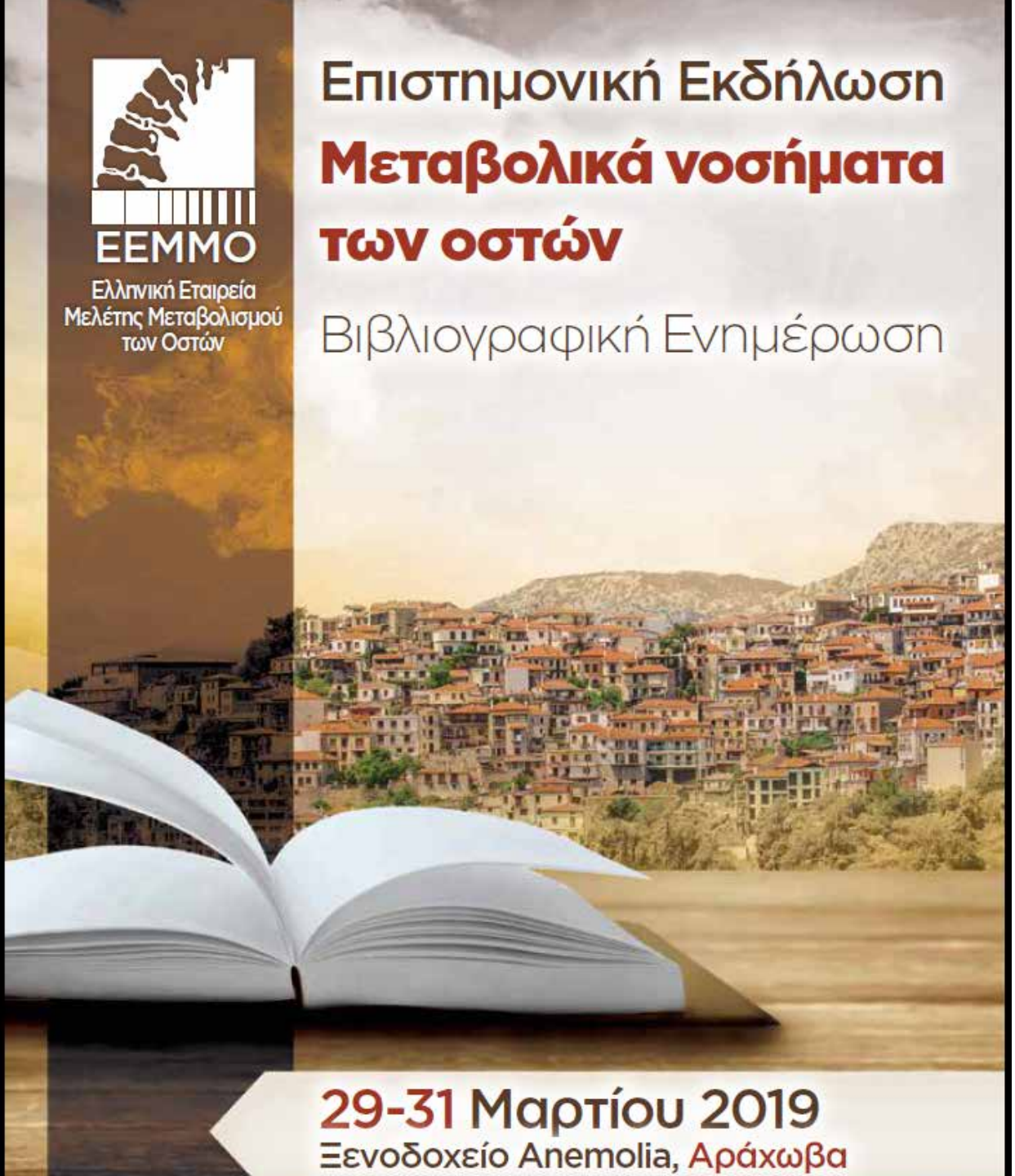
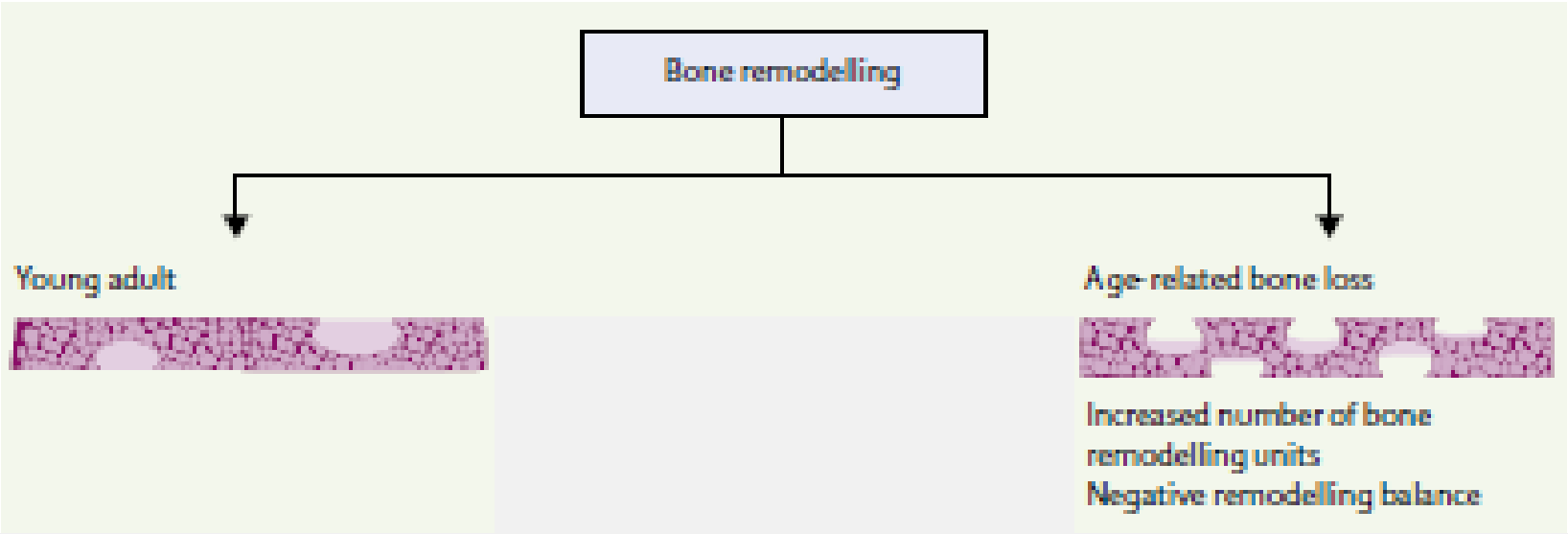


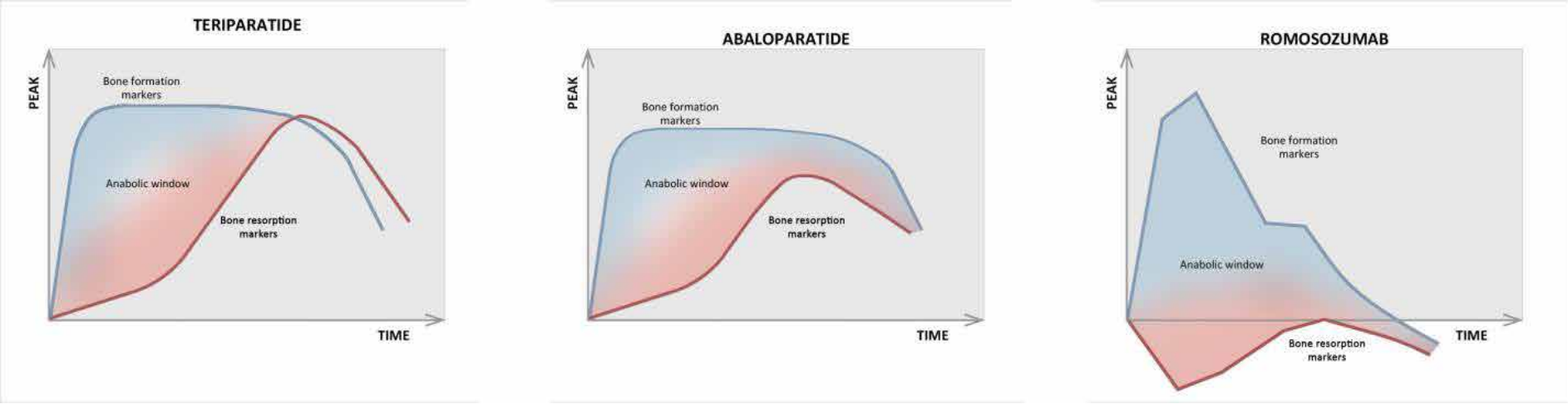
Αναβολική αγωγή οστεοπόρωσης

ΚΩΝΣΤΑΝΤΙΝΟΣ Ι. ΜΑΥΡΟΥΔΗΣ
ΕΝΔΟΚΡΙΝΟΛΟΓΟΣ
τ. Συντονιστής Διευθυντής
Ενδοκρ/λογίας Διαβήτη
& Μεταβολισμού
ΓΝΑ ¨Ασκληπιείο Βούλας¨

Effects of antiresorptive and anabolic drugs on bone remodelling and modelling



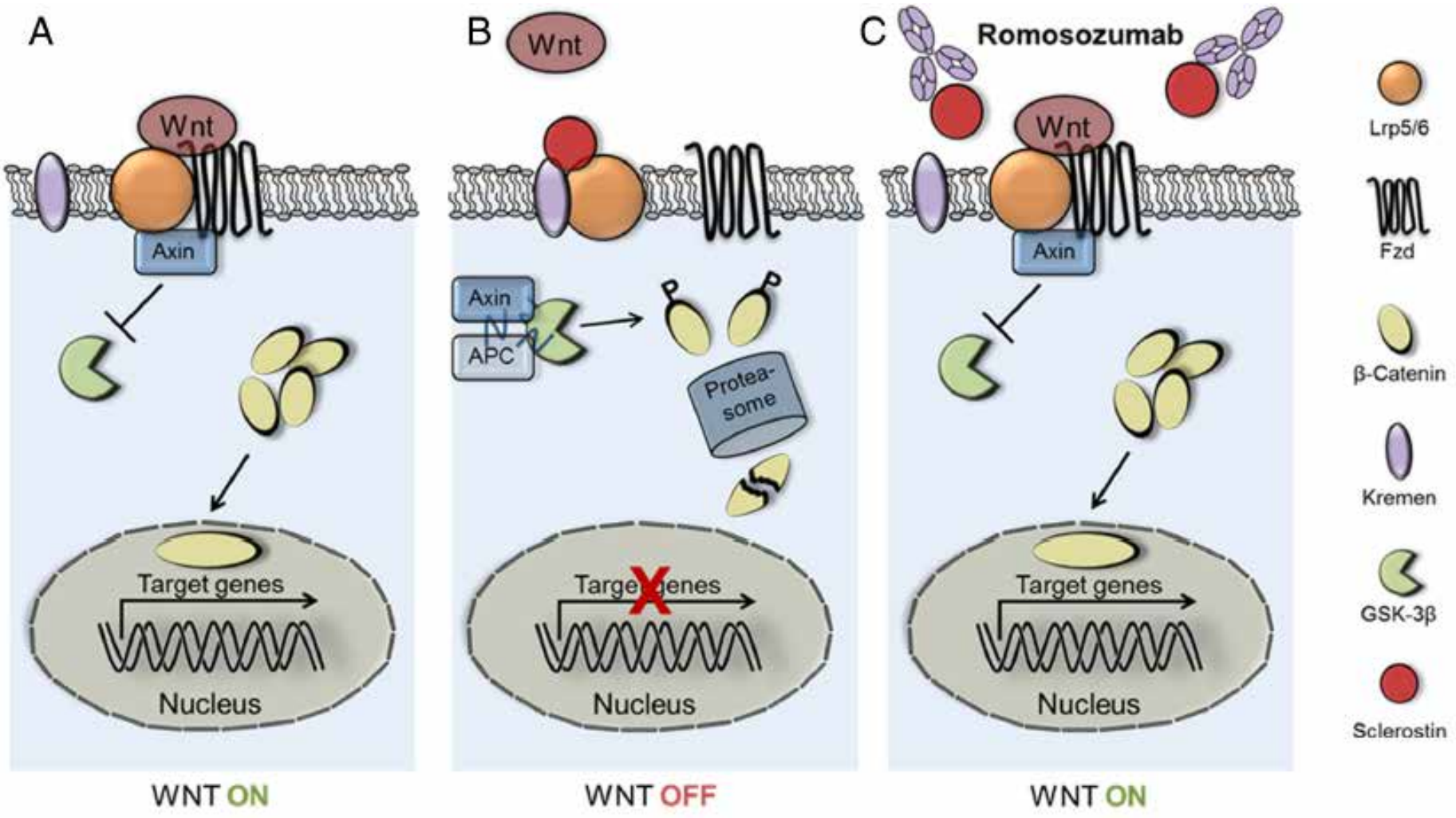
Anabolic windows for Teriparatide, Abaloparatide and Romosozumab



G. Tabacco and JP. Bilezikian. British Journal of Clinical Pharmacology

Teriparatide (TPTD) and **Abaloparatide (ABL)** are the only osteoanabolic drugs available, at this time, for treatment of osteoporosis. TPTD is a 34–amino acid fragment that is identical in its primary sequence to the 34 amino acids of full-length human parathyroid hormone [hPTH(1-84)]. ABL is identical to parathyroid hormone related peptide (PTHrP) through the first 22 residues with significantly different amino acids inserted thereafter, between residues 22 and 34. Both drugs are administered for a maximum of 24 months, and should be followed by an anti-resorptive agent to maintain gains in BMD. **Romosozumab,** a monoclonal antibody that binds to and inhibits sclerostin, **appears to have dual actions** by stimulating bone formation and reducing bone resorption.

Romosozumab is a monoclonal antibody directed against the Wnt inhibitor sclerostin



TD Rachner, LC Hofbauer, A Göbel and **E Tsourdi** *Journal of Molecular Endocrinology* (2019) **62**, R145–R154

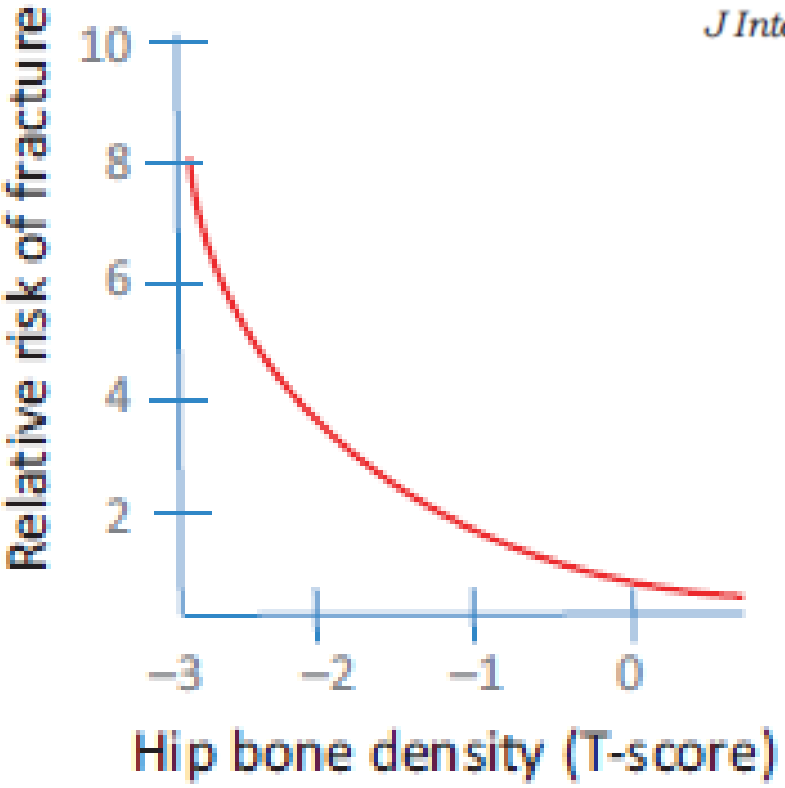
JIM Review

doi: 10.1111/joim.12873

Treating osteoporosis to prevent fractures: current concepts and future developments

Mattias Lorentzon[1,2]

J Intern Med 2019; **285**: 381–394.



The relationship between hip bone mineral density T-score and fracture risk

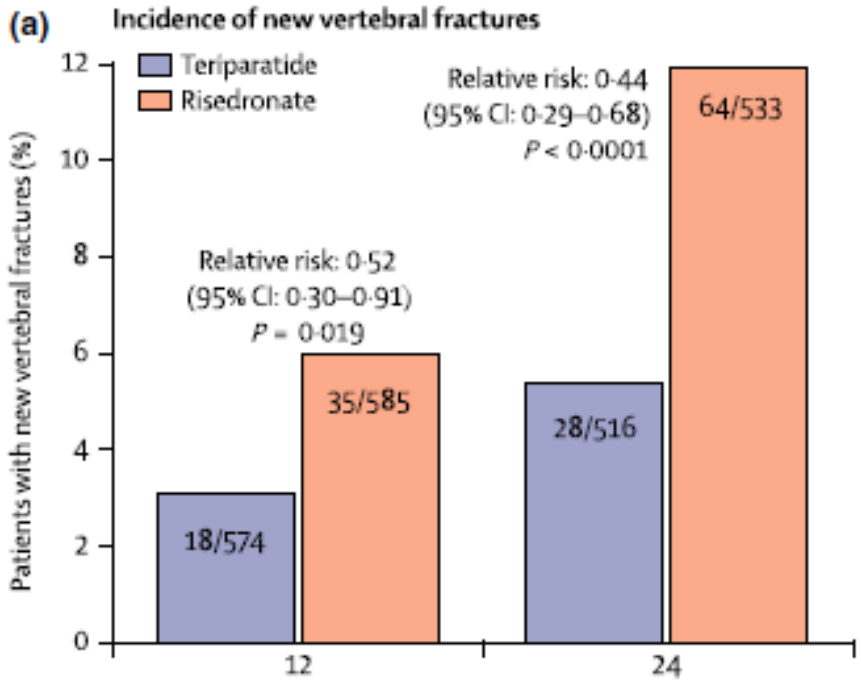
Table 1 *Effects of bone building vs. antiresorptive medications on fracture risk in postmenopausal women with osteoporosis*

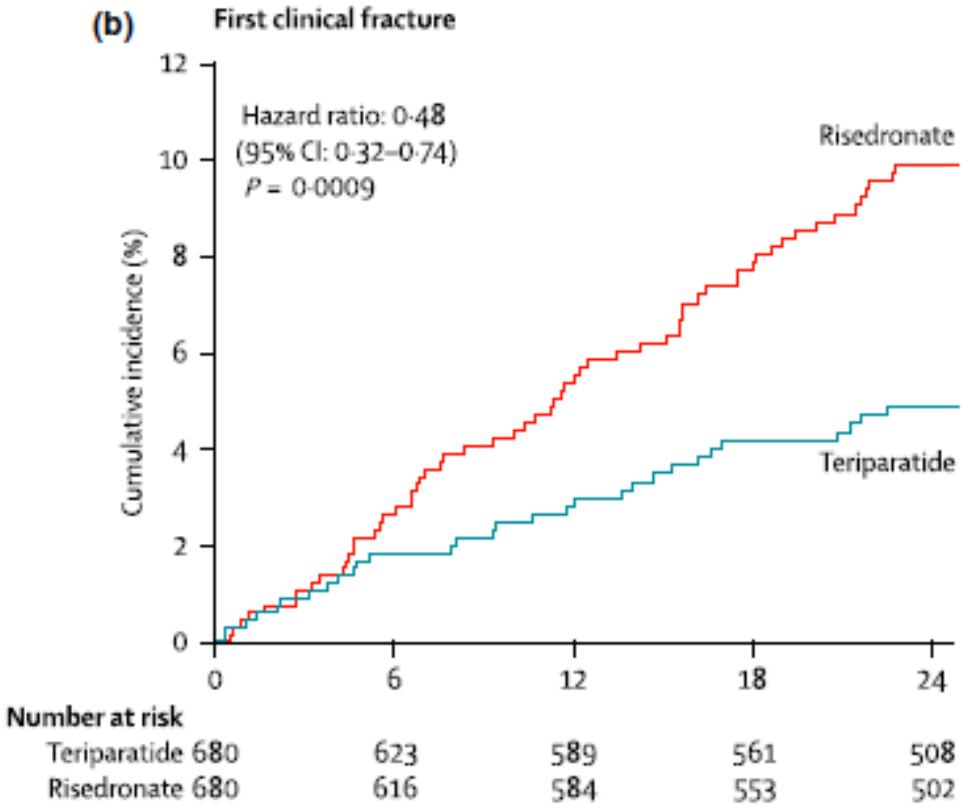
Study	Study population	Assigned treatment			Treatment effect		
ARCH [83]	PM women with osteoporosis and fragility fracture	Romosozumab to alendronate (n = 2046)	Alendronate to alendronate (n = 2047)	Treatment time (months)	ARR	RRR	P-value
	Fracture incidence						
	Vertebral	6.2%	11.9%	24	5.7%	48%	<0.001
	Nonvertebral	8.7%	10.6%	32.4[a]	1.9%	19%	0.04
	Clinical	9.7%	13.0%	32.4[a]	3.3%	27%	<0.001
	Hip	2.0%	3.2%	32.4[a]	1.2%	38%	0.02

Study	Study population	Assigned treatment			Treatment effect		
VERO [49]	PM women with ≥2 moderate or ≥1 severe vertebral fracture & a BMD T-score ≤−1.50	Teriparatide (n = 680)	Risedronate (n = 680)	Treatment time (months)	ARR	RRR	P-value
	Fracture incidence						
	Vertebral	5.4%	12.0%	24	6.6%	56%	<0.0001
	Nonvertebral	4.0%	6.1%	24	2.1%	34%	0.10
	Clinical	4.8%	9.8%	24	5.0%	52%	0.0009

ARR, Absolute risk reduction; BMD, Bone mineral density; PM, Postmenopausal; RRR, Relative risk reduction.
Adapted from [83] and [49].
[a]Denotes median ± interquartile range.

Lower risk of fractures with teriparatide than with risedronate treatment in postmenopausal women with severe osteoporosis.

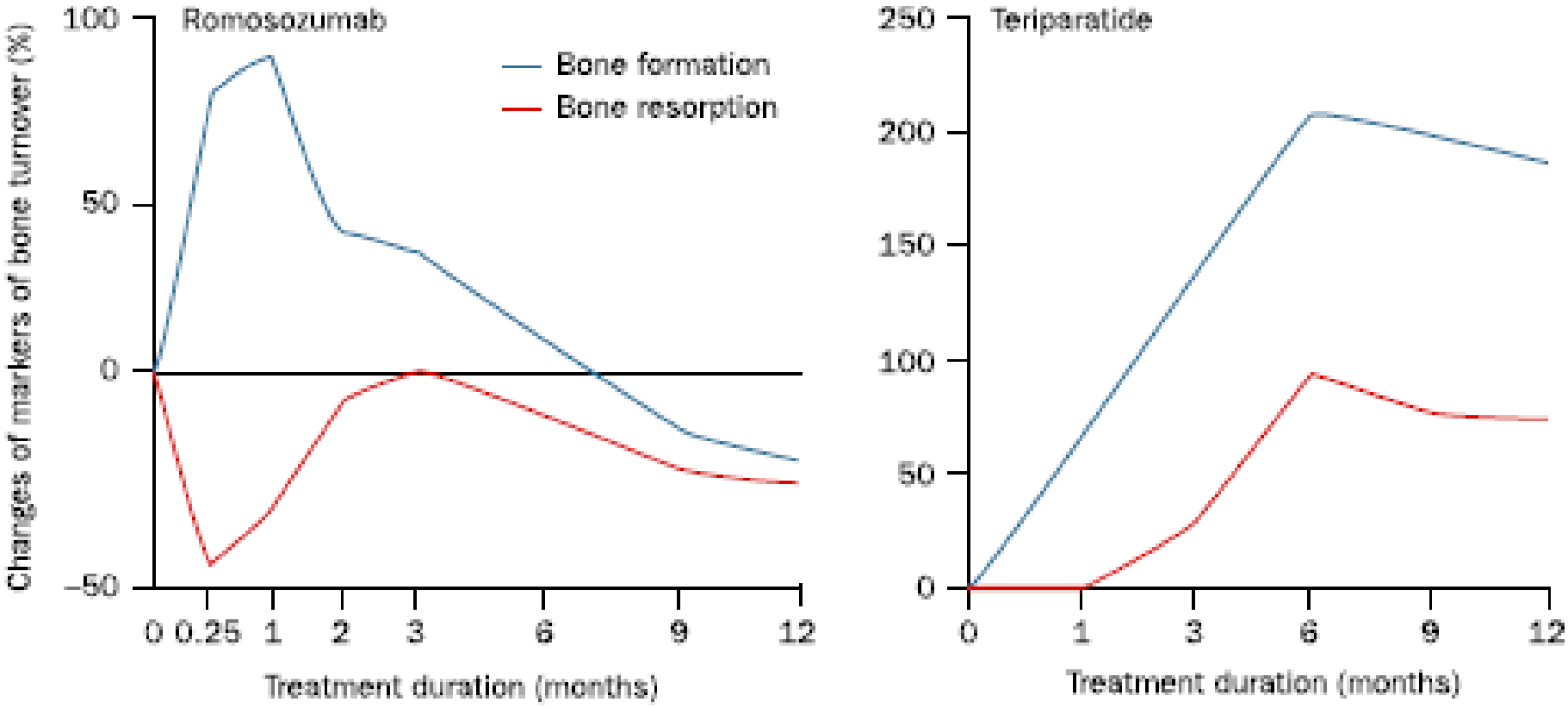




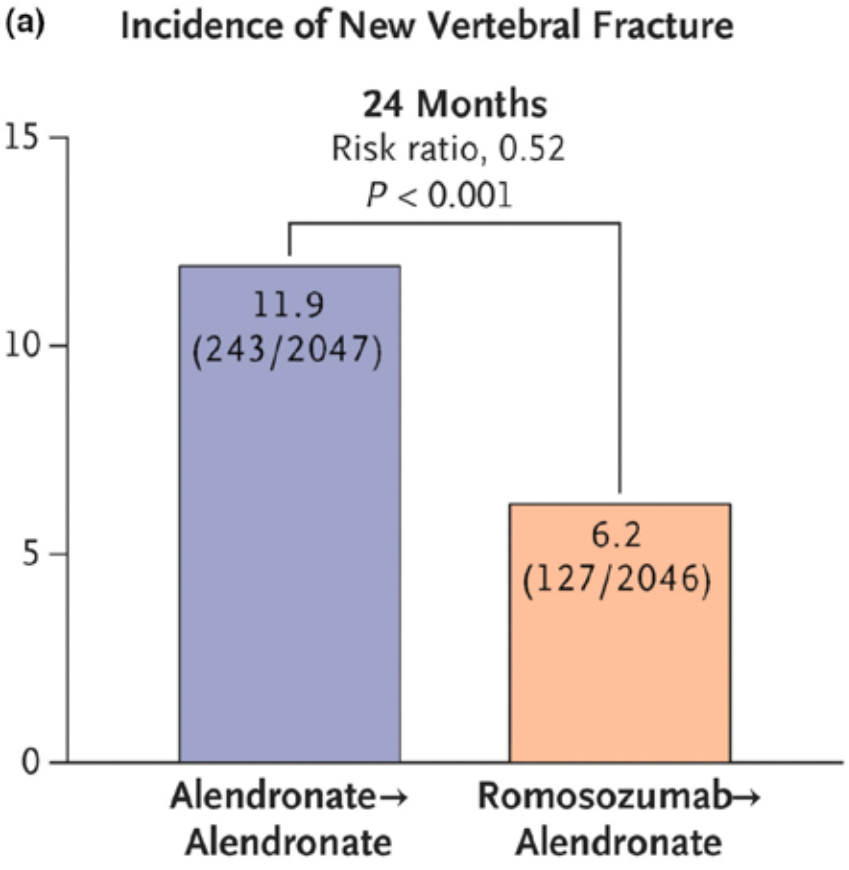
(a) Risk of vertebral fractures

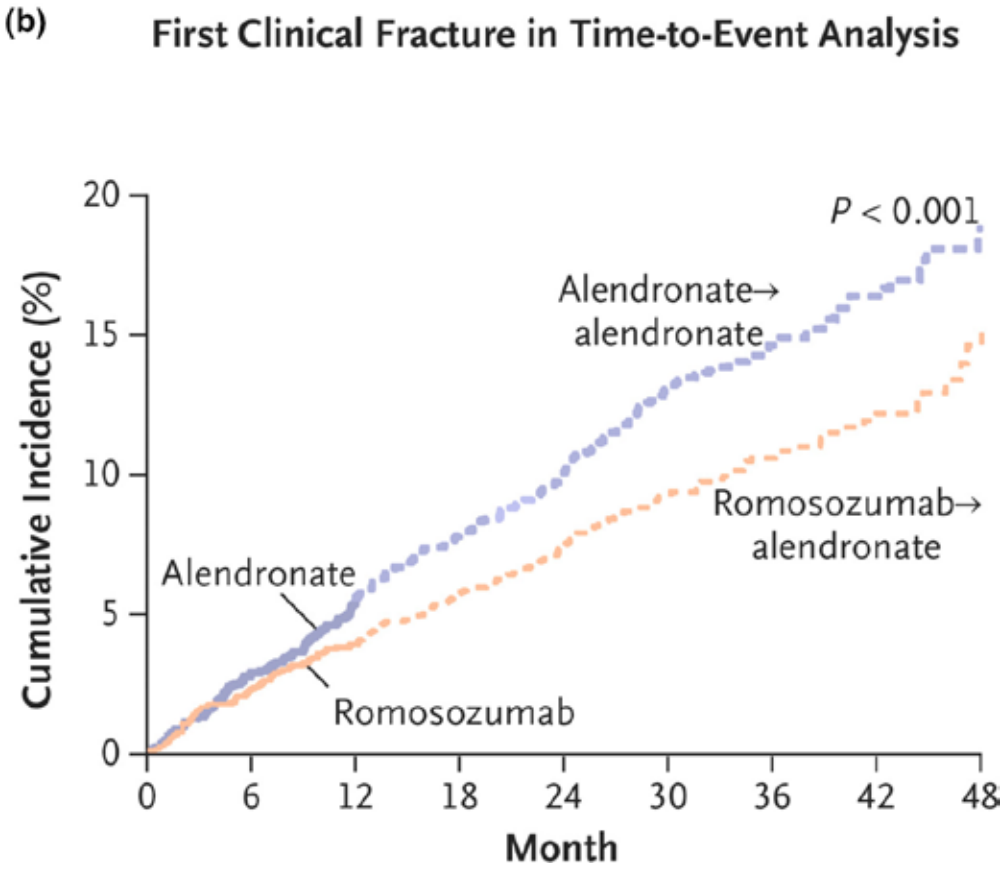
(b) Risk of clinical fractures

Schematic presentation of bone turnover with romosozumab and teriparatide treatment

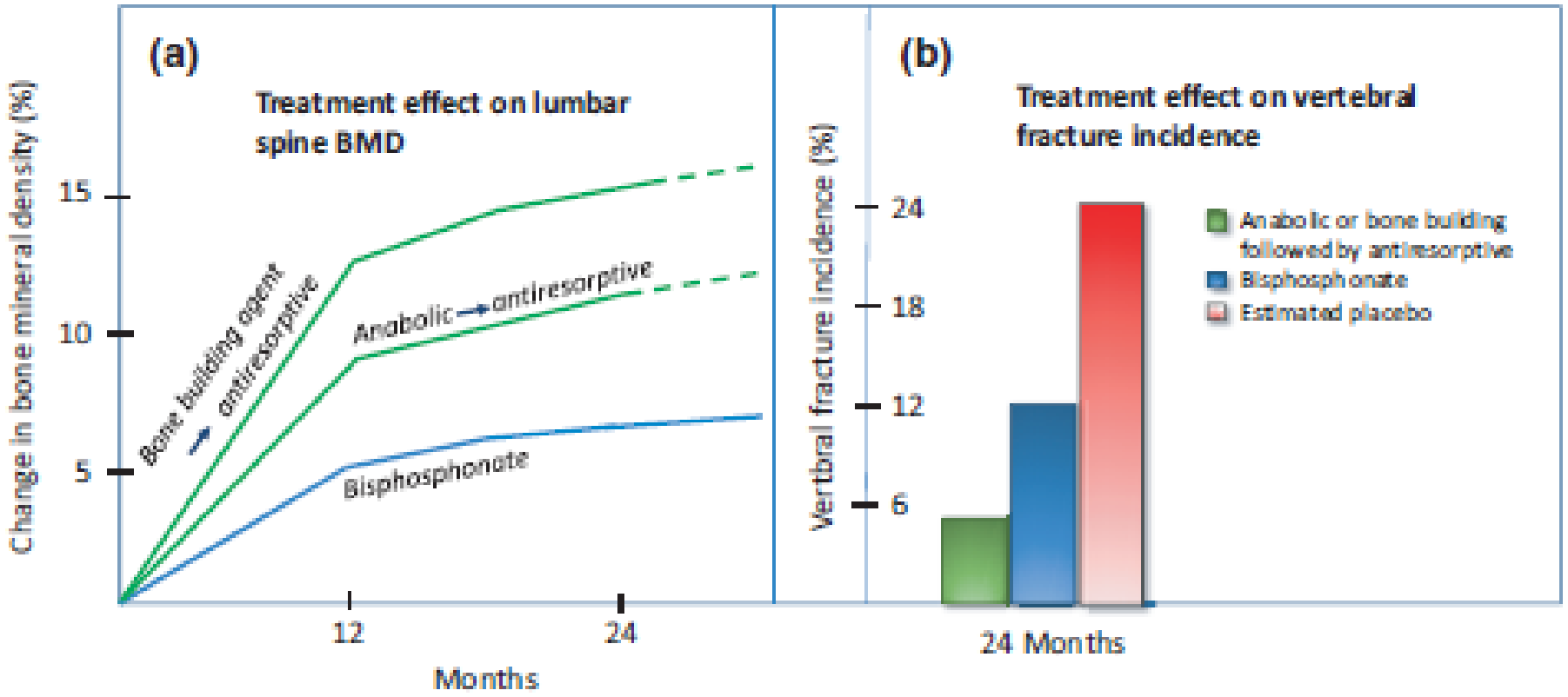


Romosozumab for 12 months followed by alendronate reduced the risk of vertebral (a) and clinical (b) fracture compared to alendronate alone in postmenopausal women with osteoporosis





Schematic illustration of the effect of an anabolic or a bone-building agent, followed by an antiresorptive on (a) spine BMD and on (b) vertebral fracture incidence



Bone 120 (2019) 1–8

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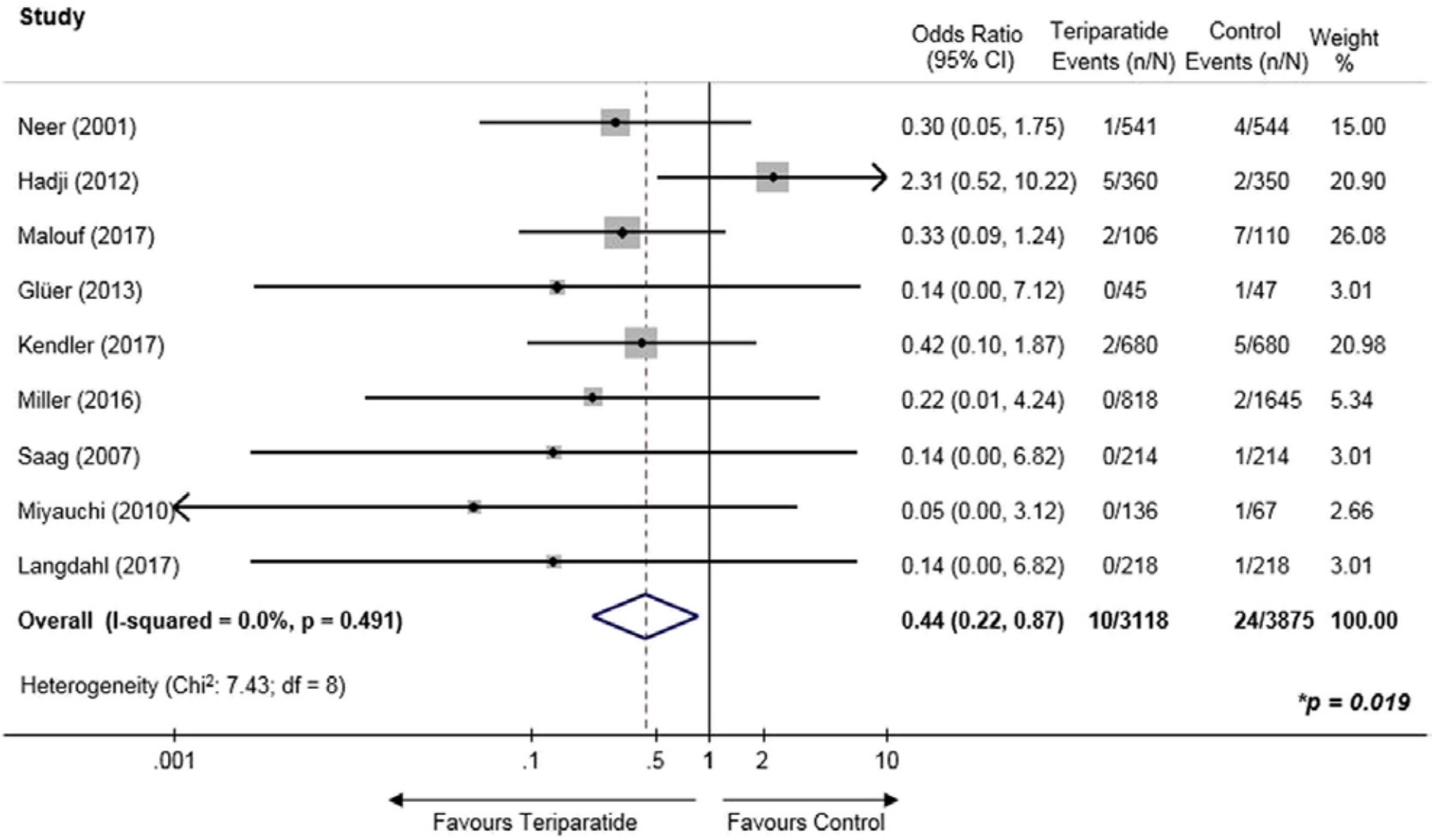
Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: A systematic review and meta-analysis

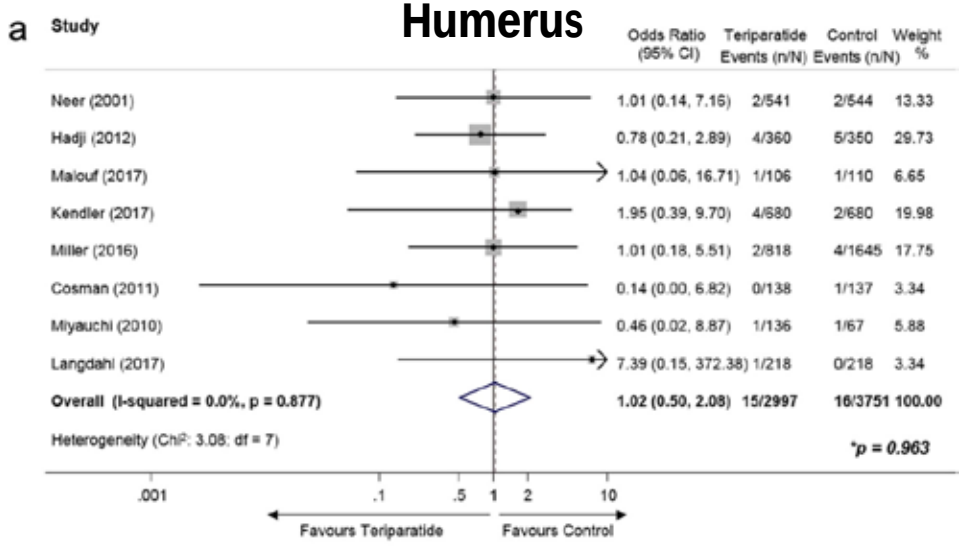
Adolfo Díez-Pérez[a,b,*], Fernando Marin[c], Erik F. Eriksen[d], David L. Kendler[e], John H. Krege[f], Miguel Delgado-Rodríguez[g,h]

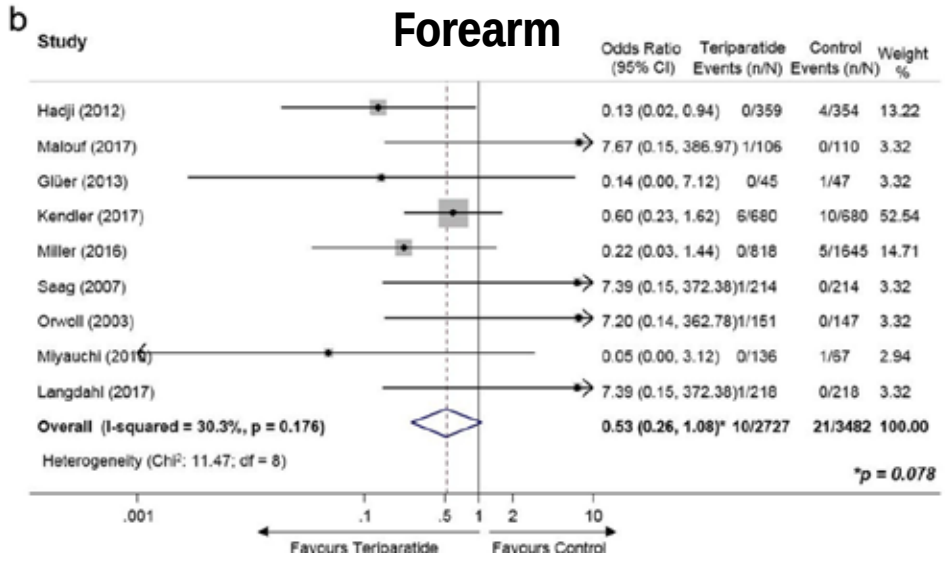
In RCTs with teriparatide, the number of patients with incident hip fractures was small and insufficiently powered to show statistically significant differences between groups. We, therefore, conducted a systematic review and meta-analysis of the efficacy of teriparatide in the reduction of hip and upper limb fractures in women and men with osteoporosis. Only RCTs that included patients with the approved treatment indications and dose for use of teriparatide were included; trials with off-label use of teriparatide were excluded. Two independent reviewers performed study selection and data extraction... 23 RCTs were included, 19 with an active-controlled arm (representing 64.9% of the patients included in the control group) and 11 double-blind, representing data on 8644 subjects, 3893 of them treated with teriparatide.

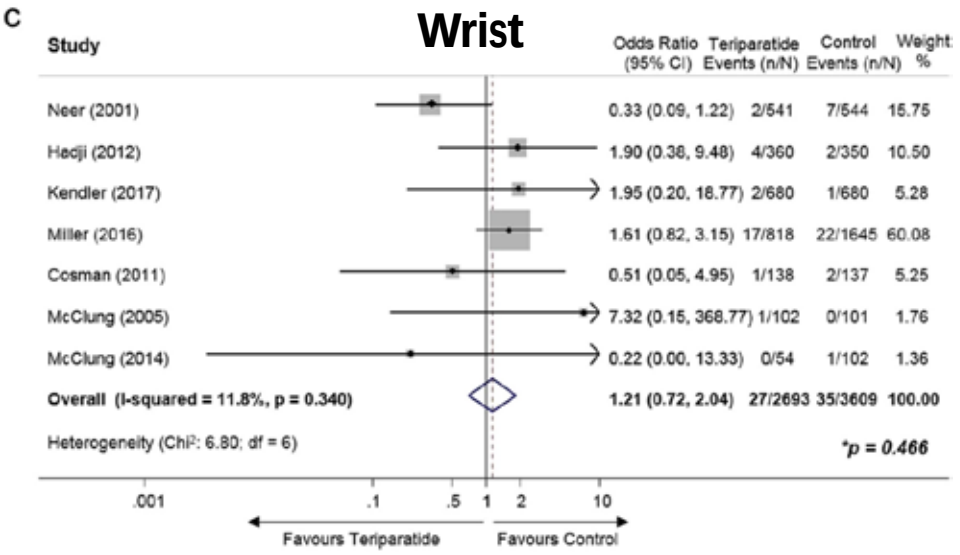
Forest plot of hip fracture outcomes



Forest plots of upper limb fracture outcomes: (a) humerus, (b) forearm, (c) wrist







Effects of teriparatide on hip and upper limb fractures in patients with osteoporosis: A systematic review and meta-analysis

Bone 120 (2019) 1–8

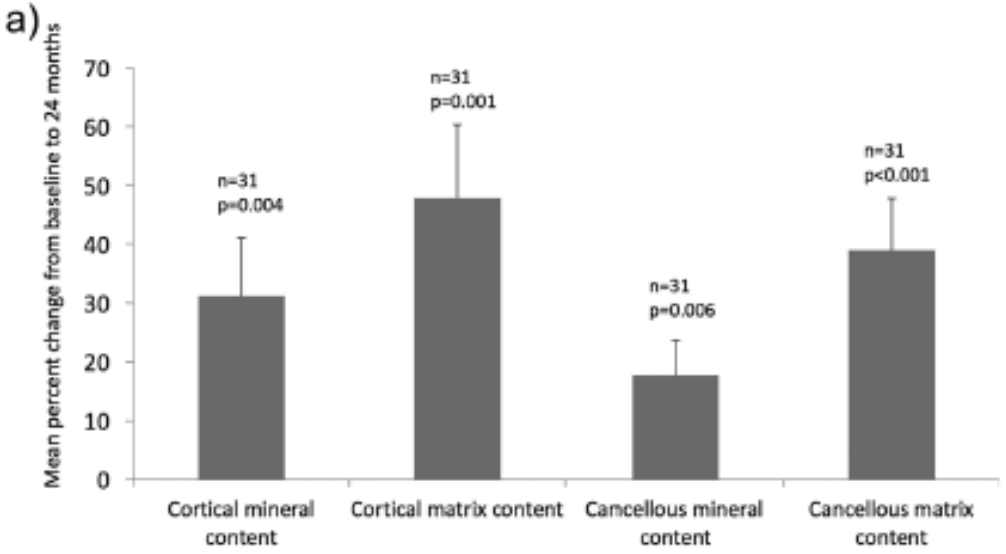
Conclusions

Our systematic review and individual-level meta-analyses of 23 randomized clinical trials comparing teriparatide to placebo or other anti-osteoporosis drugs in a total of 8644 subjects with osteoporosis in the approved indications for its clinical use, indicate that there is a significant reduction of hip fracture and a neutral effect on the pooled upper limb fractures reported. Collectively, these results support consideration of teriparatide for the treatment of osteoporosis as a first-line therapy in patients at high risk for osteoporotic fractures, although they should be interpreted in the context of the relatively small number of reported hip fractures.

Teriparatide Treatment Increases Mineral Content and Volume in Cortical and Trabecular Bone of Iliac Crest: A Comparison of Infrared Imaging With X-Ray–Based Bone Assessment Techniques

Eleftherios P Paschalis,[1] John H Krege,[2] Sonja Gamsjaeger,[1] Erik F Erik
Damon P Disch,[2] Jan J Stepan,[5] Astrid Fahrleitner-Pammer,[6] Klaus Kla
and Imre Pavo[2]

Journal of Bone and Mineral Research,
December 2018, pp 2230–2235



Conclusion

Data from this study indicate that 2 years of teriparatide treatmen leads to increased bone organi matrix and mineral content in the iliac crest. The magnitude o these increases in the iliac cres were not detected with conven tional aBMD measurements a other skeletal sites.

Osteoporos Int (2018) 29:501–506
https://doi.org/10.1007/s00198-017-4286-7

SHORT COMMUNICATION

Teriparatide for treatment of patients with bisphosphonate-associated atypical fracture of the femur

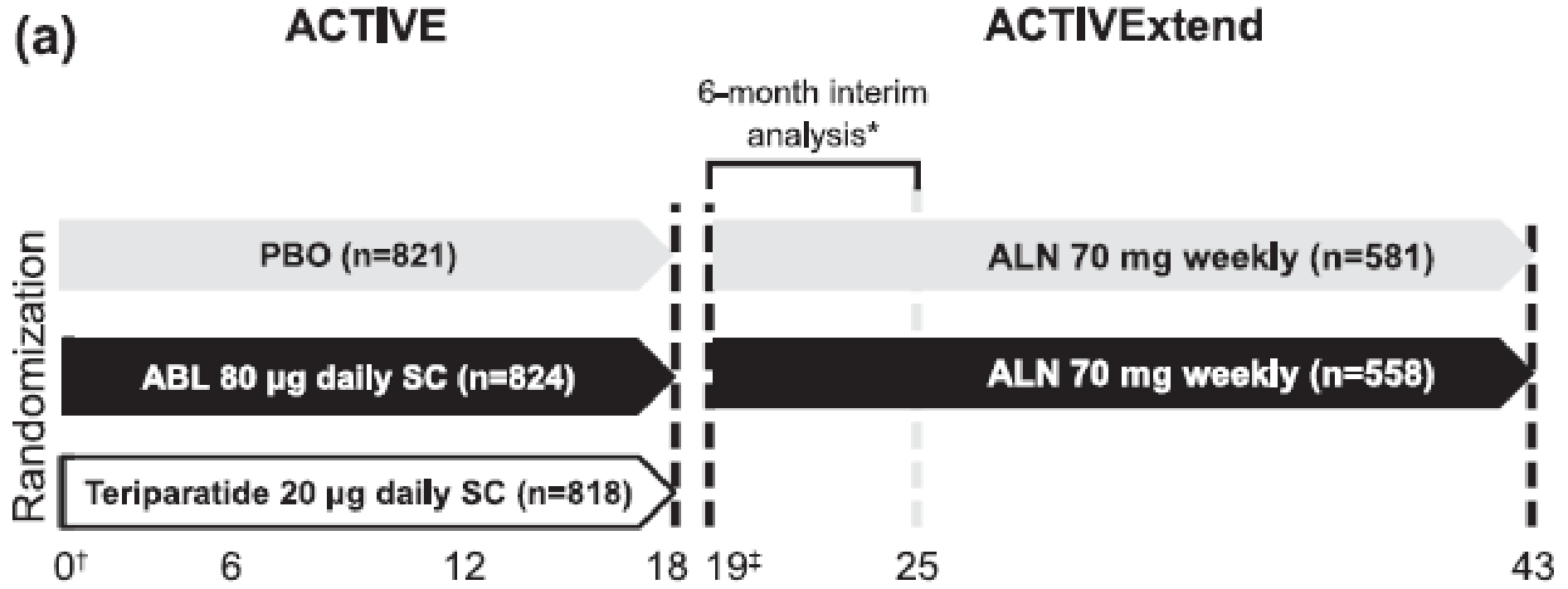
S. L. Greenspan[1] · K. Vujevich[1] · C. Britton[2] · A. Herradura[2] · G. Gruen[3] · I. Tarkin[3] · P. Siska[3] · B. Hamlin[3] · S. Perera[1]

In conclusion,
in this randomized pilot clinical trial designed to examine immediate vs delayed treatment with teriparatide for skeletal healing of an atypical femoral fracture, we found a preliminary signal for greater improvement in healing indices with immediate treatment. The treatment was well tolerated and appears to be safe. However, because this is a rare event, and numbers were small, the results must be interpreted with caution.

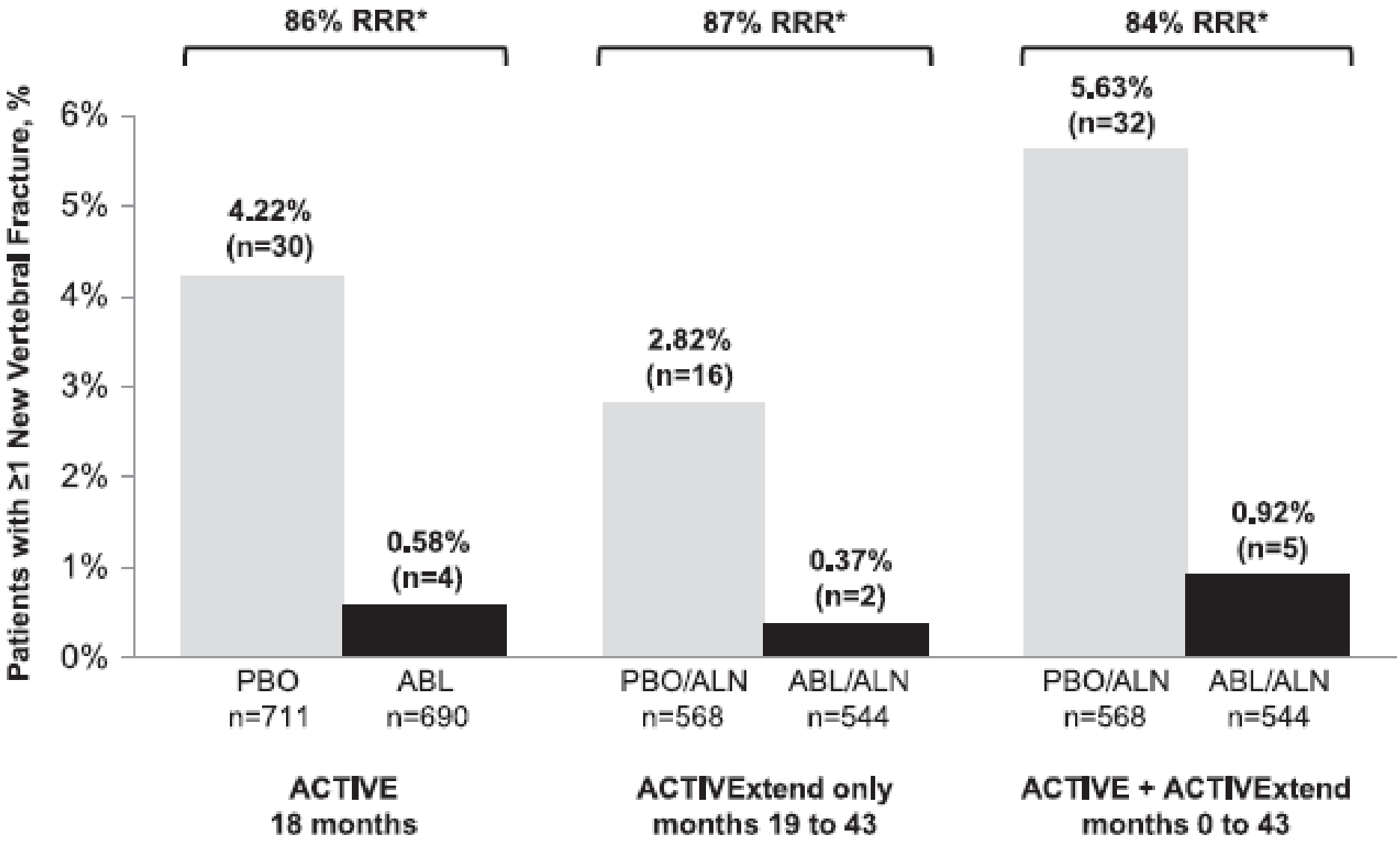
ACTIVExtend: 24 Months of Alendronate After 18 Months of Abaloparatide or Placebo for Postmenopausal Osteoporosis

J Clin Endocrinol Metab, August 2018, 103(8):2949–2957

Henry G. Bone,[1,2] Felicia Cosman,[3,4] Paul D. Miller,[5] Gregory C. Williams,[6] Gary Hattersley,[6] Ming-yi Hu,[6] Lorraine A. Fitzpatrick,[6] Bruce Mitlak,[6] Socrates Papapoulos,[7] René Rizzoli,[8] Robin K. Dore,[9] John P. Bilezikian,[10] and Kenneth G. Saag[11]



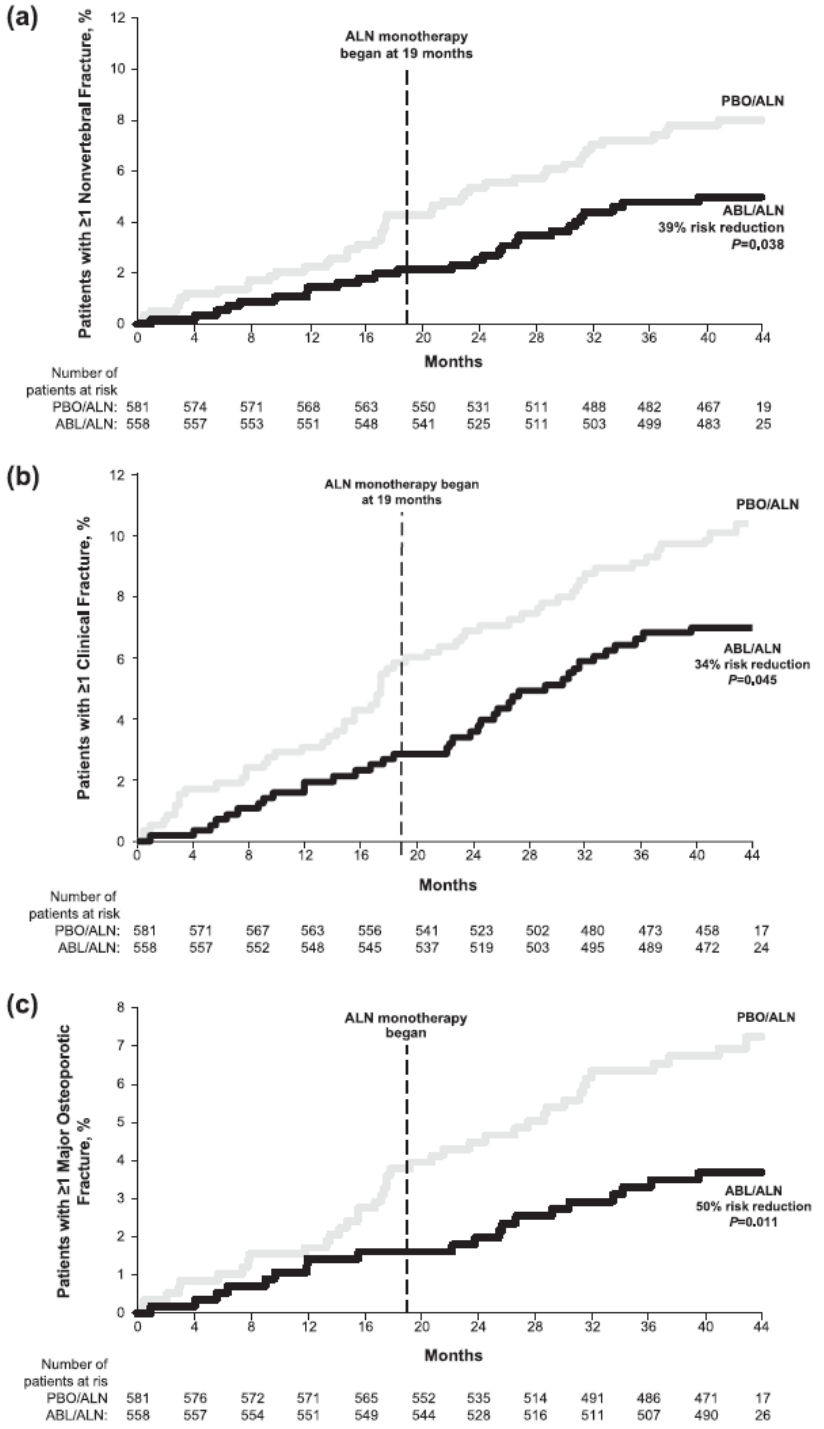
Incidence of new vertebral fractures in ACTIVE, ACTIVExtend only, and ACTIVE plus ACTIVExtend



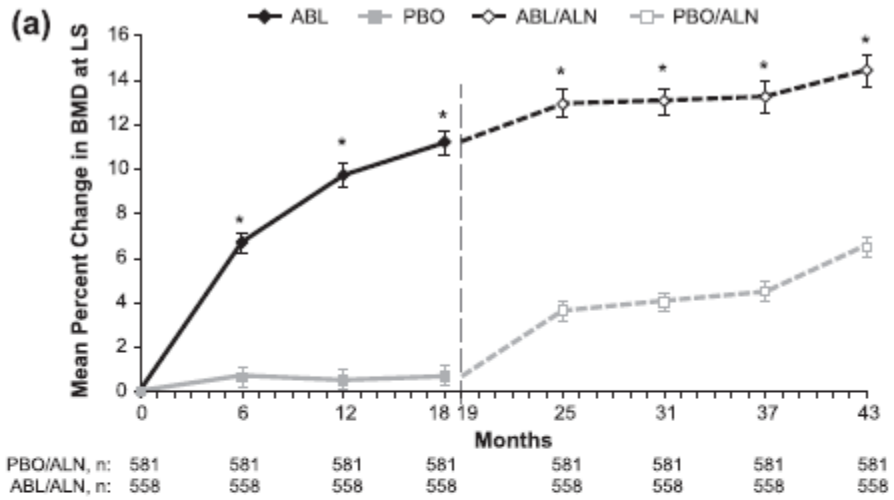
Time-to-event analyses of Nonvertebral fractures,
were defined as fractures excluding those of the spine, sternum, patella, toes, fingers, skull, and face and those with high trauma.

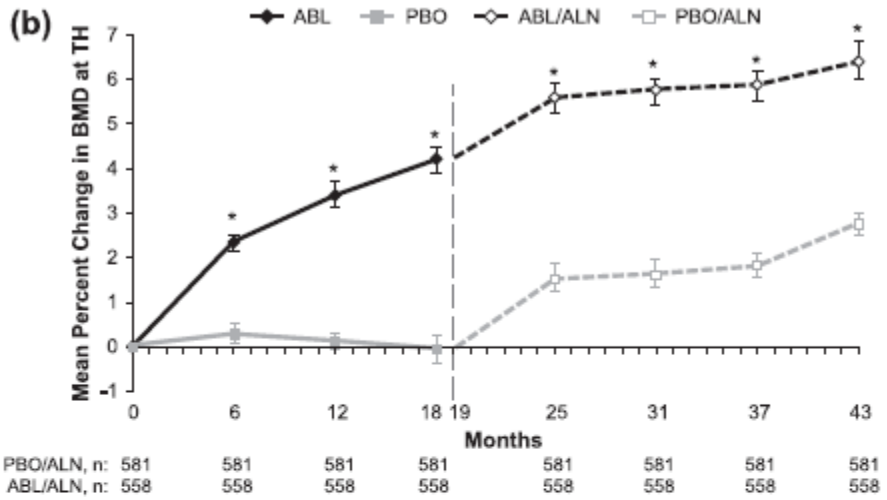
Clinical fractures,
were defined as all fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine
and
Major osteoporotic fractures
were defined as fractures of the wrist, upper arm, hip, and clinical spine

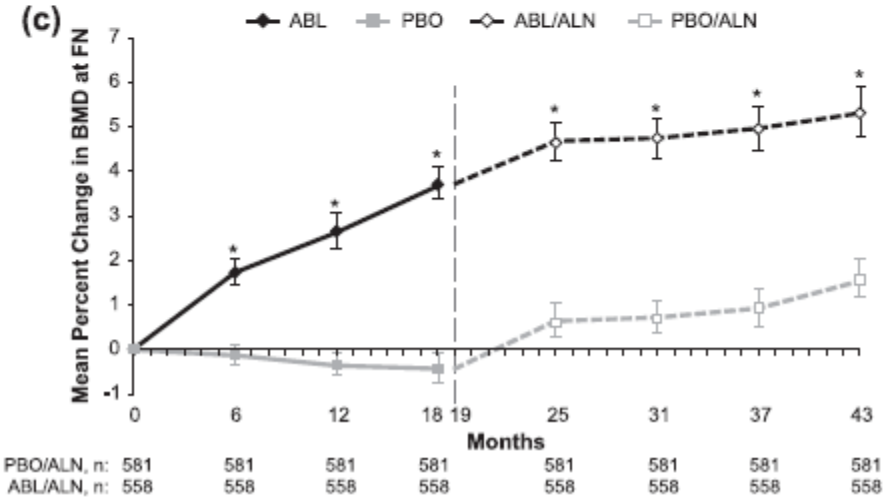
from ACTIVE baseline at mo 43.



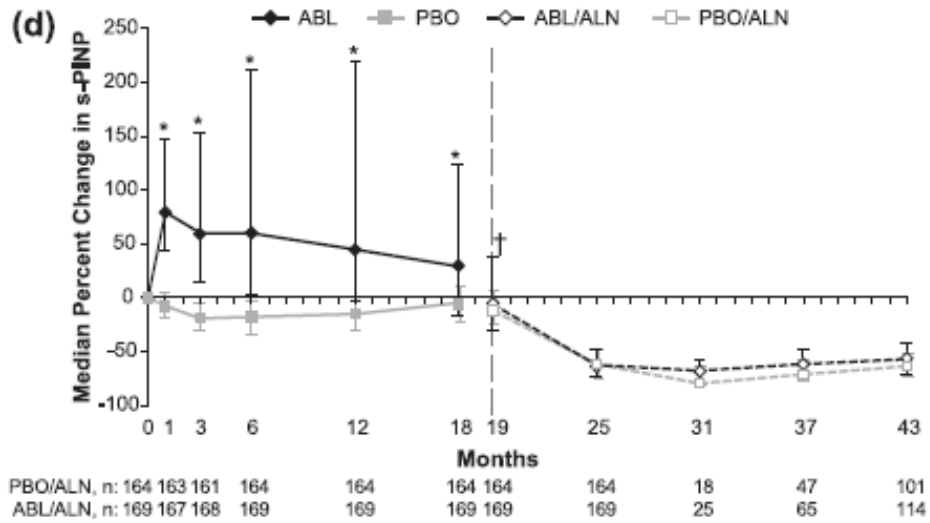
Percentage changes from ACTIVE baseline to end of ACTIVExtend in BMD

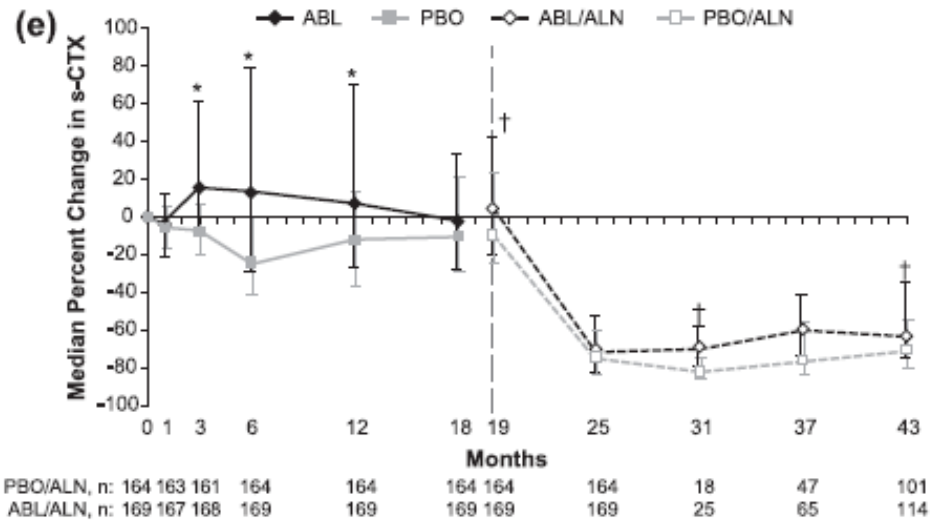






Percentage changes from ACTIVE baseline to end of ACTIVExtend in bone turnover markers

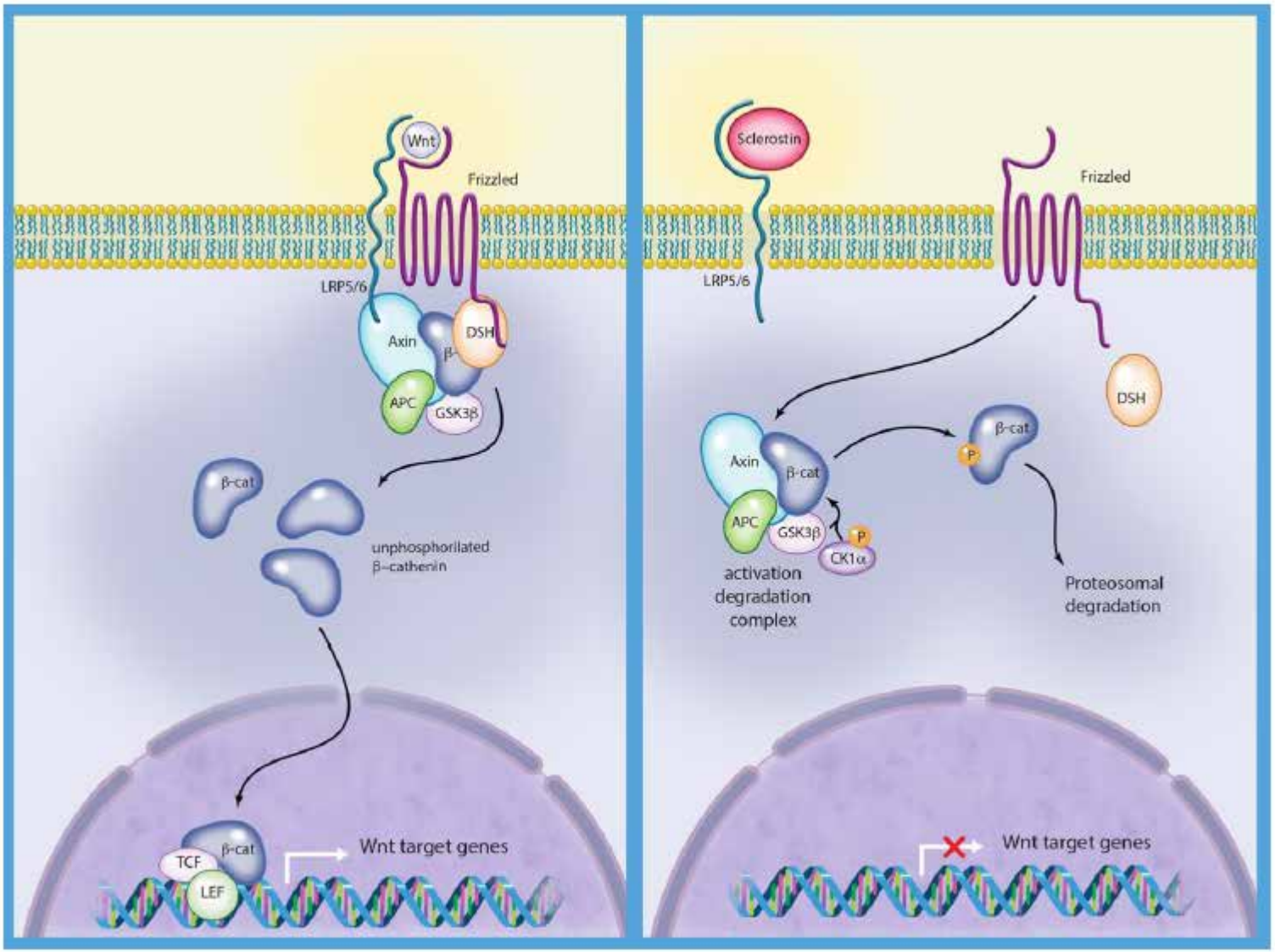




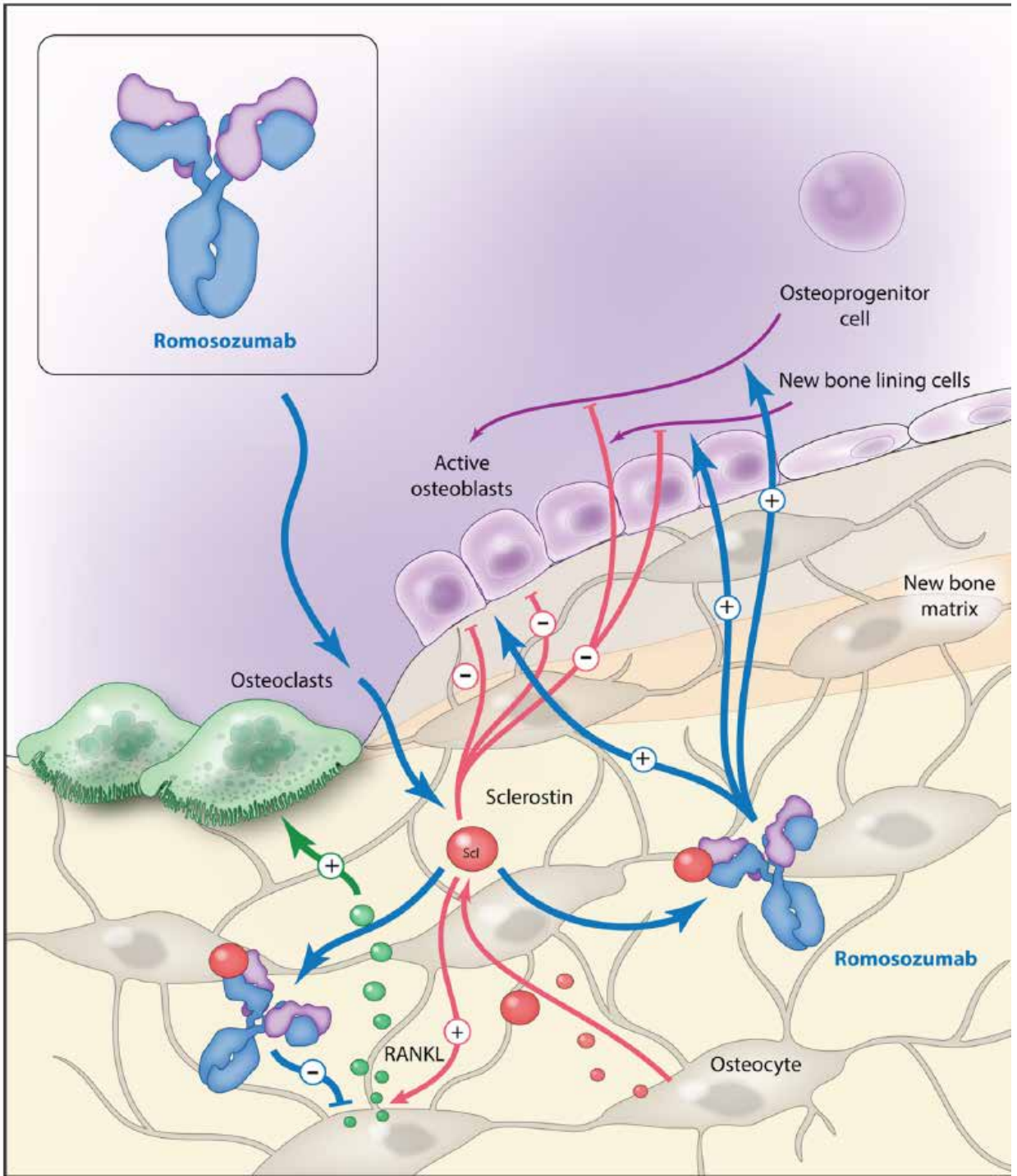
Conclusion

Eighteen months of treatment with ABL followed by 24 months of treatment with ALN reduced the risk of vertebral, nonvertebral, clinical, and major osteoporoticfractures and produced large increments in BMD of the LS, TH, and FN. These findings demonstrate that the sequence of ABL followed by ALN can be a highly efficacious treatment option for postmenopausal women who are at risk for osteoporosis-related fractures.

The clinical potential of romosozumab for the prevention of fractures in postmenopausal women with osteoporosis



Romosozumab mode of action.



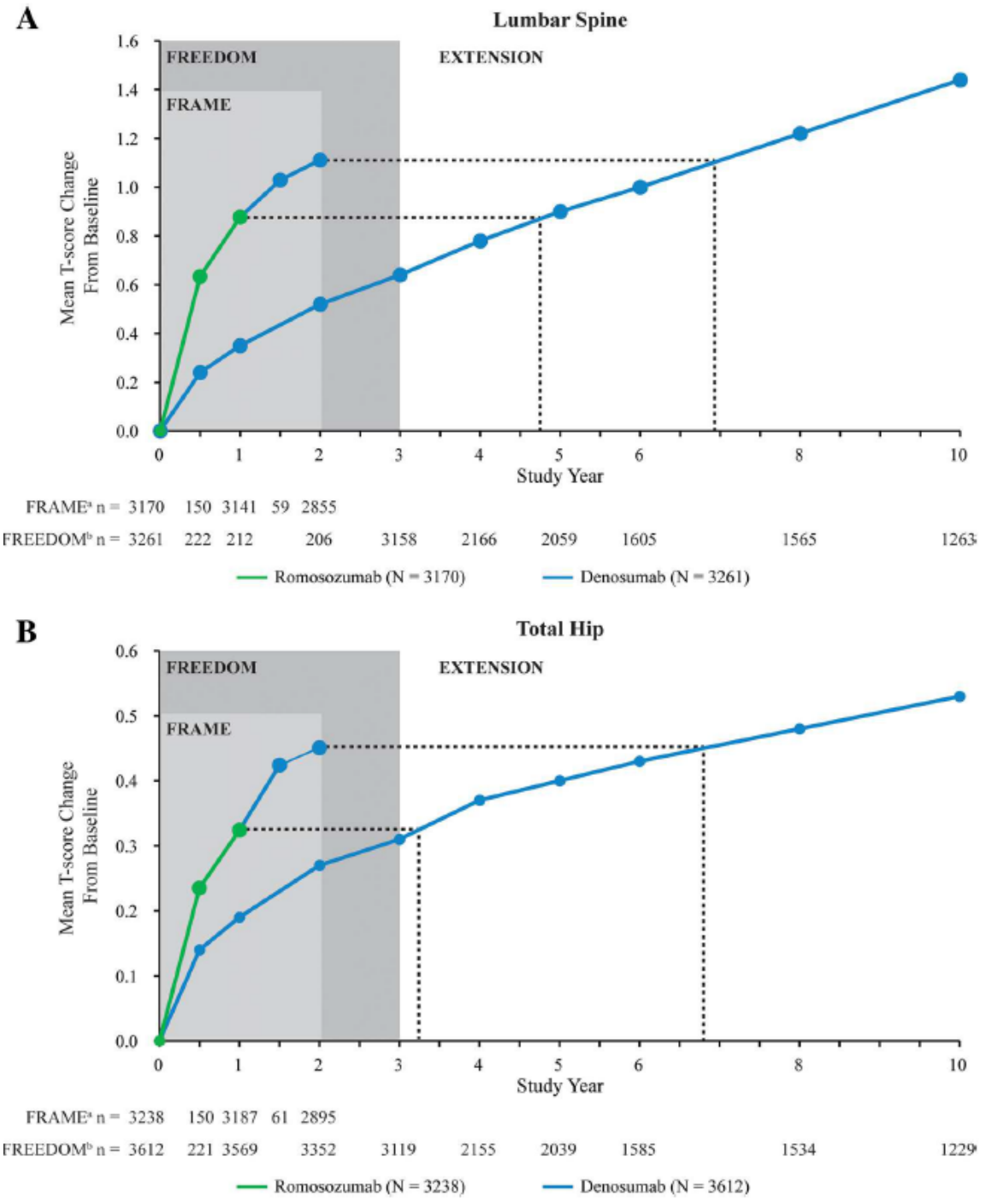
FRAME Study: The Foundation Effect of Building Bone With 1 Year of Romosozumab Leads to Continued Lower Fracture Risk After Transition to Denosumab

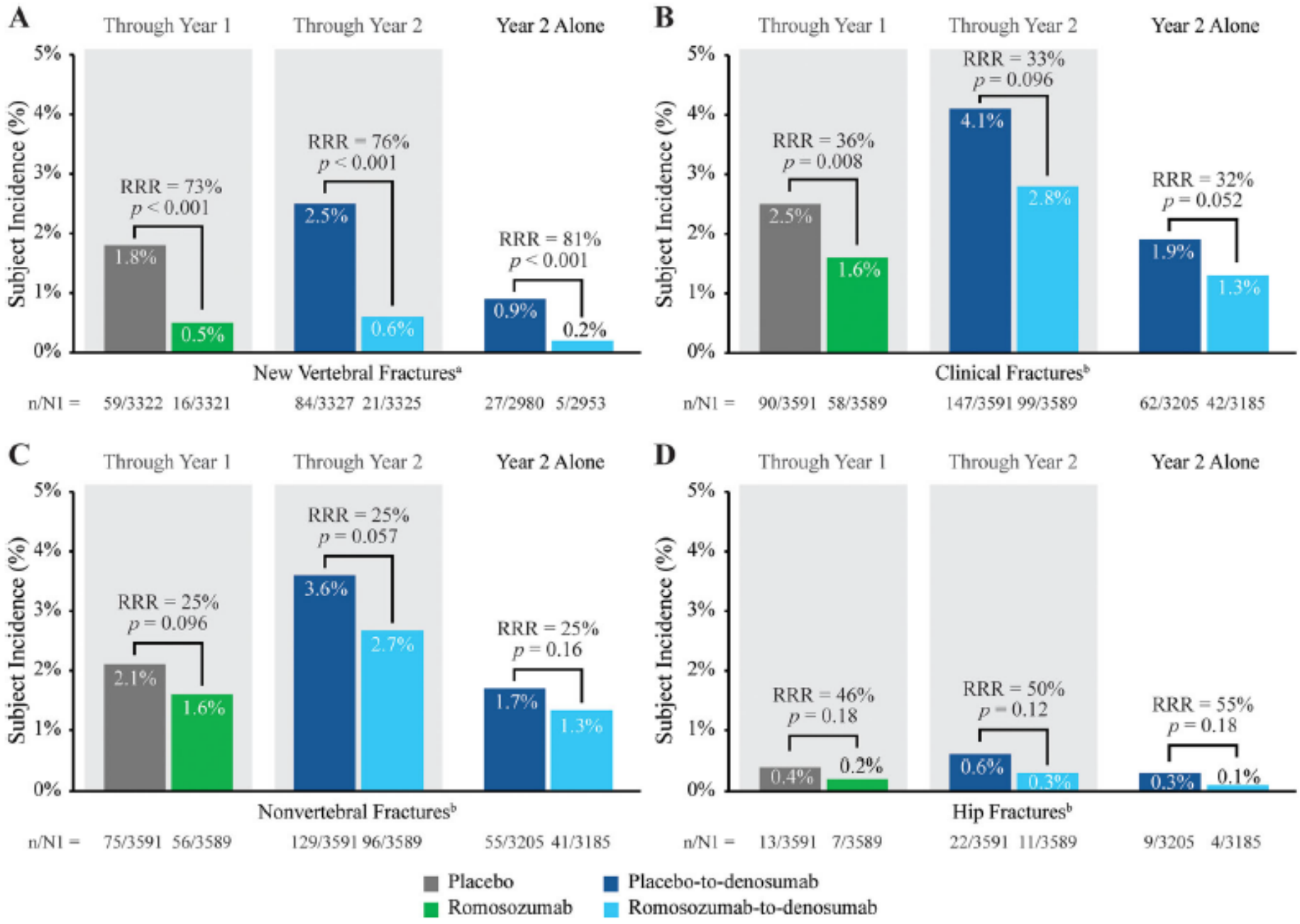
Felicia Cosman,[1,2] Daria B Crittenden,[3] Serge Ferrari,[4] Aliya Khan,[5] Nancy E Lane,[6] Kurt Lippuner,[7] Toshio Matsumoto,[8] Cassandra E Milmont,[3] Cesar Libanati,[9] and Andreas Grauer[3]

ABSTRACT

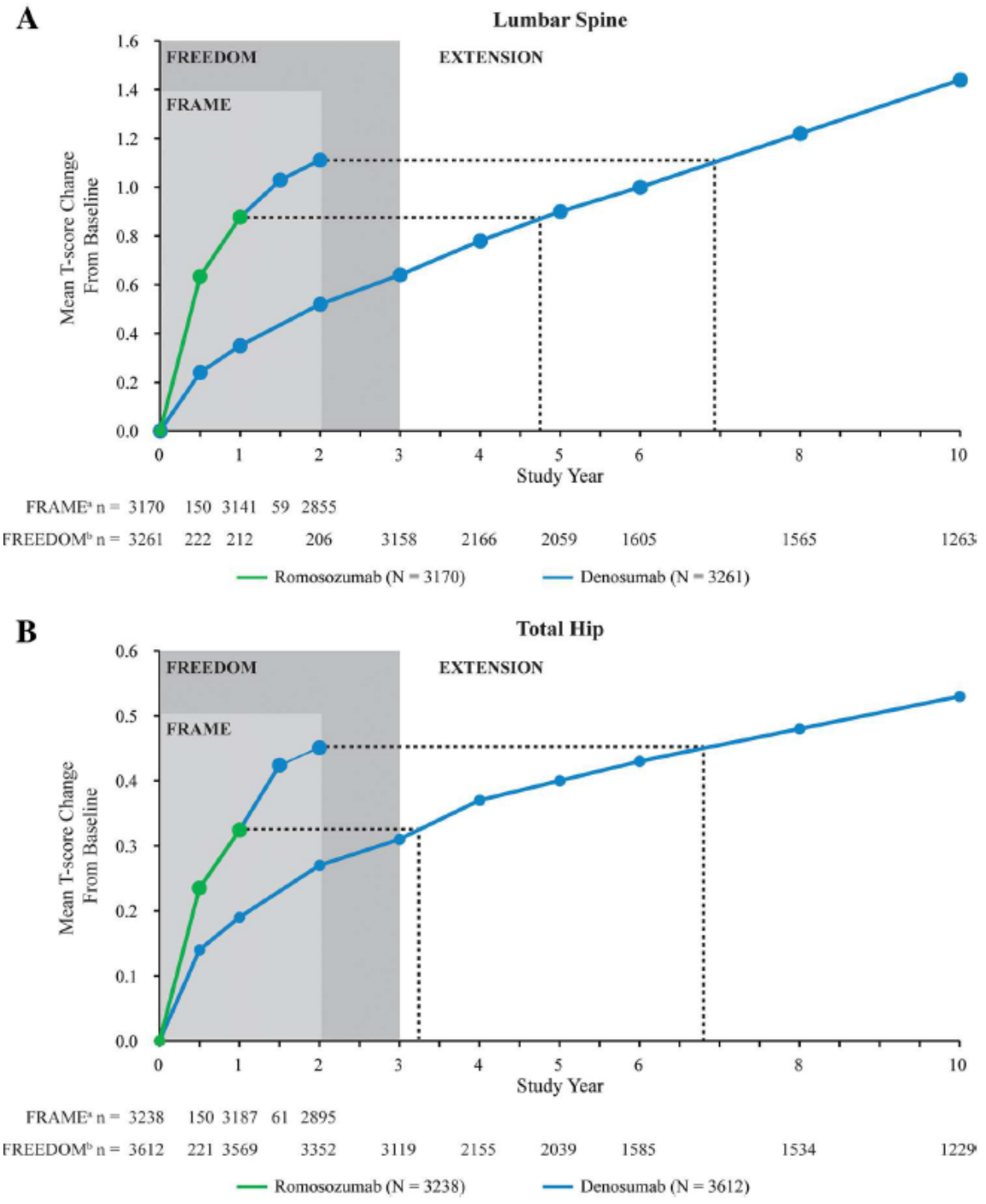
Romosozumab is a bone-forming agent with a dual effect of increasing bone formation and decreasing bone resorption. In FRActure study in postmenopausal woMen with ostEoporosis (FRAME), postmenopausal women with osteoporosis received romosozumab 210 mg s.c. or placebo once monthly for 12 months, followed by denosumab 60 mg s.c. once every 6 months in both groups for 12 months. One year of romosozumab increased spine and hip BMD by 13% and 7%, respectively, and reduced vertebral and clinical fractures with persistent fracture risk reduction upon transition to denosumab over 24 months. Here, we further characterize the BMD gains with romosozumab by quantifying the percentages of patients who responded at varying magnitudes; report the mean *T*-score changes from baseline over the 2-year study and contrast these results with the long-term BMD gains seen with denosumab during Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) and its Extension studies; and assess fracture incidence rates in year 2, when all patients received denosumab. Among 7180 patients ($n = 3591$ placebo, $n = 3589$ romosozumab), most romosozumab-treated patients experienced $\geq$3% gains in BMD from baseline at month 12 (spine, 96%; hip, 78%) compared with placebo (spine, 22%; hip, 16%). For romosozumab patients, mean absolute *T*-score increases at the spine and hip were 0.88 and 0.32, respectively, at 12 months (placebo: 0.03 and 0.01) and 1.11 and 0.45 at 24 months (placebo-to-denosumab: 0.38 and 0.17), with the 2-year gains approximating the effect of 7 years of continuous denosumab administration. Patients receiving romosozumab versus placebo in year 1 had significantly fewer vertebral fractures in year 2 (81% relative reduction; $p < 0.001$), with fewer fractures consistently observed across other fracture categories. The data support the clinical benefit of rebuilding the skeletal foundation with romosozumab before transitioning to antiresorptive therapy. *Journal of Bone and Mineral Research* Published by Wiley Periodicals, Inc.

BMD T-score increases at the (A) lumbar spine and (B) total hip in FRAME relative to FREEDOM and FREEDOM Extension




A
Through Year 1
Through Year 2
Year 2 Alone
Subject Incidence (%)
5%
4%
3%
2%
1%
0%
RRR = 73%
p < 0.001
1.8%
0.5%
RRR = 76%
p < 0.001
2.5%
0.6%
RRR = 81%
p < 0.001
0.9%
0.2%
New Vertebral Fractures[a]
n/N1 = 59/3322 16/3321 84/3327 21/3325 27/2980 5/2953
B
Through Year 1
Through Year 2
Year 2 Alone
Subject Incidence (%)
RRR = 36%
p = 0.008
2.5%
1.6%
RRR = 33%
p = 0.096
4.1%
2.8%
RRR = 32%
p = 0.052
1.9%
1.3%
Clinical Fractures[b]
n/N1 = 90/3591 58/3589 147/3591 99/3589 62/3205 42/3185
C
Through Year 1
Through Year 2
Year 2 Alone
Subject Incidence (%)
RRR = 25%
p = 0.096
2.1%
1.6%
RRR = 25%
p = 0.057
3.6%
2.7%
RRR = 25%
p = 0.16
1.7%
1.3%
Nonvertebral Fractures[b]
n/N1 = 75/3591 56/3589 129/3591 96/3589 55/3205 41/3185
D
Through Year 1
Through Year 2
Year 2 Alone
Subject Incidence (%)
RRR = 46%
p = 0.18
0.4%
0.2%
RRR = 50%
p = 0.12
0.6%
0.3%
RRR = 55%
p = 0.18
0.3%
0.1%
Hip Fractures[b]
n/N1 = 13/3591 7/3589 22/3591 11/3589 9/3205 4/3185
Placebo
Romosozumab
Placebo-to-denosumab
Romosozumab-to-denosumab

BMD T-score increases at the (A) lumbar spine and (B) total hip in FRAME relative to FREEDOM and FREEDOM Extension



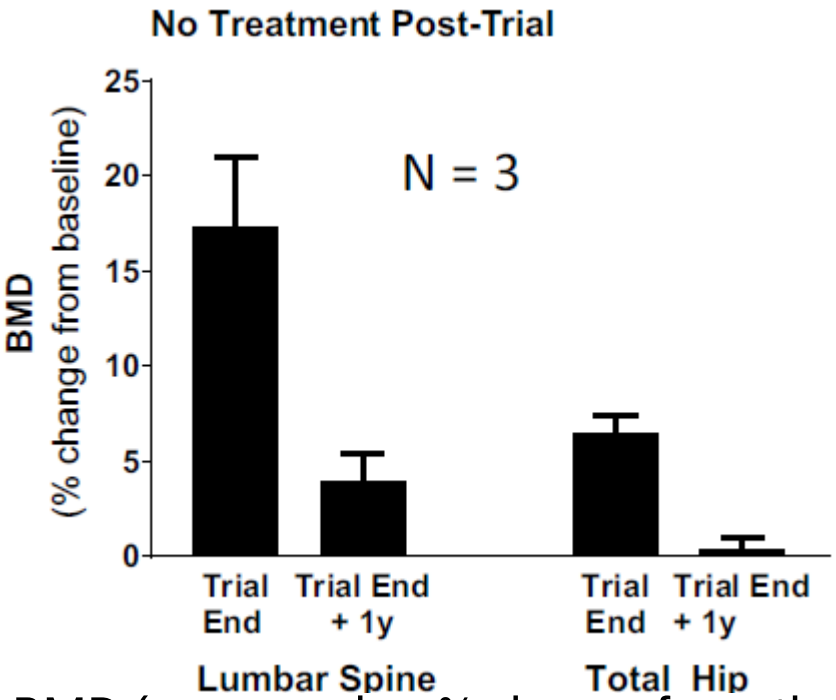
Bone Loss After Romosozumab/Denosumab: Effects of Bisphosphonates

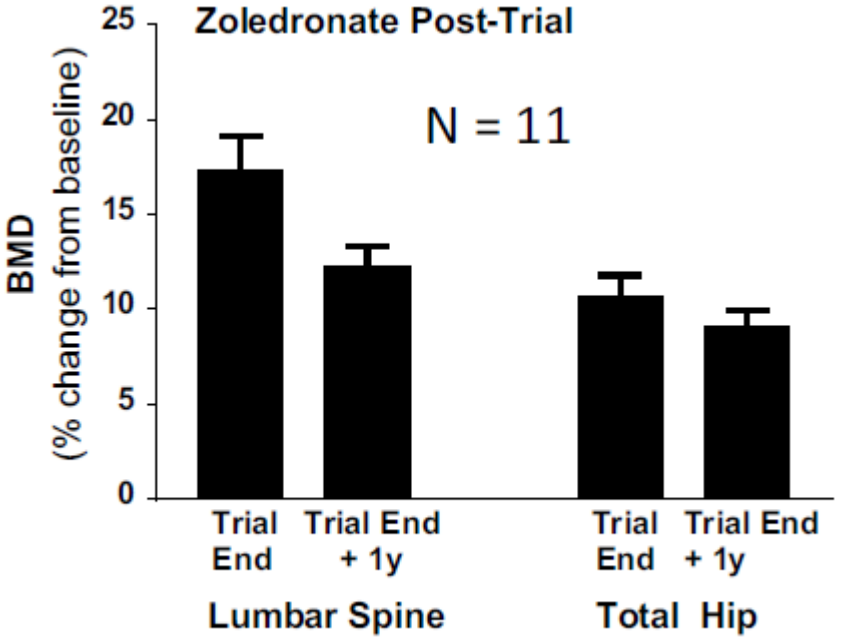
AM. Horne, B. Mihov, IR. Reid.

Calcified Tissue International (2018) 103:55–61

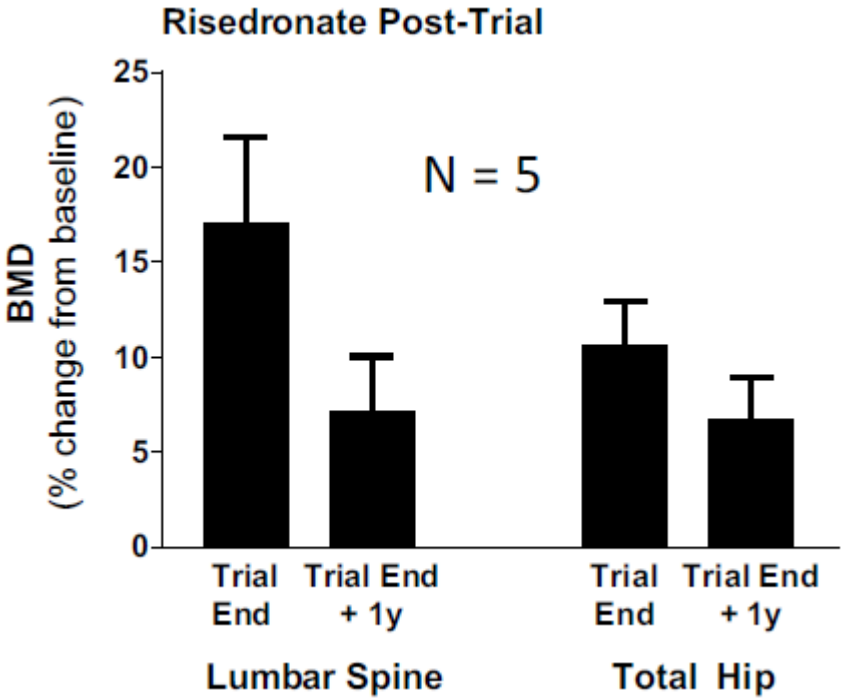
Abstract

Romosozumab and denosumab are monoclonal antibodies for the treatment of osteoporosis. Both have a rapid offset of effect resulting in loss of bone density (BMD) gained on-treatment and, in some cases, multiple vertebral fractures following treatment cessation. We recently reported disappointing results from transitioning patients from denosumab to intravenous zoledronate at the time the next denosumab injection is due. The present report re-assesses the role of bisphosphonates following the use of denosumab. In the FRAME trial, osteoporotic women were randomized to romosozumab or placebo for 1 year, then both groups were provided with open-label denosumab for the subsequent 2 years. In women completing this study at our center, we offered treatment with either oral or intravenous bisphosphonates. In the eleven women opting for intravenous treatment, zoledronate was given after a median delay of 65 days from trial-end, in the hope that this might increase skeletal uptake of the drug and, thereby, its efficacy to maintain bone density. In these women, spine BMD was 17.3% above baseline at trial-end, and still 12.3% above baseline a year later, a 73% (CI: 61%, 85%) retention of the treatment benefit. The comparable BMD figures for the total hip were 10.7 and 9.2% above baseline, a 87% (CI: 77%, 98%) retention of treatment effect. In contrast, those not receiving treatment after the conclusion of the FRAME trial lost 80–90% of the BMD gained on-trial in the following 12 months. Women treated with risedronate showed an intermediate response. In the zoledronate group, mean PINP 6 months post-FRAME was 23 ± 4 µg/L and at 12 months it was 47 ± 8 µg/L, suggesting that repeat zoledronate dosing is needed at 1 year to maintain the BMD gains. In conclusion, delaying administration of intravenous bisphosphonate when transitioning from short-term denosumab appears to increase the extent to which the gains in BMD are maintained.





BMD (expressed as % change from the baseline values at the beginning of the FRAME study) at the end of that study when Dmab was discontinued, and 1 year later. During the 1-year post trial follow-up, some patients received no treatment, some a single infusion of zoledronate administered 15–165 days after the end of the trial, and some weekly risedronate 35 mg. There was significant loss of BMD from trial-end to 1 year in all treatment groups ($P < 0.05$), except in hip BMD for those taking risedronate .



Bone Loss After Romosozumab/Denosumab: Effects of Bisphosphonates

In conclusion, delaying administration of intravenous bisphosphonate when transitioning from denosumab appears to increase the extent to which the gains in BMD are maintained.

The optimal interval remains to be defined with certainty but appears to be 7–8 months after the last denosumab injection.

The PINP results at 1 year, suggest that re-dosing with zoledronate at that time is desirable.

Continuous anti-resorptive therapy, such as an oral bisphosphonate, can probably be started at the time the next denosumab injection would have been due, since its repeated administration will allow it to be taken up by the skeleton as bone turnover progressively increases.

Romosozumab treatment in postmenopausal women with osteoporosis: a meta-analysis of randomized controlled trials

CLIMACTERIC, 2018
VOL. 21, NO. 2, 189–195

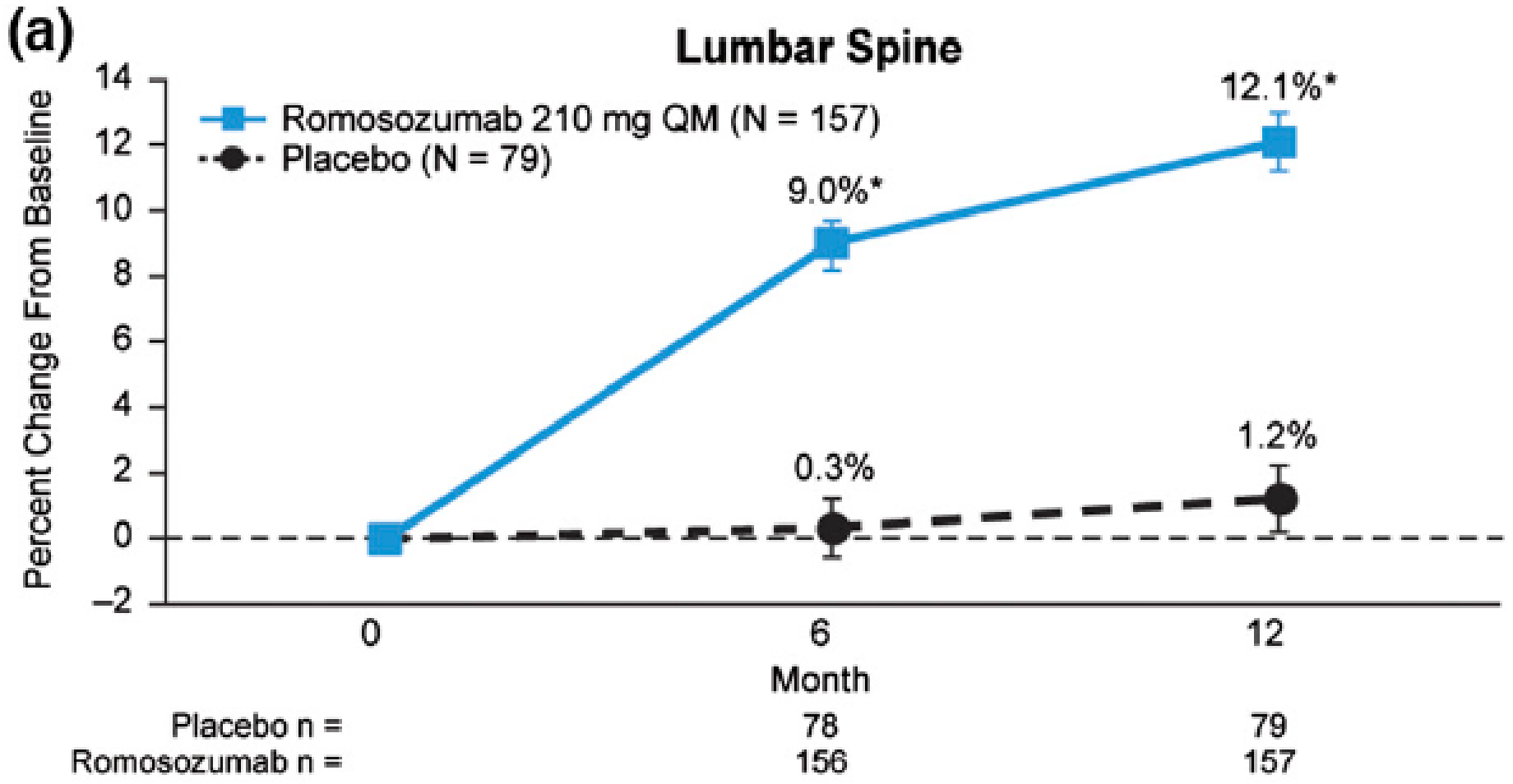
Y. Liu, Y. Cao, S. Zhang, W. Zhang, B. Zhang, Q. Tang, Z. Li & J. Wu

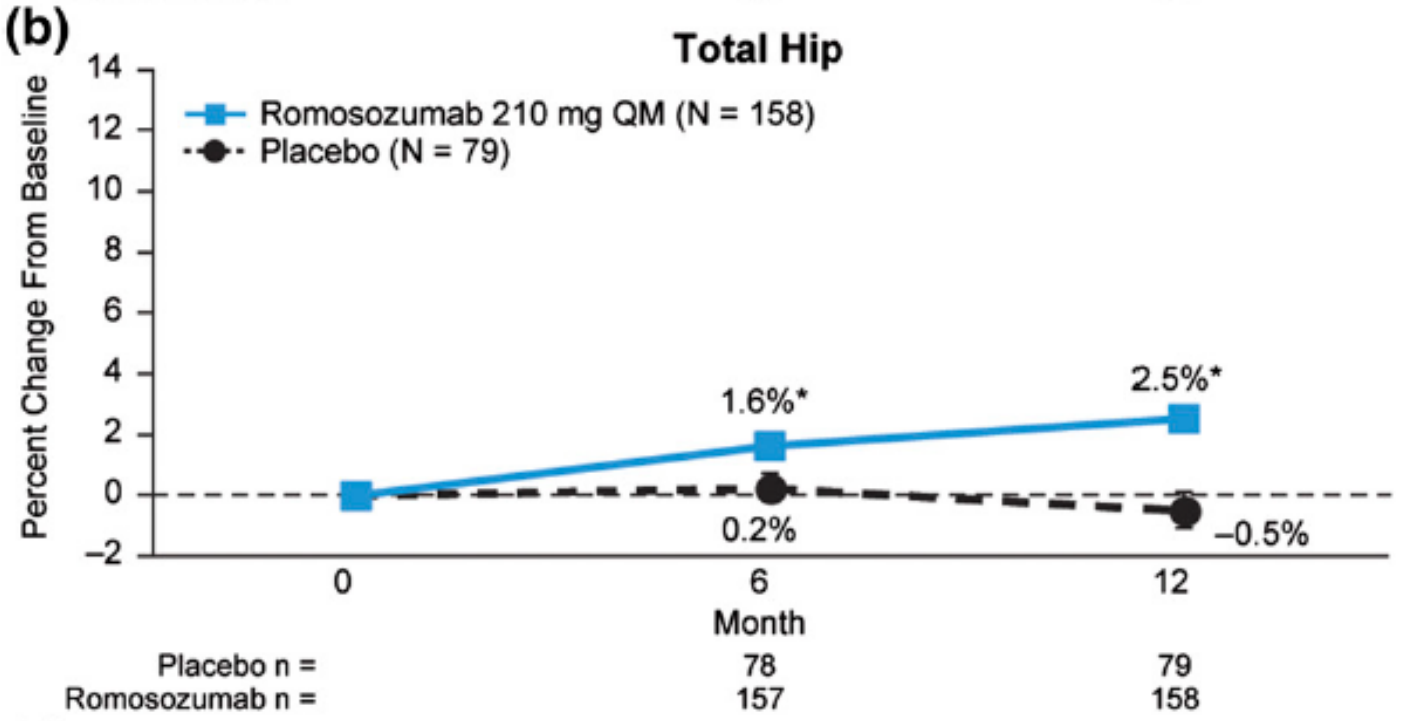
Conclusion

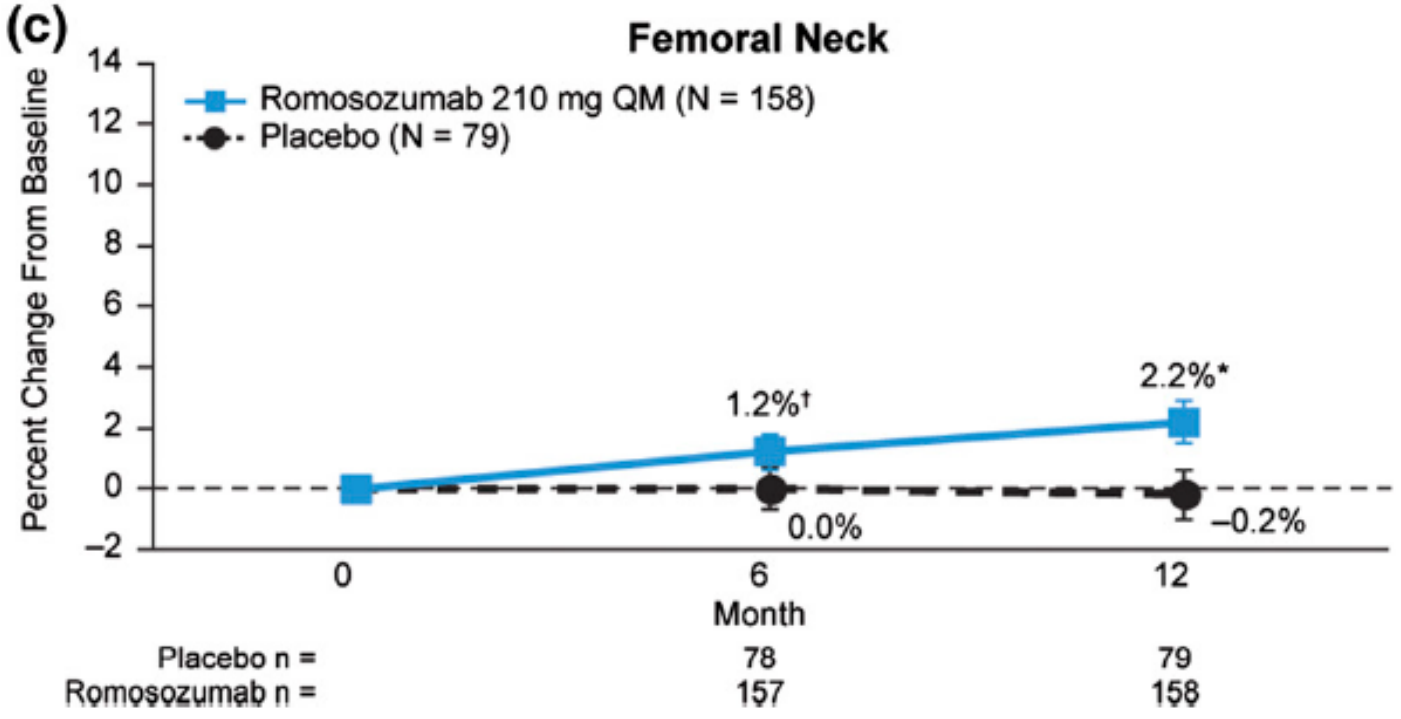
In postmenopausal women with osteoporosis who were at high risk for fracture, romosozumab treatment resulted in a significantly lower risk of fracture and showed the largest gains in BMD despite previous use of bisphosphonate. In future years, to clarify the safety of romosozumab (such as cardiovascular events), more data are needed.

A Phase III Randomized Placebo-Controlled Trial to Evaluate Efficacy and Safety of Romosozumab in Men With Osteoporosis

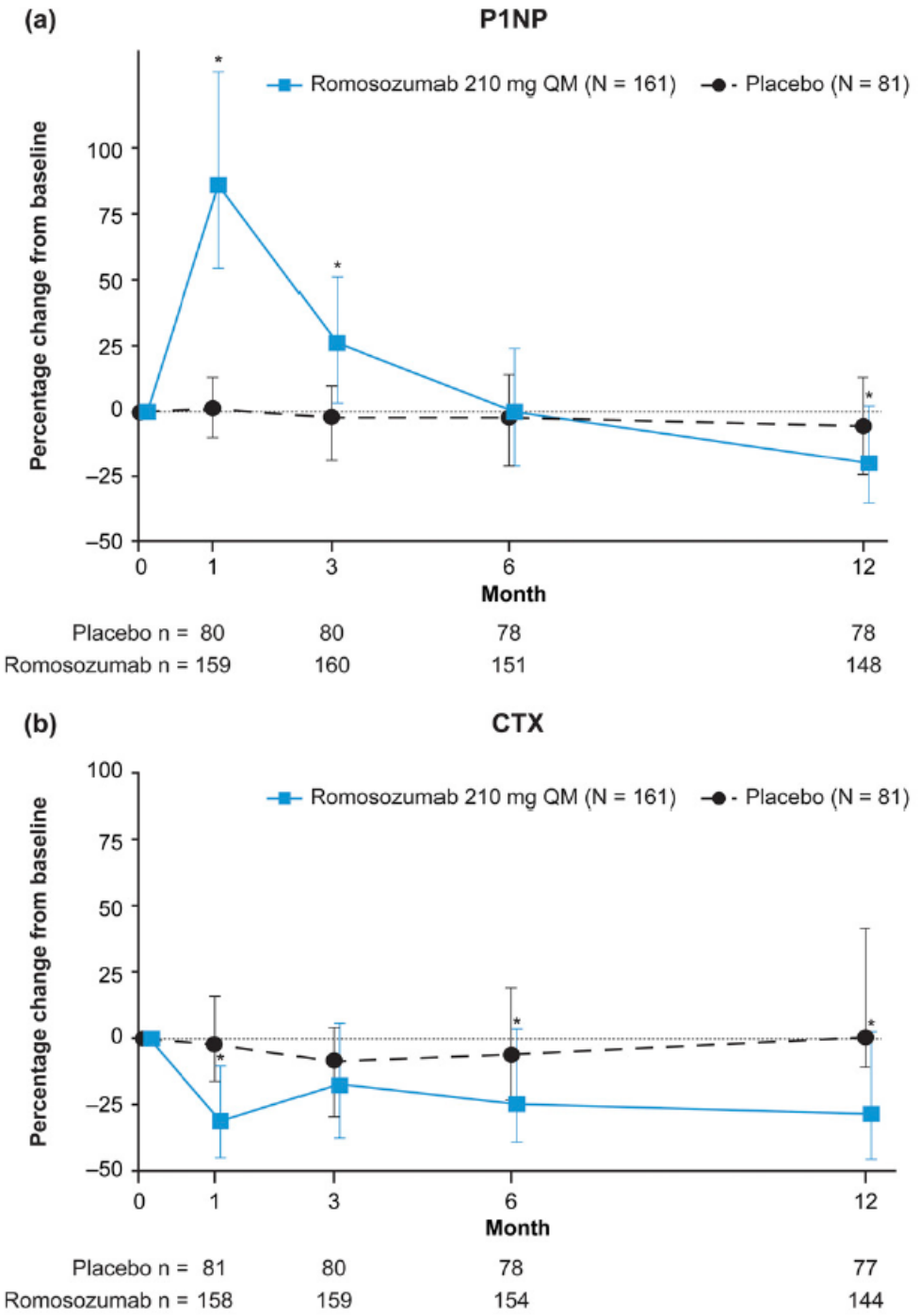
JCEM 103: 3183–3193, 2018)




(b)
Total Hip
Romosozumab 210 mg QM (N = 158)
Placebo (N = 79)
Percent Change From Baseline
14
12
10
8
6
4
2
0
–2
1.6%*
2.5%*
0.2%
–0.5%
0
6
12
Month
Placebo n =
Romosozumab n =
78
157
79
158


(c)
Femoral Neck
Romosozumab 210 mg QM (N = 158)
Placebo (N = 79)
Percent Change From Baseline
14
12
10
8
6
4
2
0
–2
1.2%†
2.2%*
0.0%
–0.2%
0
6
12
Month
Placebo n =
Romosozumab n =
78
157
79
158

Percentage change from baseline in BTMs stratified by visit. Percentage change from baseline in (a) serum P1NP and (b) serum CTX levels stratified by visit



Calcified Tissue International (2018) 103:359–371
https://doi.org/10.1007/s00223-018-0437-x

ORIGINAL RESEARCH

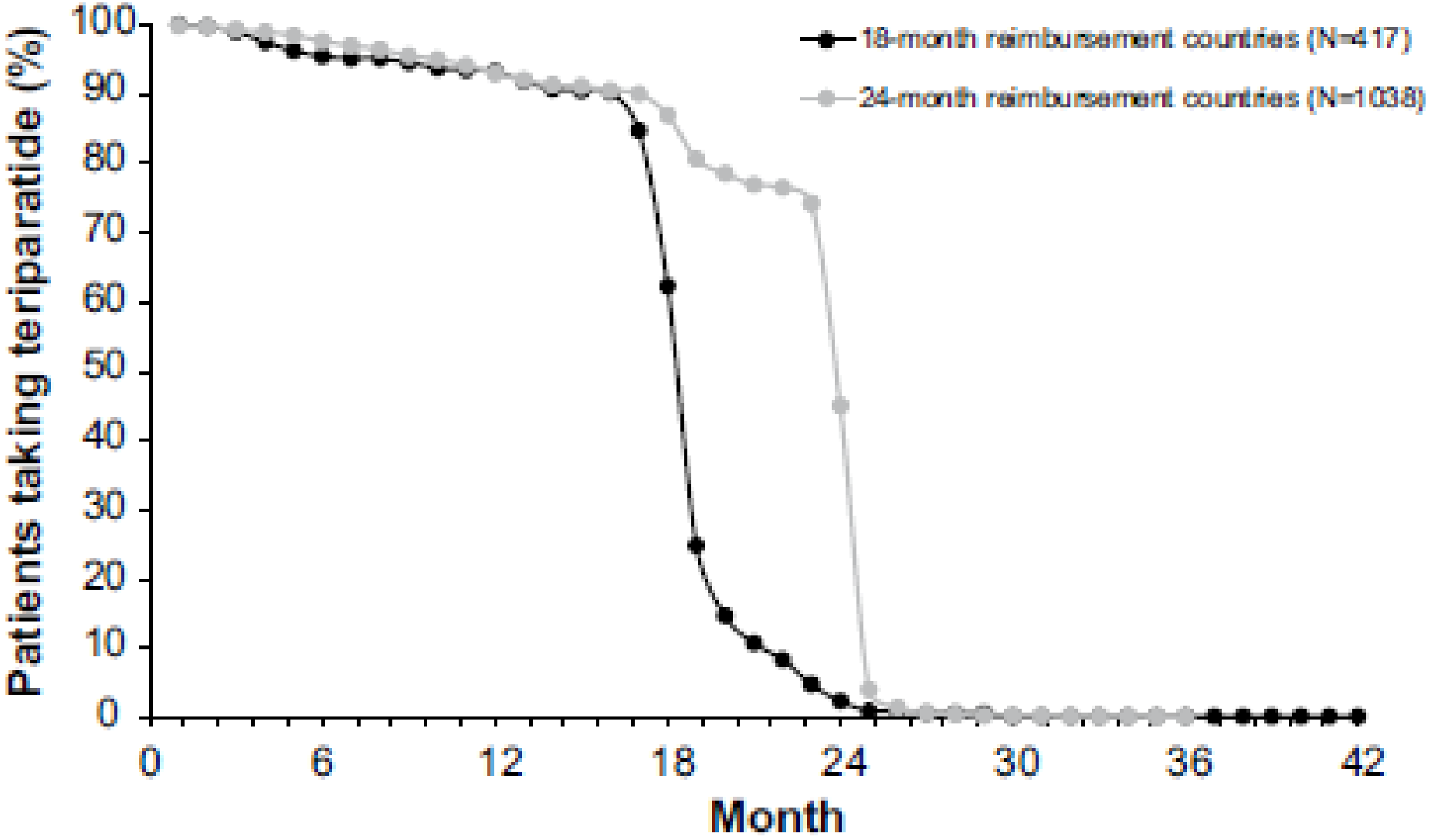
Effects of Teriparatide in Patients with Osteoporosis in Clinical Practice: 42-Month Results During and After Discontinuation of Treatment from the European Extended Forsteo® Observational Study (ExFOS)

Nicola Napoli[1] · Bente. L. Langdahl[2] · Östen Ljunggren[3] · Eric Lespessailles[4,5] · George Kapetanos[6] · Tomaz Kocjan[7] · Tatjana Nikolic[8] · Pia Eiken[9,10] · Helmut Petto[11] · Thomas Moll[11] · Erik Lindh[11] · Fernando Marin[11]

Abstract

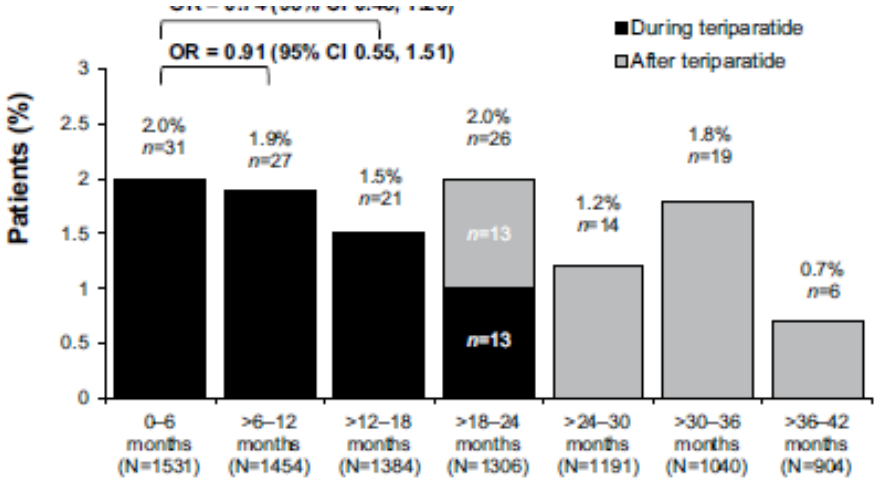
This study aimed to describe clinical outcomes in patients prescribed teriparatide and followed up for 18 months after stopping the drug in real-life conditions. The Extended Forsteo® Observational Study analysed incident clinical fractures in 6-month intervals .. Changes in back pain and health-related quality of life (HRQoL; Patients were analysed if they had a post-baseline visit, regardless of whether and for how long they took teriparatide. Of 1531patients analysed (90.7% female, mean age: 70.3 years), 76 (5.0%) never took teriparatide. Median treatment duration was 23.6 months.....

Persistence with teriparatide over time differentiated by 18- and 24-month reimbursement countries (data from Active Treatment Cohort)

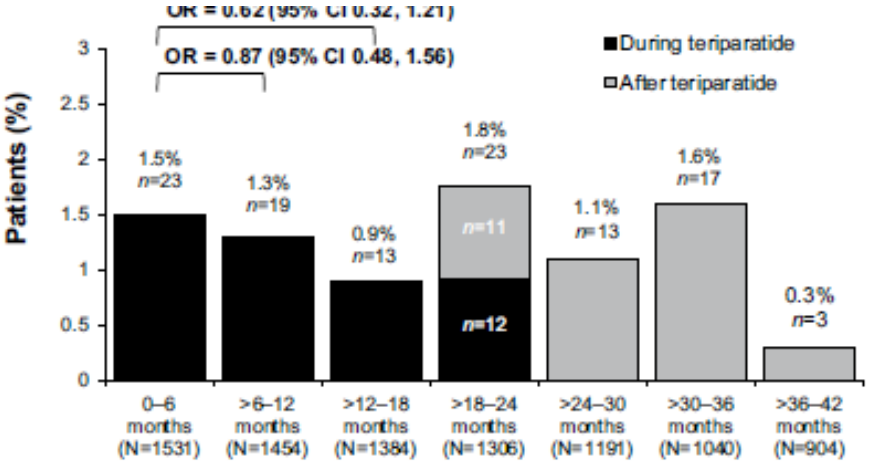


Fracture outcomes in the Total Study Cohort during and after teriparatide treatment for

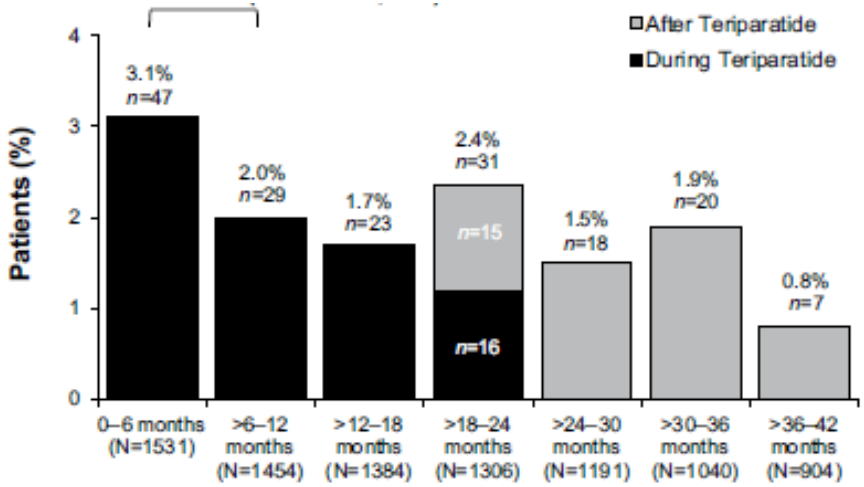
a clinical fractures



b clinical vertebral fractures

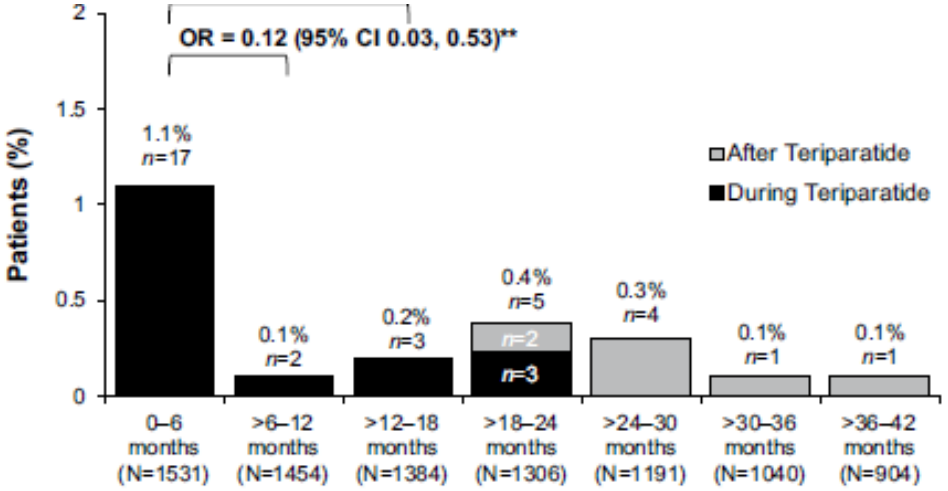


c non-vertebral fractures

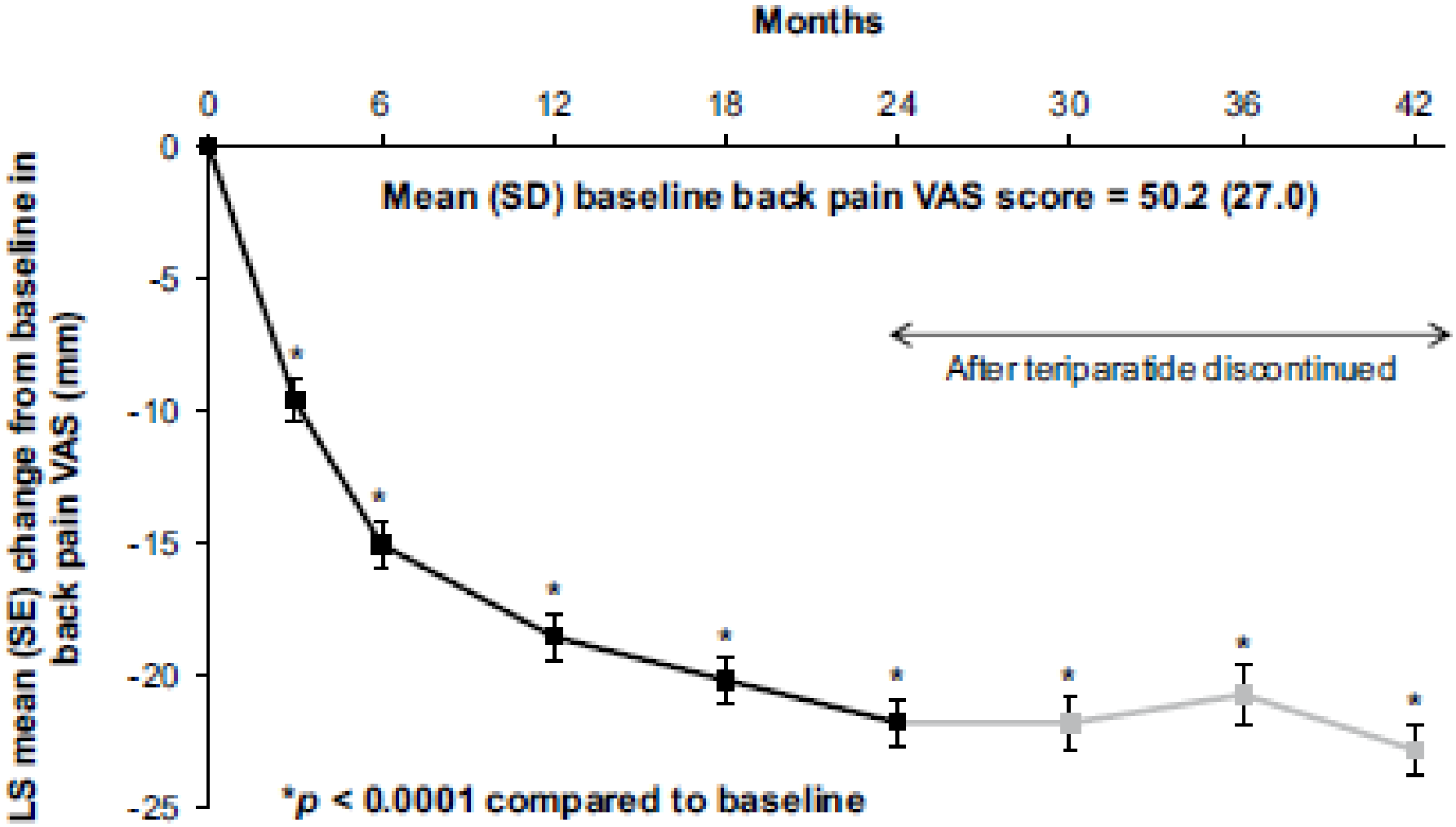


d main non-vertebral fractures

(forearm/wrist, hip, humerus, leg or ribs).



Change in back pain VAS score from baseline



Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial

Lancet 2018; 391: 230–40

David L Kendler, Fernando Marin, Cristiano A F Zerbini, Luis A Russo, Susan L Greenspan, Vit Zikan, Alicia Bagur, Jorge Malouf-Sierra, Péter Lakatos, Astrid Fahrleitner-Pammer, Eric Lespessailles, Salvatore Minisola, Jean Jacques Body, Piet Geusens, Rüdiger Möricke, Pedro López-Romero

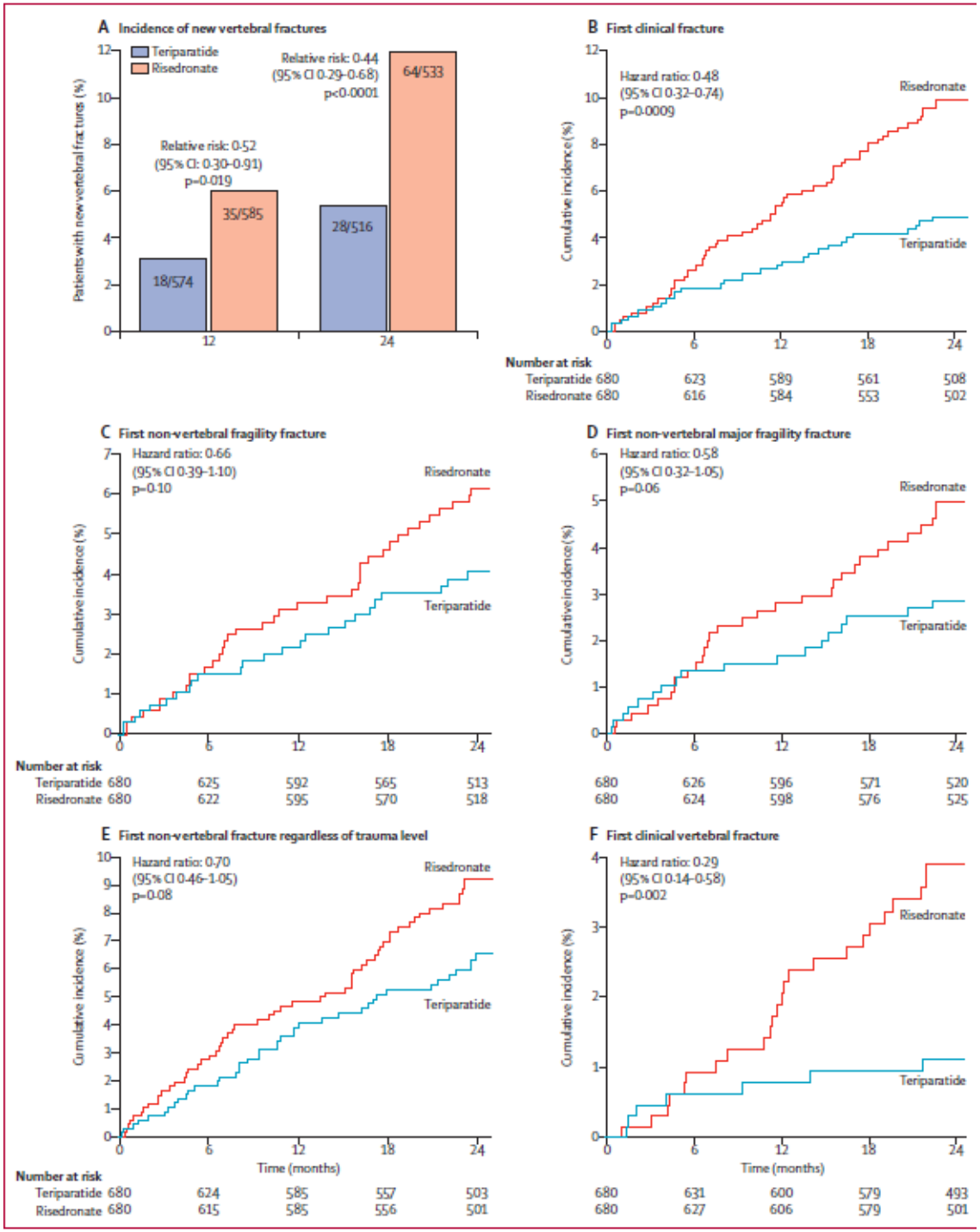
Summary

Background No clinical trials have compared osteoporosis drugs with incident fractures as the primary outcome. We compared the anti-fracture efficacy of teriparatide with risedronate in patients with severe osteoporosis.

Methods In this double-blind, double-dummy trial, we enrolled post-menopausal women with at least two moderate or one severe vertebral fracture and a bone mineral density T score of less than or equal to –1·50. Participants were randomly assigned to receive 20 µg of teriparatide once daily plus oral weekly placebo or 35 mg of oral risedronate once weekly plus daily injections of placebo for 24 months. The primary outcome was new radiographic vertebral fractures. Secondary, gated outcomes included new and worsened radiographic vertebral fractures, clinical fractures (a composite of non-vertebral and symptomatic vertebral), and non-vertebral fractures. This study is registered with ClinicalTrials.gov (NCT01709110) and EudraCT (2012-000123-41).

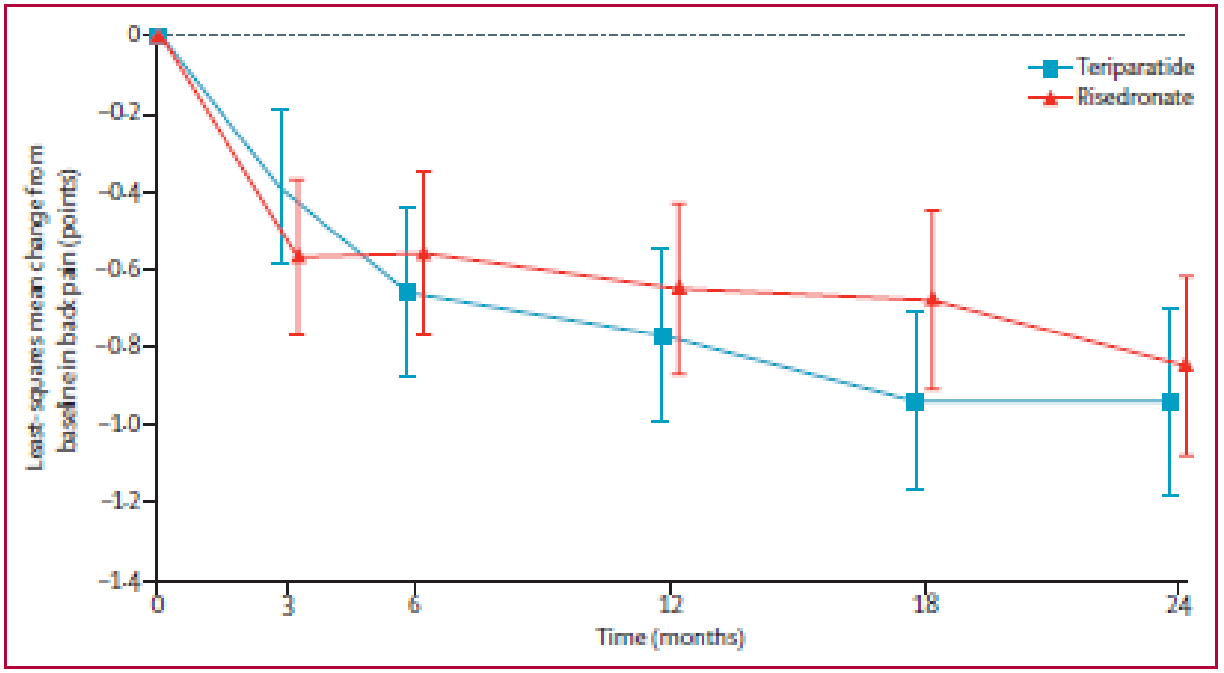
Findings We enrolled 680 patients in each group. At 24 months, new vertebral fractures occurred in 28 (5·4%) of 680 patients in the teriparatide group and 64 (12·0%) of 680 patients in the risedronate group (risk ratio 0·44, 95% CI 0·29–0·68; p<0·0001). Clinical fractures occurred in 30 (4·8%) of 680 patients in the teriparatide group compared with 61 (9·8%) of 680 in the risedronate group (hazard ratio 0·48, 95% CI 0·32–0·74; p=0·0009). Non-vertebral fragility fractures occurred in 25 (4·0%) patients in the teriparatide group and 38 (6·1%) in the risedronate group (hazard ratio 0·66; 95% CI 0·39–1·10; p=0·10).

Incidence of fractures over 24 months

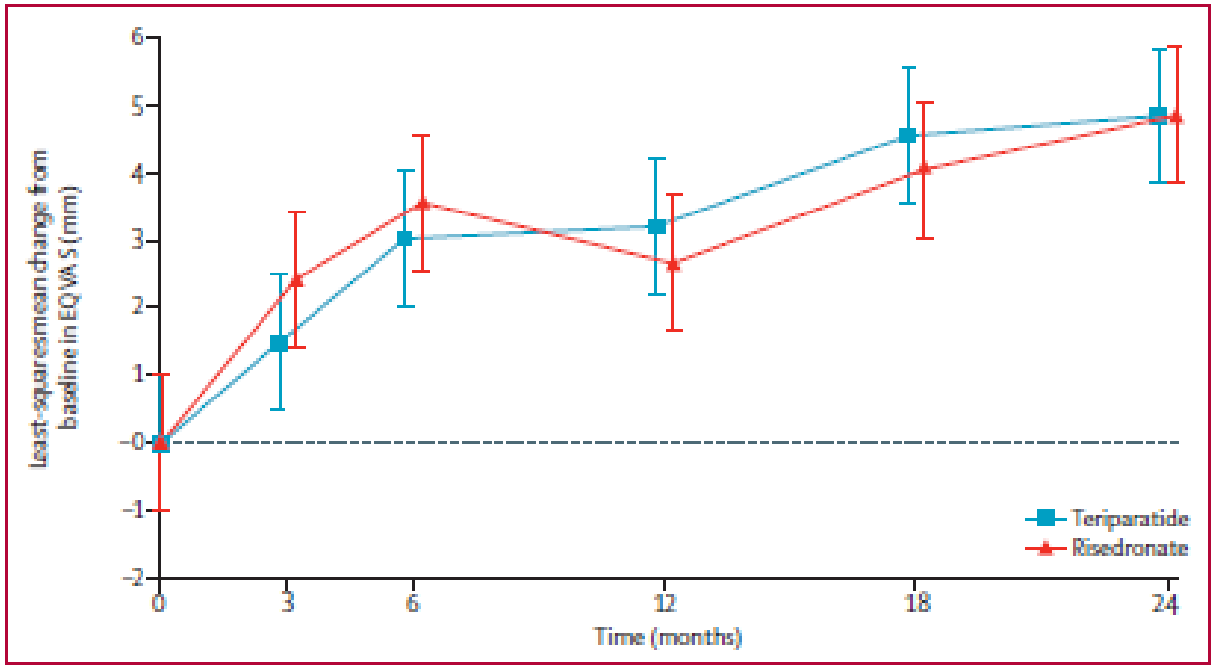


Lancet 2018; 391: 230–40

Change from baseline in back pain over 24 months (full analysis set)



Change from baseline in EQ VAS over 24 months (full analysis set)



Lancet 2018; 391: 230–40

Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial

***Lancet* 2018; 391: 230–40**

David L Kendler, Fernando Marin, Cristiano A F Zerbini, Luis A Russo, Susan L Greenspan, Vit Zikan, Alicia Bagur, Jorge Malouf-Sierra, Péter Lakatos, Astrid Fahrleitner-Pammer, Eric Lespessailles, Salvatore Minisola, Jean Jacques Body, Piet Geusens, Rüdiger Möricke, Pedro López-Romero

In conclusion, in post-menopausal women with established osteoporosis who are at high risk of fracture, treatment with teriparatide was associated with a significant reduction in the incidence of vertebral and clinical fractures compared with risedronate. Differences between groups in the incidence of non-vertebral fractures were not statistically significant. Adverse events and safety laboratory findings accorded with the safety profile of either drug. These data show that teriparatide is better at preventing fractures in patients with severe osteoporosis, and confirm previous data from clinical trials of teriparatide versus bisphosphonates with fracture as a secondary endpoint.

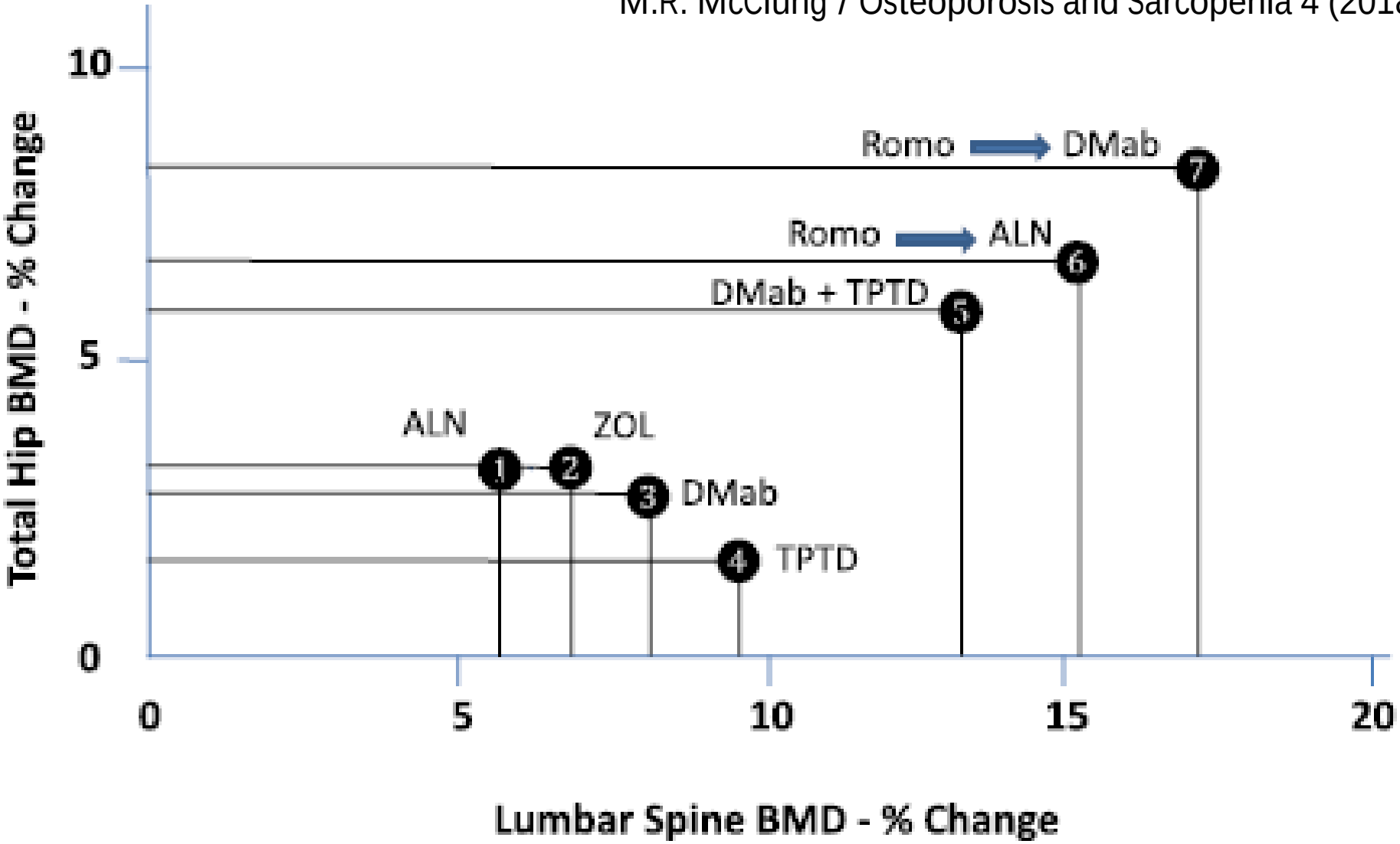
Bone-forming agents in non-responders to bisphosphonates

Juliet Compston doi.org/10.1016/ S0140-6736(17)31613-6

In clinical practice, it is not uncommon to encounter patients who despite adequate adherence to medication apparently do not respond to oral bisphosphonates, with persistently low BMD or incident fracture during treatment. Some of these patients might respond to intravenous bisphosphonate therapy, but in others switching to a drug that stimulates bone formation is a reasonable approach.

Percent changes from baseline at 24 months (M) in bone mineral density (BMD) of the lumbar spine and total hip in postmenopausal women with osteoporosis with various treatment regimens

M.R. McClung / Osteoporosis and Sarcopenia 4 (2018)



Σας ευχαριστώ

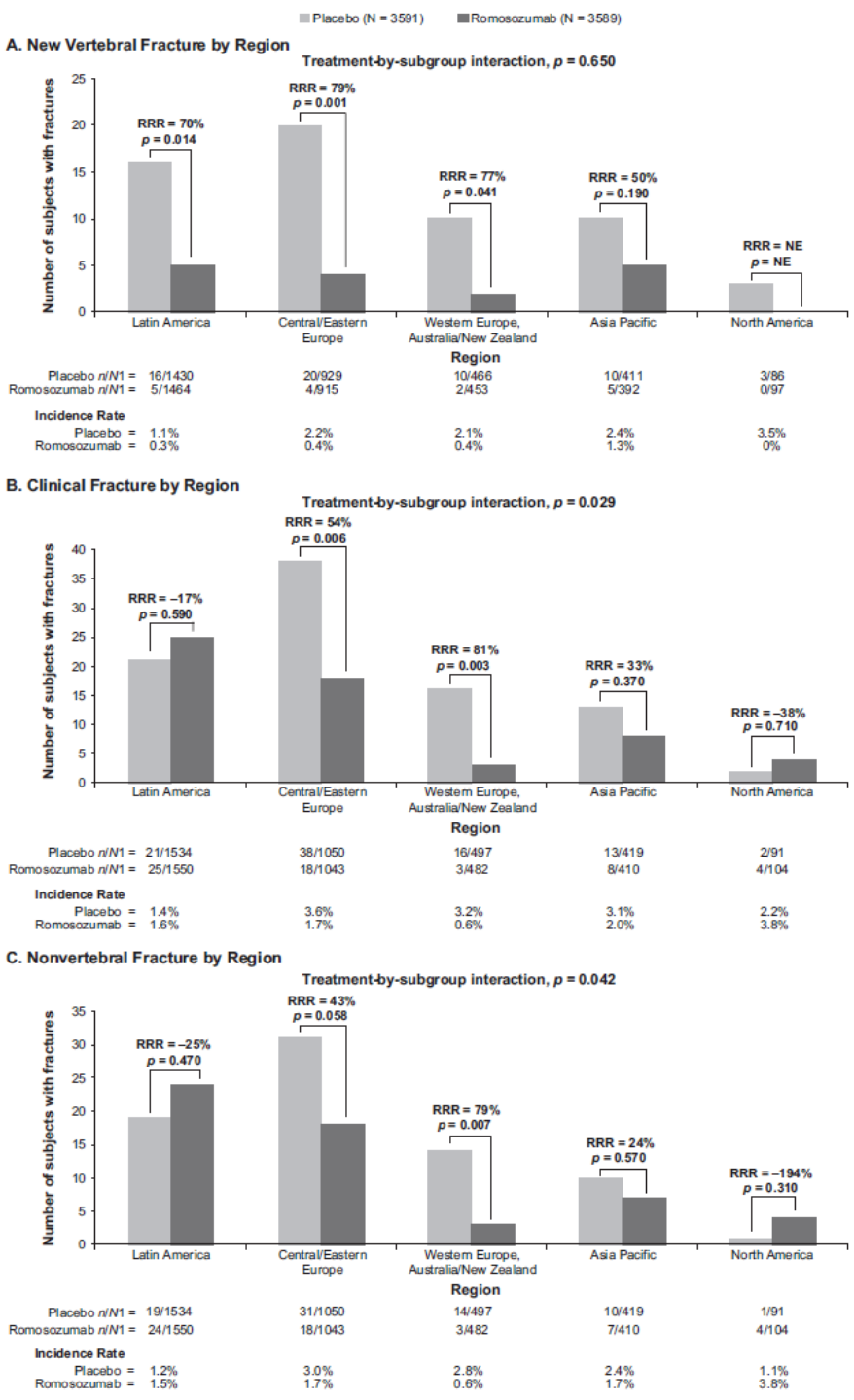
Romosozumab FRAME Study: A Post Hoc Analysis of the Role of Regional Background Fracture Risk on Nonvertebral Fracture Outcome

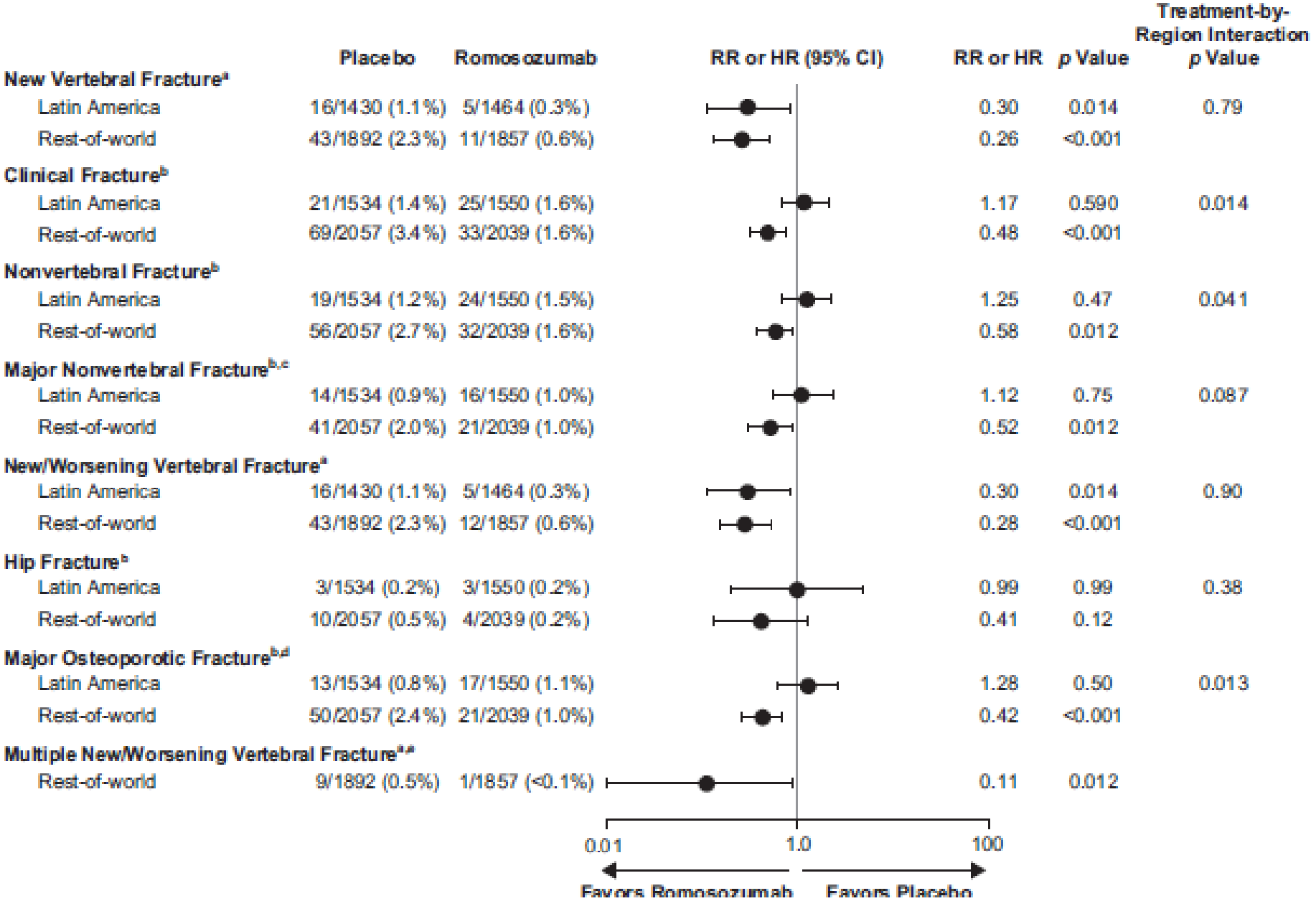
Felicia Cosman,[1] Daria B Crittenden,[2] Serge Ferrari,[3] E Michael Lewiecki,[4] Juan Jaller-Raad,[5] Cristiano Zerbini,[6] Cassandra E Milmont,[2] Paul D Meisner,[7] Cesar Libanati,[7] and Andreas Grauer[2]

ABSTRACT

In the pivotal Fracture Study in Postmenopausal Women with Osteoporosis (FRAME; NCT01575834), 1 year of the bone-forming agent romosozumab significantly reduced new vertebral and clinical fracture risk versus placebo. Nonvertebral fracture risk was not significantly reduced in the overall population, influenced by a low placebo-group fracture rate, observed particularly in the highest-enrolling region of Latin America. In year 1 of FRAME, postmenopausal women with a *T*-score of −2.5 to −3.5 at the total hip or femoral neck were randomized to subcutaneous romosozumab 210 mg or placebo once monthly for 12 months. Of 7180 randomized women, 43% were from Latin America, largely Colombia and Brazil. Prespecified analyses assessed fracture risk reductions by geographic regions. A significant treatment-by-geographic region interaction for the clinical ($p = 0.029$) and nonvertebral fracture ($p = 0.042$) endpoints led to further characterization of the Latin American population and comparison with the remaining study population, grouped post hoc as rest-of-world. Nonvertebral fracture efficacy in the overall population was also assessed by baseline fracture risk using the Fracture Risk Assessment Tool (FRAX). Romosozumab significantly and consistently reduced new vertebral fracture risk in Latin America (70% reduction; $p = 0.014$) and rest-of-world (74% reduction; $p < 0.001$). For nonvertebral fracture, risk reductions were observed in rest-of-world (42% reduction; $p = 0.012$), with no treatment effect observed in Latin America, where background nonvertebral fracture risk was low (1.2% in the placebo group). Consistent with this finding, in the overall population, greater reductions in nonvertebral fracture risk were observed among women with higher FRAX scores. These findings suggest that fracture risk assessment should consider regional factors in addition to classical risk factors, such as bone mineral density. In women at high risk for fracture, romosozumab reduced nonvertebral fracture risk within 1 year. *Journal of Bone and Mineral Research* Published by Wiley Periodicals Inc.

Number of subjects with fractures and fracture risk reduction through month 12 by region




Placebo
Romosozumab
RR or HR (95% CI)
RR or HR
p Value
Treatment-by-Region Interaction p Value
New Vertebral Fracture[a]
Latin America 16/1430 (1.1%) 5/1464 (0.3%) 0.30 0.014 0.79
Rest-of-world 43/1892 (2.3%) 11/1857 (0.6%) 0.26 <0.001
Clinical Fracture[b]
Latin America 21/1534 (1.4%) 25/1550 (1.6%) 1.17 0.590 0.014
Rest-of-world 69/2057 (3.4%) 33/2039 (1.6%) 0.48 <0.001
Nonvertebral Fracture[b]
Latin America 19/1534 (1.2%) 24/1550 (1.5%) 1.25 0.47 0.041
Rest-of-world 56/2057 (2.7%) 32/2039 (1.6%) 0.58 0.012
Major Nonvertebral Fracture[b,c]
Latin America 14/1534 (0.9%) 16/1550 (1.0%) 1.12 0.75 0.087
Rest-of-world 41/2057 (2.0%) 21/2039 (1.0%) 0.52 0.012
New/Worsening Vertebral Fracture[a]
Latin America 16/1430 (1.1%) 5/1464 (0.3%) 0.30 0.014 0.90
Rest-of-world 43/1892 (2.3%) 12/1857 (0.6%) 0.28 <0.001
Hip Fracture[b]
Latin America 3/1534 (0.2%) 3/1550 (0.2%) 0.99 0.99 0.38
Rest-of-world 10/2057 (0.5%) 4/2039 (0.2%) 0.41 0.12
Major Osteoporotic Fracture[b,d]
Latin America 13/1534 (0.8%) 17/1550 (1.1%) 1.28 0.50 0.013
Rest-of-world 50/2057 (2.4%) 21/2039 (1.0%) 0.42 <0.001
Multiple New/Worsening Vertebral Fracture[a,e]
Rest-of-world 9/1892 (0.5%) 1/1857 (<0.1%) 0.11 0.012
0.01
1.0
100
Favors Romosozumab
Favors Placebo