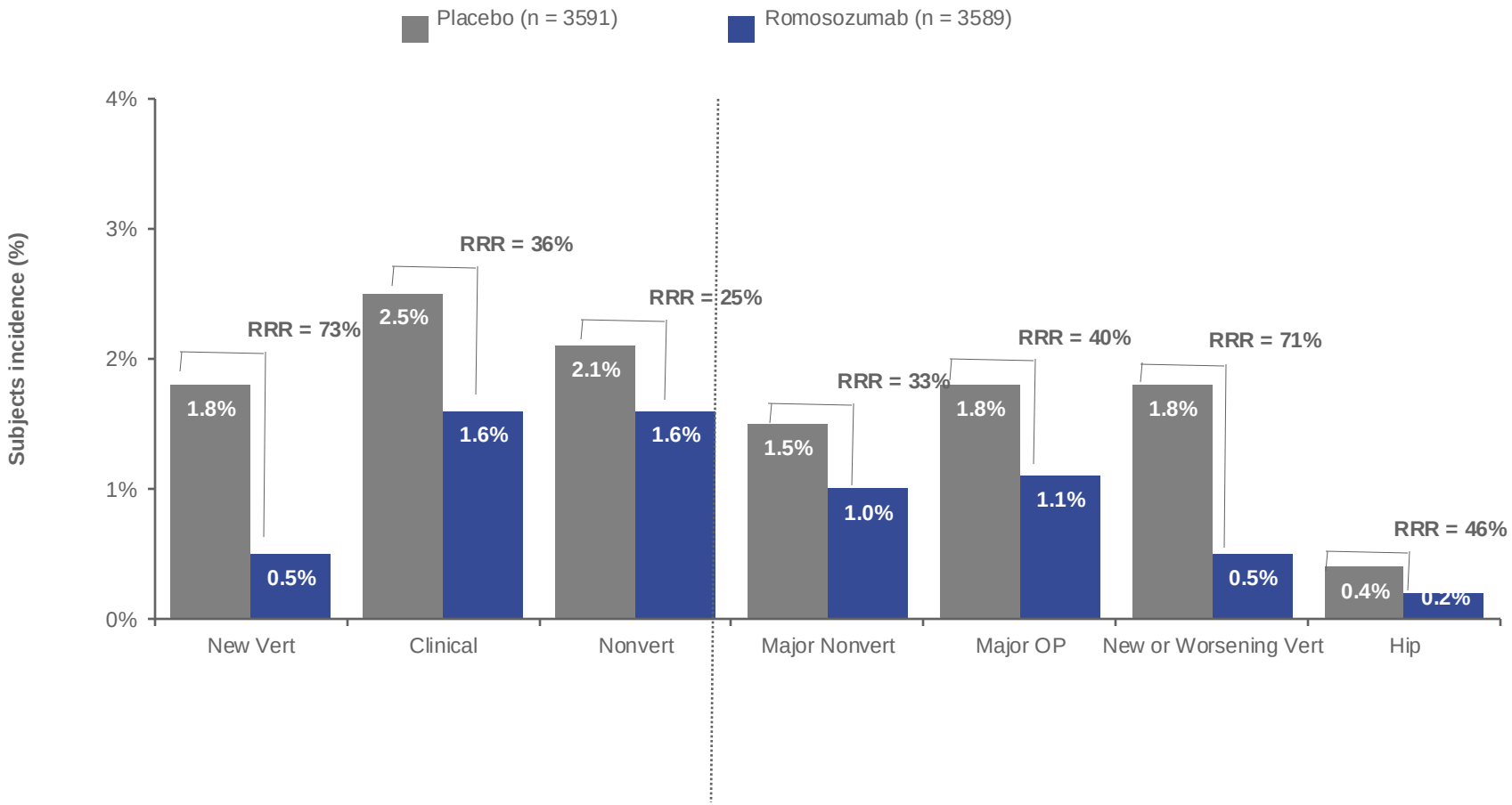


FRAME

Incidence of New Vertebral Fracture Through Month 12

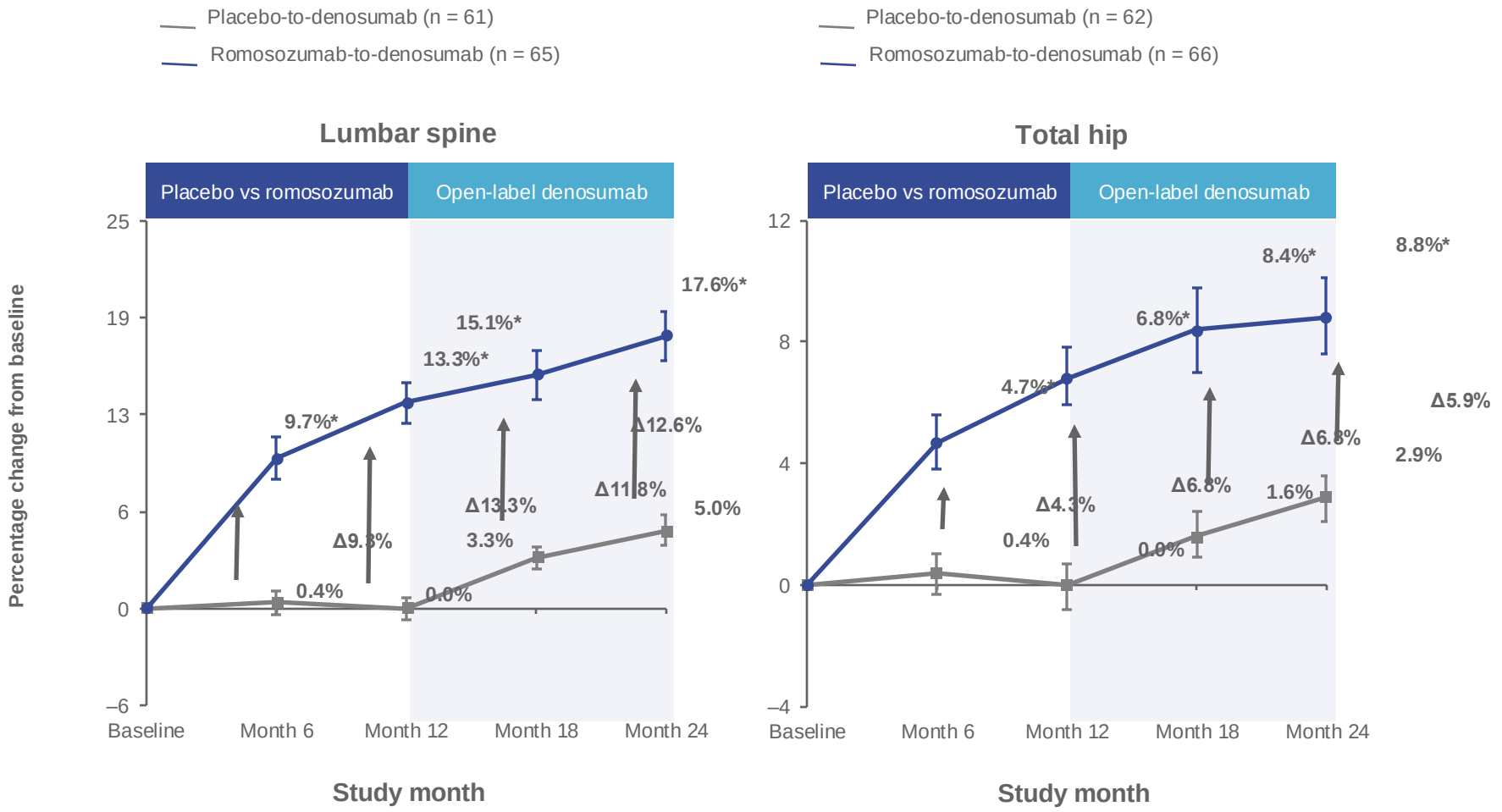


FRAME
Other Key Fracture Endpoints
Through Month 12

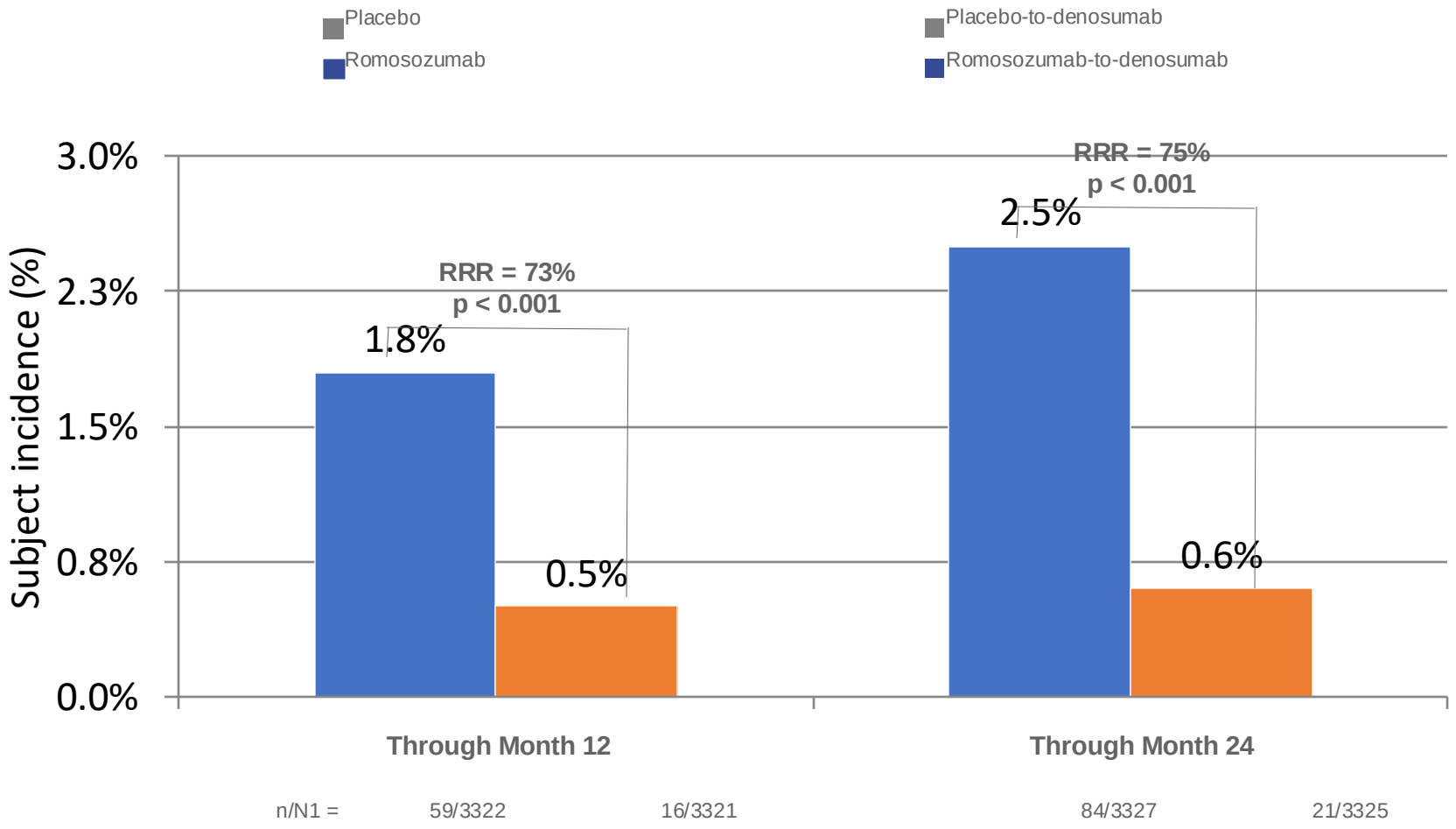


FRAME

Lumbar Spine and Total Hip BMD Through Month 24

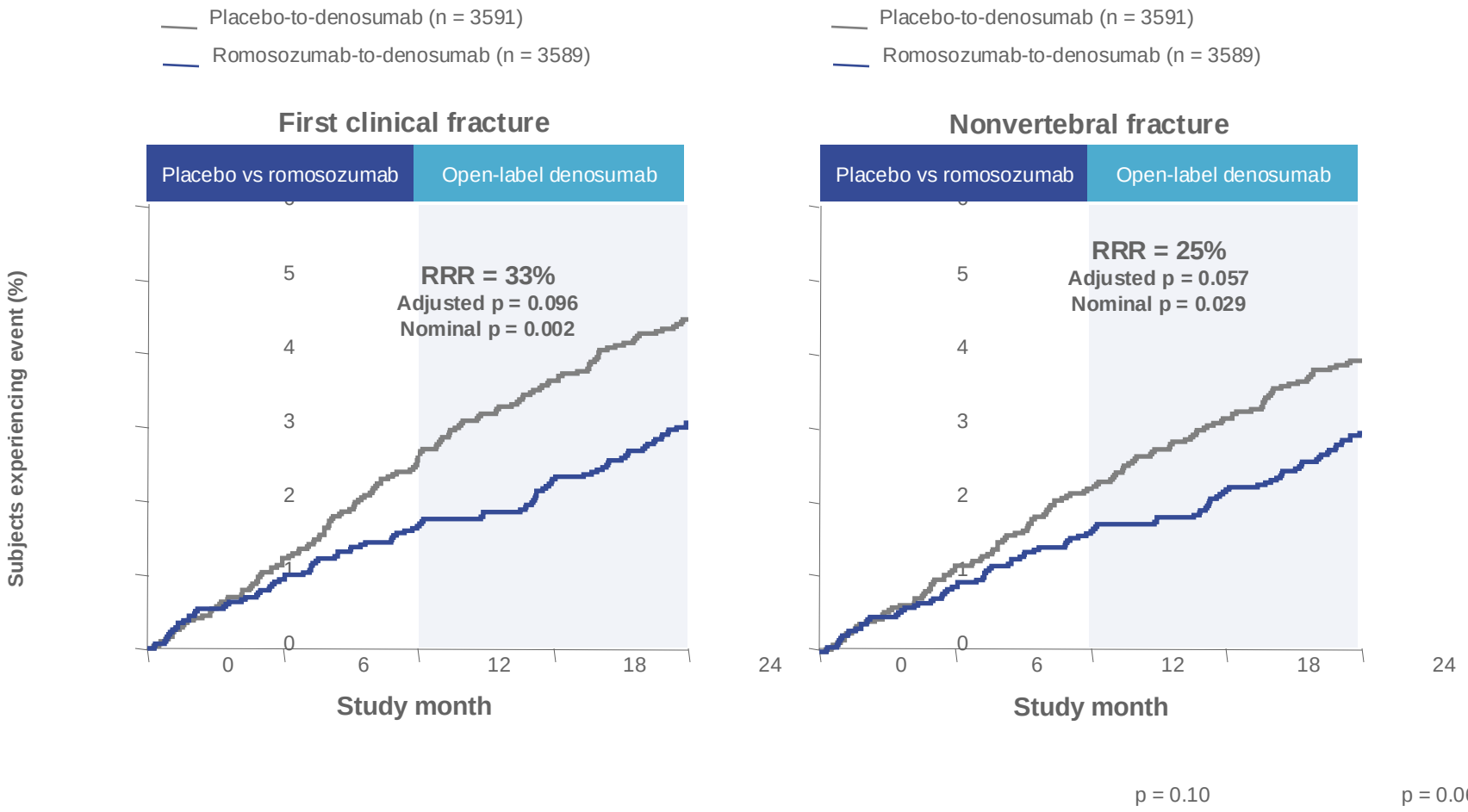


FRAME
Subject Incidence of New Vertebral Fracture Through Month 24



FRAME

Time to First Clinical Fracture and Nonvertebral Fracture Through Month 24



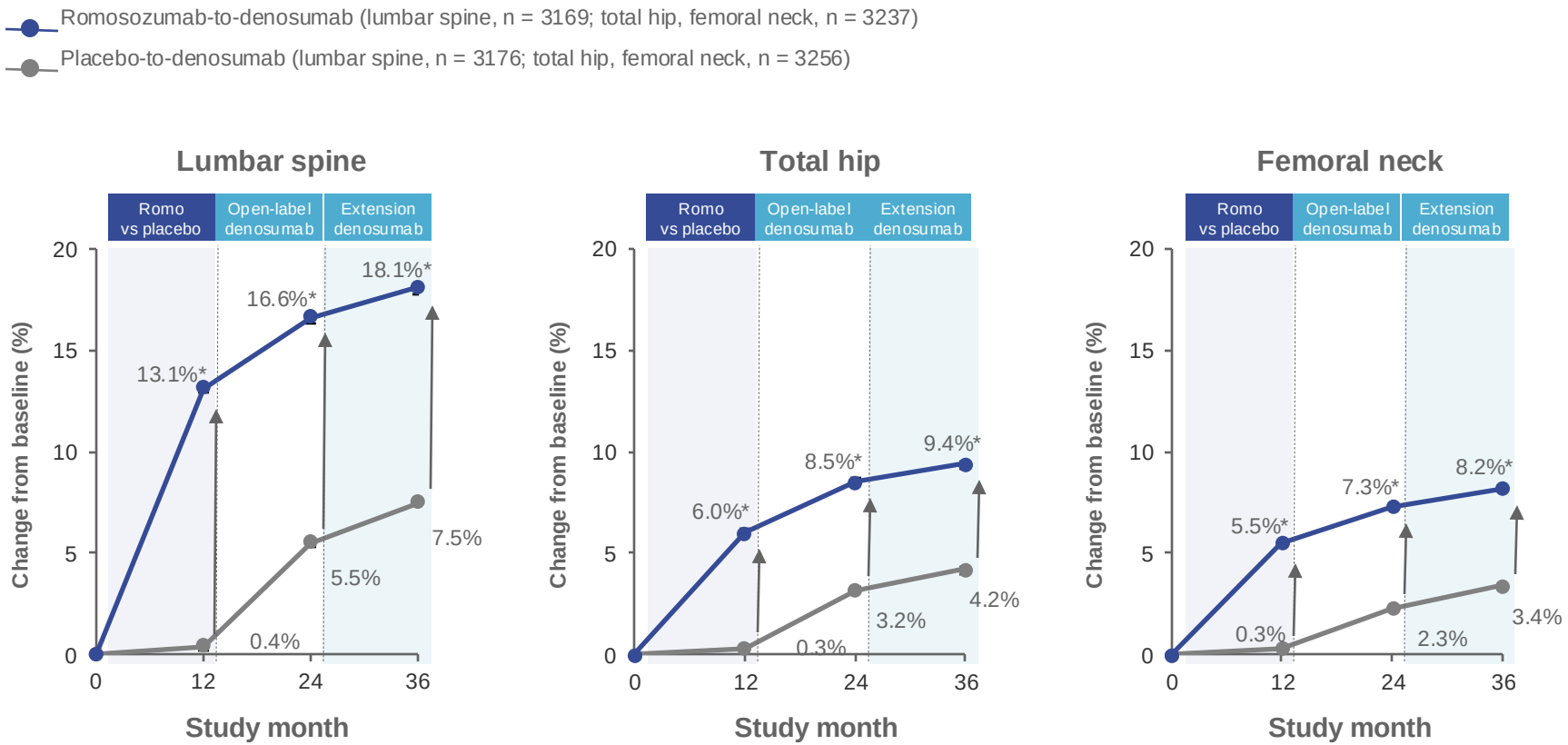
One Year of Romosozumab Followed by Two Years of Denosumab Maintains Fracture Risk Reductions: Results of the FRAME Extension Study

M Lewiecki, RV Dinavahi, M Lazaretti-Castro, PR Ebeling, JD Adachi, A Miyauchi, E Gielen, CE Milmont, C Libanati, A Grauer

J Bone Miner Res 2019;34:419–28.

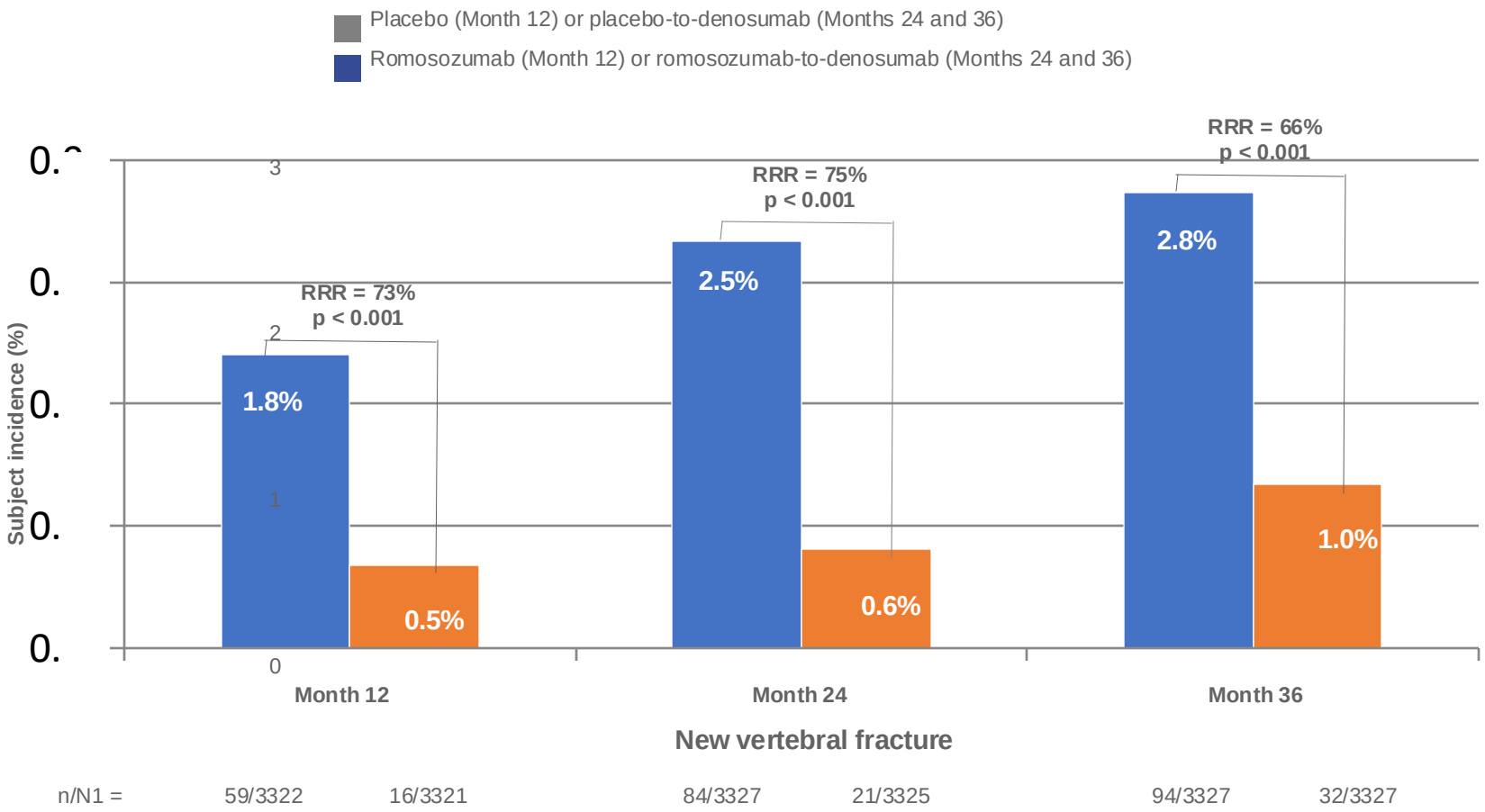
FRAME

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



FRAME

New Vertebral Fracture Incidence Through Month 12, 24 and 36

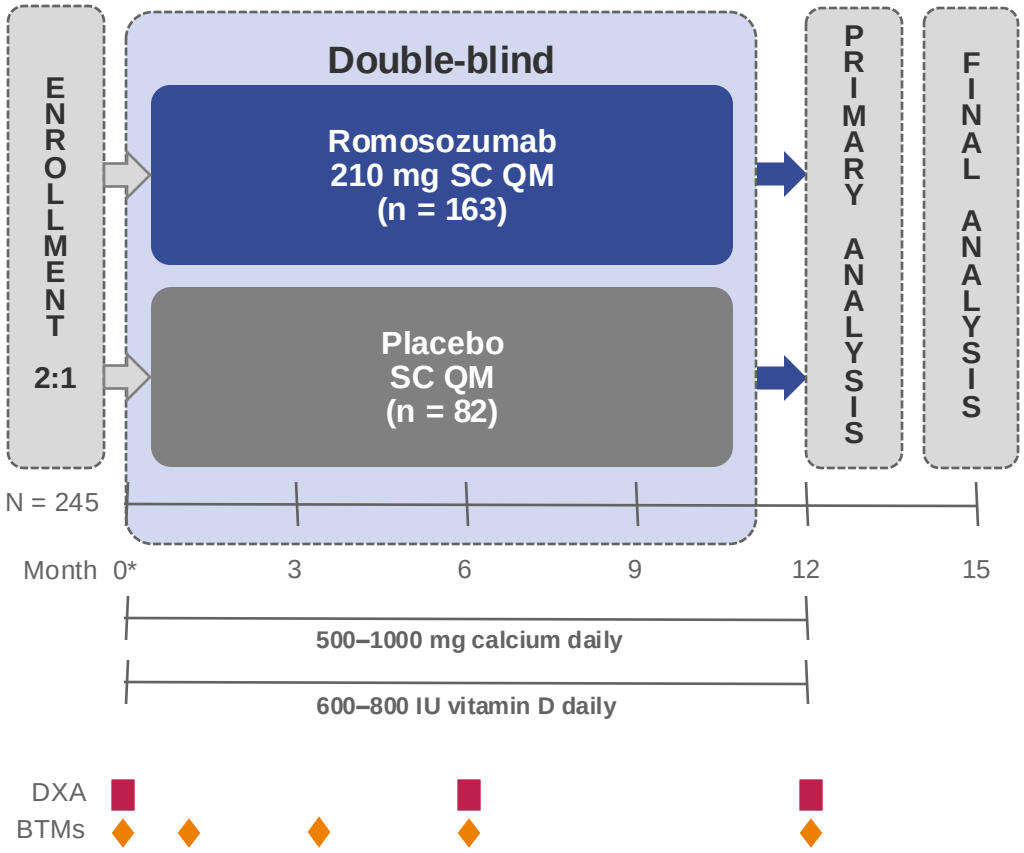


Phase III – BRIDGE

Romosozumab vs placebo in men with osteoporosis

BRIDGE Study Design

PlaceBo-controlled study evaluating the efficacy and safety of romosozumab in treating men with osteoporosis



Inclusion:

- Men age 55–90 years with increased risk of fracture:
  - BMD T-score ≤ –2.5 at lumbar spine, total hip, or femoral neck, or
  - BMD T-score ≤ –1.5 at the lumbar spine, total hip, or femoral neck and a history of fragility nonvertebral fracture or vertebral fracture

Exclusion:

- Subjects with BMD T-score ≤ –3.5 at total hip or femoral neck, or history of hip fractures
- Subjects with recent osteoporosis therapy

Primary endpoints:

- Δ lumbar spine BMD by DXA at 12 months

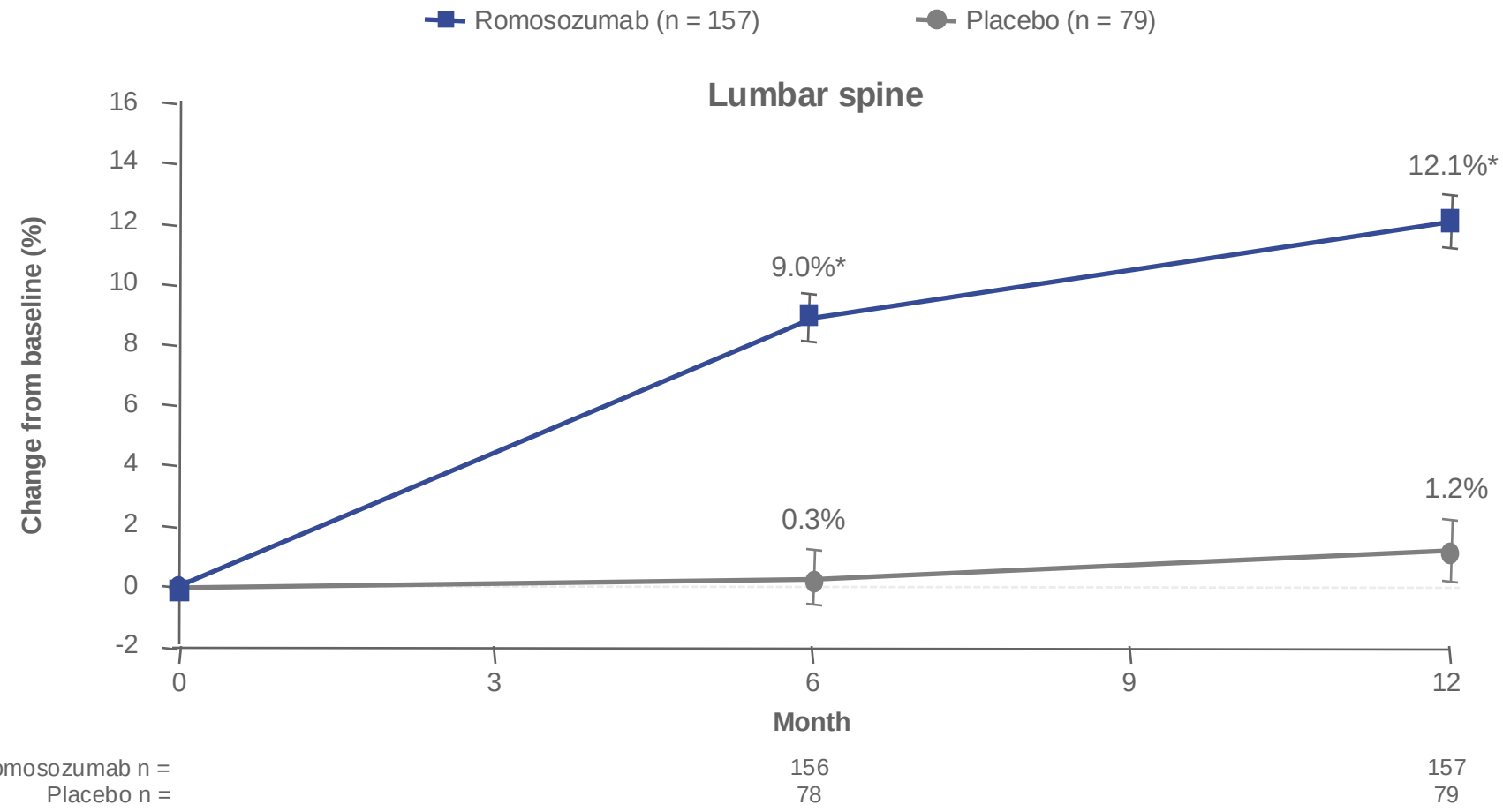
Secondary fracture endpoints:

- Δ BMD by DXA at 12 months (total hip, femoral neck)
- Δ BMD by DXA at 6 months (lumbar spine, total hip, femoral neck)

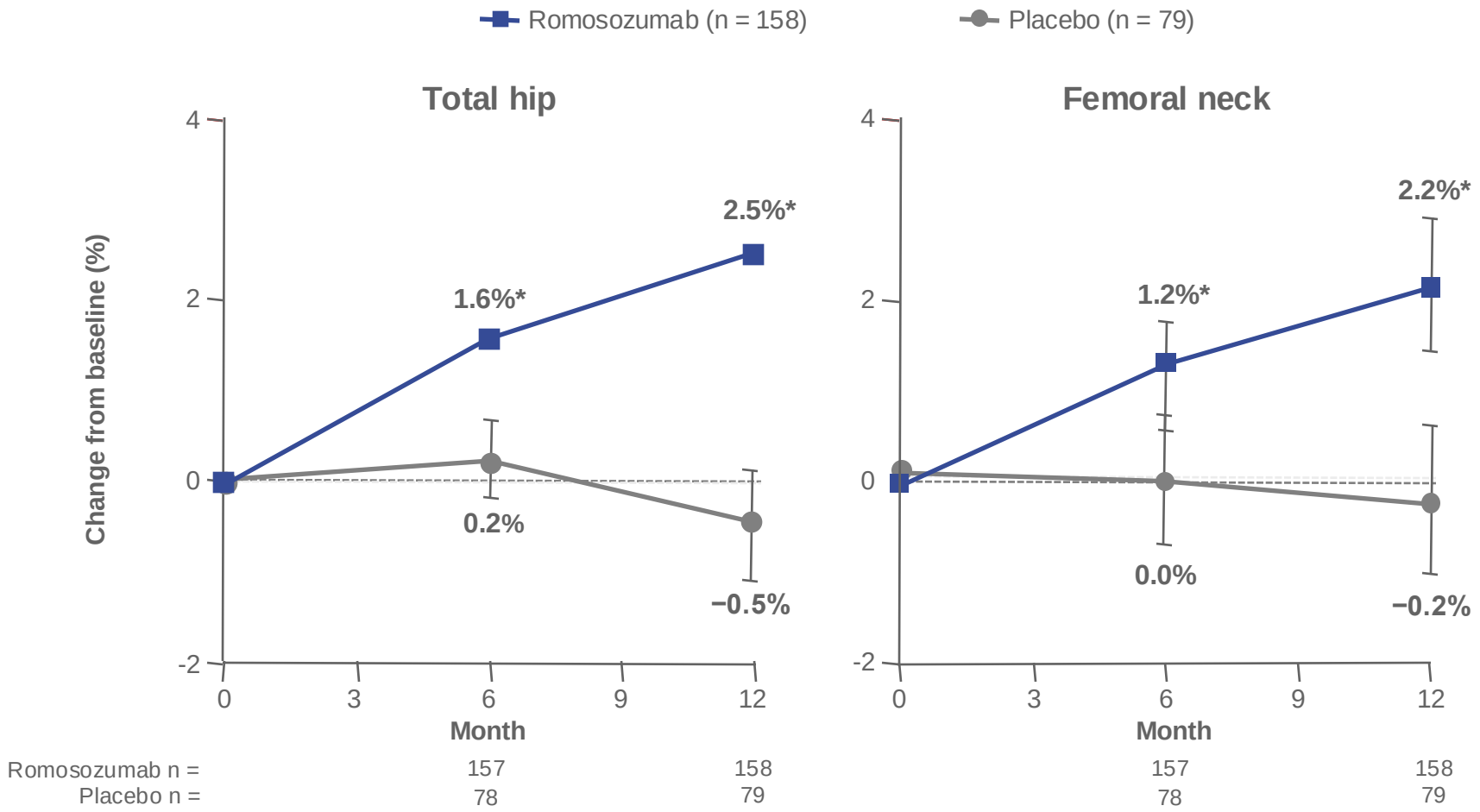
Exploratory endpoints:

- Δ serum BTMs
- Bone histology and histomorphometry parameters

BRIDGE: Percentage Change From Baseline in BMD by Visit



BRIDGE: Percentage Change From Baseline in BMD by Visit



Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

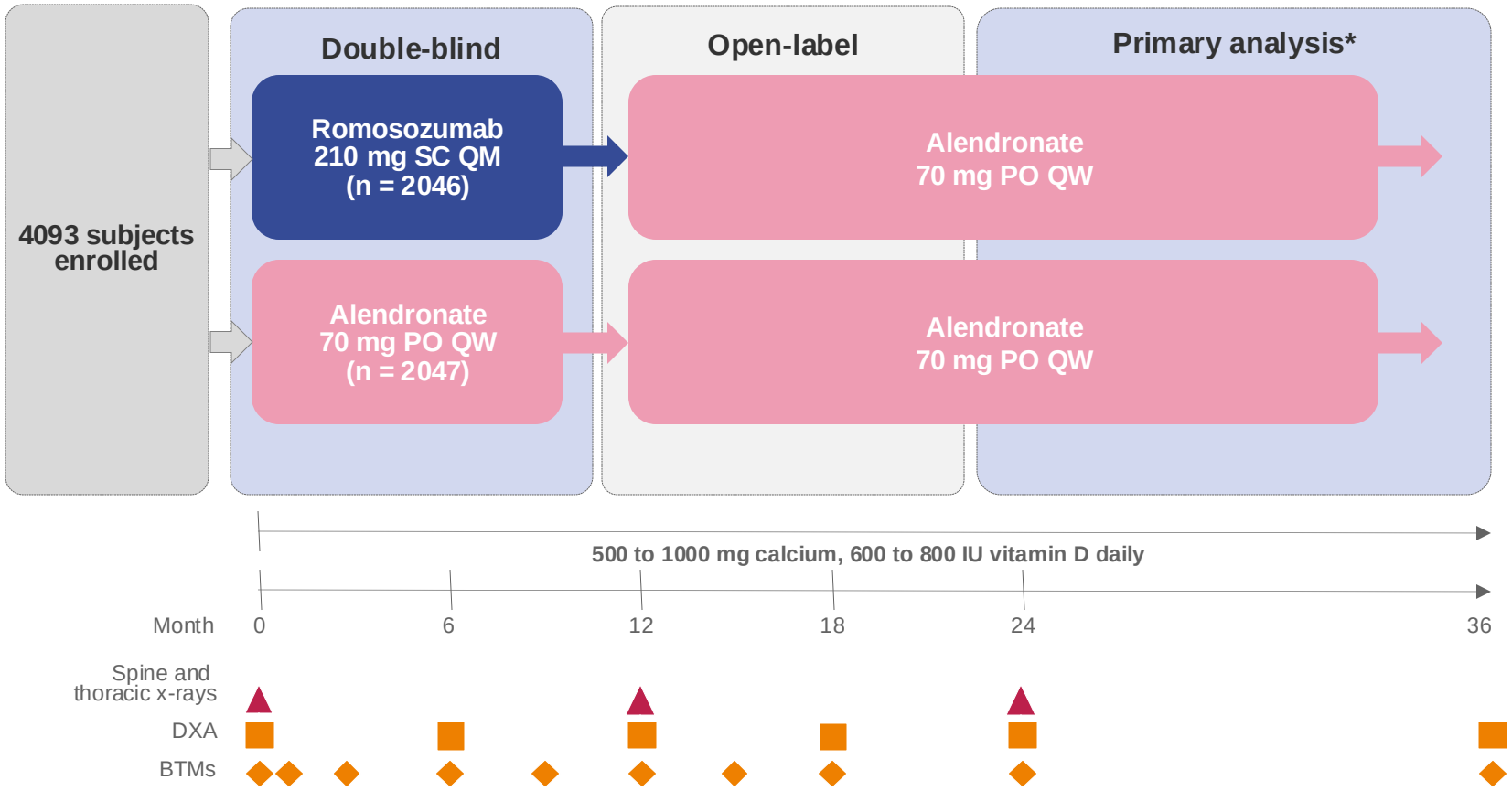
Active-contRolled fraCture study in postmenopausal women with osteoporosis at High risk of fracture (ARCH)

KG Saag, J Petersen, ML Brandi, AC Karaplis, M Lorentzon, T Thomas, J Maddox, M Fan, PD Meisner, A Grauer

N Engl J Med 2017;377:1417–27.

ARCH Phase III Study Design

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

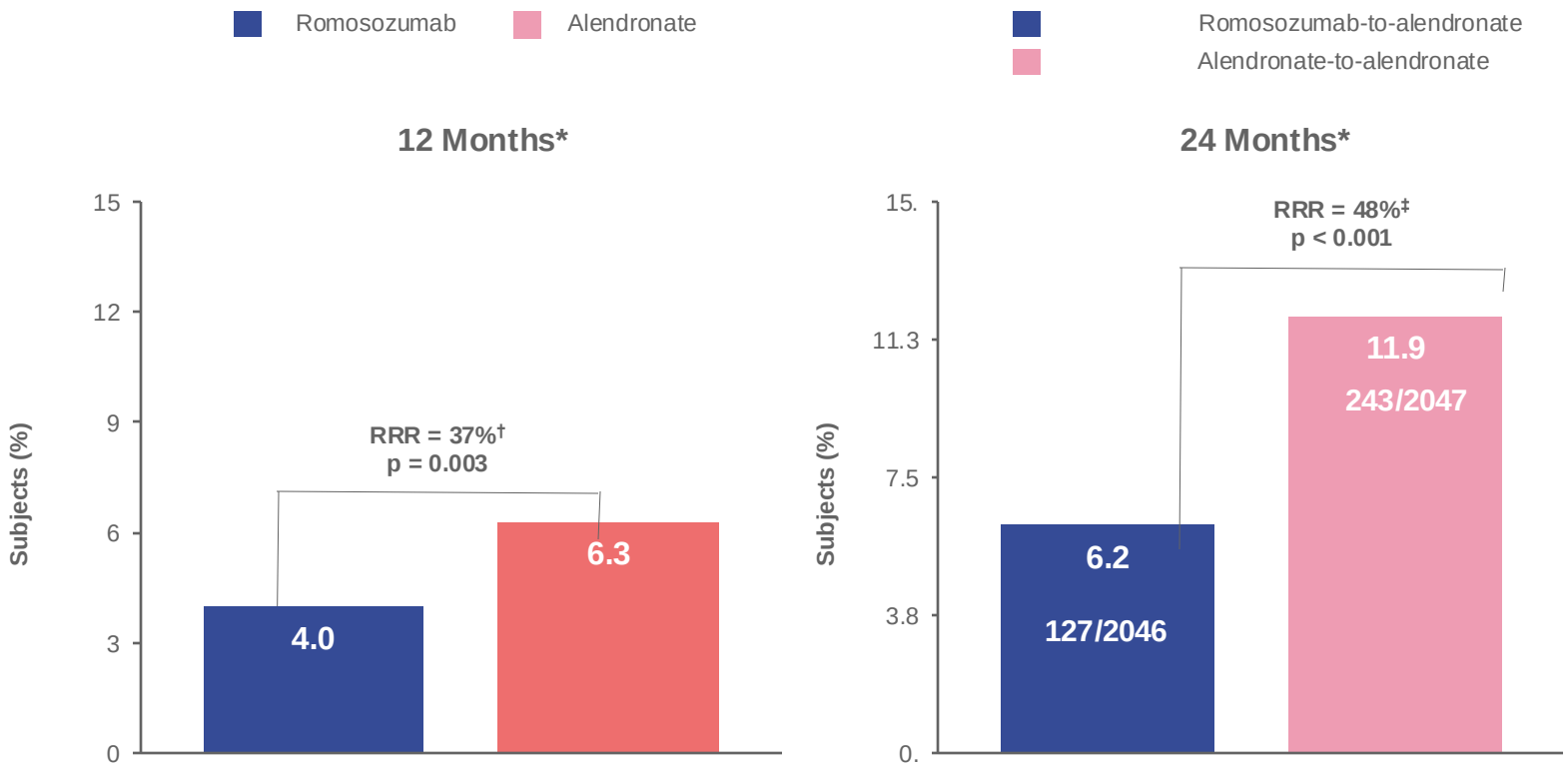


ARCH: Primary and Key Secondary Endpoints

Primary endpoints	• Subject incidence of new vertebral fracture through 24 months • Subject incidence of clinical fracture (nonvertebral and symptomatic vertebral fracture) at primary analysis
Key secondary endpoints	• Subject incidence of nonvertebral fracture at primary analysis BMD at the lumbar spine, total hip and femoral neck at 12 and 24 months
Other secondary/ exploratory endpoints	• Hip fracture, major osteoporotic fracture and other fracture categories at primary analysis

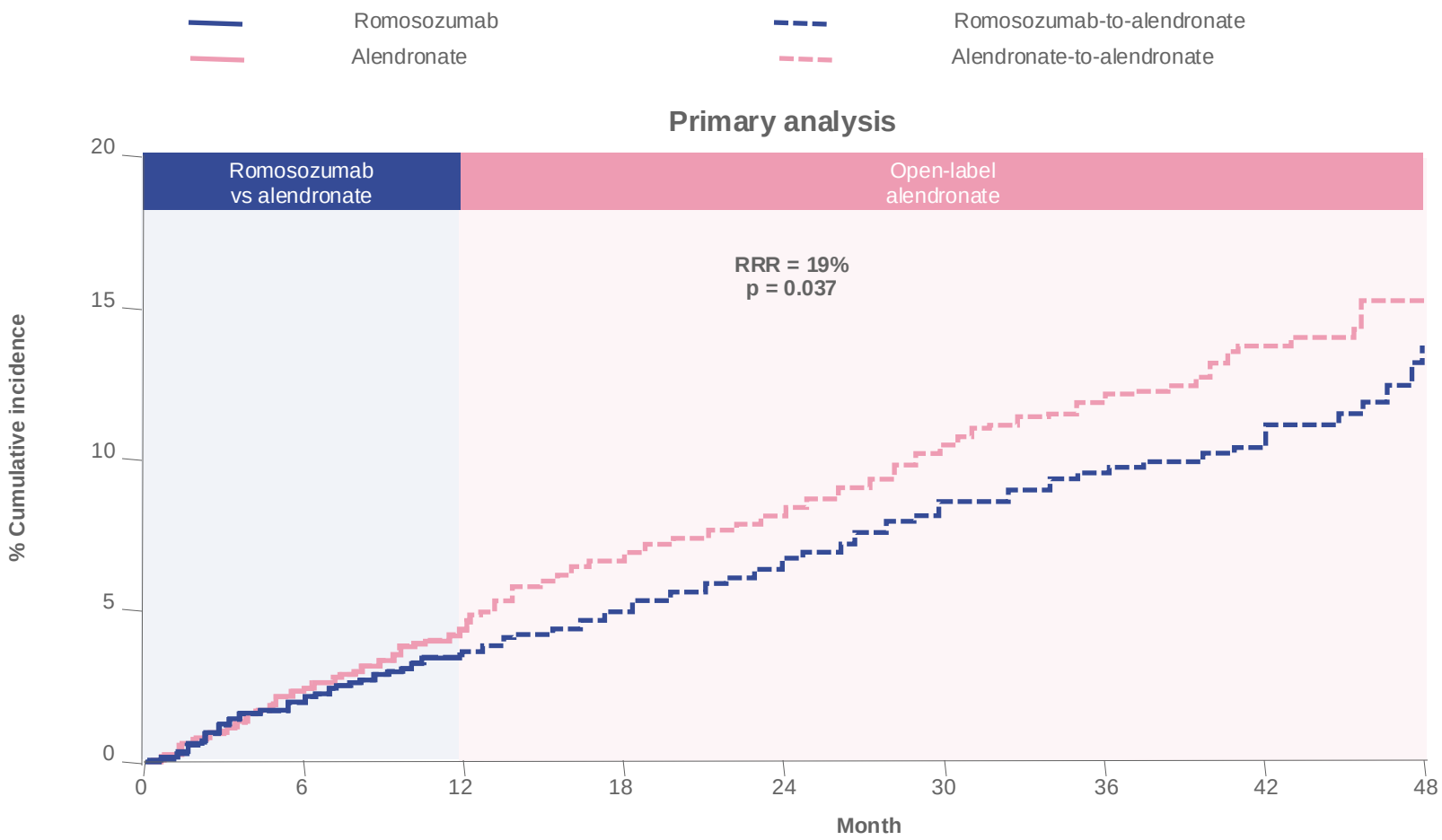
Primary Endpoint **ARCH**

Incidence of New Vertebral Fracture Through Month 24



ARCH

Incidence of Nonvertebral Fractures* at Primary Analysis



ARCH: Adverse Events and Events of Interest

	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%)

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%)‡

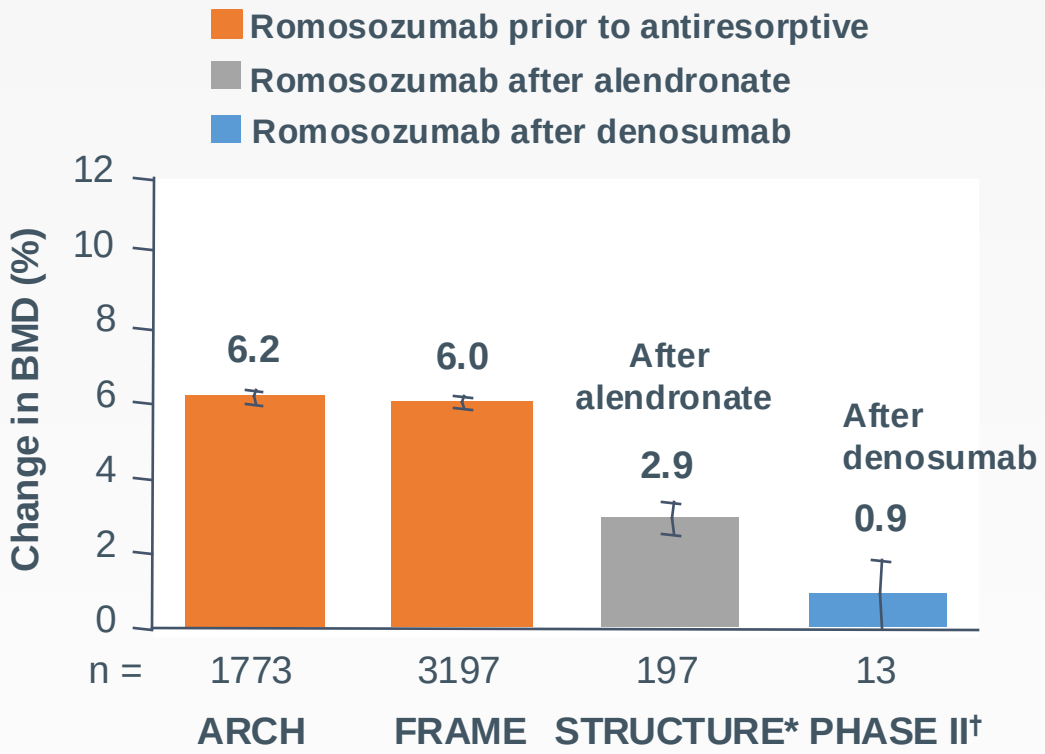
*Incidence rates at the time of the primary analysis were cumulative and included all events in the double-blind and open-label period (to February 27 2017) in patients who received at least one dose of open-label alendronate.
†Serious CV adverse events were adjudicated by the Duke Clinical Research 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.

The importance of treatment sequence

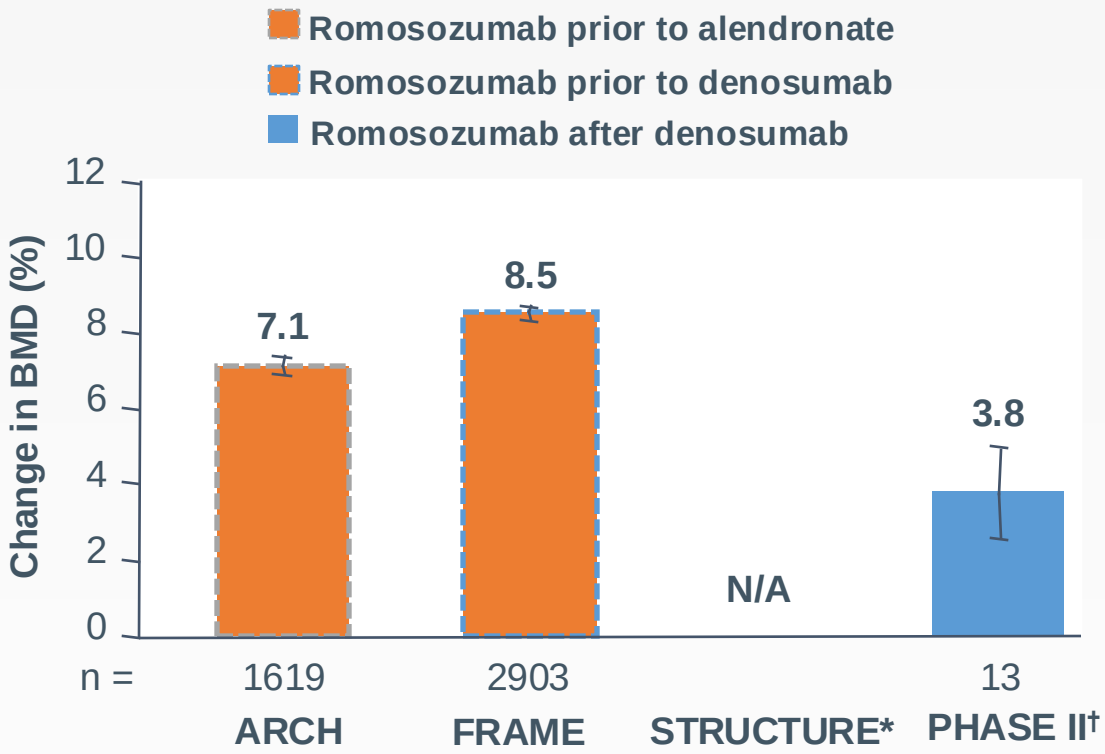
Romosozumab and antiresorptive treatment: The importance of treatment sequence (post-hoc analysis)

Total hip BMD[1]

1-year gains with romosozumab



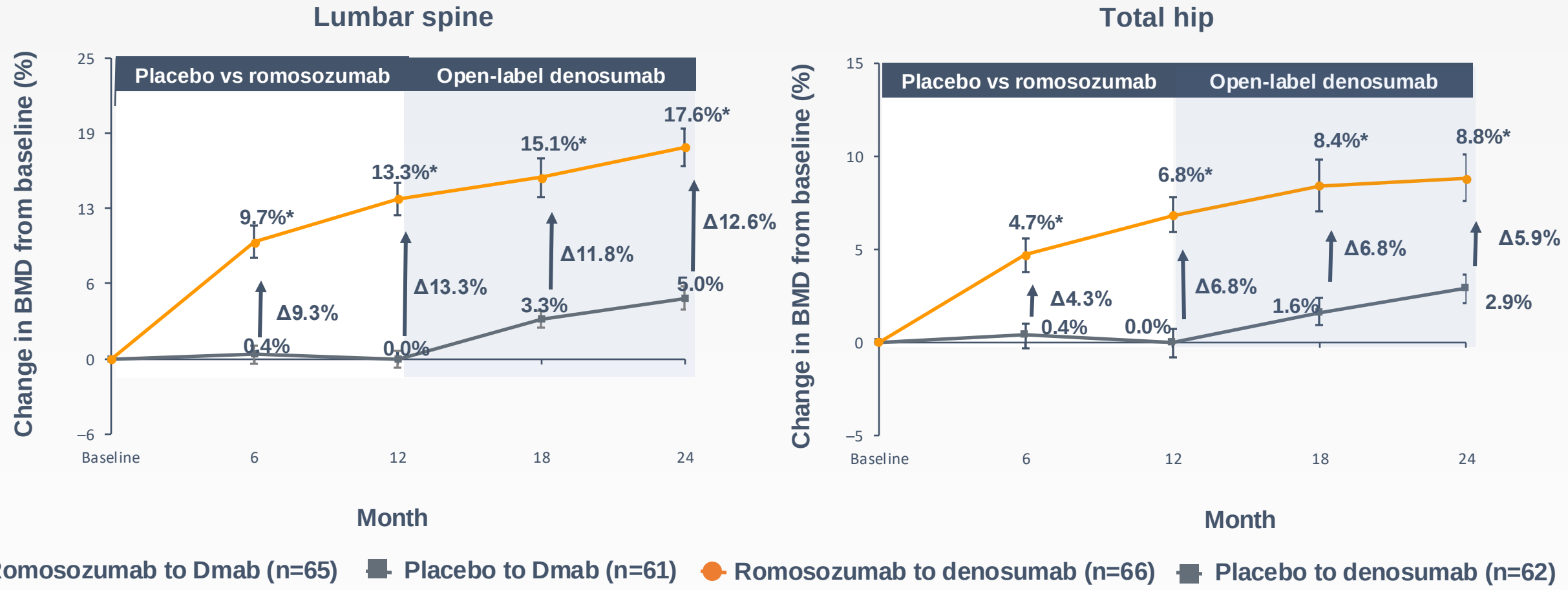
2-year cumulative gains after sequential therapy



In the EU, romosozumab is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.
Please refer to your local Prescribing Information or Summary of Product Characteristics for more information.

Error bars are 95% CI. n = number of patients who received romosozumab and had lumbar spine BMD measurements at baseline and at specified timepoints. *Patients had received oral bisphosphonate for ≥3 years before screening and alendronate (70 mg QW) ≥1 year immediately before screening; BMD was not measured in the 1 year of alendronate before romosozumab. †Patients received placebo during Months 0–24, denosumab during Months 24–36 and romosozumab during Months 36–48; cumulative gains are relative to the Month 24 baseline. Patients with a low BMD (an LS, TH or FN T-score of ≤–2.0 and ≥–3.5 at each of the three sites) were enrolled.[2] ARCH, Active-Controlled Fracture Study In Postmenopausal Women With Osteoporosis At High Risk; BMD, bone mineral density; CI, confidence interval; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; FN, femoral neck; LS, lumbar spine; N/A; not applicable; QW, weekly; TH, total hip. 1. Cosman F, et al. Osteoporos Int. 2022;33:1243–1256; 2. McClung MR, et al. N Engl J Med. 2014;370:412–420. Figures adapted with permission from Cosman F, et al. Osteoporos Int. 2022;33:1243–1256.

FRAME: Lumbar spine and total hip BMD through Month 24



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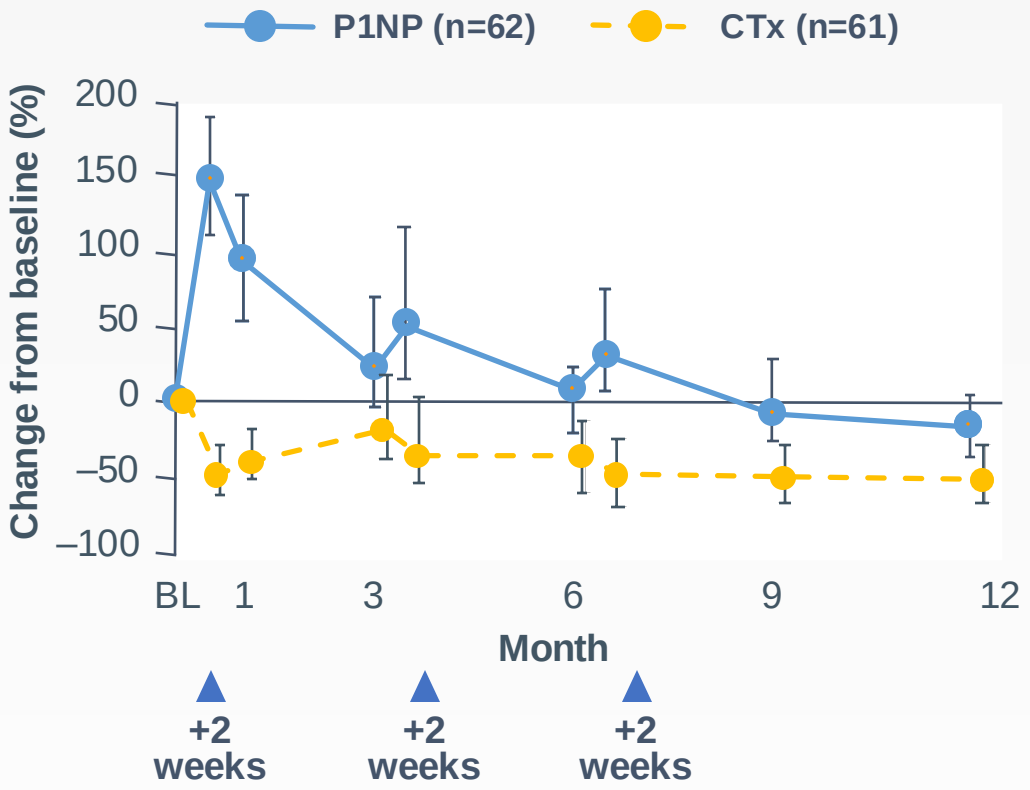
*p<0.001 compared with placebo. Data are least-squares mean (95% CI) adjusted for relevant baseline covariates.
BMD, bone mineral density; CI, confidence interval; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis.
Cosman F, et al. N Engl J Med. 2016;375:1532–43.

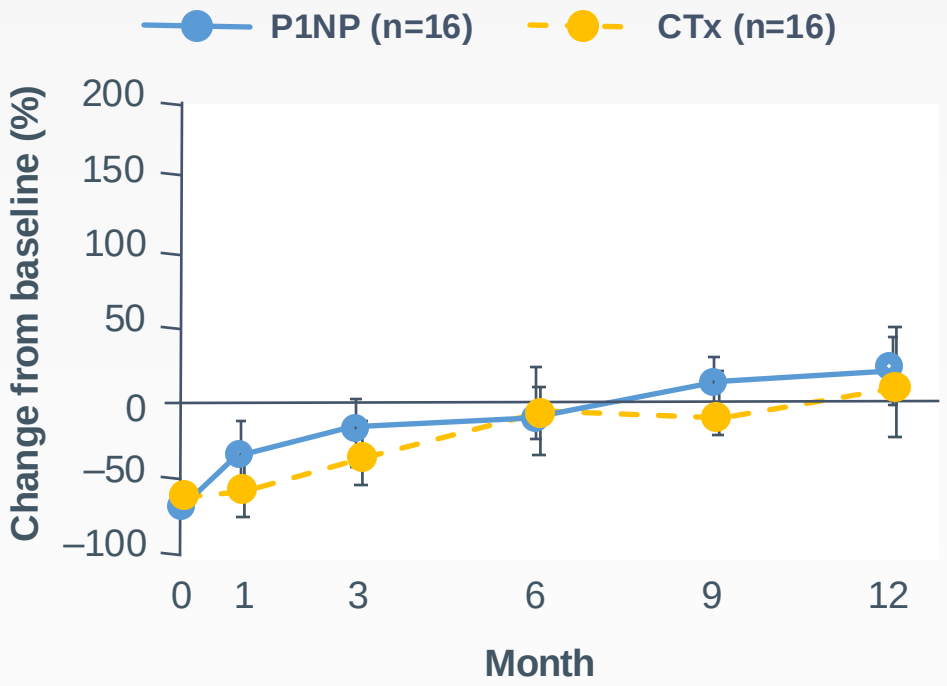
FRAME and Phase II Extension: BTMs through Month 12

P1NP and CTx

12 months of romosozumab (FRAME)[1]



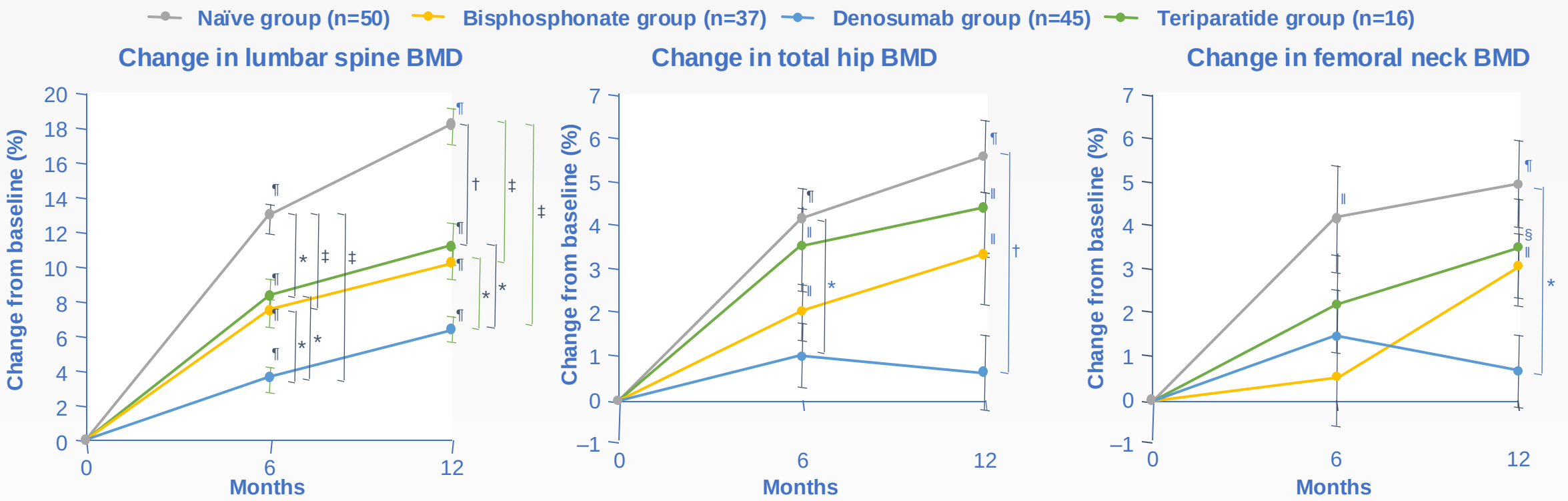
12 months of romosozumab after denosumab (Phase II Extension)[2]*



Data are median and interquartile range. *For the Phase II extension, baseline (Month 0) is at Month 36 of the study when patients had previously received 24 months of placebo followed by 12 months of denosumab. In the Phase II study, patients with a low BMD (an LS, TH or FN T-score of ≤–2.0 and ≥–3.5 at each of the three sites) were enrolled. BL, baseline; BTM, bone turnover marker; CTx, serum C-telopeptide of type 1 collagen; FRAME, Fracture Study in Postmenopausal Women with Osteoporosis; P1NP, serum procollagen type 1 N-terminal propeptide. 1. Cosman F, *et al. N Engl J Med* 2016 375:1532–43; 2. McClung MR, et al. N Engl J Med. 2021;5:e10512. Left figure adapted from Cosman F, *et al. N Engl J Med* 2016 375:1532–43. Right figure adapted from McClung MR, et al. N Engl J Med. 2021;5:e10512.

Real-world data from Japan: Effects of prior treatment on BMD with romosozumab treatment

Change in BMD from baseline with 12 months of romosozumab following pre-treatment with either bisphosphonate therapy, denosumab, teriparatide or no osteoporosis treatment[1]



In Japan, romosozumab is indicated for the treatment of osteoporosis in patients at high risk of fracture[2]

In the EU, romosozumab is indicated for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture.
Please refer to your local Prescribing Information or Summary of Product Characteristics for more information.

Data are mean (standard error). This study was a prospective, observational, multicentre study in which 148 postmenopausal patients who were treatment-naïve or previously treated with bisphosphonates, denosumab or teriparatide were switched to romosozumab. *p<0.05, †p<0.01, ‡p<0.001; difference between the two indicated groups. §p<0.05, ‖p<0.01, ¶p<0.001; change from baseline within each treatment group.
BMD, bone mineral density; LS, lumbar spine.1. Ebina B, et al. Joint Bone Spine. 2021; 88:105219; 2. Amgen. EVENITY® (romosozumab) receives approval in Japan for the treatment of osteoporosis in patients at high risk of fracture. https://www.amgen.com/newsroom/press-releases/2019/01/evenity-romosozumab-receives-approval-in-japan-for-the-treatment-of-osteoporosis-in-patients-at-high-risk-of-fracture. Accessed on April 2023. Figures adapted with permission from Ebina B, et al. Joint Bone Spine. 2021; 88:105219.

Safety considerations

ARCH: Incidence of adverse events

Incidence, n (%)	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)

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*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 ≥1 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 pre-specified Medical Dictionary for Regulatory Activities search strategies. §Pre-specified events were osteoarthritis, spinal osteoarthritis, exostosis, arthritis, polyarthritis, arthropathy, mono-arthritis 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%), haemorrhage (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.

ARCH, Active-Controlled Fracture Study In Postmenopausal Women With Osteoporosis At High Risk. Saag KG, et al. N Engl J Med. 2017;377:1417–1427. Table adapted from Saag KG, et al. N Engl J Med. 2017;377:1417–1427.

Conclusions

Romosozumab provides a rapid reduction in the risk of vertebral and clinical fractures in postmenopausal women at very high risk of fracture[1]

Initiating therapy with romosozumab, followed by an antiresorptive, provides greater BMD gains than the reverse sequence[1–3]

- There is some blunting of BMD gains when using romosozumab after antiresorptives, but the BMD gain is still positive[2]

Romosozumab is contraindicated after a stroke or MI[4]