



VIII CONVEGNO PONTINO  
SULLE PATOLOGIE  
OSTEOMETABOLICHE

15 - 16 Ottobre 2021 - Sabaudia (LT)

Romosozumab  
Evidenze cliniche e criteri di utilizzo

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UOS Malattie Metaboliche

# Sclerostina, Romosozumab una lunga storia....

*Nel 2010, un ricercatore che studiava una popolazione di sudafricani con origini olandesi in cui molti membri avevano anomalie alle ossa,*

*Chiese in un incontro pubblico se qualcuno di loro aveva mai avuto un incidente.....*

*Un uomo alzò la mano per raccontare:*

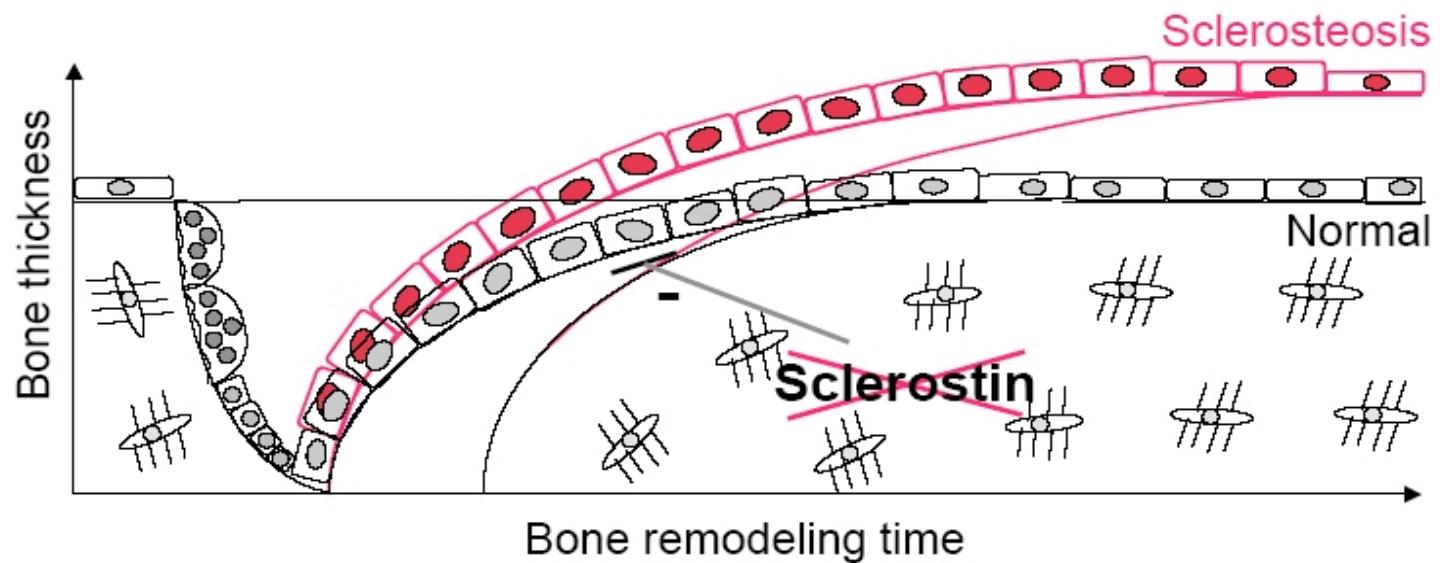
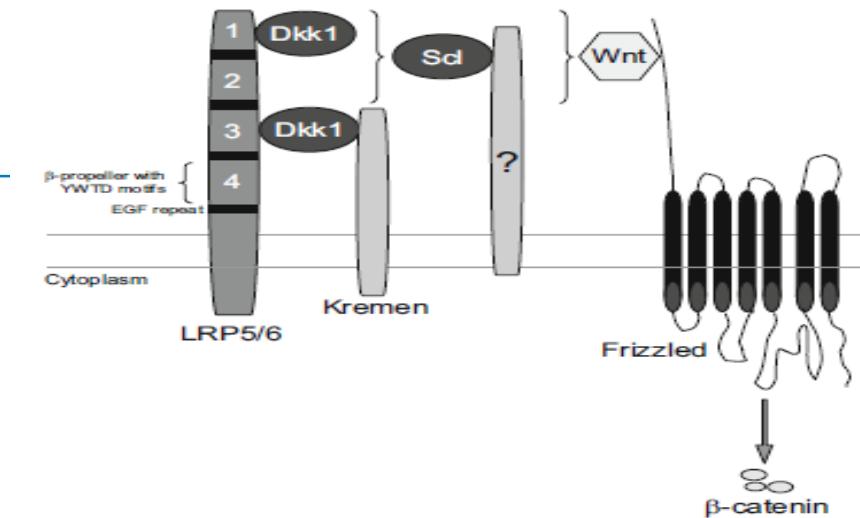
**“stavo attraversando la strada con mio fratello quando una Mercedes ci è venuta addosso”.** E che cosa è successo?

**“Avresti dovuto vedere la Mercedes”** è stata la risposta.

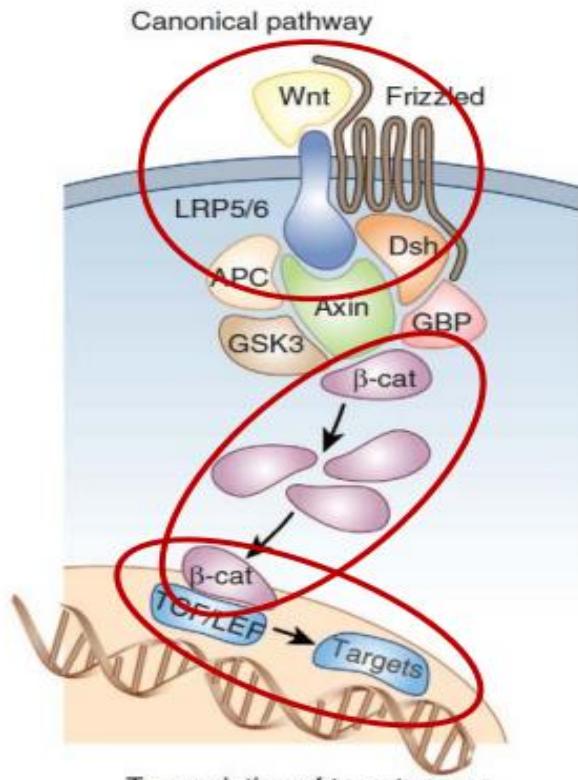
# The Osteocyte as the New Discovery of Therapeutic Options in Rare Bone Diseases

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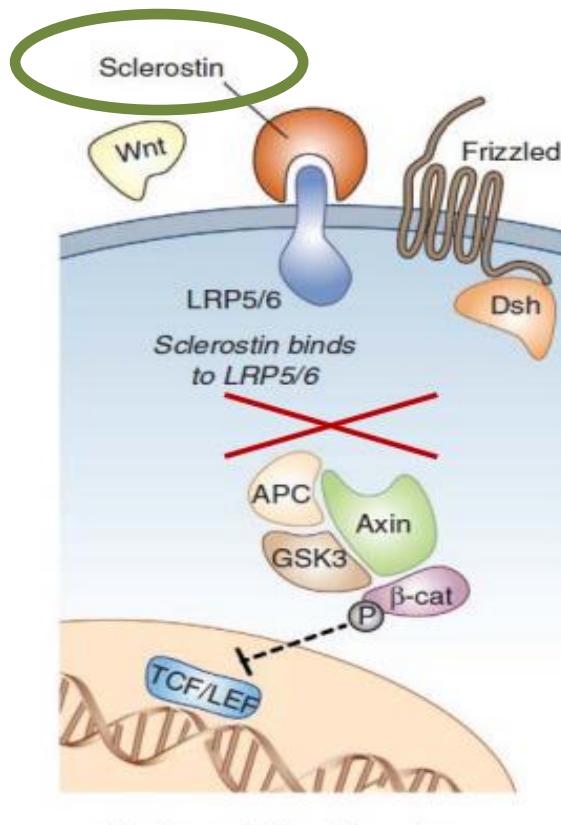




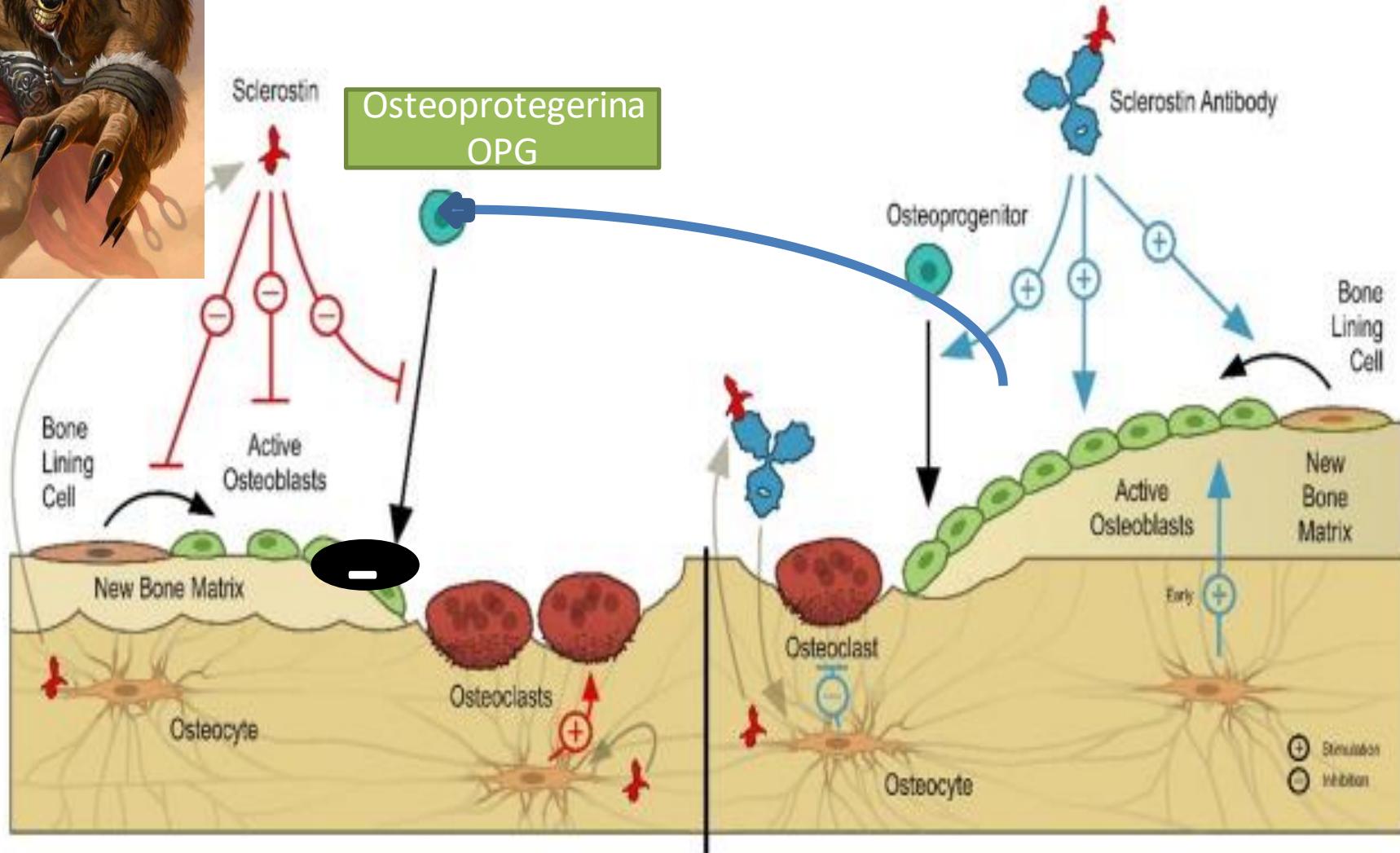
# Sclerostina e via canonica del WNT



Differenziazione, proliferazione e sopravvivenza degli osteoblasti, aumento della formazione ossea



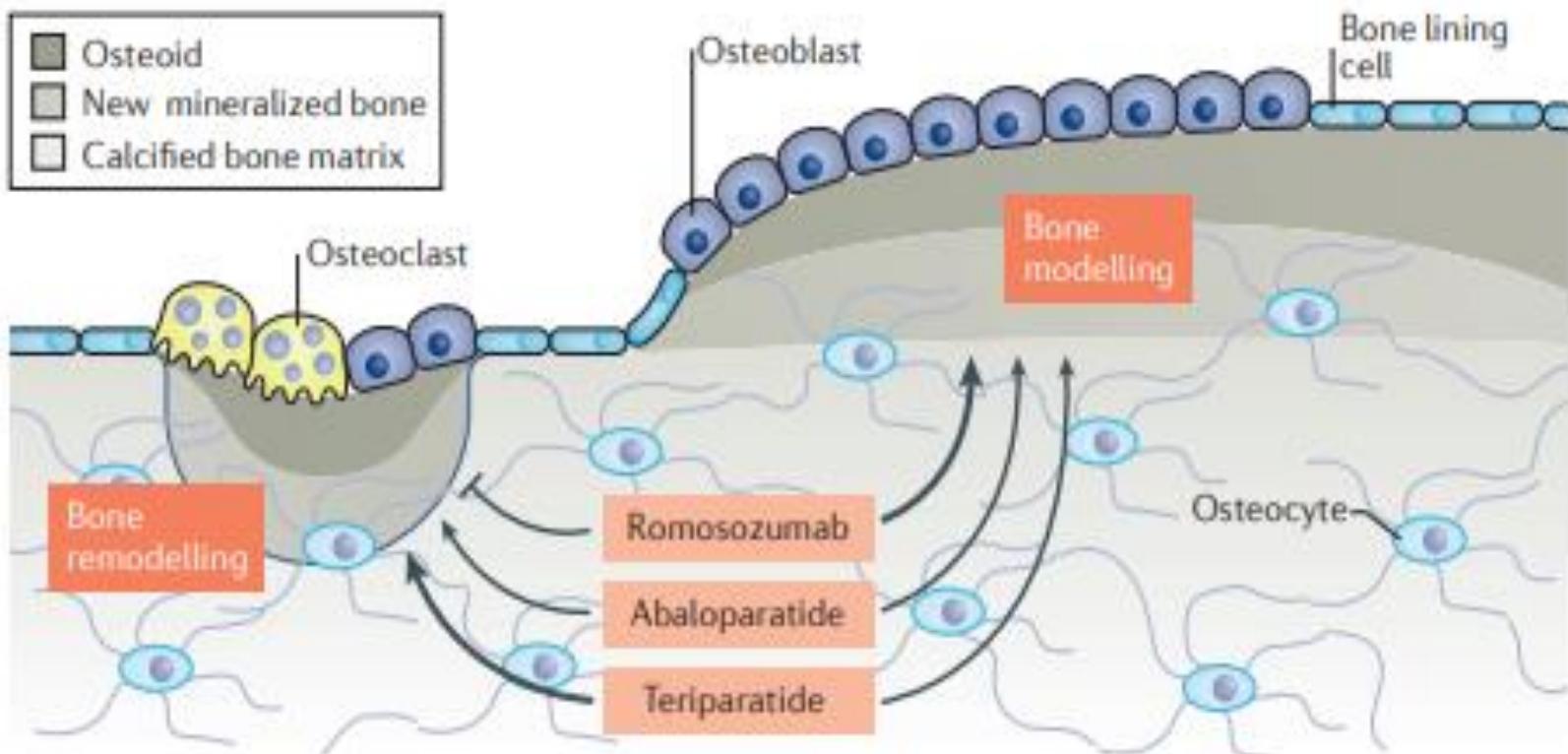
Evenepoel P, Kidney Int 2015





# ROMOSOZUMAB

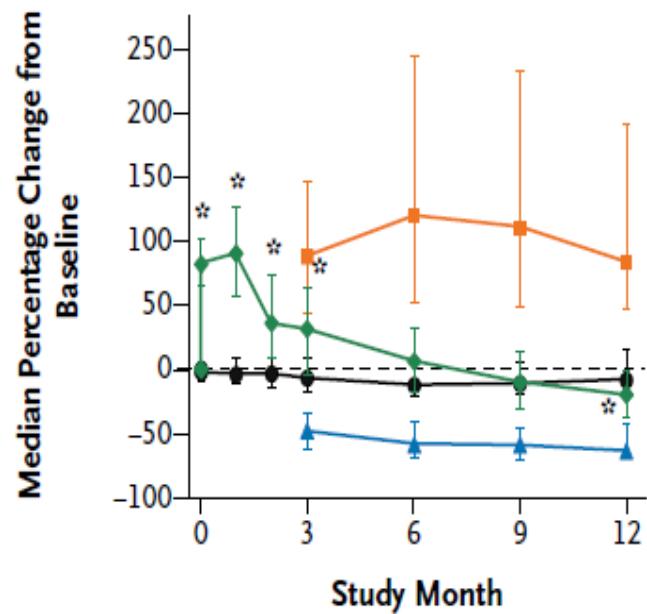
## MECCANISMO DI AZIONE



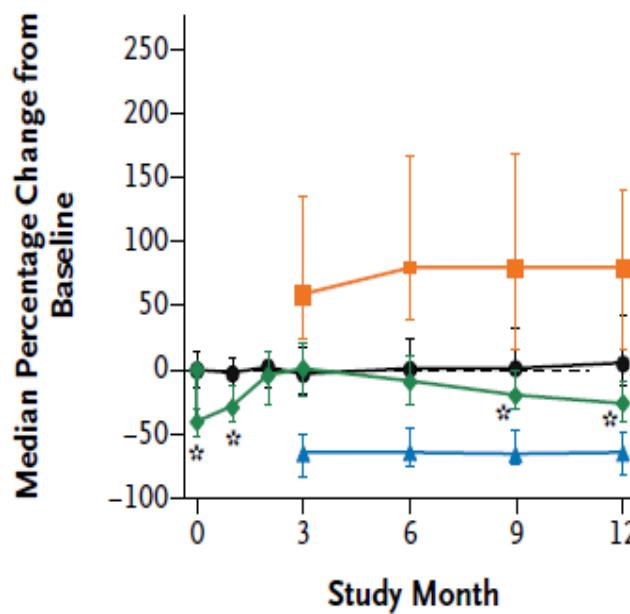
# Romosozumab in Postmenopausal Women with Low Bone Mineral Density

● Placebo    ■ Alendronate    □ Teriparatide    ● 210 mg of Romosozumab monthly

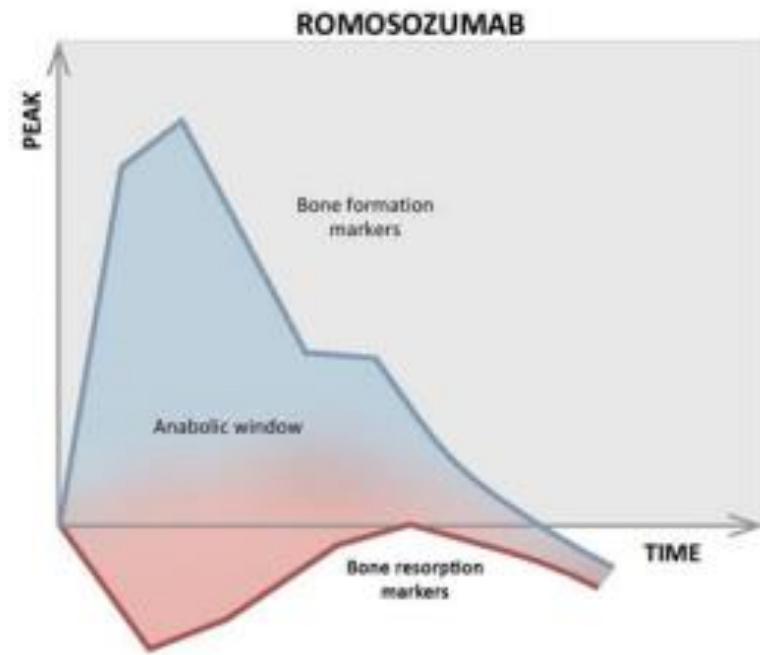
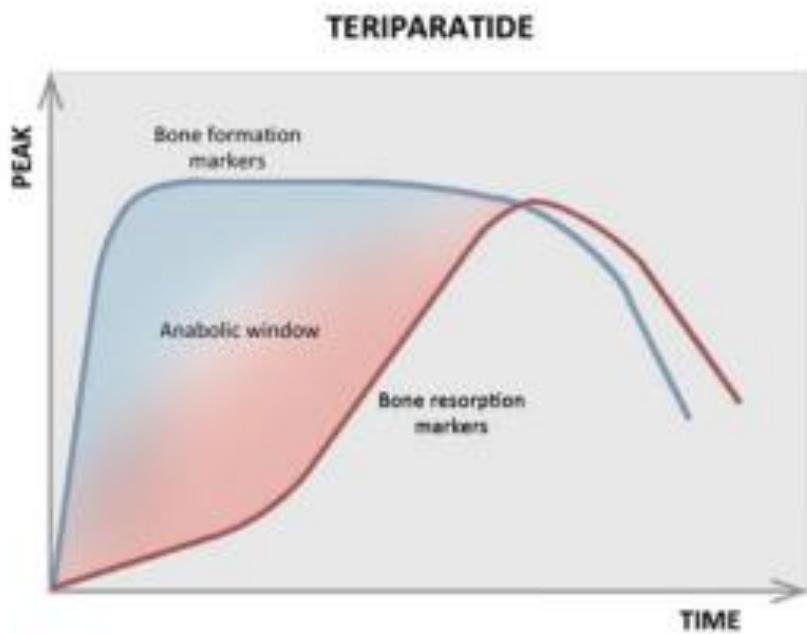
A P1NP



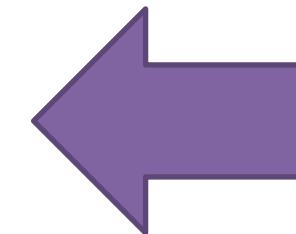
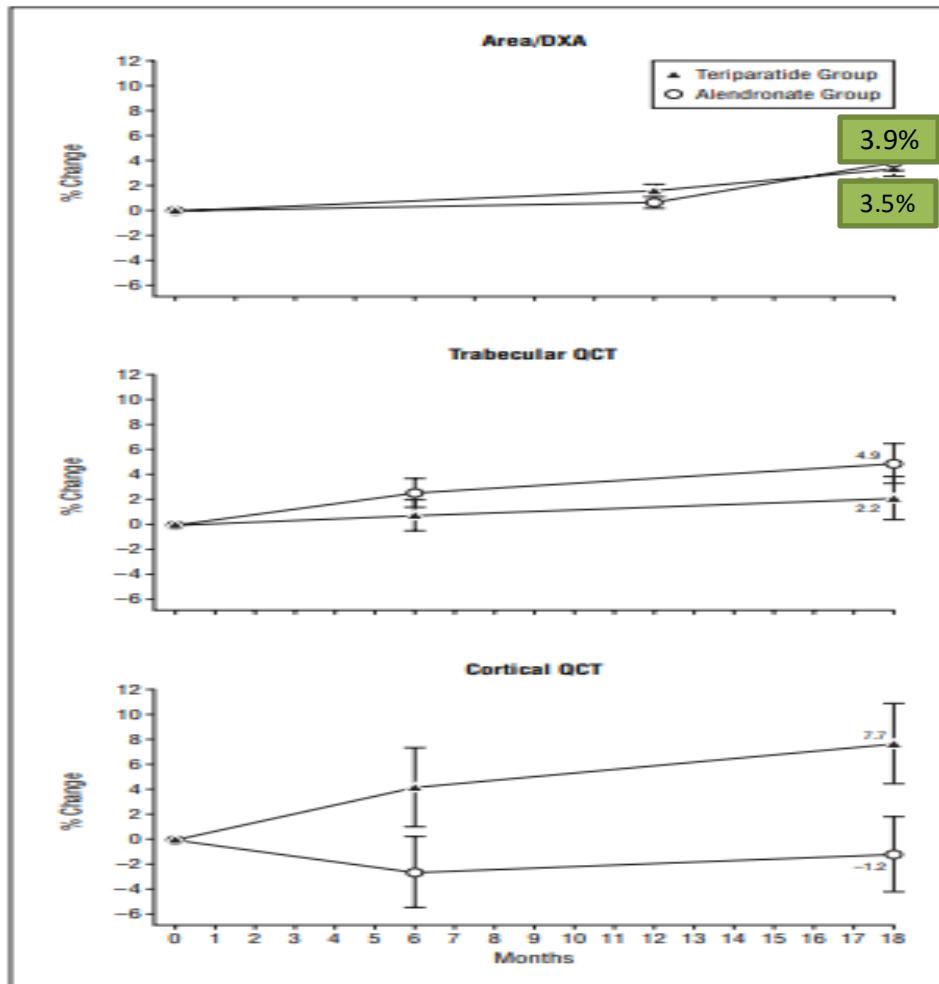
B  $\beta$ -CTX



# LA FINESTRA ANABOLICA

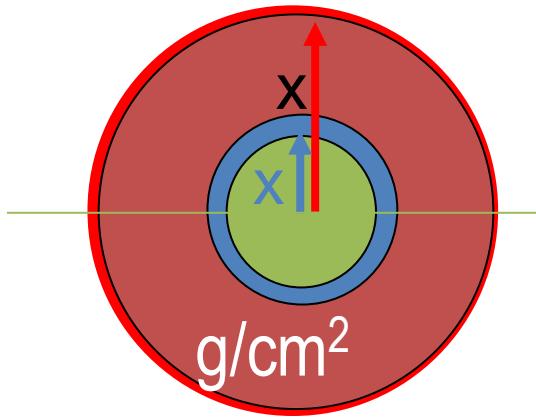


# Opposite Bone Remodeling Effects of Teriparatide and Alendronate in Increasing Bone Mass

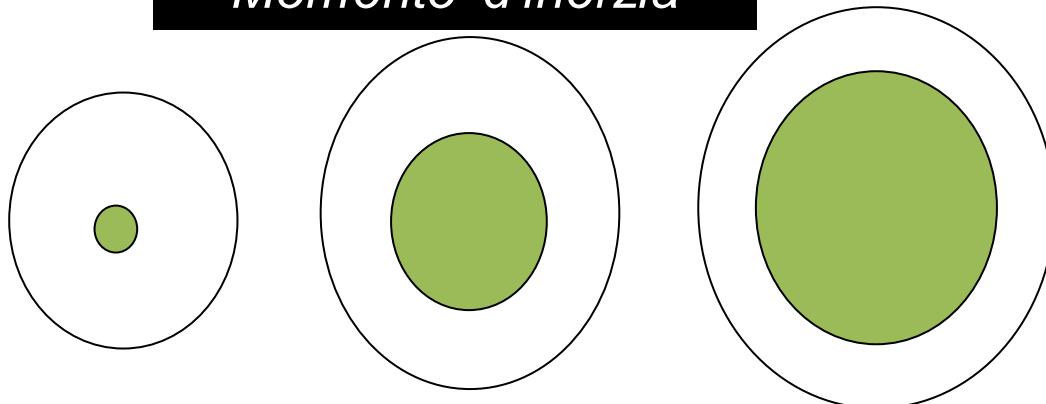


# PARATORMONE: GEOMETRIA

L'osso rosso  
è meglio" di quello  
verde  
perchè è più lontano  
dall'asse neutro



"Cross-Sectional Moment of Inertia"  
distribuzione della massa nello spazio  
È una funzione del quadrato della distanza  
dall'asse neutro

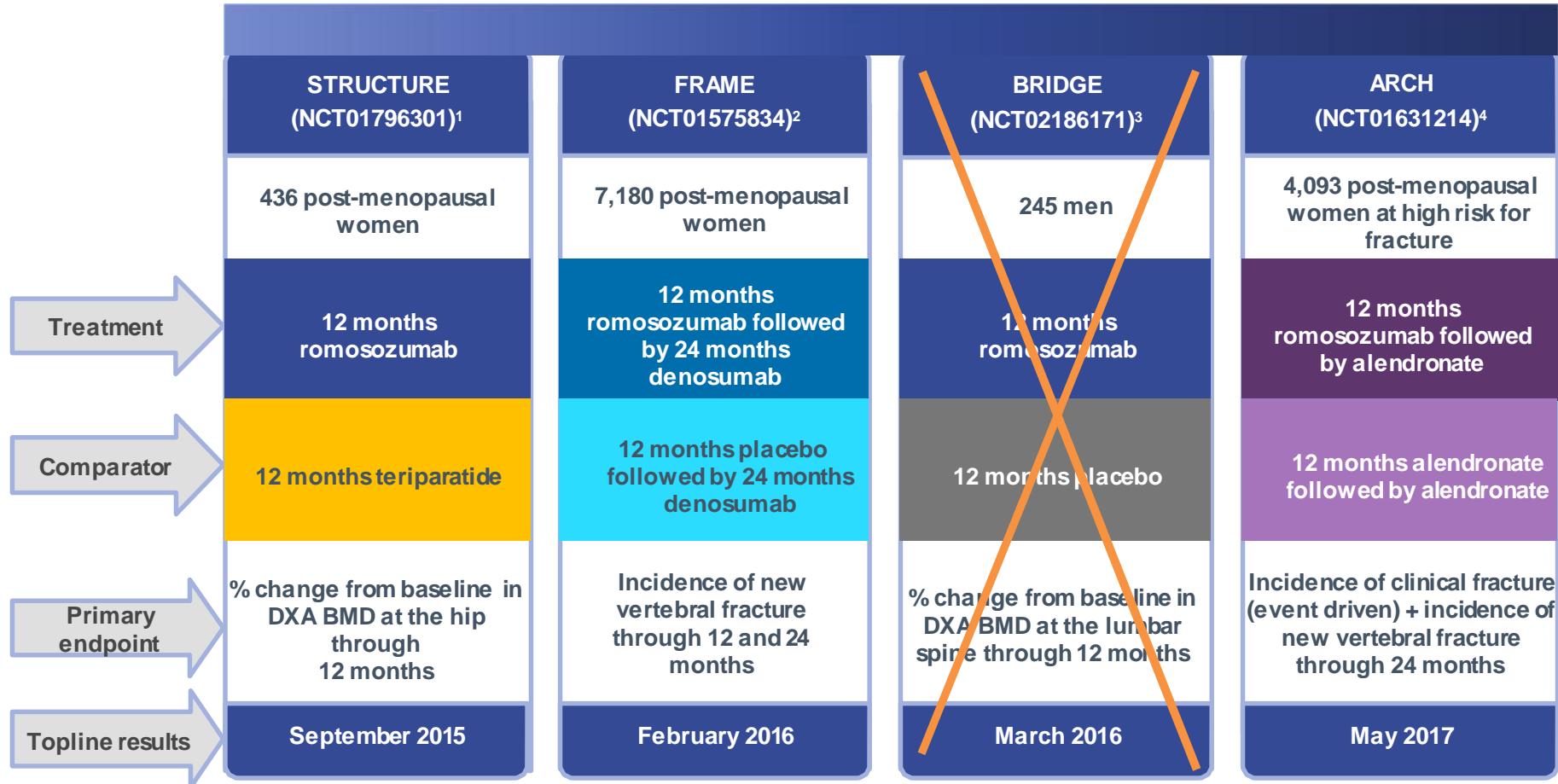


Area (cm <sup>2</sup> )	2.77	2.77	2.77
CSMI (cm <sup>4</sup> )	0.61	1.06	1.54
Bending Strength	100%	149%	193%

OSSO CORTICALE

# Romosozumab Phase 3 clinical trials

Più di 10,000 donne in menopausa affette da osteoporosi sono state studiate



# Romosozumab Treatment in Postmenopausal Women with Osteoporosis

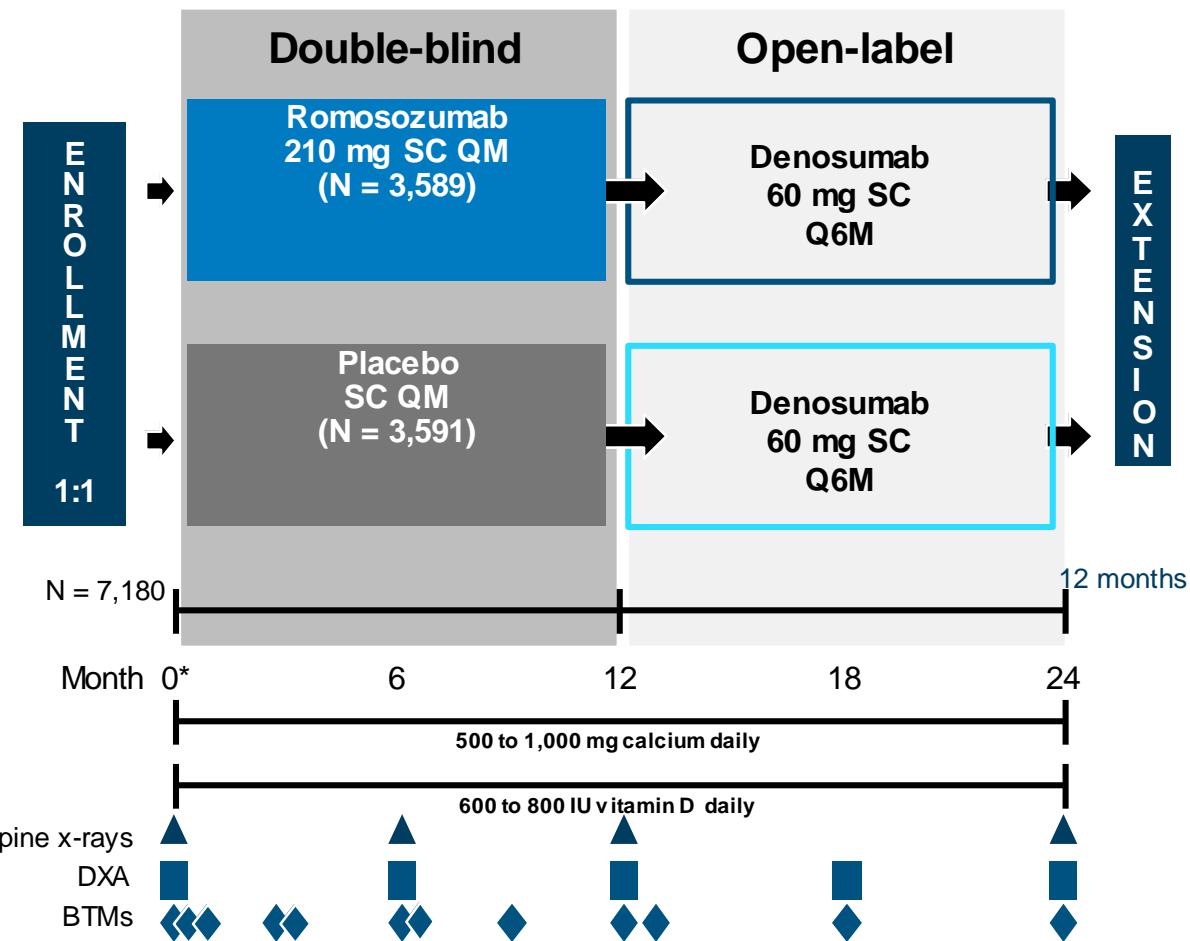
*FRA*cture Study in Postmenopausal WoMen with OstEoporosis (FRAME)

FRAME is a phase 3, randomized, placebo-controlled FRActure study in postmenopausal woMen with ostEoporosis<sup>2</sup>



# FRAME Phase 3 Study Design

*FRA*cture study in postmenopausal wo*M*en with ost*E*oporosis



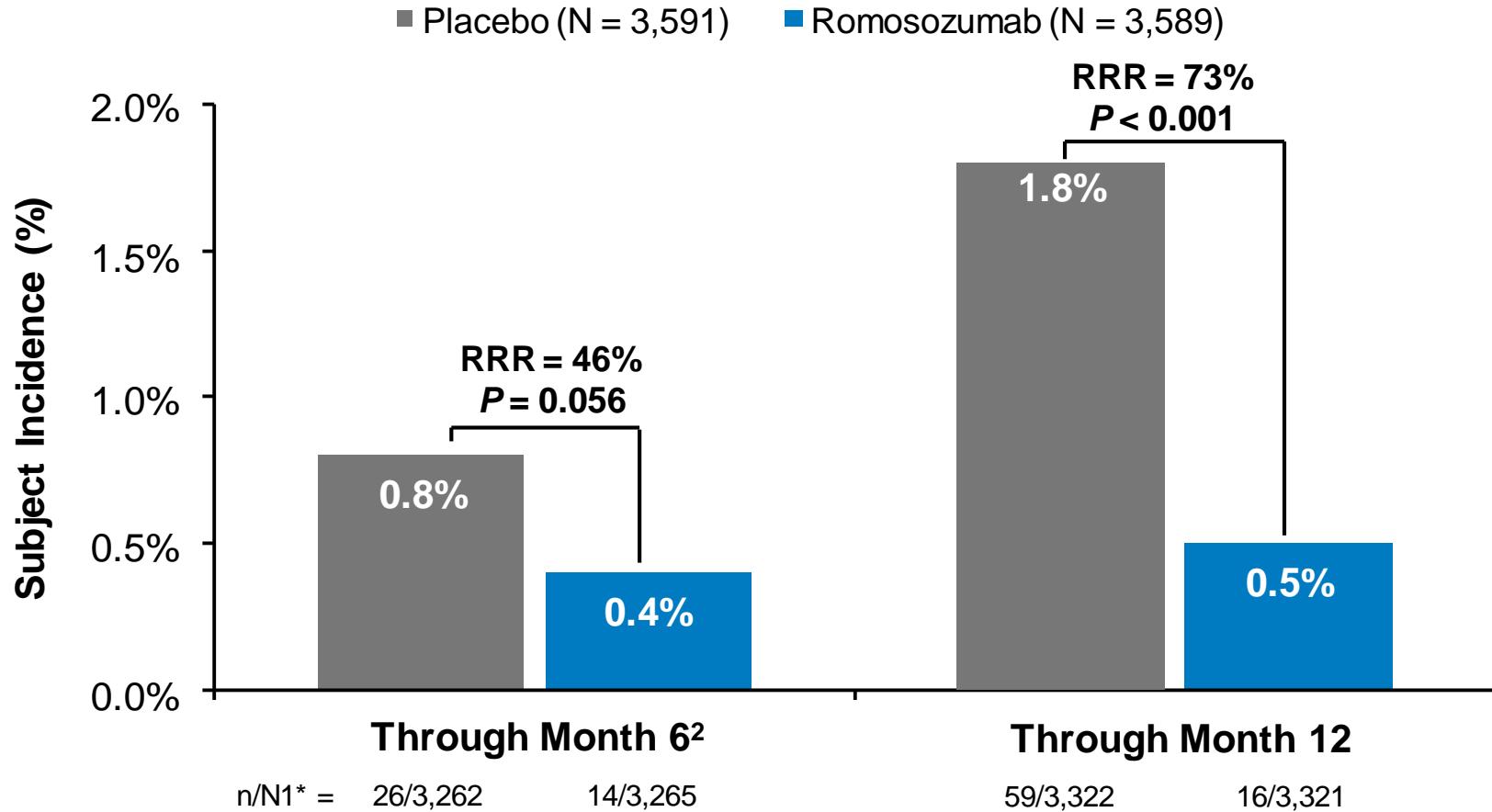
**Co-Primary Endpoints:**

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

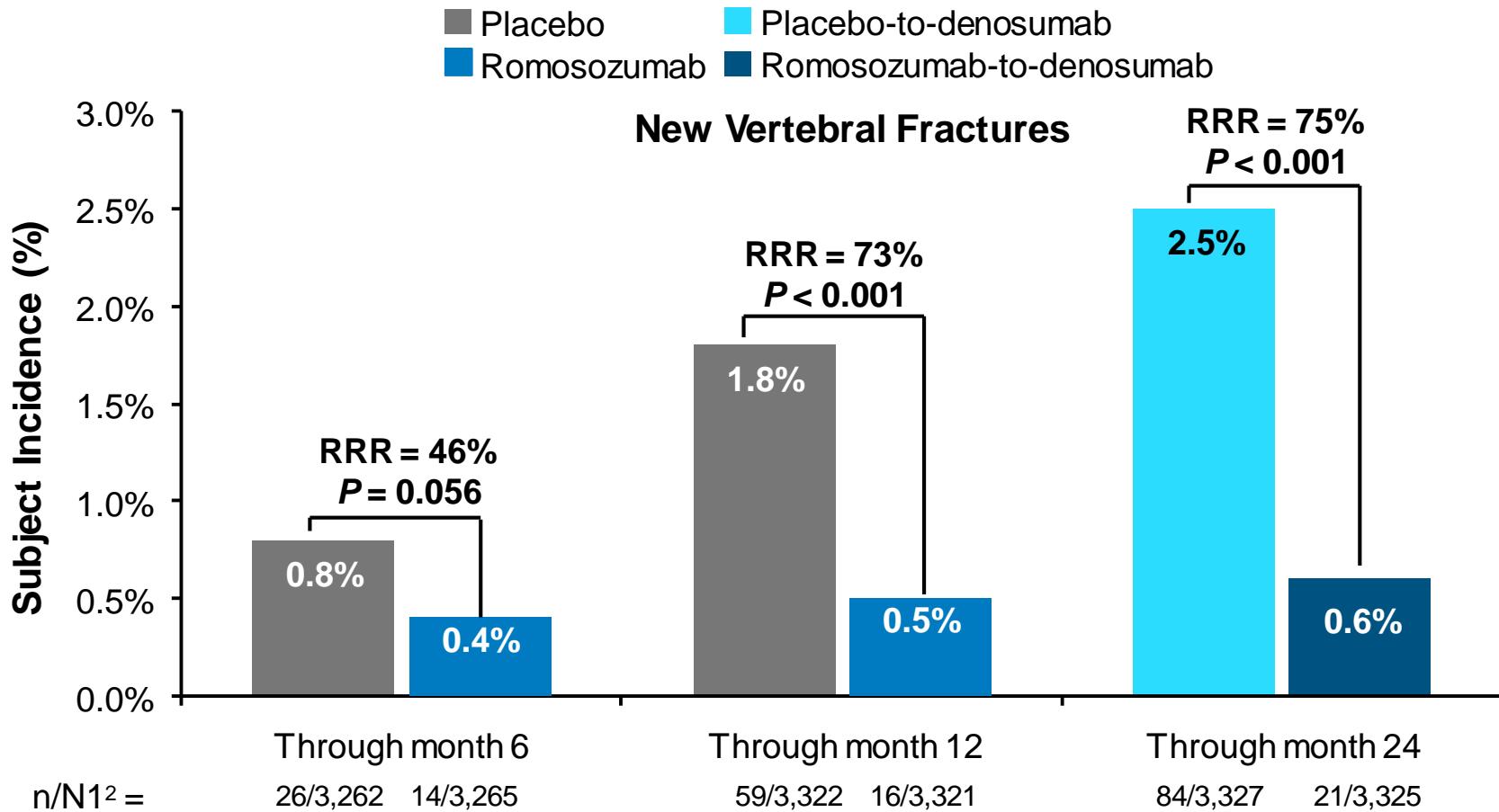
**Secondary Fracture Endpoints:**

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

# Incidenza di nuove fratture vertebrali a 12 mesi

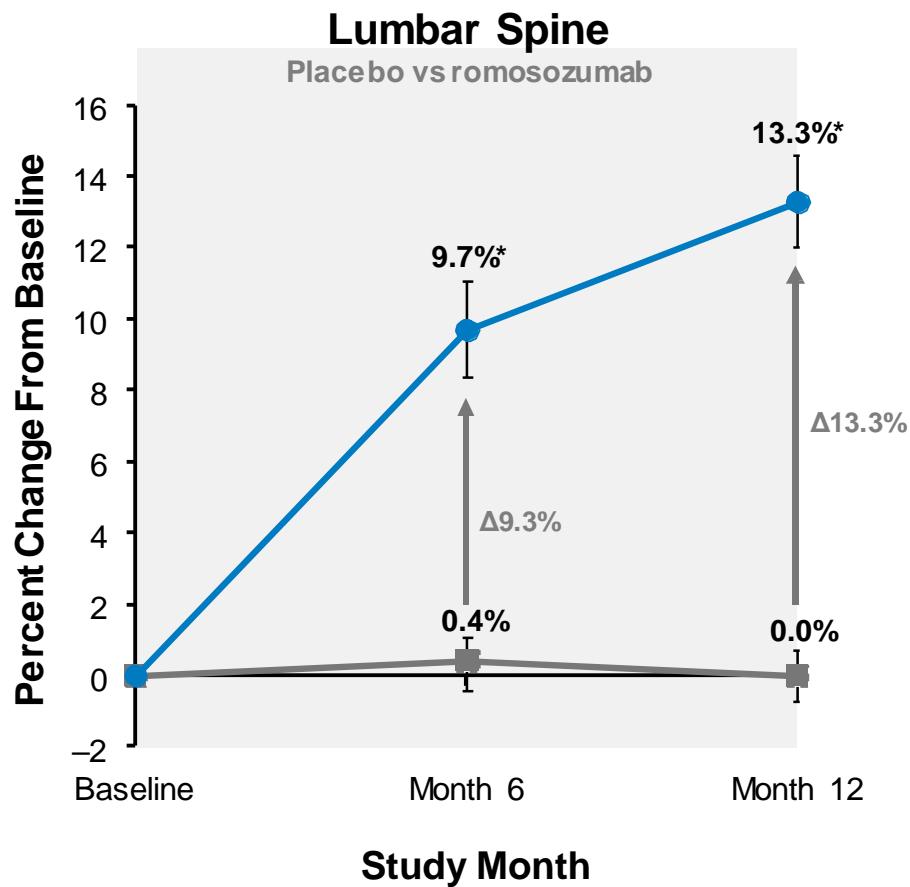


# Nuove fratture vertebrali a 24 mesi

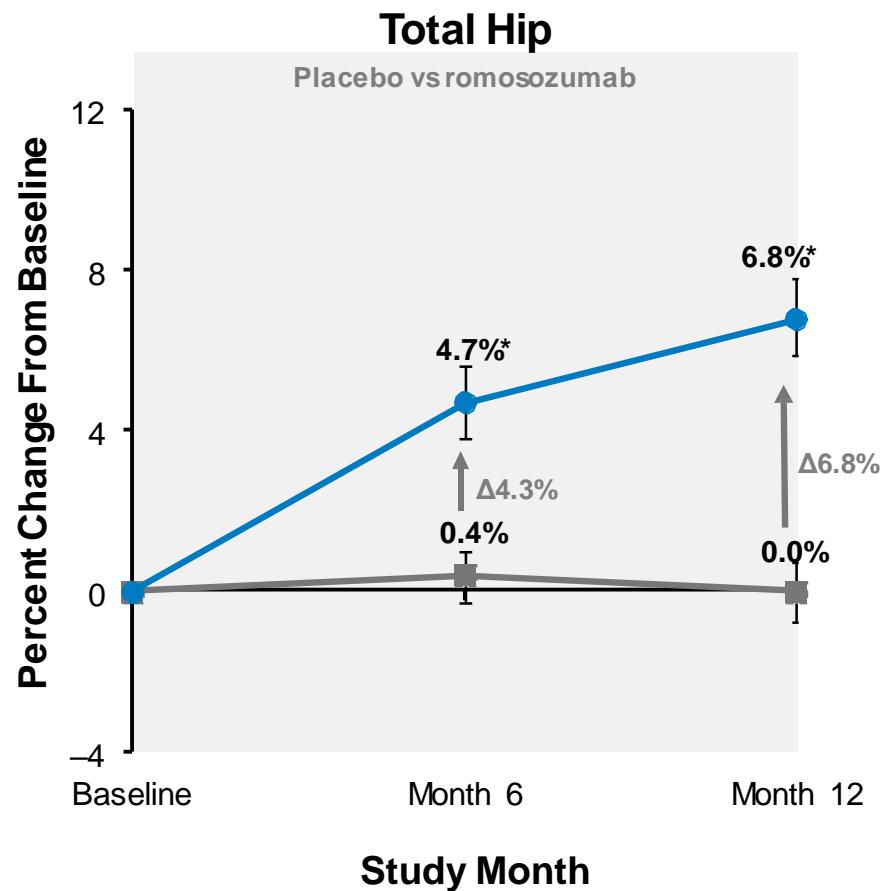


# BMD lombare e femorale a 12 mesi

— Placebo (N = 61)  
— Romosozumab (N = 65)

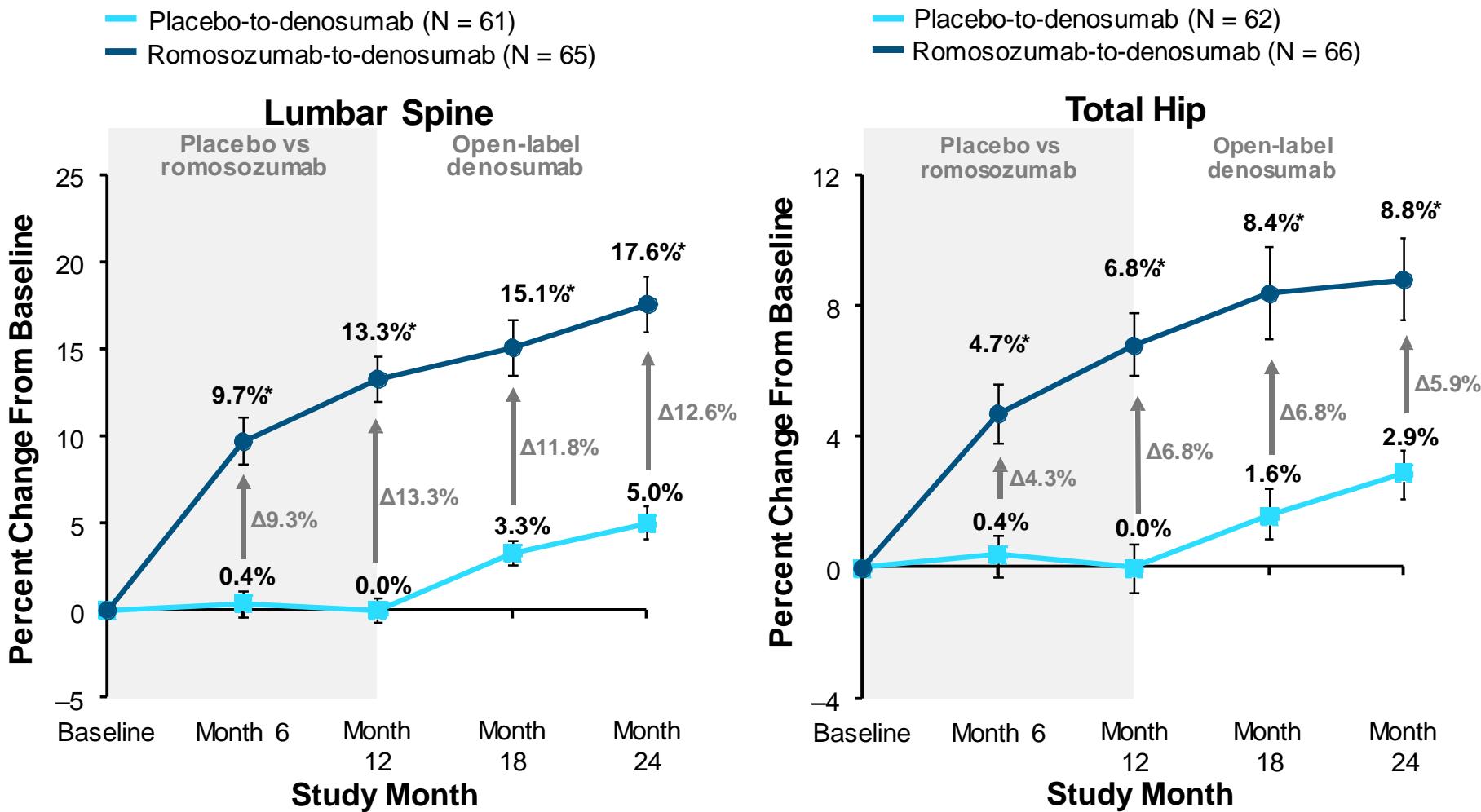


— Placebo (N = 62)  
— Romosozumab (N = 66)

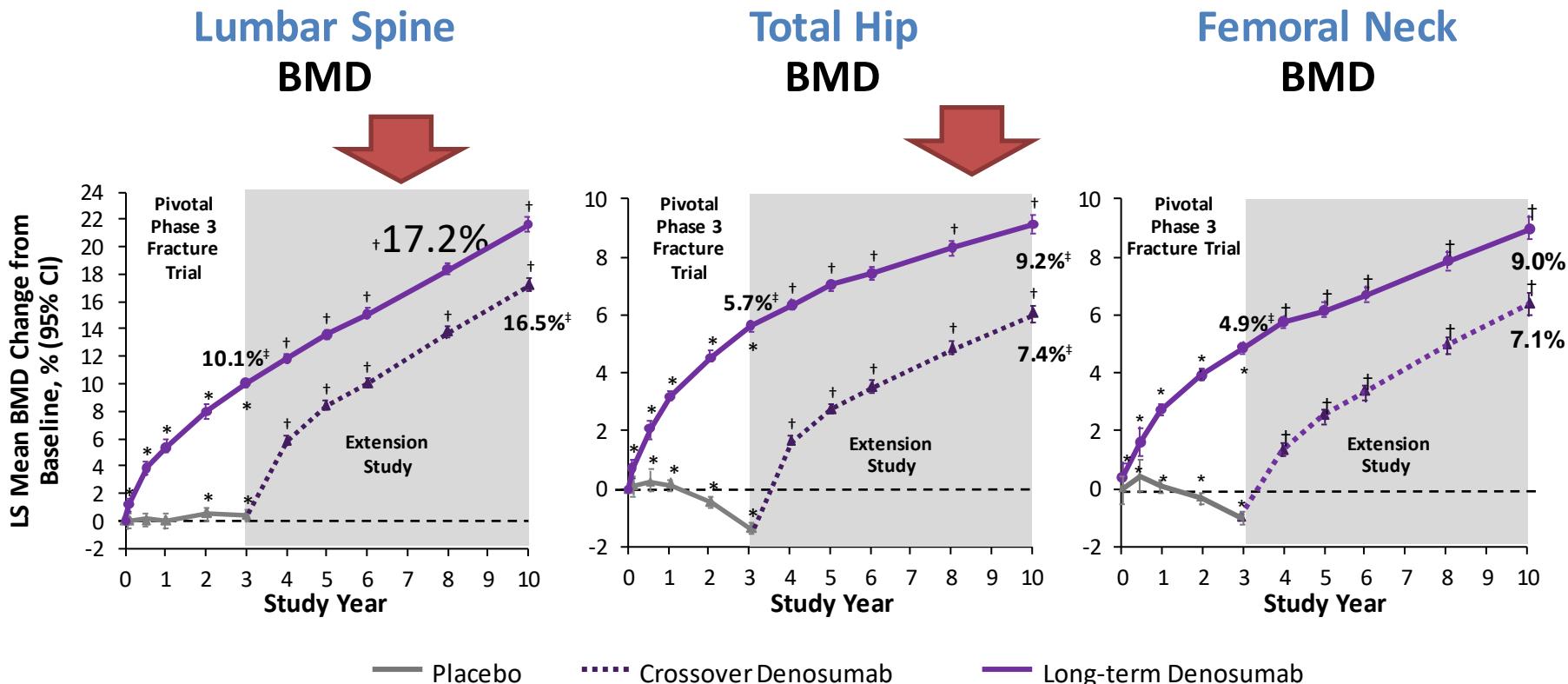


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# BMD lombare e femorale a 24 mesi



# Denosumab fino a 10 anni risulta in un continuo e progressivo incremento del BMD in sede lombare e femorale<sup>1</sup>



# Summary

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- Romosozumab per 12 mesi comparato al placebo (RRR):
  - Nuove fratture vertebrali: 73% ( $P < 0.001$ )
  - Fratture cliniche: 36% ( $P = 0.008$ )
  - Fratture non vertebrali: 25% ( $P = 0.096$ )
- In 24 mesi, romosozumab--denosumab comparato con placebo--denosumab (RRR):
  - Nuove fratture vertebrali: 75% ( $P < 0.001$ )
  - Fratture cliniche: 33% (nominal  $P = 0.002$ ; adjusted  $P = 0.096$ )
  - Fratture non vertebrali: 25% (nominal  $P = 0.029$ ; adjusted  $P = 0.057$ )

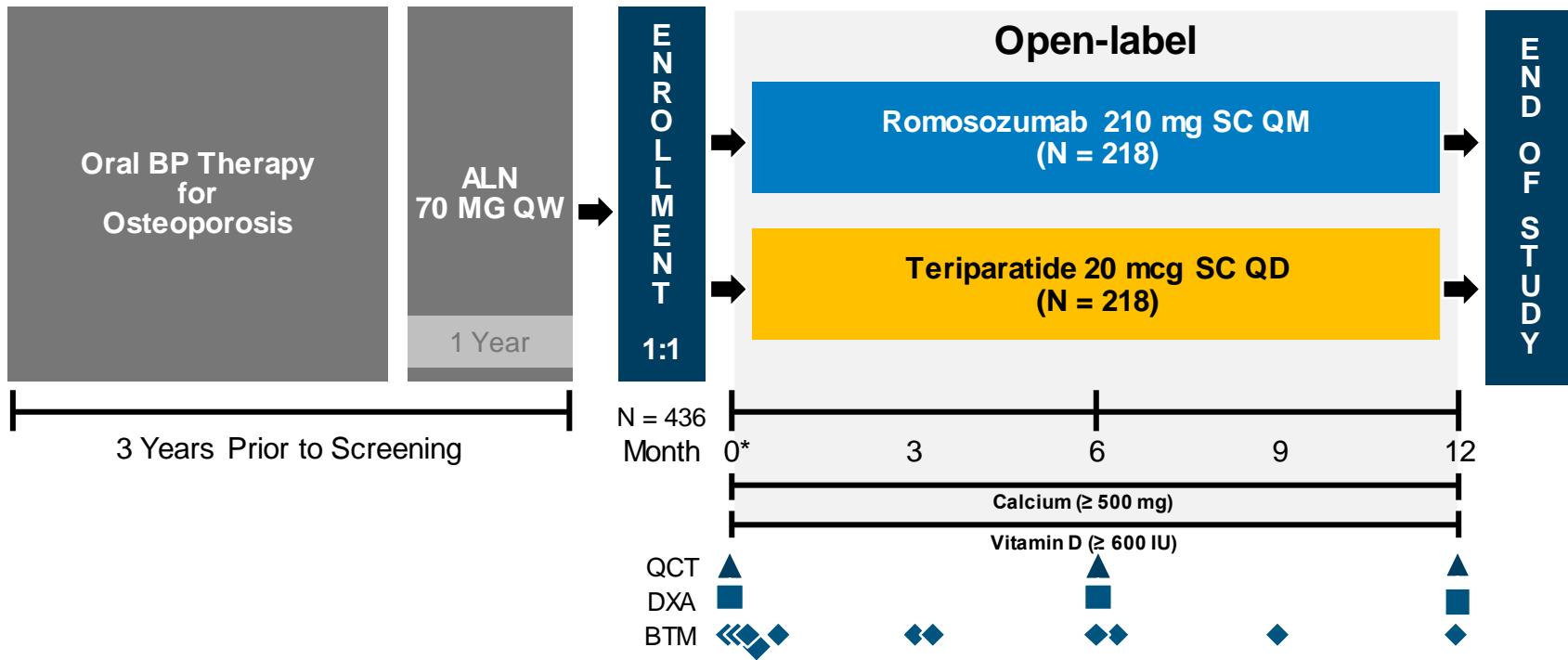
# Romosozumab vs Teriparatide in Postmenopausal Women with Osteoporosis Transitioning from Oral Bisphosphonate Therapy: A Randomized Open-Label Phase 3 Trial

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



# STRUCTURE Fase 3: disegno dello studio



# Criteri di elegibilità

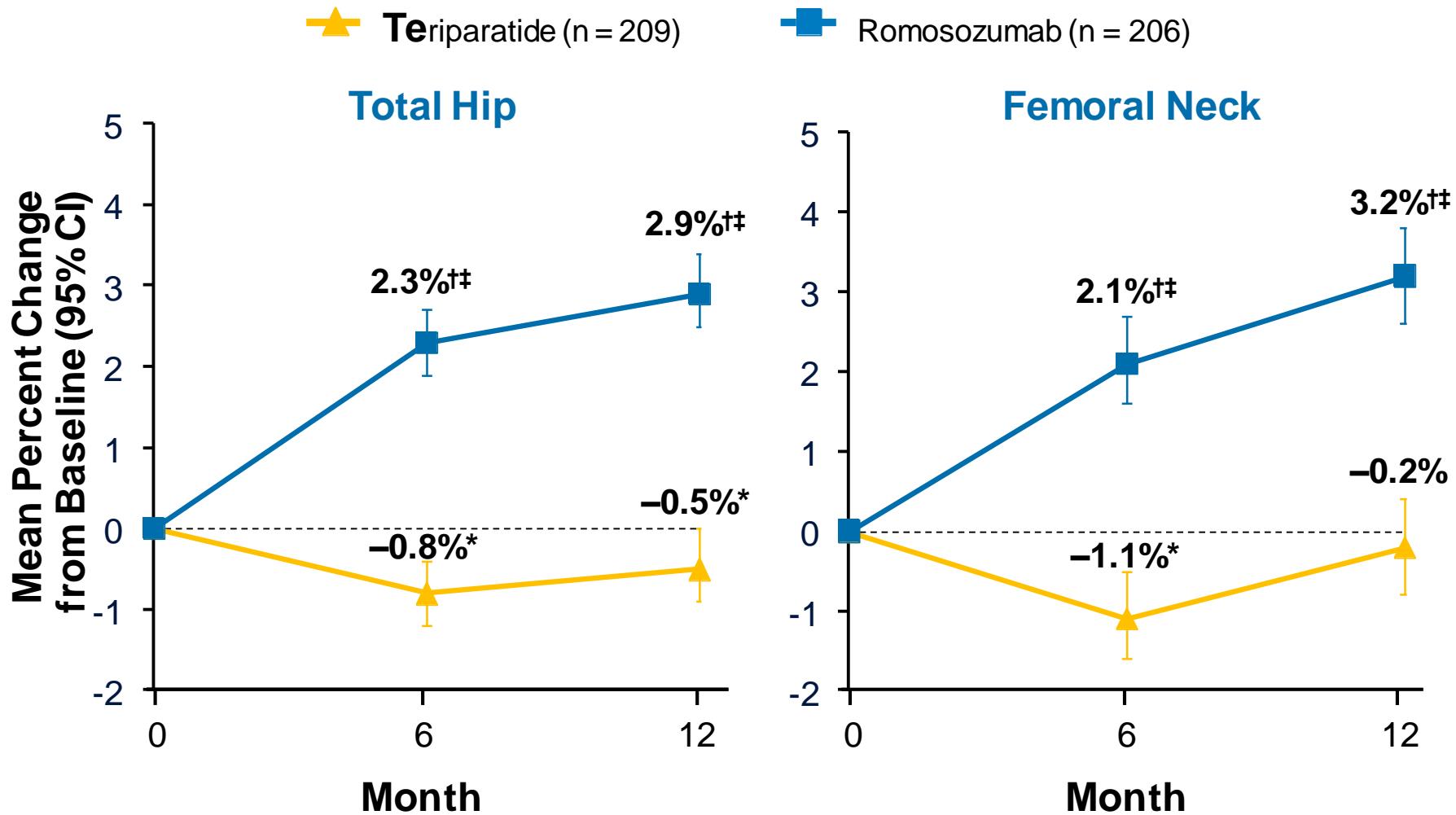
<b>Criteri di Inclusione</b>	<ul style="list-style-type: none"><li>• Donne in menopausa con età tra 55 e 90</li><li>• BMD T-score <math>\leq -2.5</math> in sede femorale o lombare</li><li>• Storia di fratture vertebrali o non vertebrali dopo l'età di 50 anni</li><li>• Bifosfonati orali assunti per <math>\geq 3</math> anni</li></ul>
<b>Criteri di esclusione</b>	<ul style="list-style-type: none"><li>• Recente uso di agenti che modificano il metabolismo osseo</li><li>• Storia di altre malattie osteometaboliche</li></ul>

# Primary and Key Secondary Endpoints

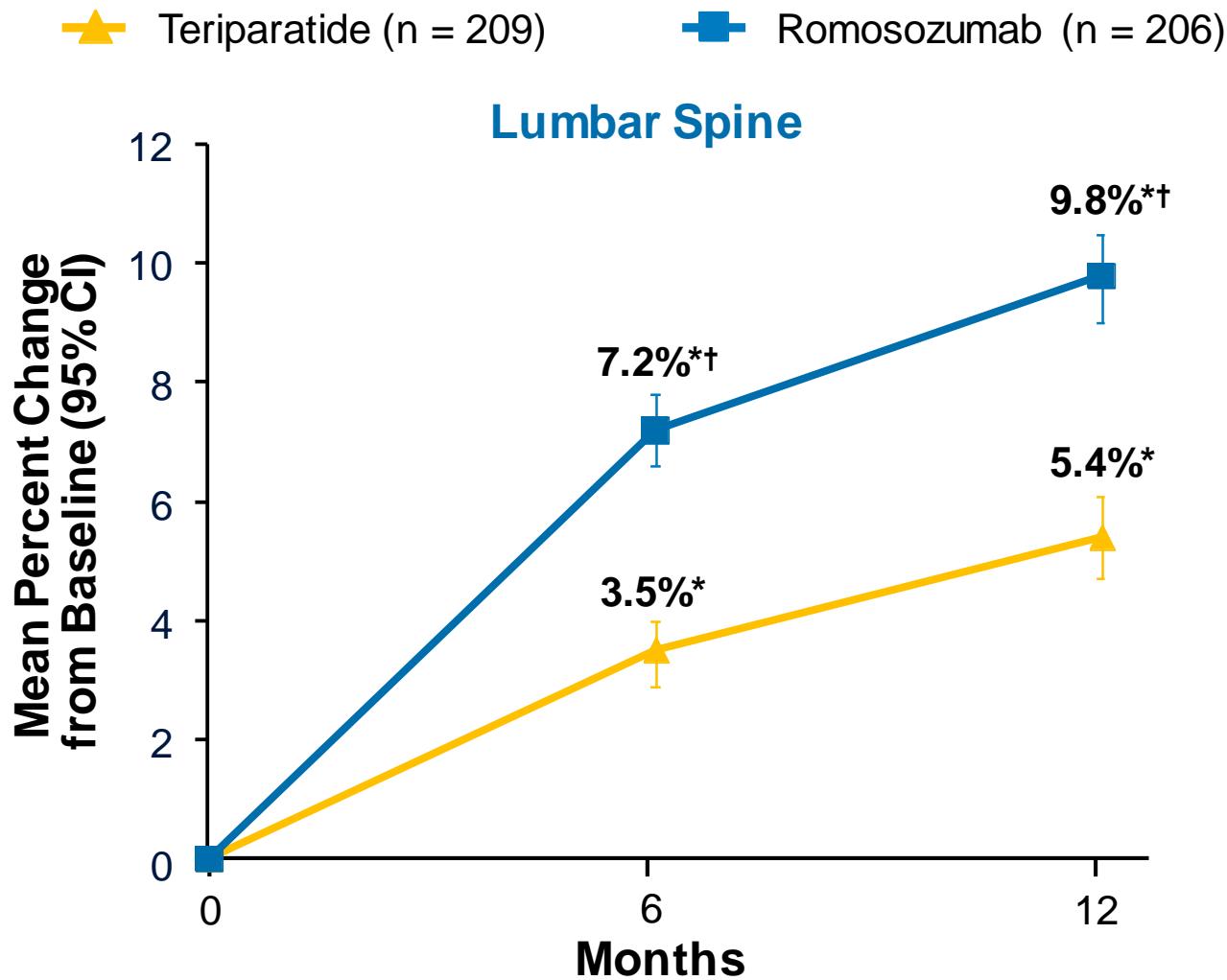
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<b>End-point primario</b>	<ul style="list-style-type: none"><li>• Percentuale di cambiamento rispetto al basale della BMD in sede lombare e femorale a 6 e 12 mesi</li></ul>
<b>KeyEnd-points secondari</b>	<ul style="list-style-type: none"><li>• Percentuale di cambiamento rispetto al basale della hip strength valutata tramite FEA a 6 e 12 mesi</li><li>• Percentuale di cambiamento rispetto al basale della BMC valutata in sede femorale con esame QCT a 6 e 12 mesi</li></ul>

# DEXA in sede femorale a 6 e 12 mesi



# DEXA in sede lombare a 6 e 12 mesi



# SAFETY A 12 MESI

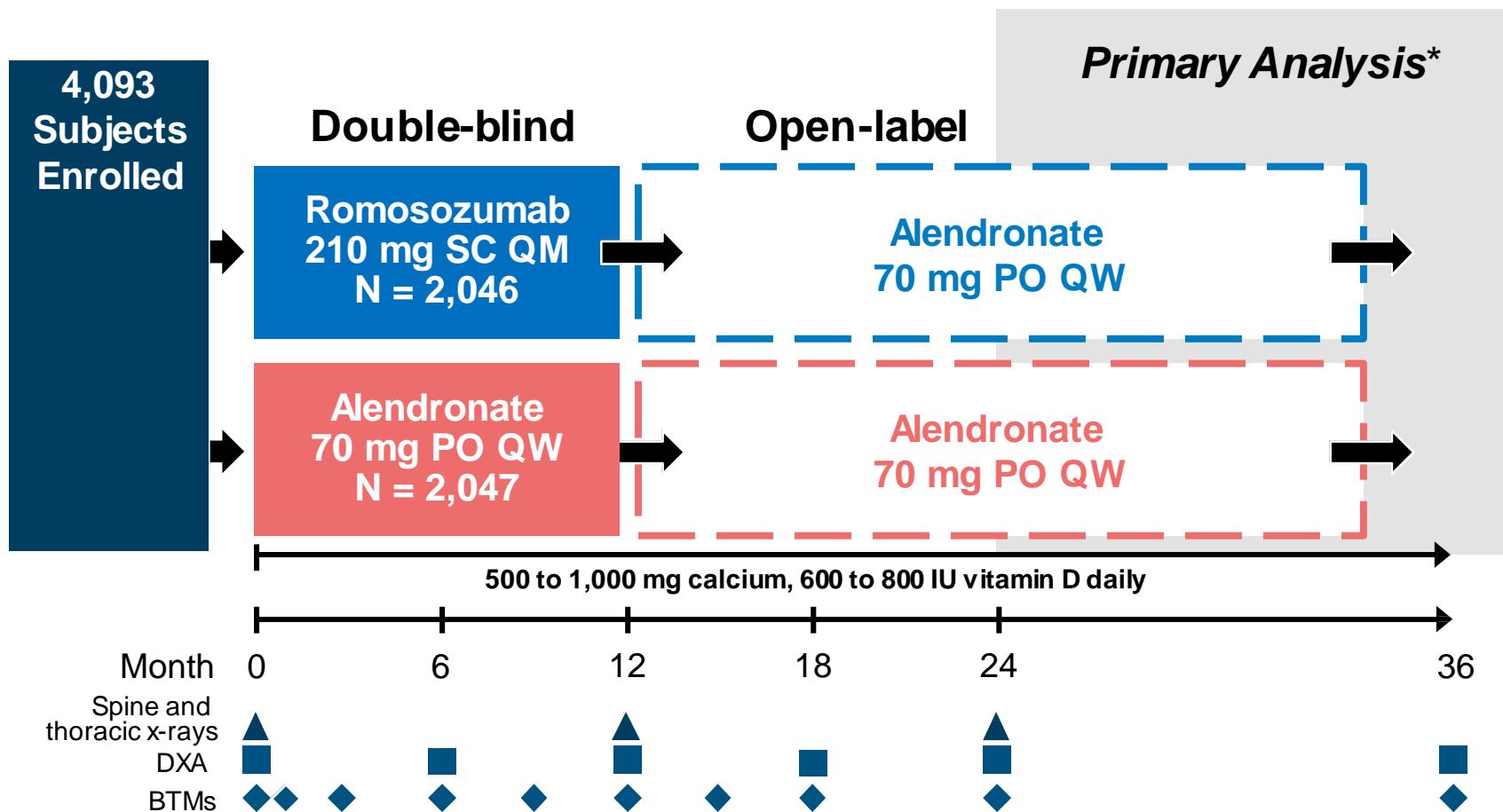
	Teriparatide (n = 214)	Romosozumab (n = 218)
<b>All adverse events</b>	148 (69%)	164 (75%)
<b>Serious adverse events</b>	23 (11%)	17 (8%)
<b>Adverse events</b>		
<b>Arthralgia*</b>	13 (6%)	22 (10%)
<b>Hypercalcaemia*</b>	22 (10%)	2 (< 1%)
<b>Hypocalcaemia†</b>	0	3 (1%)
<b>Injection-site reaction†</b>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

# 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)*



# ARCH Phase 3 : disegno dello studio

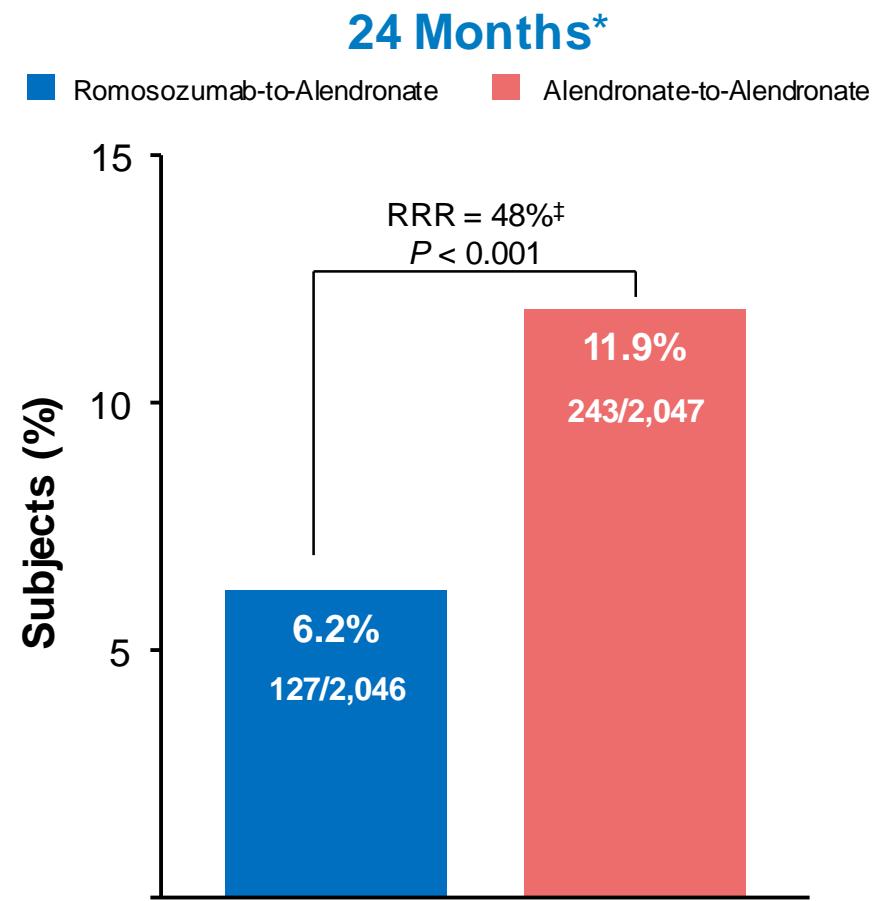
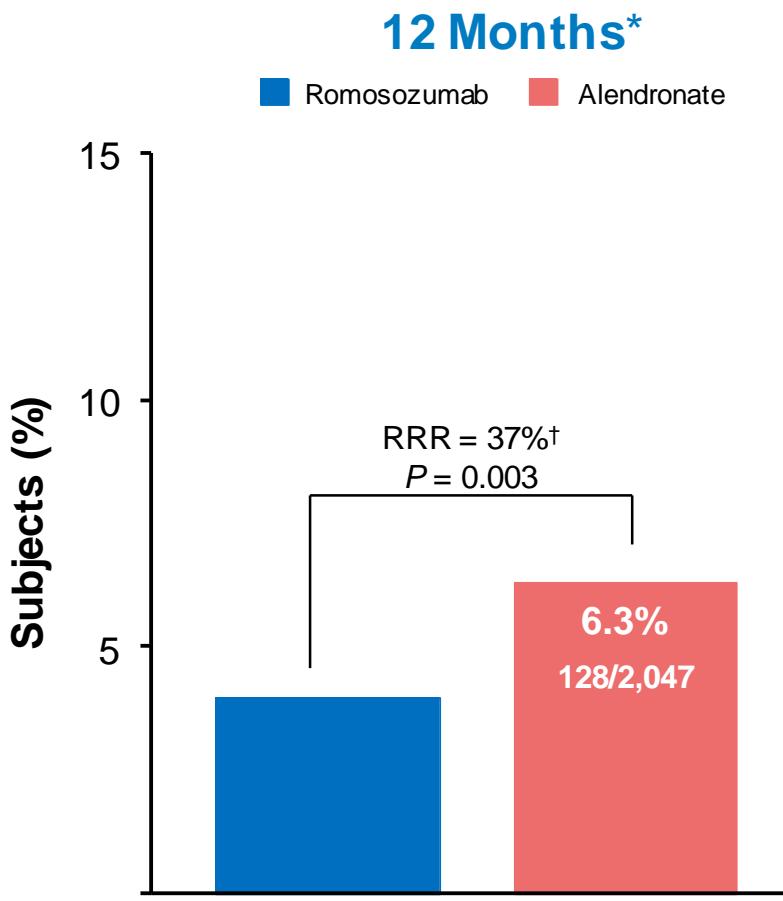


# Endpoints primari e secondari

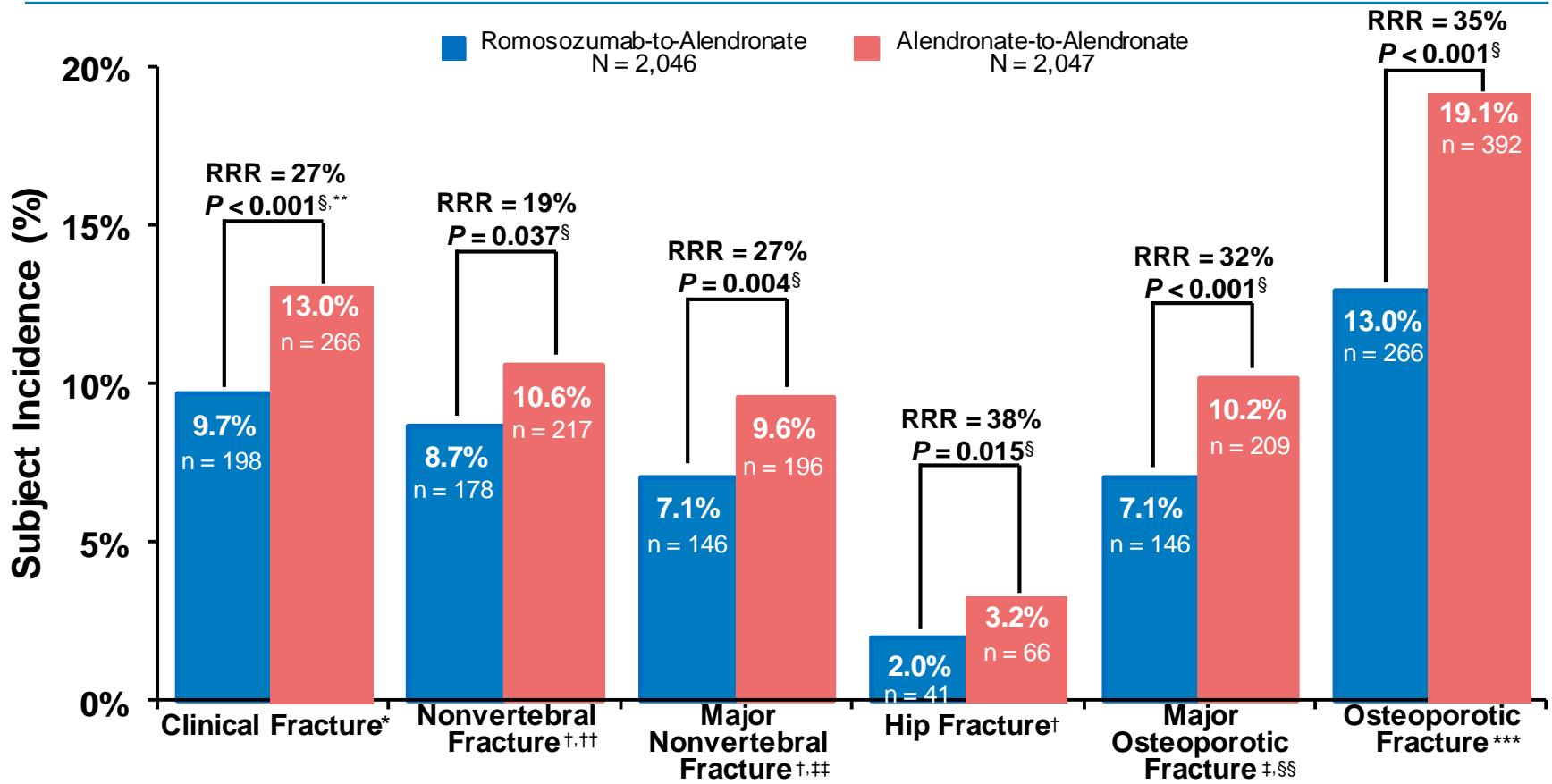
<b>Primary Endpoints</b>	<ul style="list-style-type: none"><li>• Nuove fratture vertebrali a 12 mesi</li><li>• Incidenza di fratture cliniche, sia vertebrali che non vertebrali</li></ul>
<b>Key Secondary Endpoints</b>	<ul style="list-style-type: none"><li>• BMD a 12 e 24 mesi in sede lombare, femorale</li></ul>
<b>Other Secondary/Exploratory Endpoints</b>	<ul style="list-style-type: none"><li>• Incidenza di Frattura di femore ed altre fratture maggiori</li></ul>

## *Primary Endpoint*

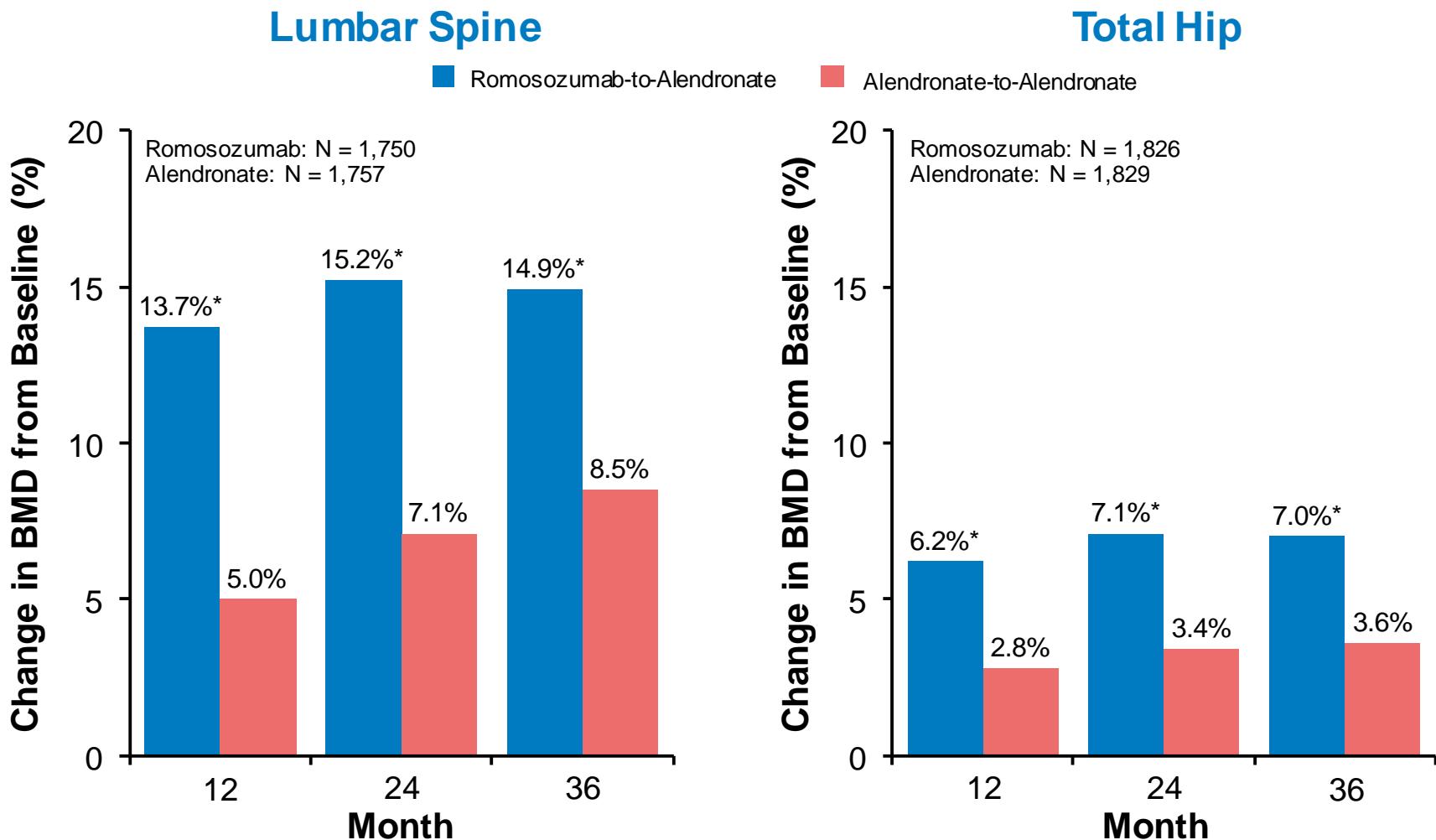
# Incidenza di nuove fratture vertebrali a 12 e 24 mesi



# Fratture Cliniche



# BMD lombare e femorale a 36 mesi



# Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

Event	Month 12: Double-Blind Period		Primary Analysis: Double-Blind and Open-Label Period <sup>a</sup>	
	Alendronate (N=2014)	Romosozumab (N=2040)	Alendronate to Alendronate (N=2014)	Romosozumab to Alendronate (N=2040)
			<i>number of patients (percent)</i>	
Adverse event during treatment	1584 (78.6)	1544 (75.7)	1784 (88.6)	1766 (86.6)
Back pain <sup>†</sup>	228 (11.3)	186 (9.1)	393 (19.5)	329 (16.1)
Nasopharyngitis <sup>†</sup>	218 (10.8)	213 (10.4)	373 (18.5)	363 (17.8)
Serious adverse event	278 (13.8)	262 (12.8)	605 (30.0)	586 (28.7)
Adjudicated serious cardiovascular event <sup>‡</sup>	38 (1.9)	50 (2.5)	122 (6.1)	133 (6.5)
Cardiac ischemic event	6 (0.3)	16 (0.8)	20 (1.0)	30 (1.5)
Cerebrovascular event	7 (0.3)	16 (0.8)	27 (1.3)	45 (2.2)
Heart failure	8 (0.4)	4 (0.2)	23 (1.1)	12 (0.6)
Death	12 (0.6)	17 (0.8)	55 (2.7)	58 (2.8)
Noncoronary revascularization	5 (0.2)	3 (0.1)	10 (0.5)	6 (0.3)
Peripheral vascular ischemic event not requiring revascularization	2 (<0.1)	0	5 (0.2)	2 (<0.1)
Death	21 (1.0) <sup>§</sup>	30 (1.5)	90 (4.5) <sup>§</sup>	90 (4.4)
Event leading to discontinuation of trial regimen	64 (3.2)	70 (3.4)	146 (7.2)	133 (6.5)
Event leading to discontinuation of trial participation	27 (1.3)	30 (1.5)	43 (2.1)	47 (2.3)
Event of interest <sup>¶</sup>				
Osteoarthritis <sup>  </sup>	146 (7.2)	138 (6.8)	268 (13.3)	247 (12.1)
Hypersensitivity	118 (5.9)	122 (6.0)	185 (9.2)	205 (10.0)
Injection-site reaction <sup>**</sup>	53 (2.6)	90 (4.4)	53 (2.6)	90 (4.4)
Cancer	28 (1.4)	31 (1.5)	85 (4.2)	84 (4.1)
Hyperostosis <sup>††</sup>	12 (0.6)	2 (<0.1)	27 (1.3)	23 (1.1)
Hypocalcemia	1 (<0.1)	1 (<0.1)	1 (<0.1)	4 (0.2)
Atypical femoral fracture <sup>‡</sup>	0	0	4 (0.2)	2 (<0.1)
Osteonecrosis of the jaw <sup>‡</sup>	0	0	1 (<0.1)	1 (<0.1)

# Efficacy and safety of Romosozumab in treatment for low bone mineral density: a systematic review and meta-analysis

Outcome	Comparison	Certainty assessment						No. of patients		Effect	Certainty
		No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison relative (95% CI)	
Death	Placebo vs. Romo 210	3	RCT	Not serious	Not serious	Not serious	Not serious	None	3801	3720	0.85 (0.5 to 1.45)
	Placebo vs. Romo 70	2	RCT	Not serious	Not serious	Not serious	Not serious	None	114	115	0.25 (0.03 to 2.26)
Hypersensitivity	Placebo vs. Romo 210	2	RCT	Not serious	Not serious	Not serious	Not serious	None	3638	3654	1.02 (0.85 to 1.23)
	Alendronate vs. Romo 210	2	RCT	Not serious	Not serious	Not serious	Not serious	None	2098	2098	0.57 (0.41 to 0.8)
Injection-site reaction	Placebo vs. Romo 210	4	RCT	Not serious	Not serious	Not serious	Not serious	None	3864	3783	0.55 (0.43 to 0.69)
	Teriparatide vs. Romo 210	2	RCT	Not serious	Not serious	Not serious	Not serious	None	270	273	0.33 (0.14 to 0.79)
Osteoarthritis	Placebo vs. Romo 210	3	RCT	Serious	Not serious	Not serious	Not serious	None	3815	3736	0.74 (0.25 to 2.2)
Cancer	Placebo vs. Romo 210	3	RCT	Not serious	Not serious	Not serious	Not serious	None	3815	3736	1.16 (0.82 to 1.63)
Any adverse event	Alendronate vs. Romo 210	2	RCT	Not serious	Not serious	Not serious	Not serious	None	2098	2098	1.12 (0.97 to 1.29)
	Placebo vs. Romo 140	2	RCT	Very serious	Not serious	Not serious	Not serious	None	114	115	0.45 (0.11 to 1.91)
	Placebo vs. Romo 210	4	RCT	Serious	Not serious	Not serious	Not serious	None	3864	3783	0.77 (0.43 to 1.36)
	Placebo vs. Romo 70	2	RCT	Serious	Not serious	Not serious	Not serious	None	114	115	0.21 (0.02 to 1.94)
Adverse event leading to discontinuation of study drug	Teriparatide vs. Romo 210	2	RCT	Not serious	Not serious	Not serious	Not serious	None	270	273	0.65 (0.45 to 0.95)
	Placebo vs. Romo 210	3	RCT	Not serious	Not serious	Not serious	Not serious	None	3815	3736	1.08 (0.72 to 1.6)
Adjudicated cardiovascular death	Placebo vs. Romo 210	2	RCT	Not serious	Not serious	Not serious	Not serious	None	3744	3657	0.89 (0.46 to 1.74)
Adjudicated serious cardiovascular event	Placebo vs. Romo 210	2	RCT	Not serious	Not serious	Not serious	Not serious	None	3744	3657	0.89 (0.59 to 1.34)

# TAKE HOME MESSAGES

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Romosozumab è un anticorpo monoclonale che esplica effetti anabolici ma anche di tipo antiriassorbitivi che sembrano diventare preponderanti nel lungo periodo

I trial clinici ne hanno dimostrato una più chiara efficacia in termini di riduzione di fratture sia vertebrali, non vertebrali e femorali oltre che aumento della BMD rispetto a comparatori «gold standard» quali alendronato e teriparatide

Nonostante la assunzione per un solo anno, gli effetti antifratturativi e della BMD aumentano progressivamente dopo switch a denosumab o allo stesso alendronato

Gli aumenti densitometrici e l'efficacia anti-fratturativa sono così rapidi che anche in termini di costo-efficacia la imminente immissione in commercio di tale terapia potrebbe stravolgere le attuali flow-churt terapeutiche ministeriali (nota 79)

La safety è risultata buona anche se il possibile potenziale effetto «cardiovascolare» della molecola probabilmente ne limiterà l'utilizzo a pazienti con problematiche cardiologiche/neurologiche di una certa consistenza