ASU FC
Azienda sanitaria universitaria Friuli Centrale
REGIONE AUTONOMA FRIULI VENEZIA GIULIA

SOC ENDOCRINOLOGIA
Dipartimento di Area Oncologica
P.O. Santa Maria della Misericordia di Udine
Direttore dott. Fabio Vescini

Abaloparatide

Fabio Vescini

Che cos'è

Archives of Endocrinology and Metabolism
OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF ENDOCRINOLOGY AND METABOLISM

Bandeira L, Lewiecki EM. Anabolic therapy for osteoporosis: update on efficacy and safety. 2022 Nov 11;66(5):707-716.

È un **peptide sintetico,** analogo del peptide correlato all'ormone paratiroideo **PTHrP** (1-34).

È perciò un farmaco **osteoanabolico.**

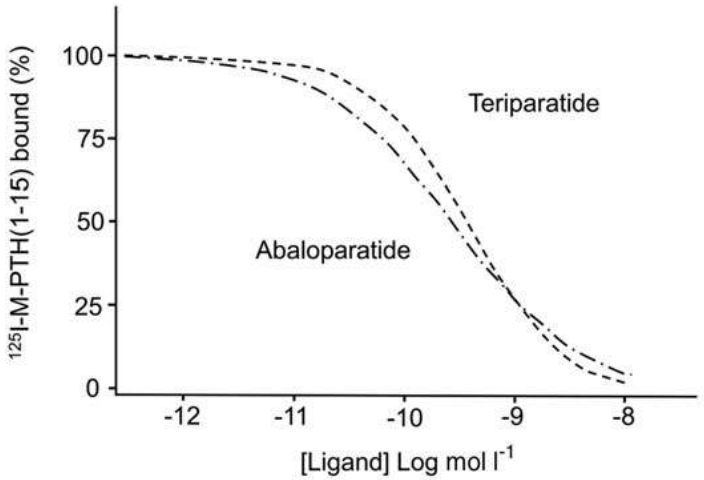
Table 1. Summary of selected properties of interest for three approved anabolic compounds for treatment of osteoporosis

Property	Teriparatide	Abaloparatide	Romosozumab
Regulatory approval	2002	2017	2019
Molecule	PTH(1-34)	PTHrP(1-34)	Humanized Monoclonal Antibody
Mechanism	PTH receptor agonist	PTH receptor agonist	Anti-sclerostin
Bone formation	Increases	Increases	Increases
Bone resorption	Increases	Increases	Decreases
Dose	20 mcg SC daily	80 mcg SC daily	210 mg SC monthly
Duration limit	24 months*	24 months lifetime	12 months (may repeat)

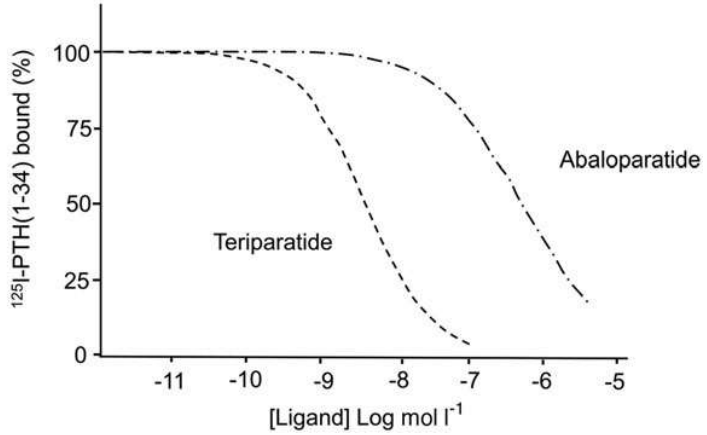
ITALY (AIFA)
18 months lifetime

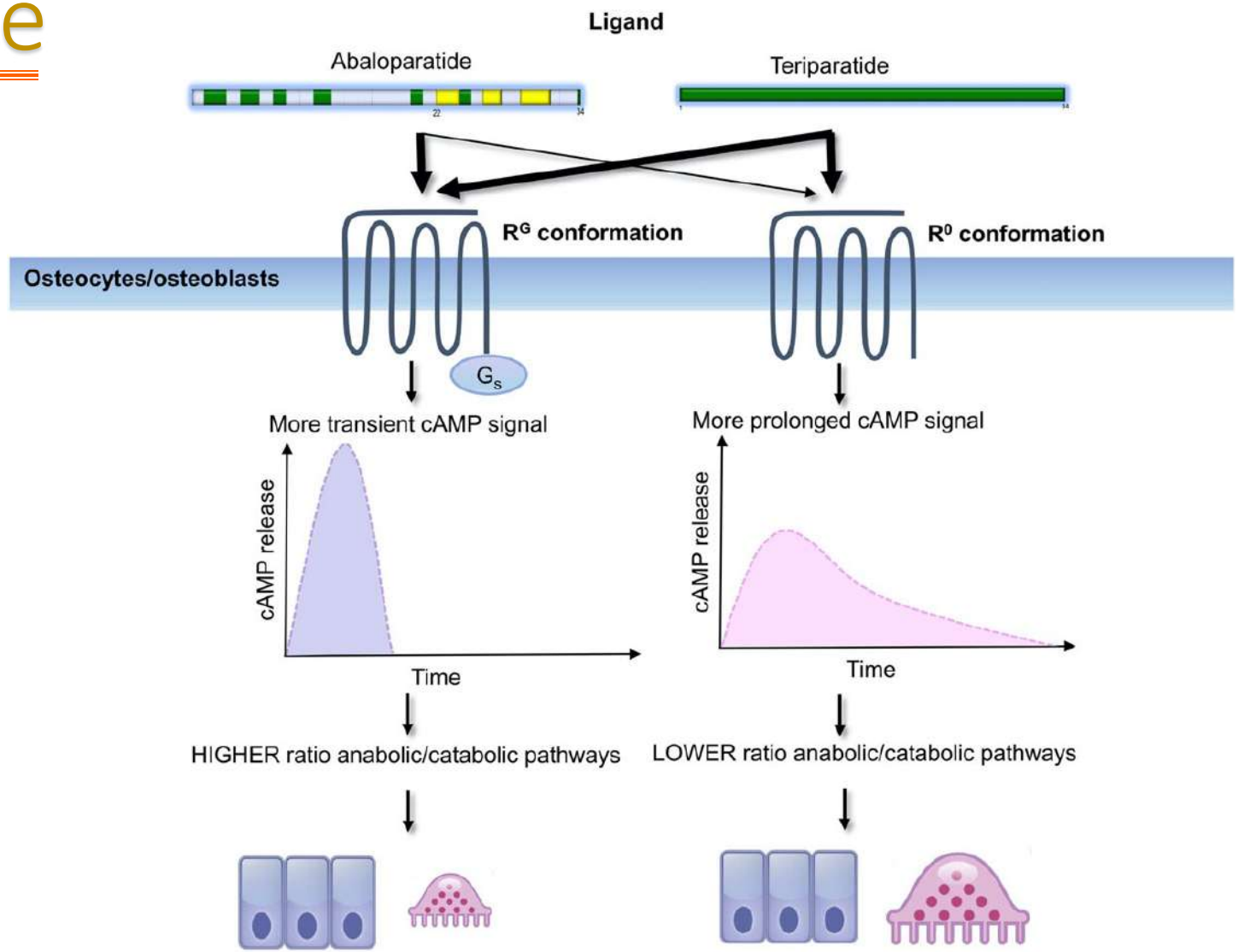
Meccanismo d'azione

R^G conformation of the PTH1R
(Associated with a more transient binding of the ligand)



R^0 conformation of the PTH1R
(Associated with more prolonged binding of the ligand)

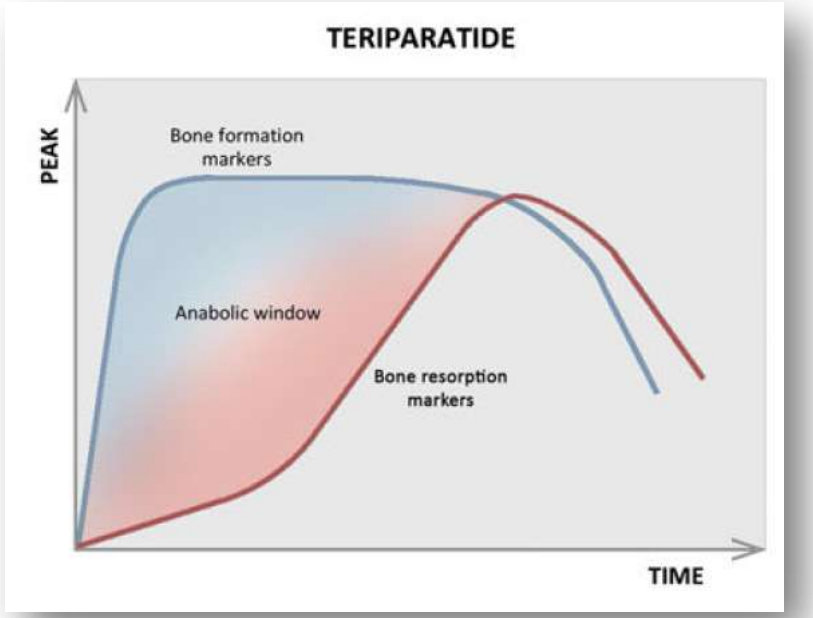




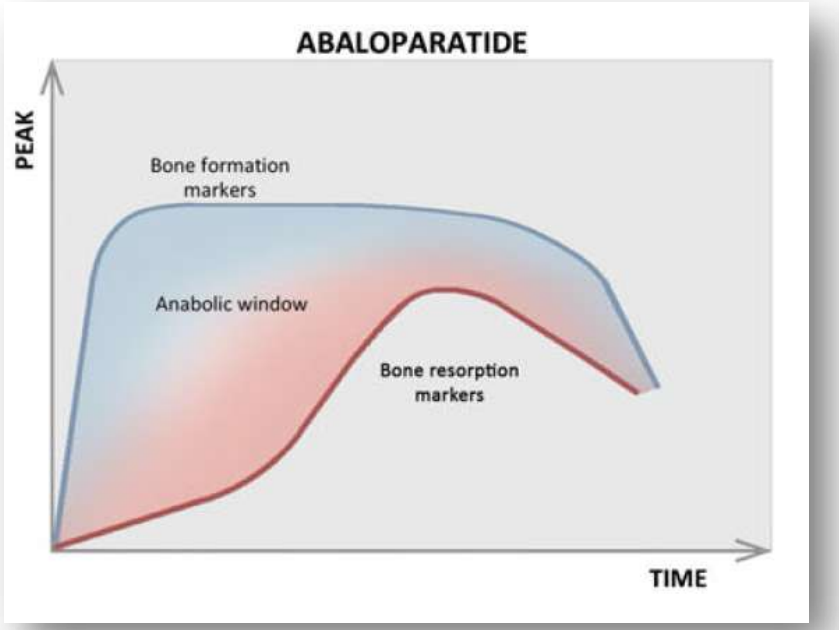
AZIONE ANABOLICA

Tay D, et al. Optimal dosing and delivery of parathyroid hormone and its analogues for osteoporosis and hypoparathyroidism - translating the pharmacology. Br J Clin Pharmacol. 2018 Feb;84(2):252-267.

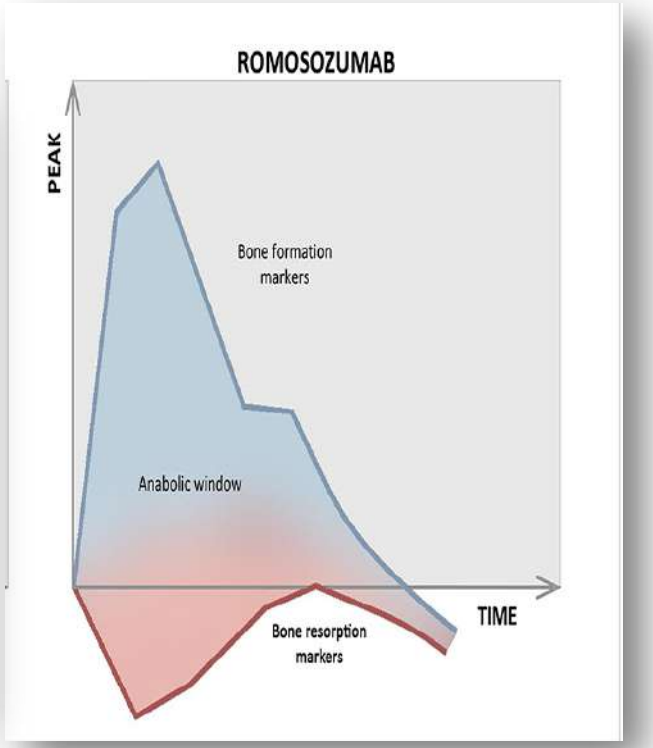
Anabolic window



Teriparatide first stimulates bone formation followed by a later increase in bone resorption.



Abaloparatide, compared with teriparatide, shows a lower rate of bone formation and bone resorption, but a higher net anabolic effect.



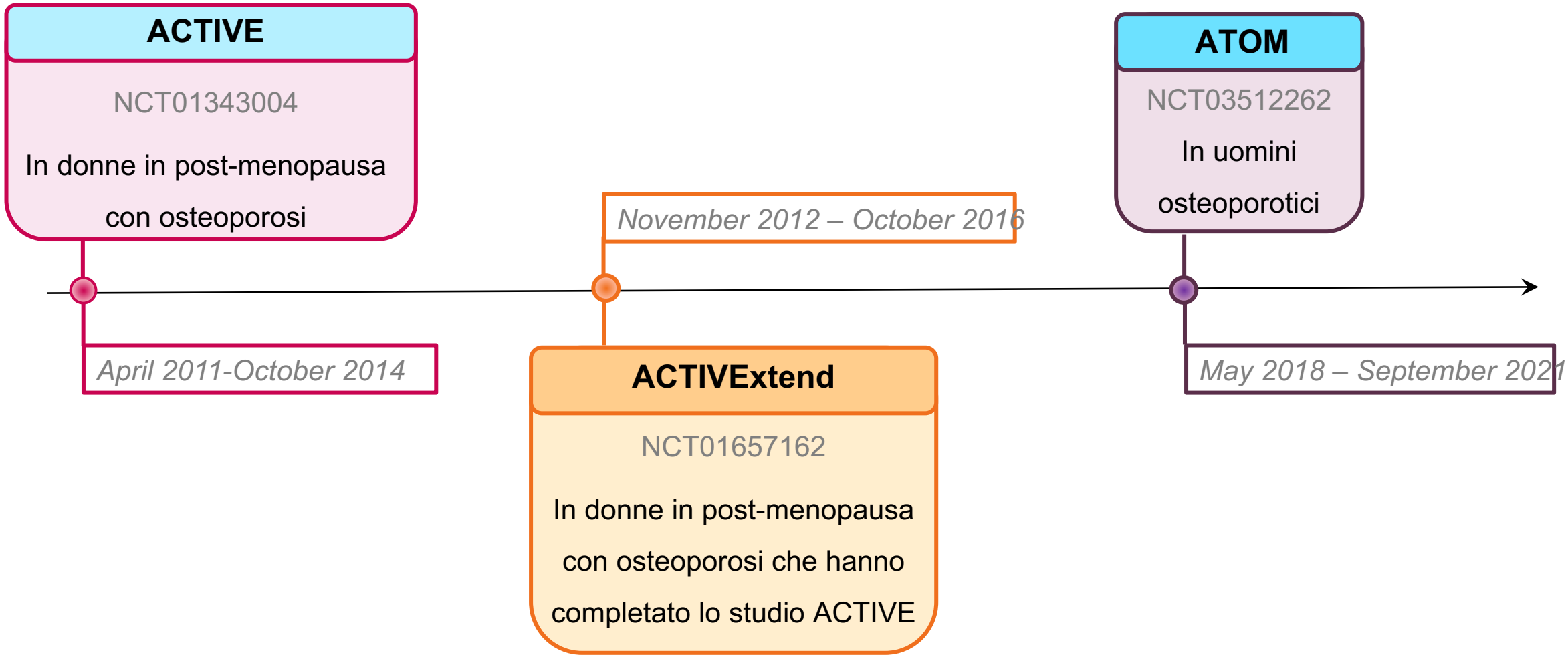
Fast increase in bone formation and anti-resorption, followed by a fast decrease in both after 12 months treatment with romosozumab

Adapted from Tabacco G et al, Br J Clin Pharmacol 2019;85:1084-1094

Abaloparatide

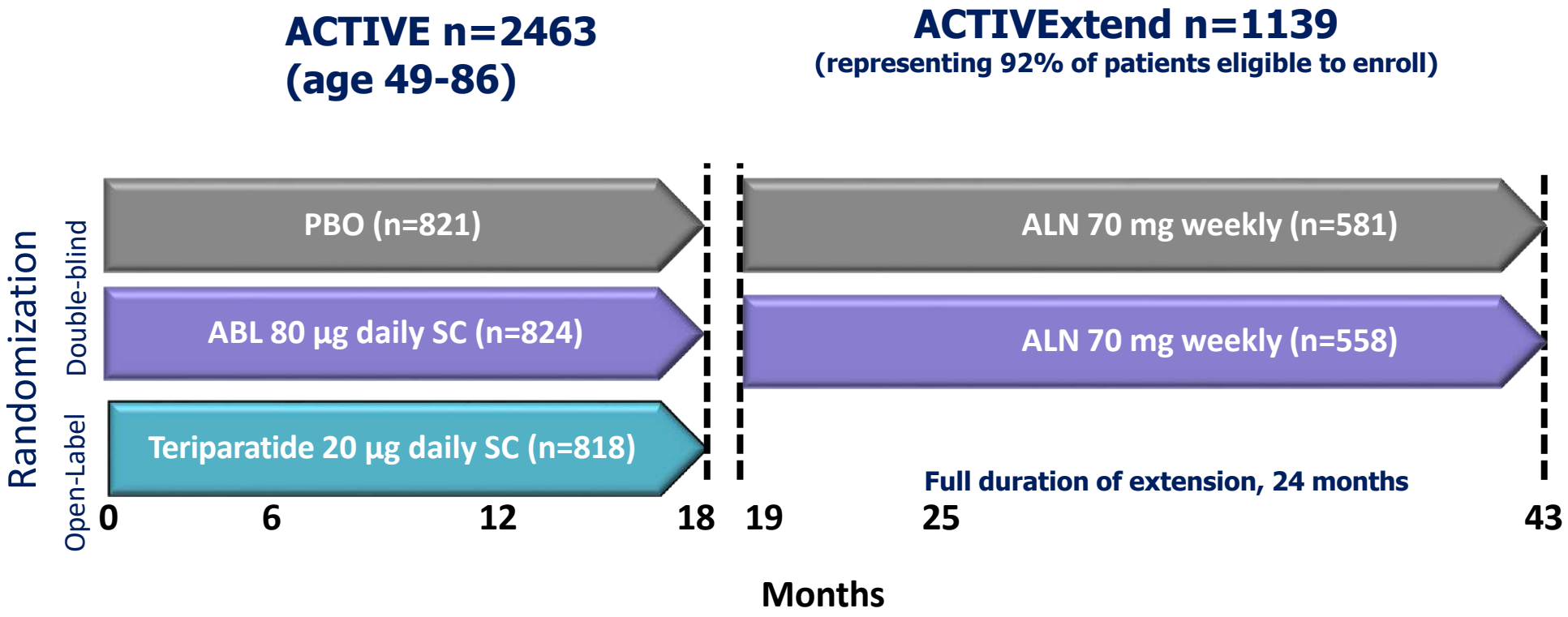
CLINICAL DEVELOPMENT PROGRAM

Trials


ACTIVE
NCT01343004
In donne in post-menopausa con osteoporosi
April 2011-October 2014
November 2012 – October 2016
ACTIVExtend
NCT01657162
In donne in post-menopausa con osteoporosi che hanno completato lo studio ACTIVE
ATOM
NCT03512262
In uomini osteoporotici
May 2018 – September 2021

Abaloparatide – Clinical Development

Pivotal phase III trials: ACTIVE[1] and ACTIVExtend[2]



Efficacy Endpoints

Fracture Outcomes

Vertebral
(primary endpoint)

Nonvertebral
(secondary endpoint)

Clinical
(exploratory endpoint)

Major osteoporotic
(exploratory endpoint)

BMD

Total hip

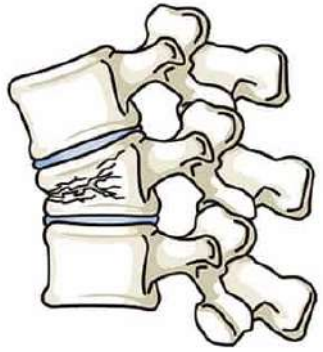
Femoral neck

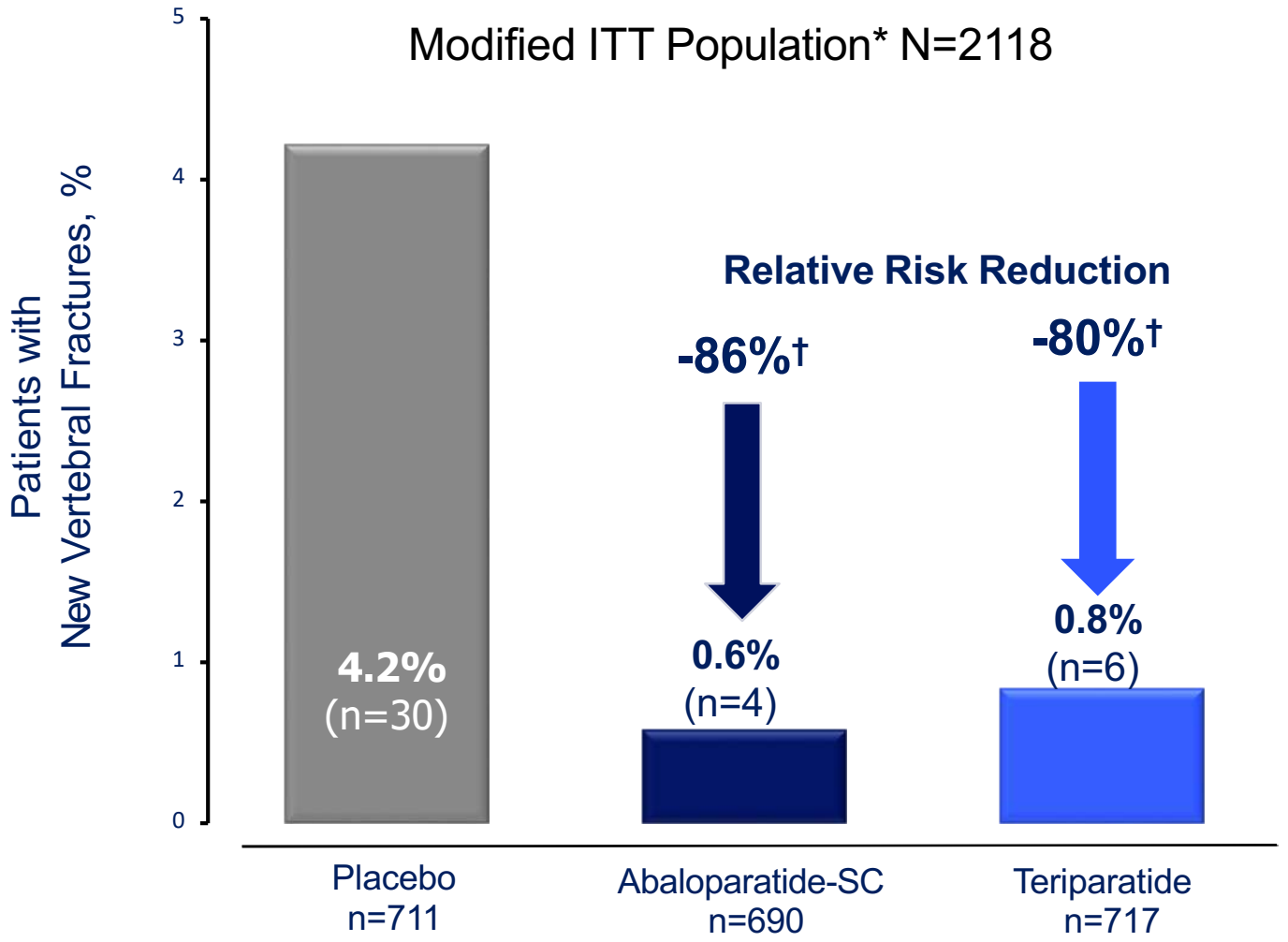
Lumbar spine

Patient inclusion criteria: Postmenopausal women, aged 49 to 86 years, with BMD ≤ -2.5 and < -5.0 T score at the lumbar spine or femoral neck together with radiologic evidence of at least 2 mild vertebral fractures or at least 1 moderate vertebral fracture

1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

ACTIVE Study
Risk Reduction of New Vertebral Fractures (*Primary endpoint*)



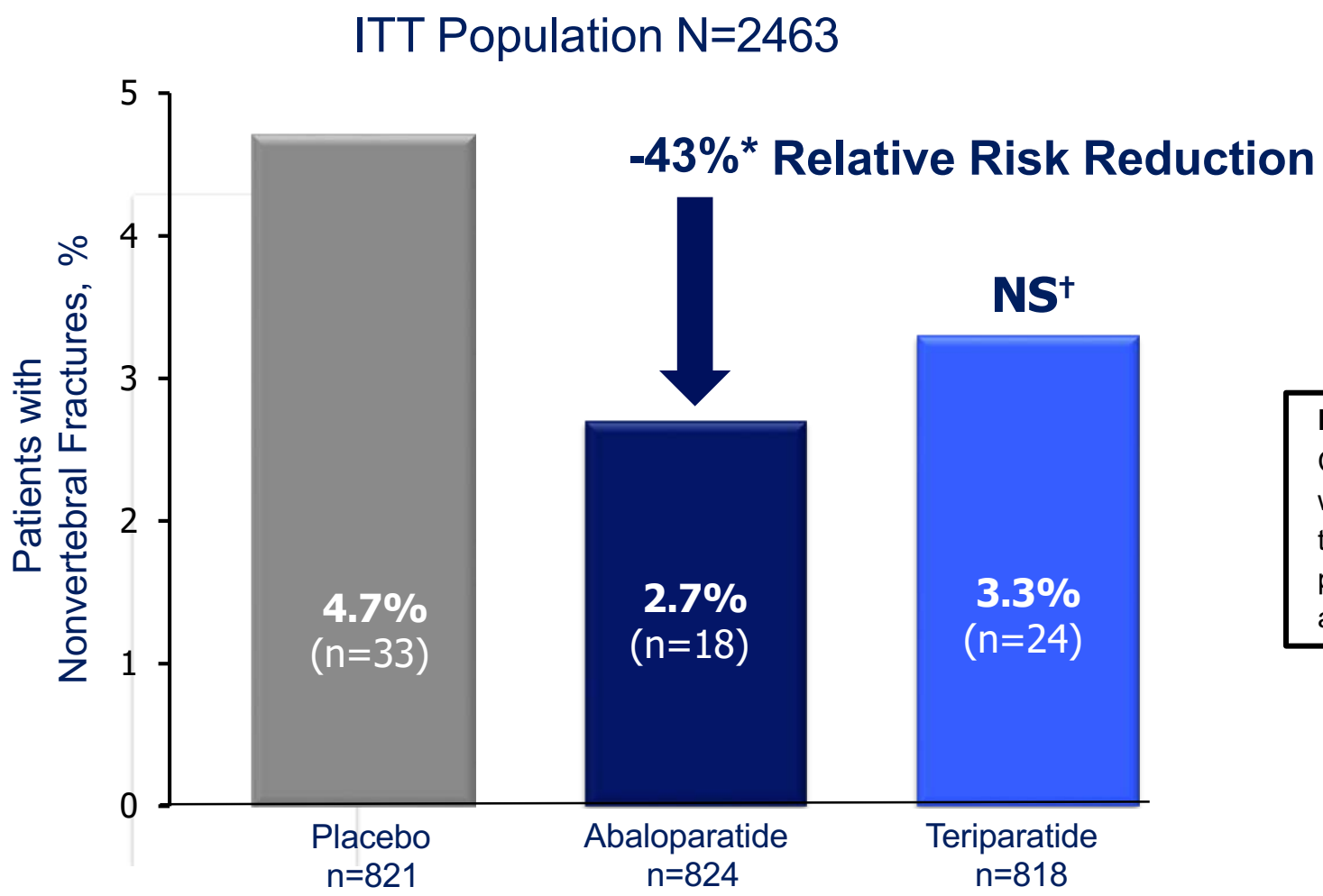


New vertebral fractures:
Morphometric fractures assessed by blinded radiographic review[2]

*Includes all ITT patients who had pretreatment and postbaseline evaluable radiologic assessments.
†$P < 0.001$ vs placebo. *P* values were not adjusted for multiple comparisons.

1. Miller et al. JAMA 2016(7);316:722-733
2. Genant HK et al. J Bone Miner Res. 1993;8:1137-1148. 2. Kanis JA on behalf of the World Health Organization Scientific Group (2007). FRAX WHO Fracture Risk Assessment Tool. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. Available at: https://www.shef.ac.uk/FRAX/.

ACTIVE Study
Risk Reduction of Nonvertebral Fractures (*Secondary endpoint*)



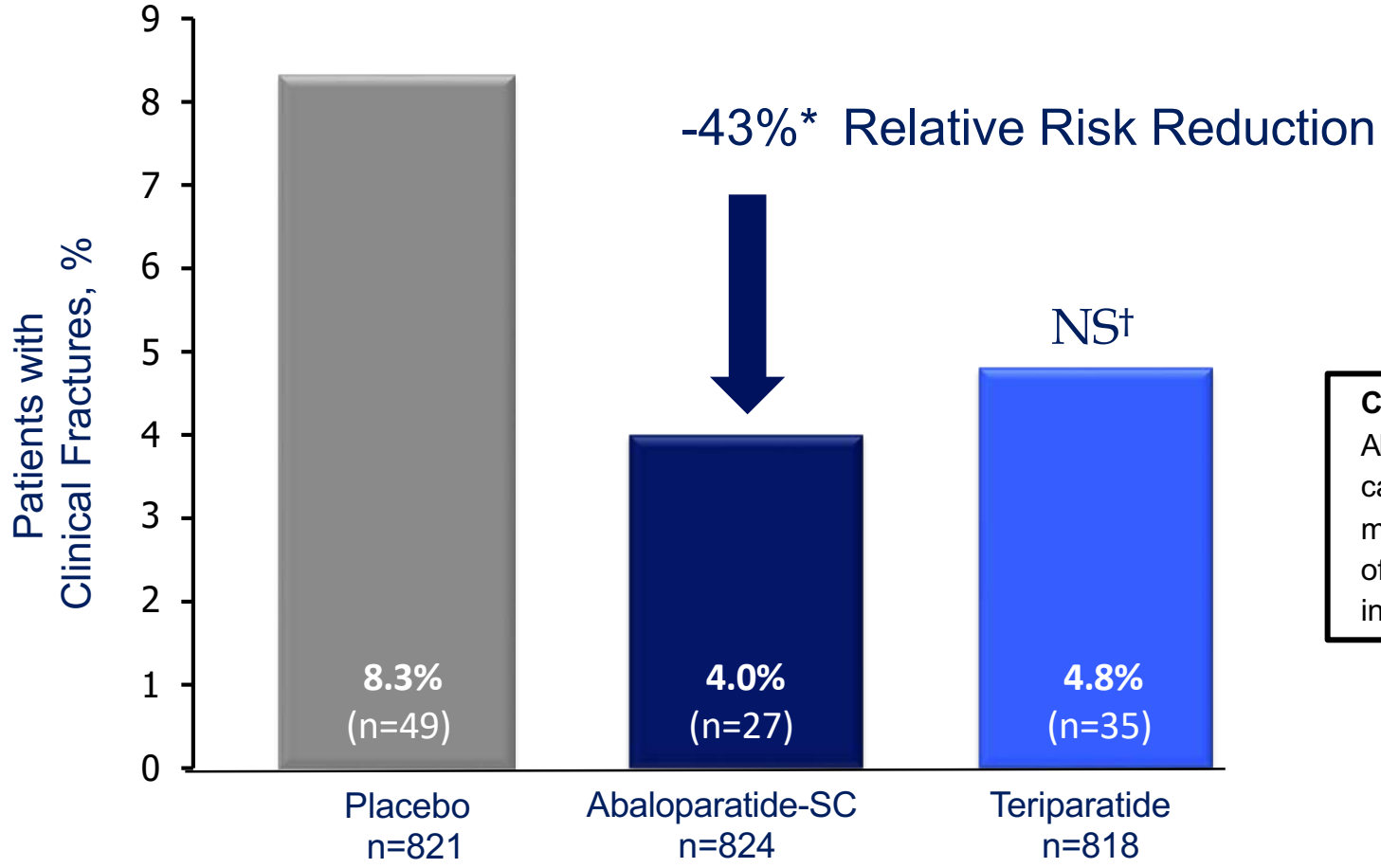
Nonvertebral fractures:
Clinical fractures associated with low trauma, excluding those of the spine, sternum, patella, toes, fingers, skull, and face

*P = 0.049 vs placebo; †NS vs placebo
Based on cumulative Kaplan-Meier estimates ITT at 19 months.

In the EU SmPC nonvertebral fracture risk reduction is not significant

Miller et al. JAMA 2016(7);316:722-733

ACTIVE Study
Risk Reduction of Clinical Fractures (*preplanned exploratory endpoint*)



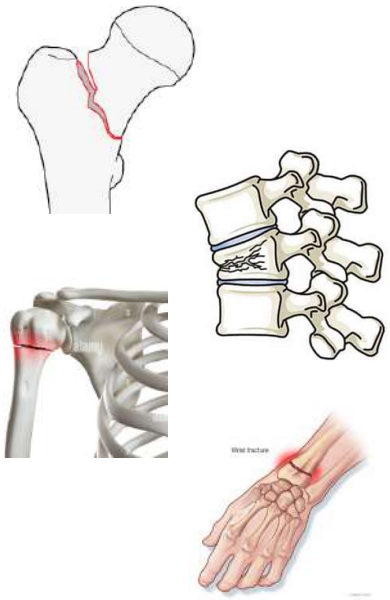
Clinical fractures:
All fractures that would cause a patient to seek medical care, regardless of the level of trauma, including clinical spine

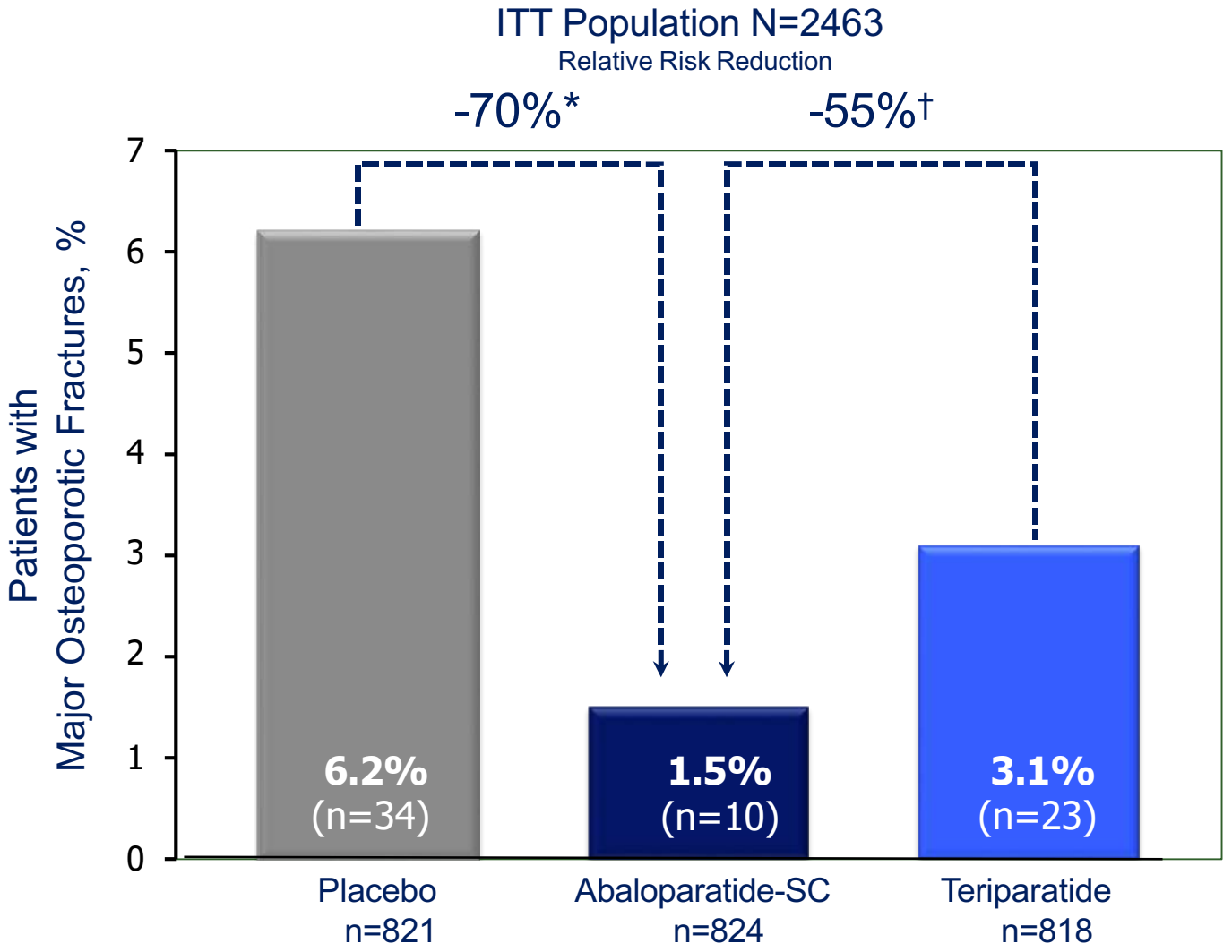
*P = 0.02 vs placebo; †NS vs placebo. P values were not adjusted for multiple comparisons Based on cumulative Kaplan-Meier estimates ITT at 19 months.

In the EU SmPC clinical fracture risk reduction is not significant

Miller et al. JAMA 2016(7);316:722-733

ACTIVE Study
Risk Reduction of Major Osteoporotic Fractures (*preplanned exploratory endpoint*)





Major osteoporotic fractures:
High- or low-trauma fractures of the **upper arm, wrist, hip, or clinical spine**[2]

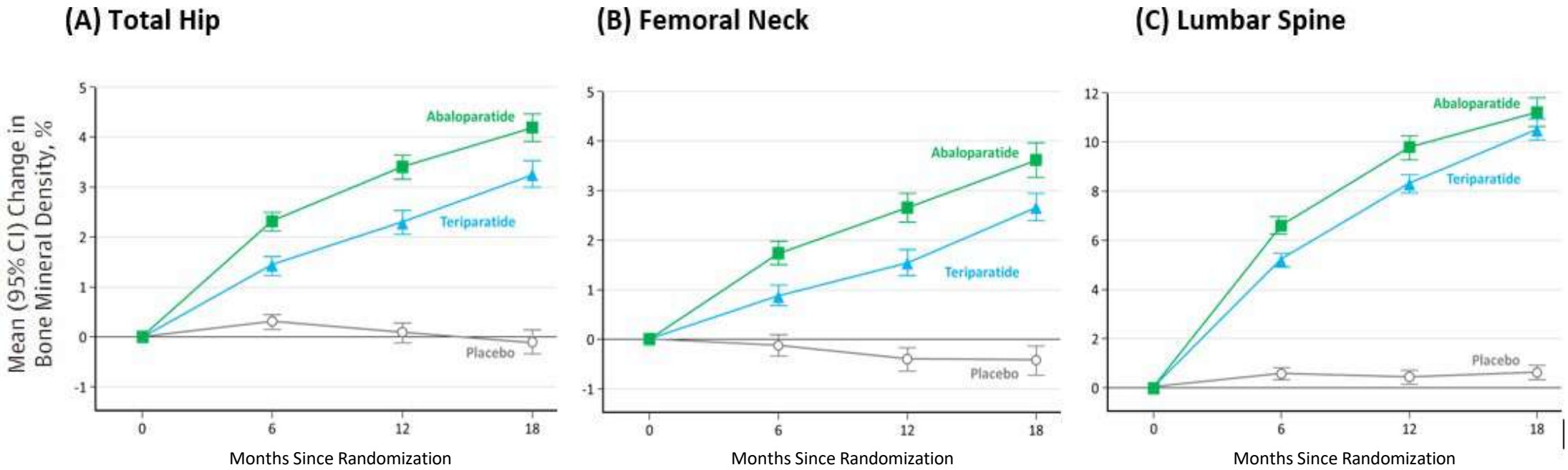
*P < 0.001, abaloparatide-SC vs placebo; †P = 0.03, abaloparatide-SC vs teriparatide; NS, teriparatide vs placebo.

Based on cumulative Kaplan-Meier estimates ITT at 19 months.

1.Miller et al. JAMA 2016(7);316:722-733
2. FRAX® is a risk assessment instrument, developed by the University of Sheffield, and is a registered trademark of Sheffield

ACTIVE Study
Change from baseline in Bone Mineral Density (BMD)

ITT Population N=2463



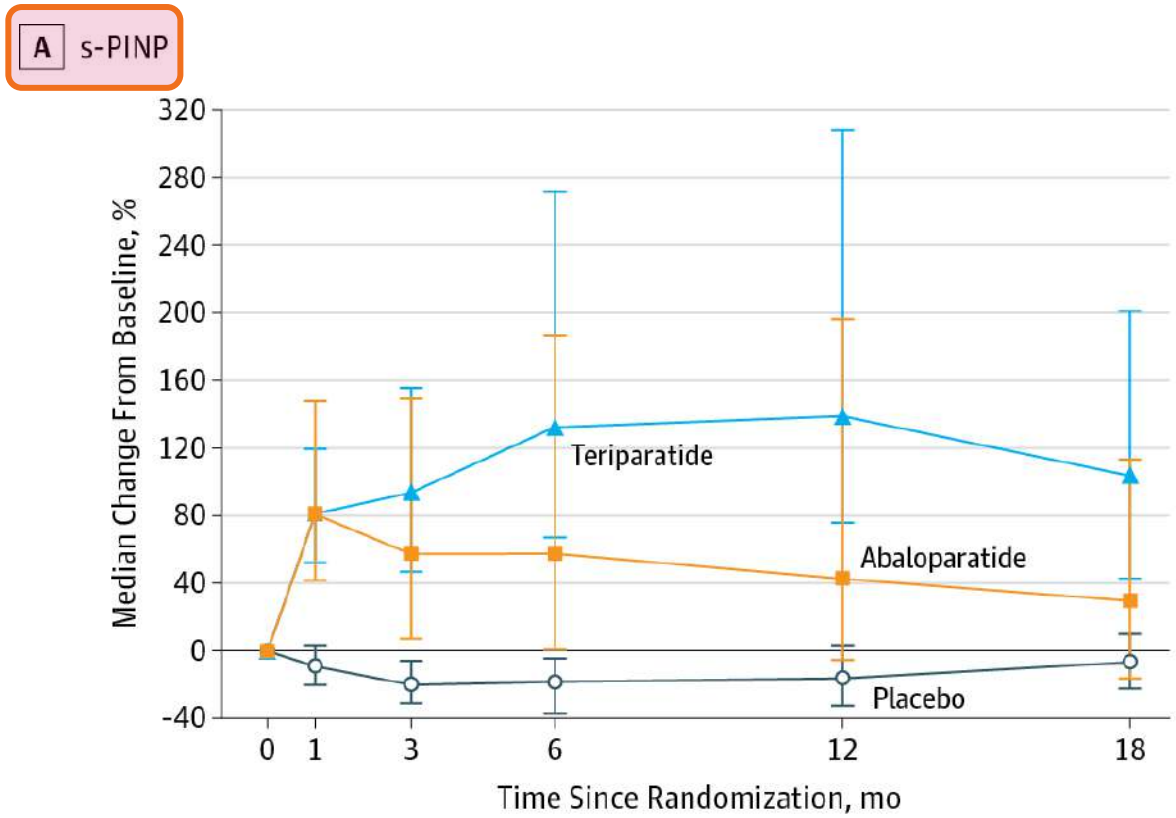
No. of participants evaluated												
Abaloparatide	822	736	651	615	822	736	651	615	823	738	652	617
Placebo	820	762	693	651	820	762	693	651	821	764	694	650
Teriparatide	818	754	705	660	818	754	705	660	818	755	704	665

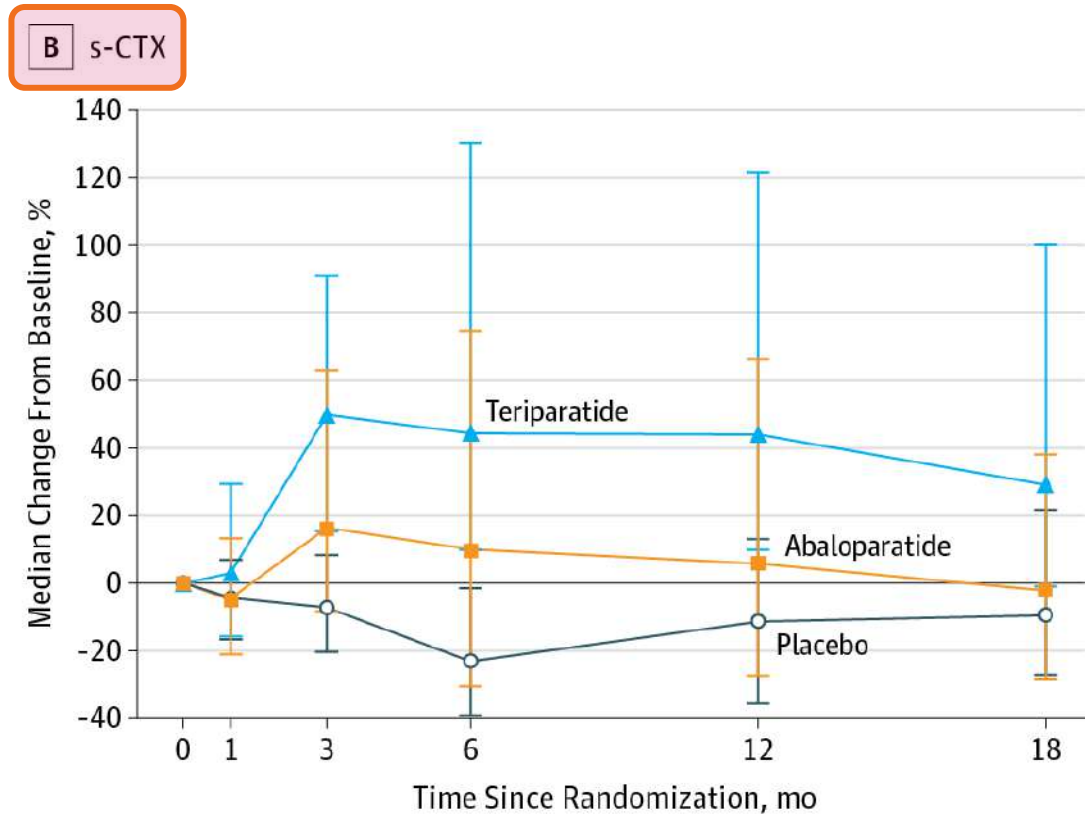
Improvements in bone mineral density associated with abaloparatide were significantly greater than with placebo at all 3 sites and at all time points ($P < .001$).

Improvements with teriparatide were significantly greater than with placebo at all 3 sites at all time points ($P < .001$). Improvements with abaloparatide were significantly greater than those with teriparatide at the total hip and femoral neck at all time points ($P < .001$) and at lumbar spine at 6 and 12 months ($P < .001$). Error bars indicate 95% CIs.

Miller et al. JAMA 2016(7);316:722-733

Studio ACTIVE





No. of participants evaluated

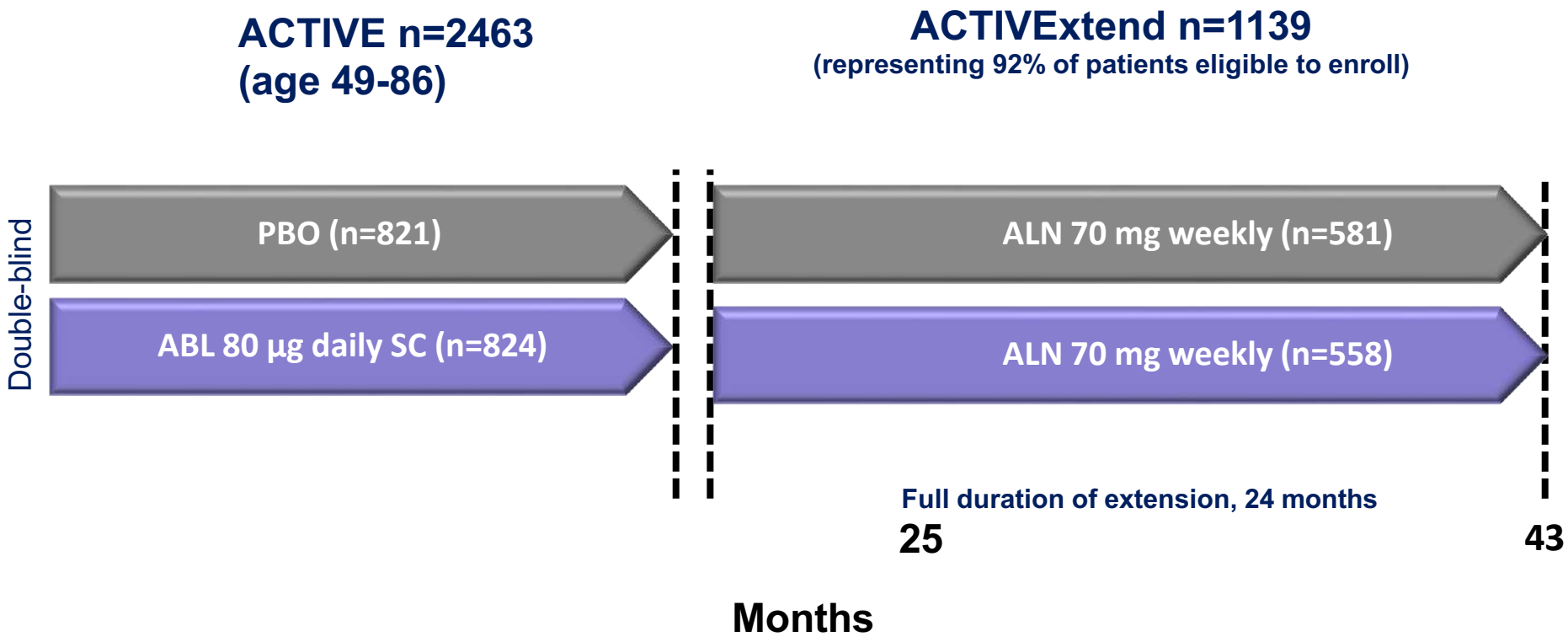
Abaloparatide	189	187	187	189	189	189
Placebo	184	183	181	184	184	184
Teriparatide	227	227	227	227	227	227

Abaloparatide	189	187	187	189	189	189
Placebo	184	183	181	184	184	184
Teriparatide	227	227	227	227	227	227

Miller PD, Hattersley G, Riis BJ, et al. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316(7):722-733.

Abaloparatide – Clinical Development

Pivotal phase III trials: ACTIVE[1] and ACTIVExtend[2]



Efficacy Endpoints

Fracture Outcomes

Vertebral
(primary endpoint)

Nonvertebral
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Clinical
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Major osteoporotic
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BMD

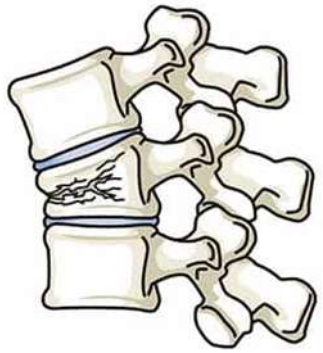
Total hip

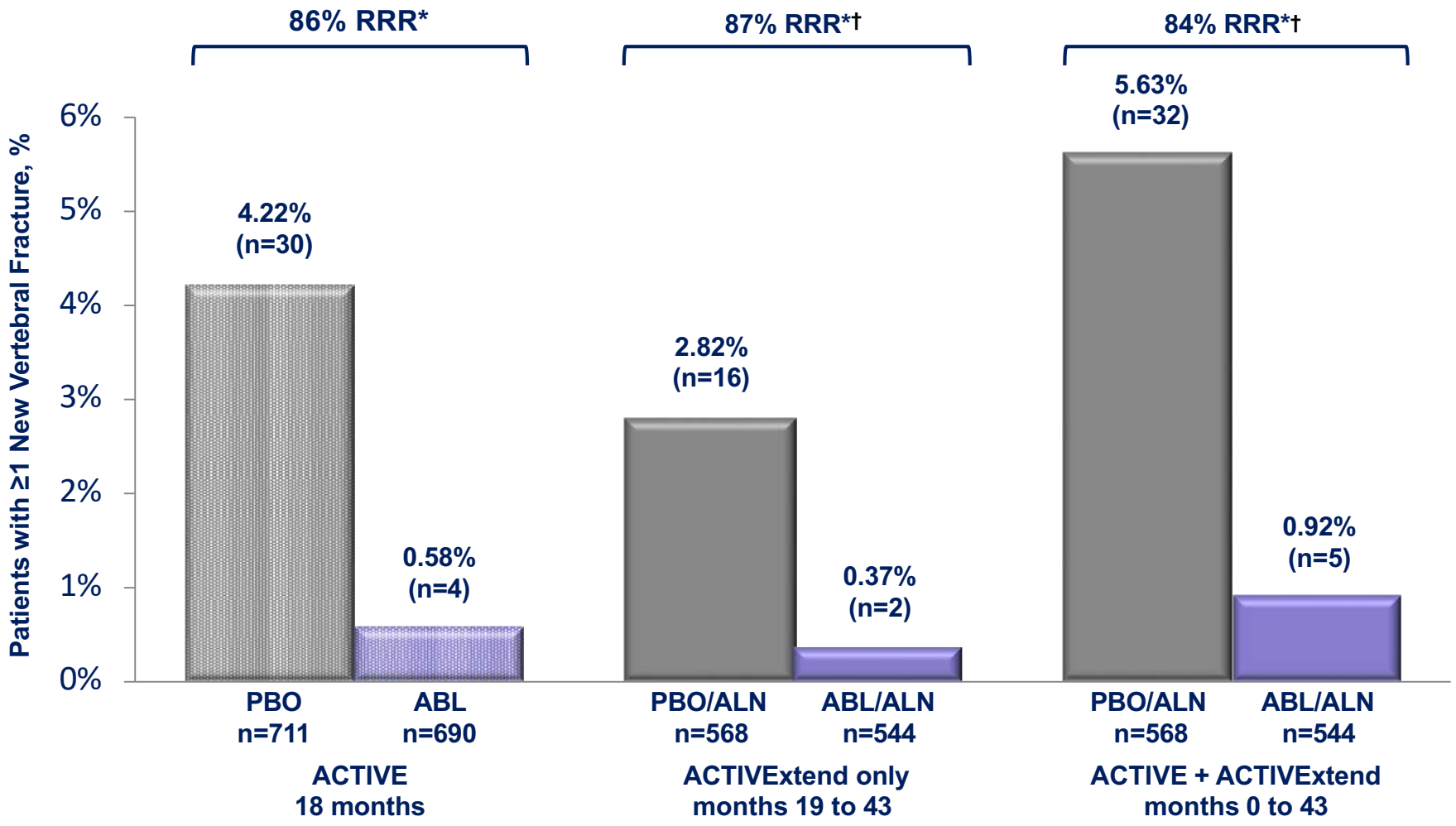
Femoral neck

Lumbar spine

1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

ACTIVE + ACTIVExtend Studies - New Vertebral Fracture Risk Reduction





*$P \leq 0.001$ for ABL vs PBO and for ABL/ALN vs PBO/ALN

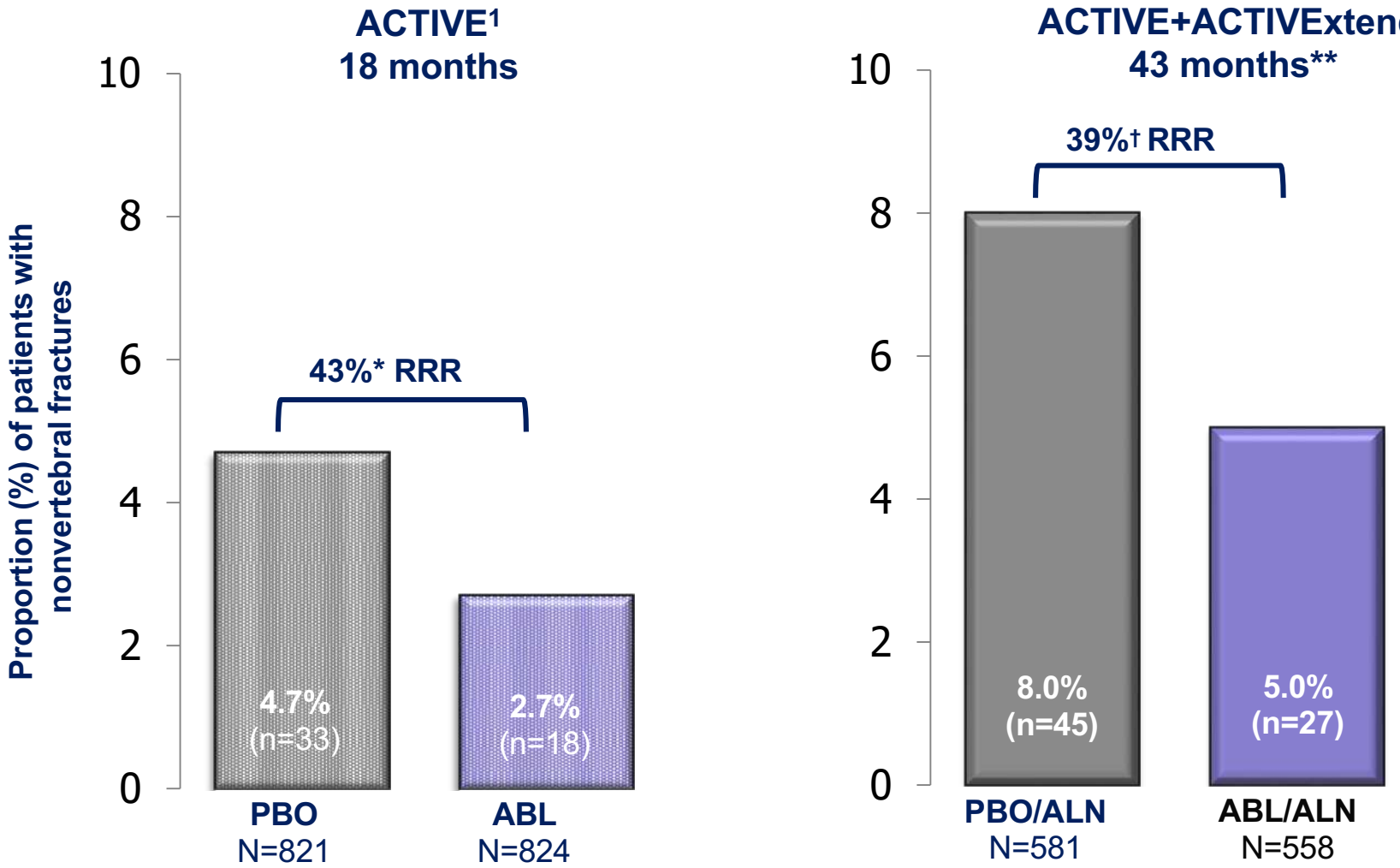
† No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37, and 43

ABL, abaloparatide; **ALN**, alendronate; **mITT**, modified intent to treat; **PBO**, placebo; **RRR**, relative risk reduction

ACTIVE findings were reported by Miller et al JAMA 2016

1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

ACTIVE + ACTIVExtend Studies - Nonvertebral Fracture Risk Reduction

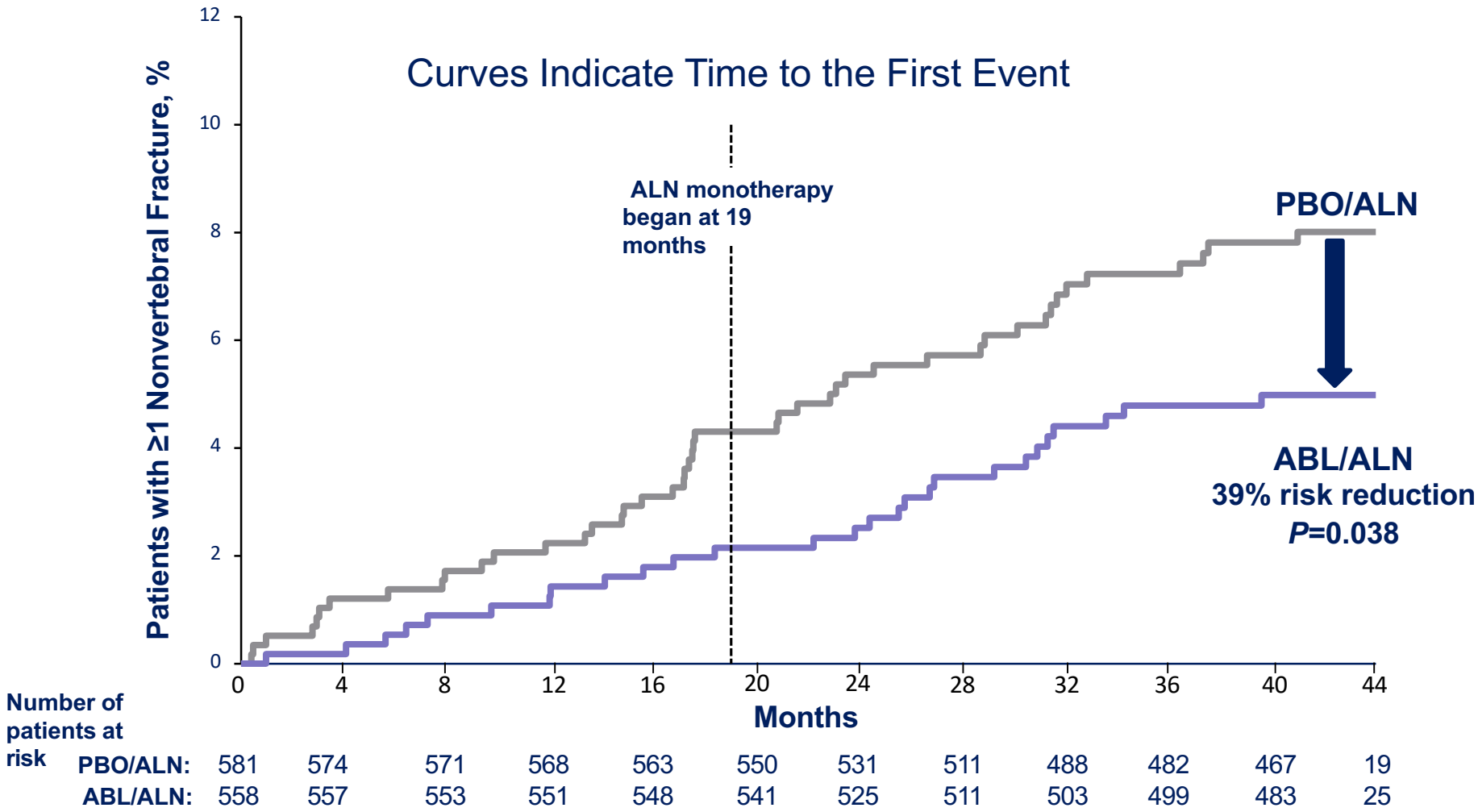


*P = 0.049 vs PBO; †Hazard ratio, 0.61; 95% CI, 0.38 to 0.98; logrank P = 0.038 vs PBO/ALN
ABL, abaloparatide; **ALN**, alendronate; **PBO**, placebo; **RRR**, relative risk reduction

** No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37, and 43

1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

ACTIVE + ACTIVExtend Studies - Nonvertebral Fracture Risk Reduction

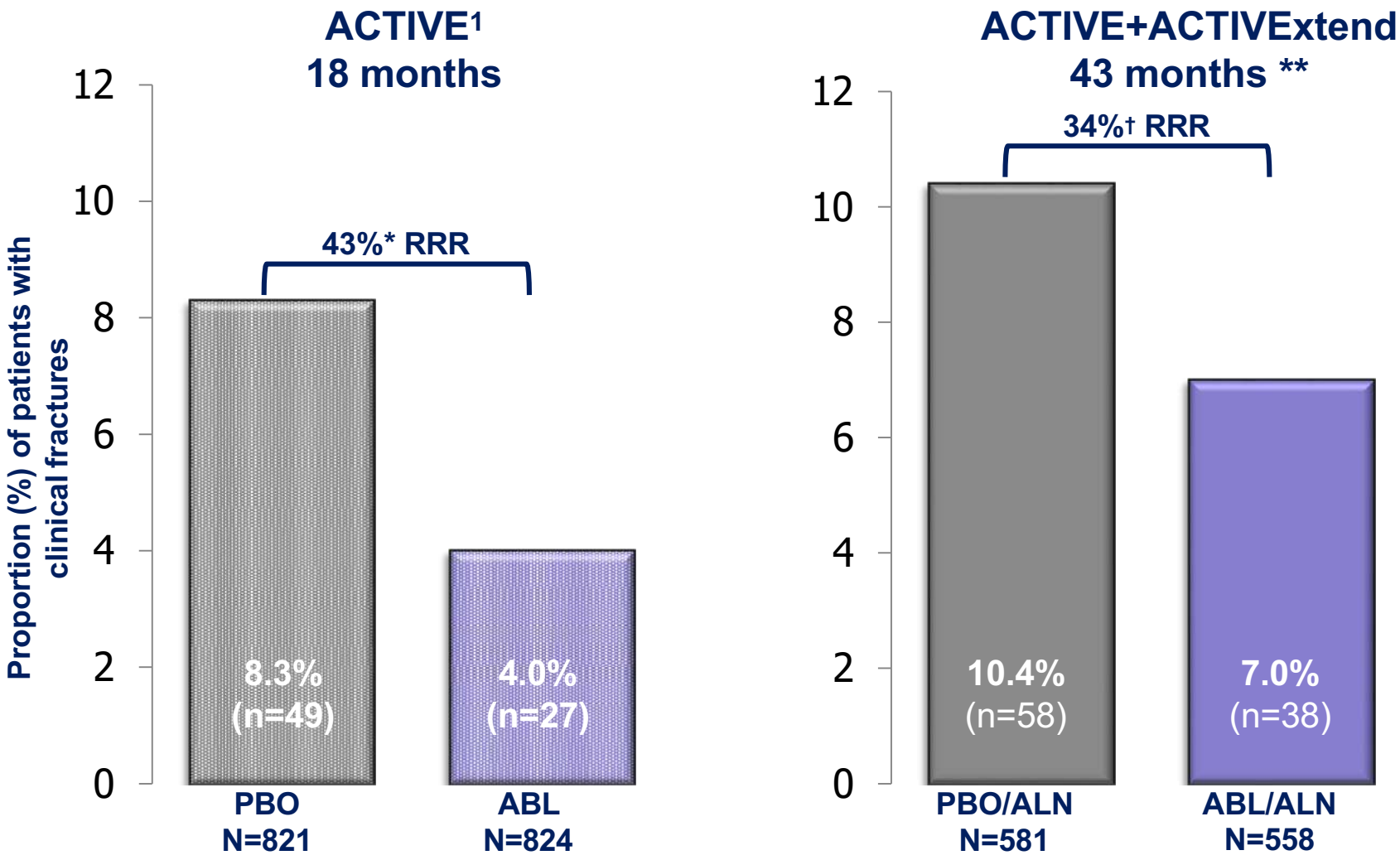


ABL, abaloparatide; **ALN**, alendronate; **PBO**, placebo.

- Kaplan-Meier estimates were calculated at 43 months
- No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37 and 43.

1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

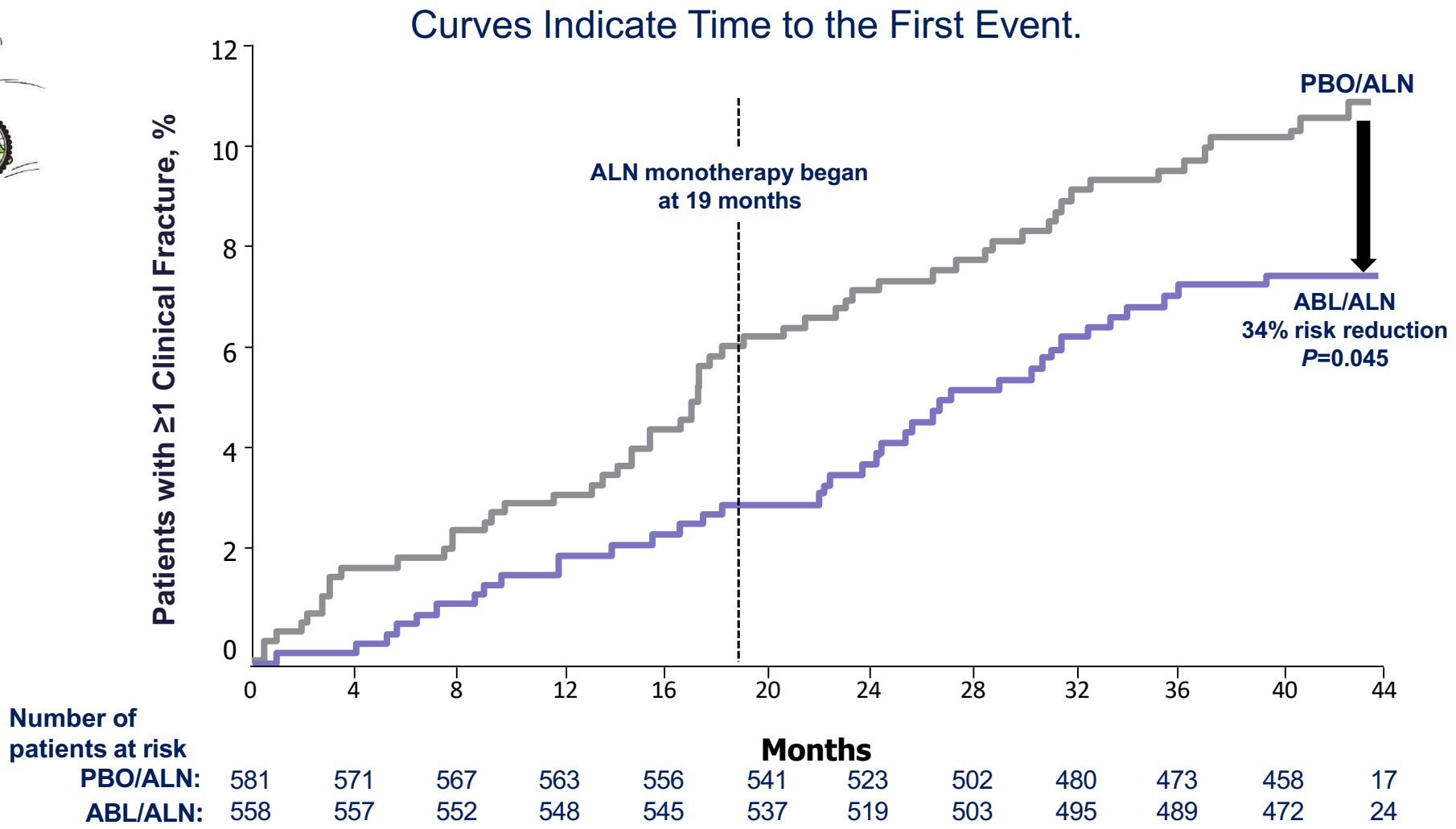
ACTIVE + ACTIVExtend Studies - Clinical Fracture Risk Reduction



*P = 0.02 vs PBO; †Hazard ratio, 0.66; 95% CI, 0.44 to 0.99; logrank P = 0.0447 vs PBO/ALN
ABL, abaloparatide; **ALN**, alendronate; **PBO**, placebo; **RRR**, relative risk reduction
** No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37, and 43

1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

ACTIVE + ACTIVExtend Studies - Clinical Fracture Risk Reduction



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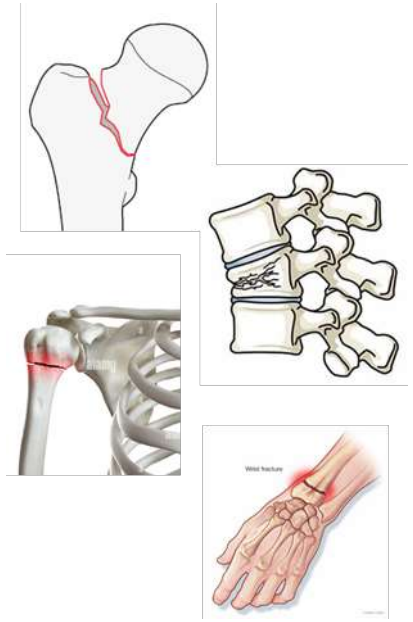
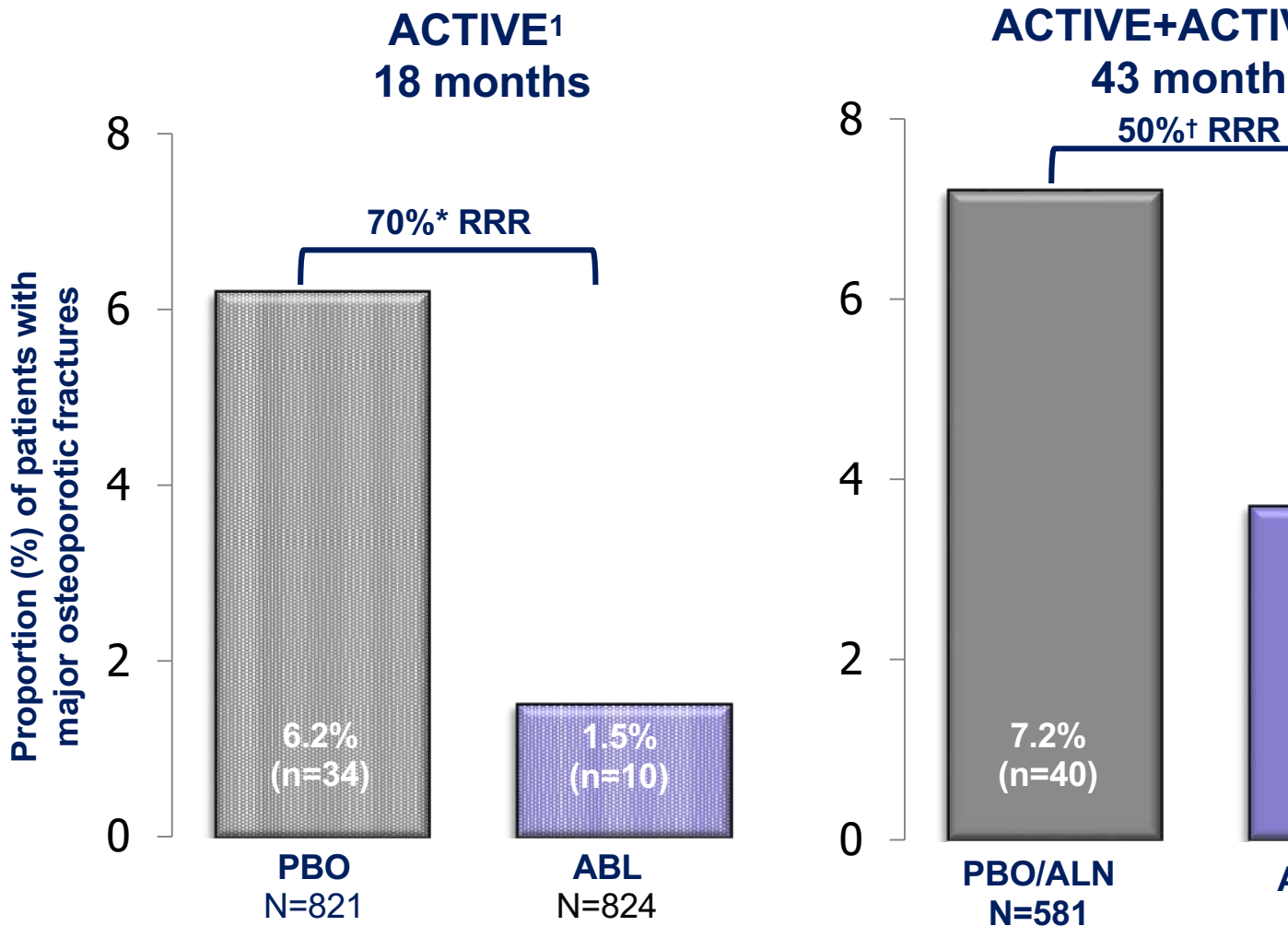
1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

ACTIVE + ACTIVExtend Studies - Major Osteoporotic Fracture Risk Reduction

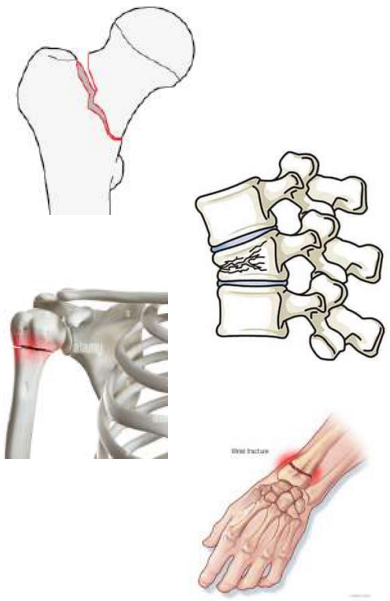




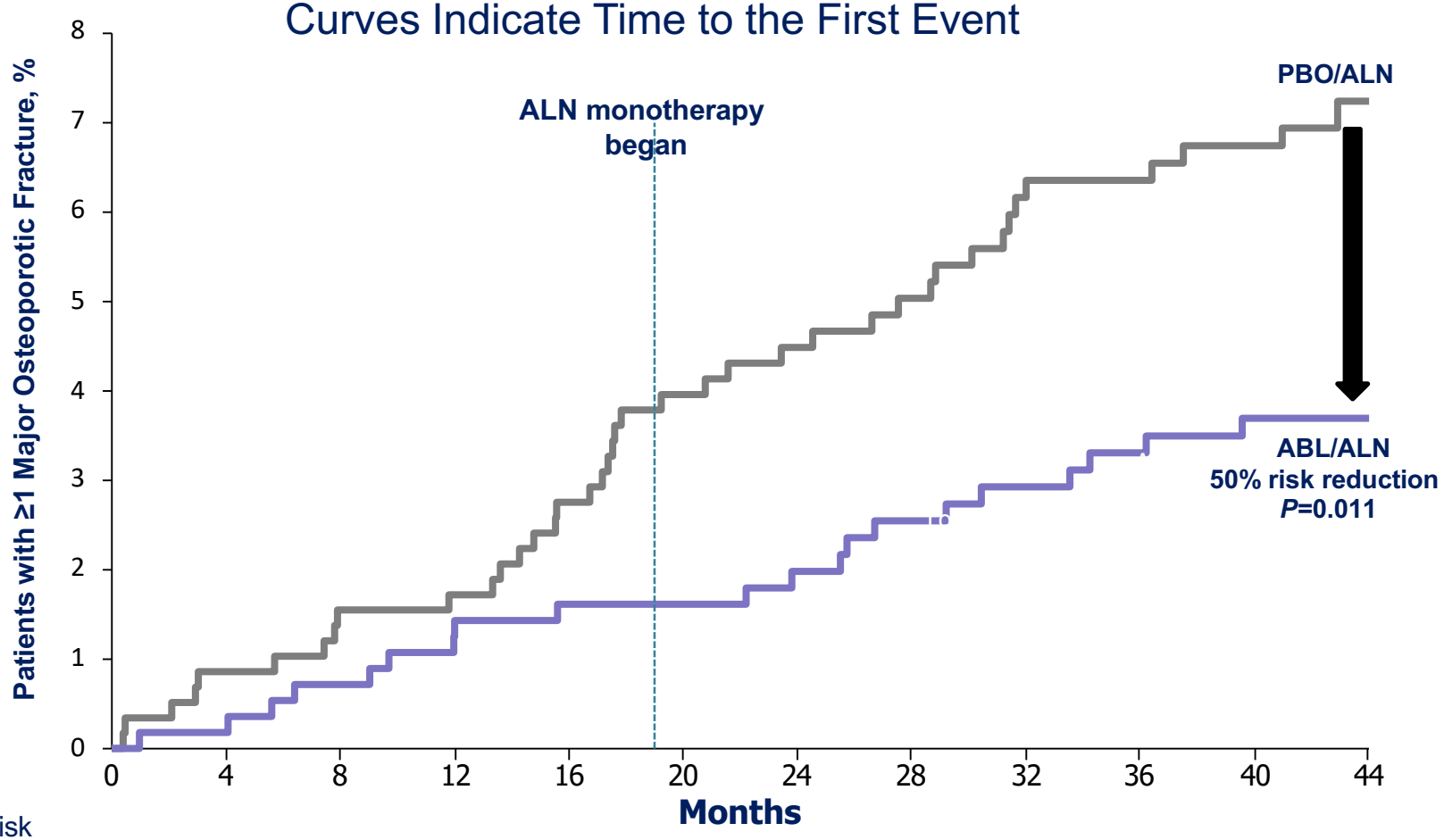
*P = 0.001 vs PBO; †Hazard ratio, 0.50; 95% CI, 0.30 to 0.86; logrank P = 0.011 vs PBO/ALN
ABL, abaloparatide; **ALN**, alendronate; **PBO**, placebo; **RRR**, relative risk reduction
** No statistical adjustments for multiple comparisons were made to additional subsequent analyses for Months 31, 37, and 43

1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

ACTIVE + ACTIVExtend Studies - Major Osteoporotic Fracture Risk Reduction



Curves Indicate Time to the First Event



Number of patients at risk

PBO/ALN:	581	576	572	571	565	552	535	514	491	486	471	17
ABL/ALN:	558	557	554	551	549	544	528	516	511	507	490	26

ABL, abaloparatide; **ALN**, alendronate; **PBO**, placebo.

- Kaplan-Meier estimates were calculated at 43 months
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1. Miller et al. JAMA 2016(7);316:722-733; 2. Bone 18;103(8):2949–2957

Eventi avversi

	Placebo n=820	Abaloparatide-SC n=822	Teriparatide (open label) n=818
All treatment-emergent adverse events	87.6%	89.4%	88.9%
Serious treatment-emergent adverse events	11.0%	9.7%	10.0%
Deaths	0.6%	0.4%	0.4%
Adverse events leading to discontinuation	6.1%	9.9%	6.8%
Discontinuation due to >7.0% BMD decrease	6.5%	0.5%	0.6%
Hypercalcemia (prespecified)*	0.4%	3.4%†‡	6.4%‡
Hypercalciuria	9.0%	11.3%	12.5%
Dizziness	6.1%	10.0%	7.3%
Arthralgia	9.8%	8.6%	8.6%
Back Pain	10.0%	8.5%	7.2%
Nausea	3.0%	8.3%	5.1%
Upper respiratory tract infection	7.7%	8.3%	8.9%
Headache	6.0%	7.5%	6.2%
Hypertension	6.6%	7.2%	5.0%
Influenza	4.8%	6.3%	4.2%
Nasopharyngitis	8.0%	5.8%	6.5%
Urinary tract infection	4.6%	5.2%	5.0%
Palpitations	0.4%	5.1%	1.6%

*Serum albumin-corrected calcium value ≥10.7 mg/dL at any time point, prespecified safety endpoint.

†P = 0.006 abaloparatide-SC vs teriparatide;

‡P < 0.001 vs placebo.

P values were not adjusted for multiple comparisons

Miller et al. *JAMA.* 2016;316(7):722-733

Eventi avversi

Archives of Endocrinology and Metabolism
OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF ENDOCRINOLOGY AND METABOLISM

Bandeira L, Lewiecki EM. Anabolic therapy for osteoporosis: update on efficacy and safety. 2022 Nov 11;66(5):707-716.

Table 1. Summary of selected properties of interest for three approved anabolic compounds for treatment of osteoporosis

Property	Teriparatide	Abaloparatide	Romosozumab
Rat osteosarcoma	Yes	Yes	No
Warning to avoid in patients at high risk for osteosarcoma	Yes	Yes	No
Warning to avoid in patients with myocardial infarction or stroke in the past year	No	No	Yes

*Branded teriparatide (Forteo) for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture.

PTH: parathyroid hormone; PTHrP: PTH related protein; SC: subcutaneous; GIO: glucocorticoid induced osteoporosis.

Abaloparatide RWE Study

Study objectives

To evaluate the real-world comparative effectiveness on Non-Vertebral Fractures* and comparative Cardiovascular Safety** of abaloparatide versus teriparatide during the 19-month period after treatment initiation.

***Nonvertebral fracture event:** hip, pelvis shoulder (including clavicle and humerus), radius/ulna (including radius and/or ulna and forearm), wrist (including unspecified wrist, wrist/hand, carpal, triquetrum, lunate, capitate, hamate, pisiform, etc.), femur, tibia/fibula, and ankle.

****MACE**: Nonfatal MI, nonfatal stroke or CV death, with and without heart failure following hospitalisation within the 18 months after treatment initiation while on therapy plus 30-day follow up.

Cosman F et al Osteoporosis International https://doi.org/10.1007/s00198-022-06413-y

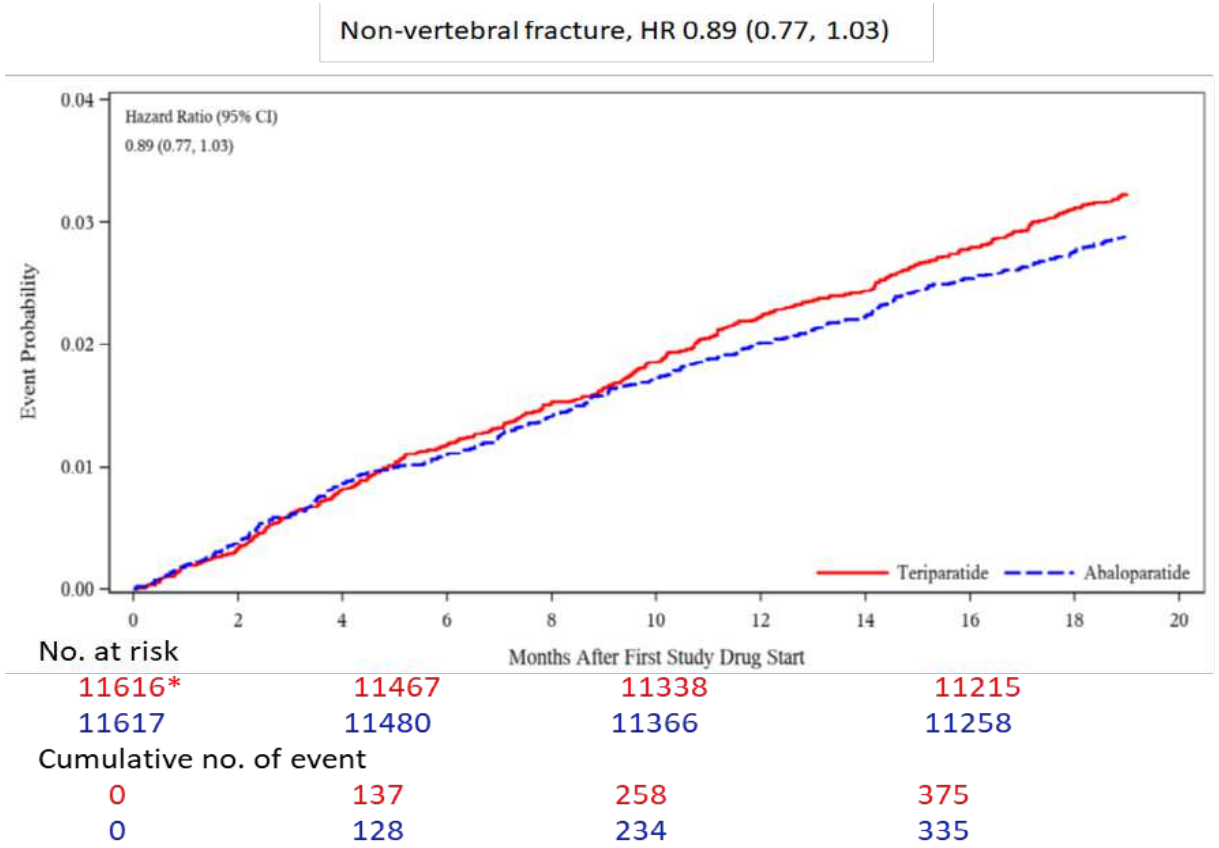
Time to first nonvertebral fracture (NVF)

Primary effectiveness endpoint

Over 19 months, 335 patients on abaloparatide and 375 patients on teriparatide had a NVF.

Estimated new NVF rate was comparable for abaloparatide vs teriparatide (2.9% vs 3.2%) *P* = 0.13.

Noninferiority for abaloparatide was established versus teriparatide on time to first NVF (Upper bound 95% CI HR = 1.03 <1.3).



*One Teriparatide patient (ID=214407410) with death date prior to index date is excluded from the analysis. Intent to treat analysis: observational period is from index date to the 18 months + 30 days, regardless when study drug ends.

Cosman F et al Osteoporosis International https://doi.org/10.1007/s00198-022-06413-y

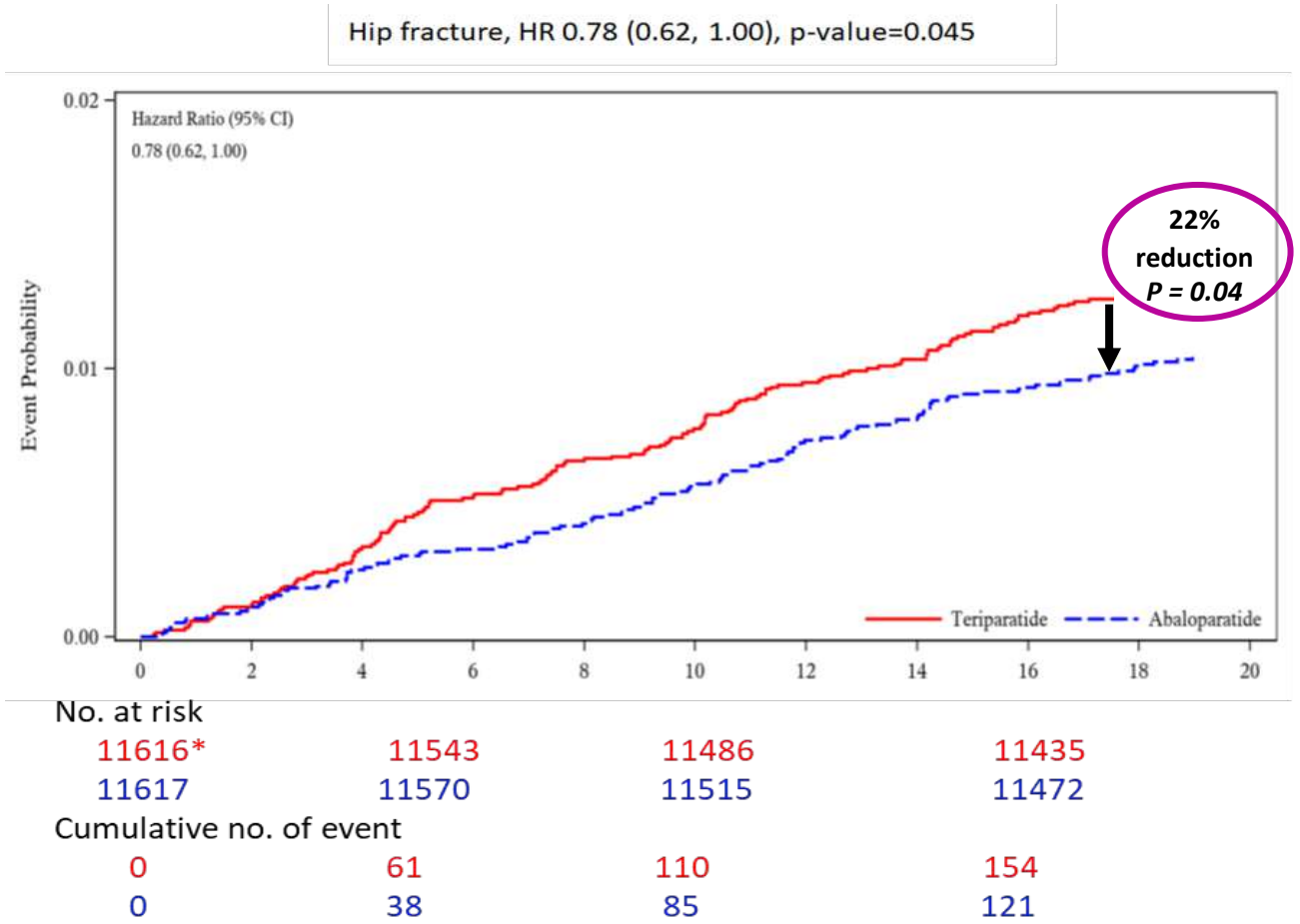
Abaloparatide significantly reduced the risk for hip fractures compared to teriparatide

Over 19 months, 121 patients on abaloparatide and 154 patients on teriparatide had a hip fracture.

The risk for hip fractures was reduced 22% for abaloparatide.

New event rate for hip fracture was lower with abaloparatide vs teriparatide (1.0% vs 1.3%) *P* = 0.04

Sensitivity analysis: when limited to patients with >12 months of consecutive treatment exposure, HR was in favour of abaloparatide 0.57 (0.35, 0.94).



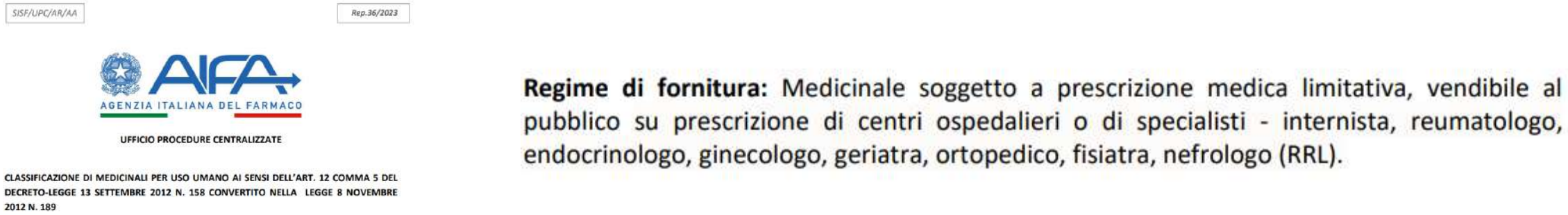
*One Teriparatide patient (ID=214407410) with death date prior to index date is excluded from the analysis. Intent to treat analysis: observational period is from index date to the 18 months + 30 days, regardless when study drug ends.

Cosman F et al Osteoporosis International https://doi.org/10.1007/s00198-022-06413-y

Indicazioni

Table 1. Summary of selected properties of interest for three approved anabolic compounds for treatment of osteoporosis

Property	Teriparatide	Abaloparatide	Romosozumab
Indications	Postmenopausal osteoporosis Male osteoporosis GIO	Postmenopausal osteoporosis	Postmenopausal osteoporosis



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Rep.36/2023

AIFA AGENZIA ITALIANA DEL FARMACO

UFFICIO PROCEDURE CENTRALIZZATE

CLASSIFICAZIONE DI MEDICINALI PER USO UMANO AI SENSI DELL'ART. 12 COMMA 5 DEL DECRETO-LEGGE 13 SETTEMBRE 2012 N. 158 CONVERTITO NELLA LEGGE 8 NOVEMBRE 2012 N. 189

Regime di fornitura: Medicinale soggetto a prescrizione medica limitativa, vendibile al pubblico su prescrizione di centri ospedalieri o di specialisti - internista, reumatologo, endocrinologo, ginecologo, geriatra, ortopedico, fisiatra, nefrologo (RRL).

Al termine del periodo massimo (18 mesi) deve seguire un **trattamento antiriassorbitivo** per mantenere i risultati sulla BMD.

thank you
danke
gracias
merci
obrigado
bedankt
dziękuję
teşekkür ederim
go raibh maith agat
mochchakkeram
ngiyabonga
tapadh leat
спасибо
謝謝
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