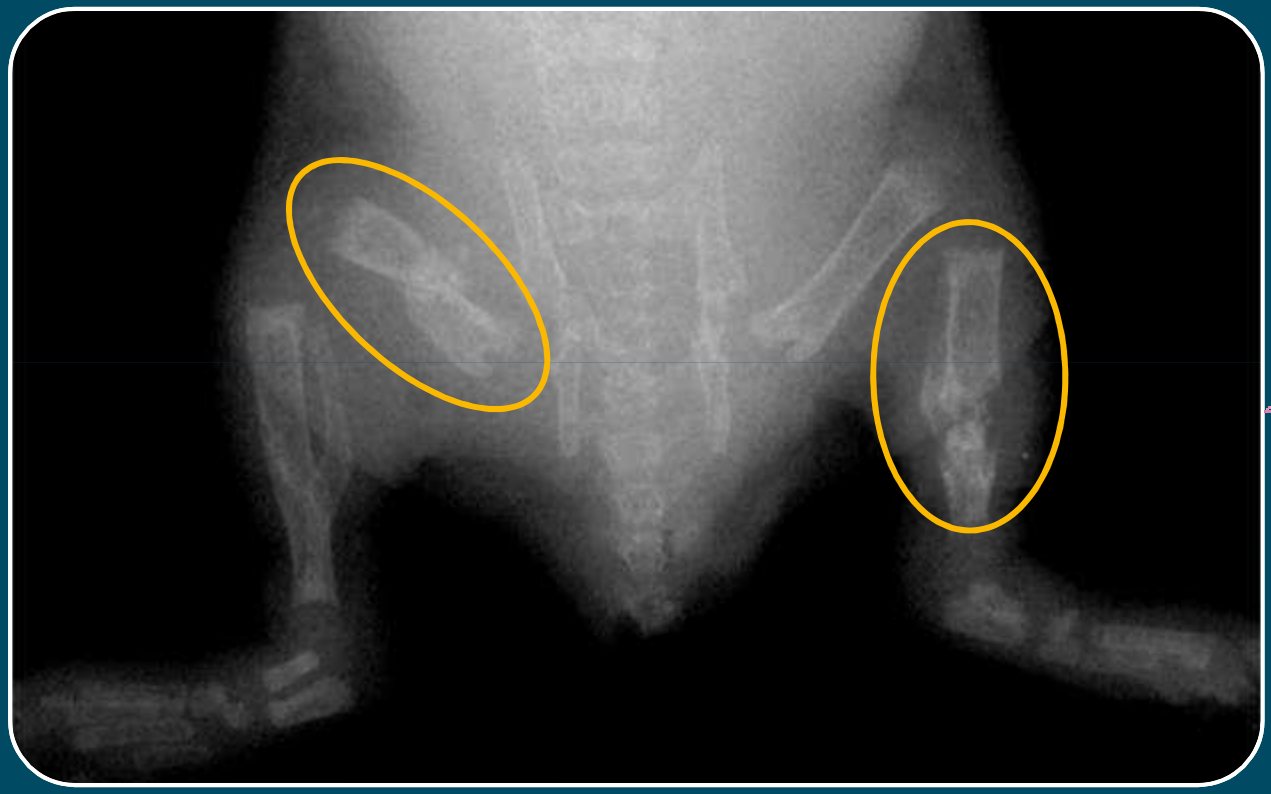
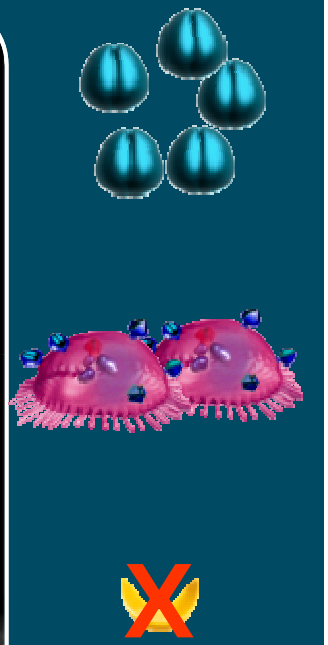
Eficacia y Seguridad de Denosumab en OPM

Contenidos

- Via del Ligando RANK
- Mecanismo de acción de Denosumab
- Estudios según perfiles de pacientes
  1. Paciente recientemente diagnosticada
  2. Paciente en tratamiento con Bifosfonatos
  3. Paciente con mala adherencia
  4. Paciente añosa

Unopposed RANK Ligand Activity Causes Long Bone Fragility Fractures





Radiograph of 1-month-old OPG knockout mouse with spontaneous fragility fractures

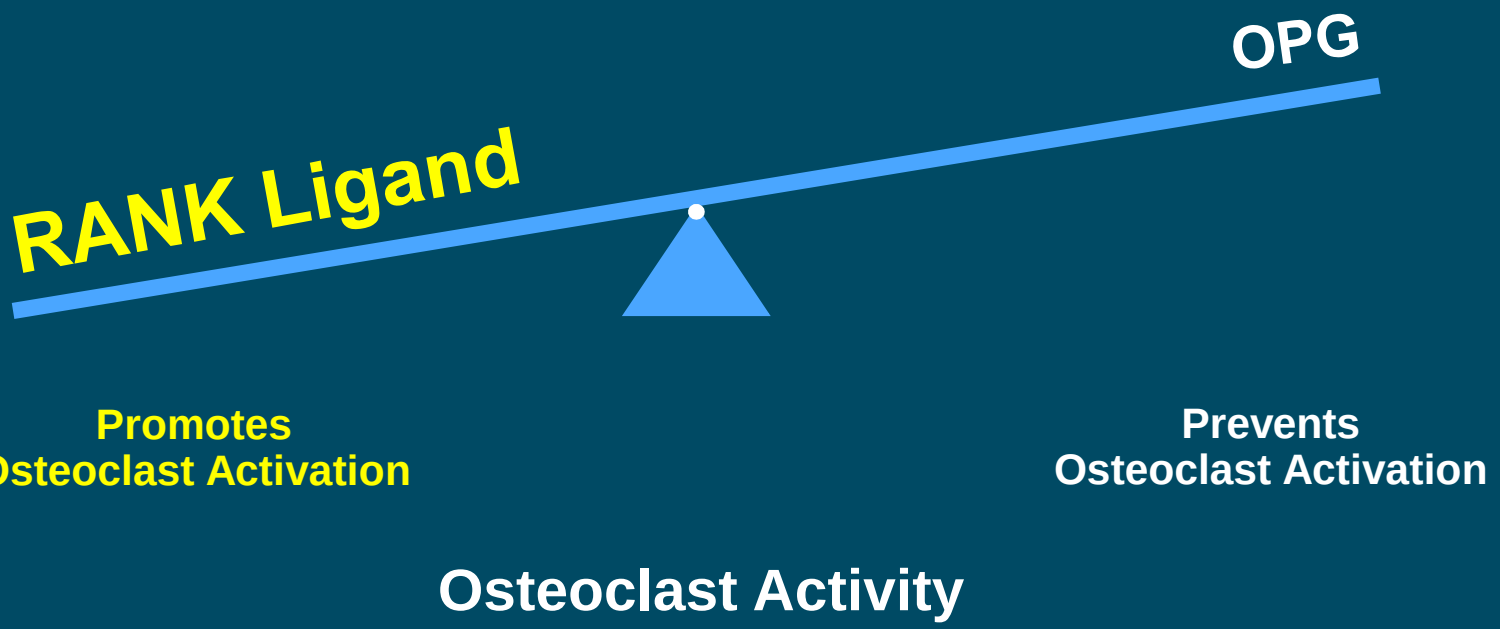
Bucay N, *et al. Genes Dev* 1998;12:1260–1268. Reprinted with permission.

Role of OPG in the Regulation of BMD

Bolon B, *et al. Arthritis Rheum* 2002;46:3121–3135.

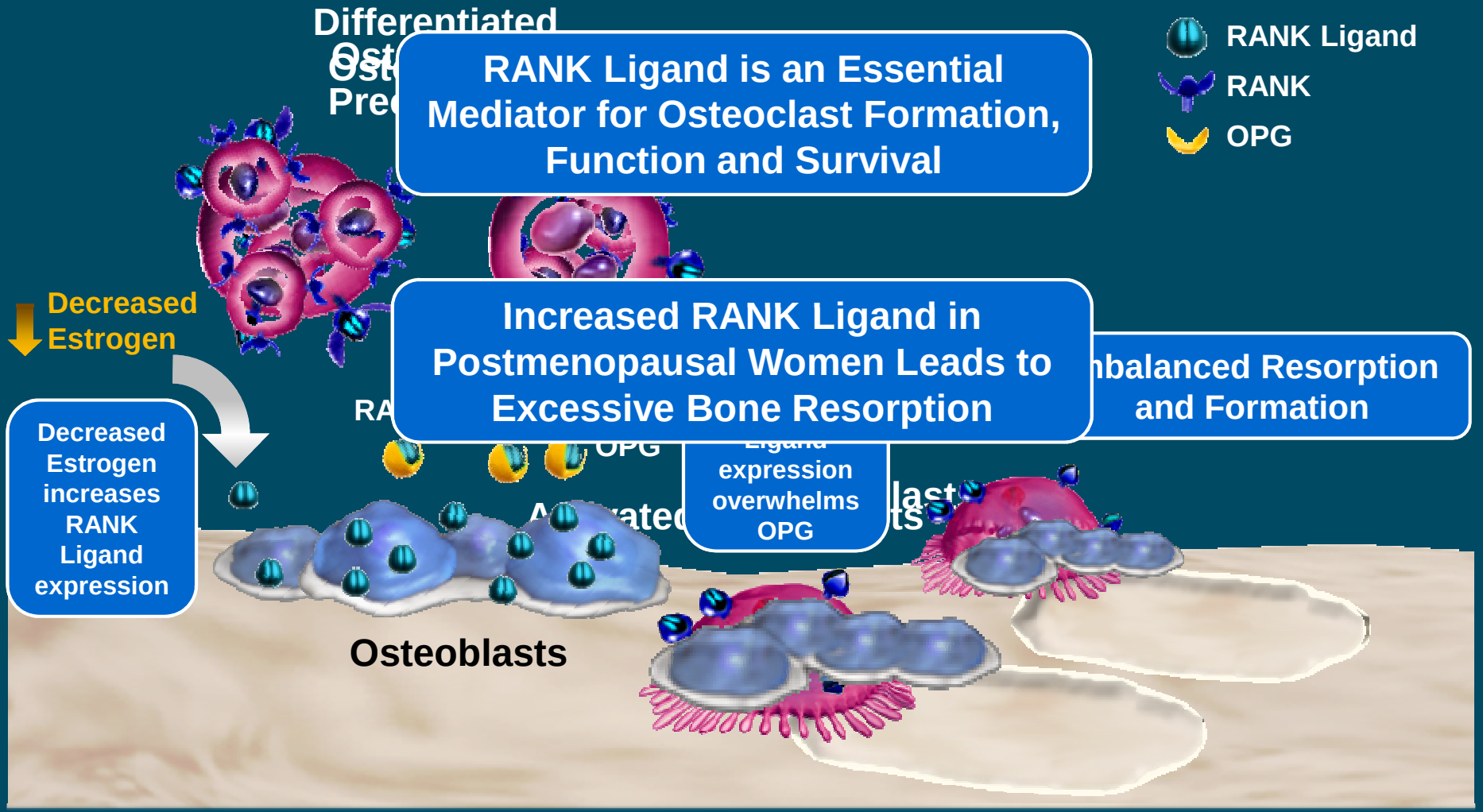
Increased RANK Ligand/OPG Ratio Promotes Bone Loss

- Alterations of the RANK Ligand/OPG ratio are critical in the pathogenesis of bone diseases that result from increased bone resorption



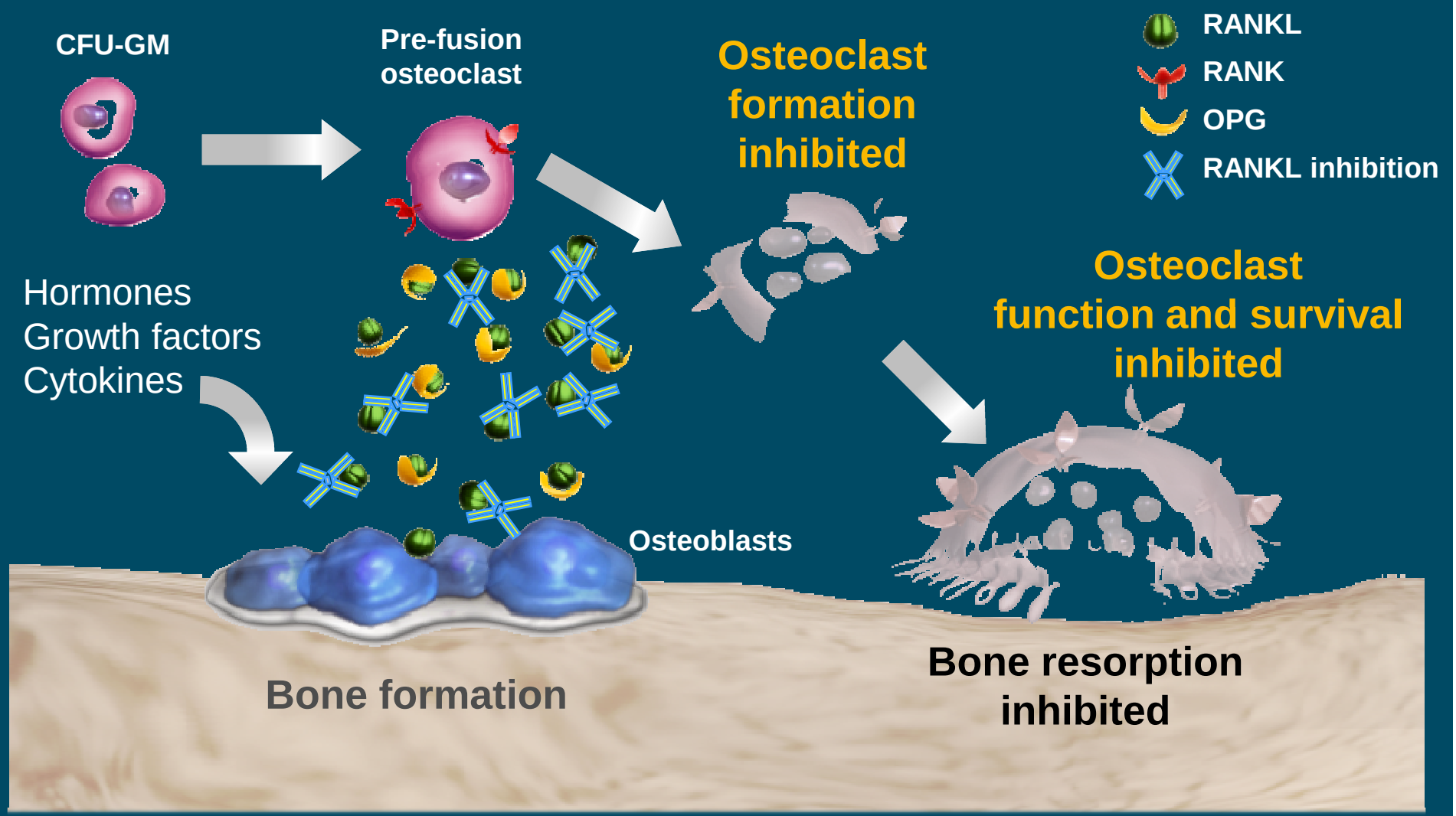
Adapted from: Hofbauer L, *et al. JAMA* 2004;292:490–495.

Reduction in Estrogen Increases RANK Ligand Expression, Causing Increased Bone Resorption



Adapted from the following: Boyle WJ, *et al. Nature* 2003;423:337–342.
Eghbali-Fatourechi G, *et al. J Clin Invest* 2003;111:1221–1230.

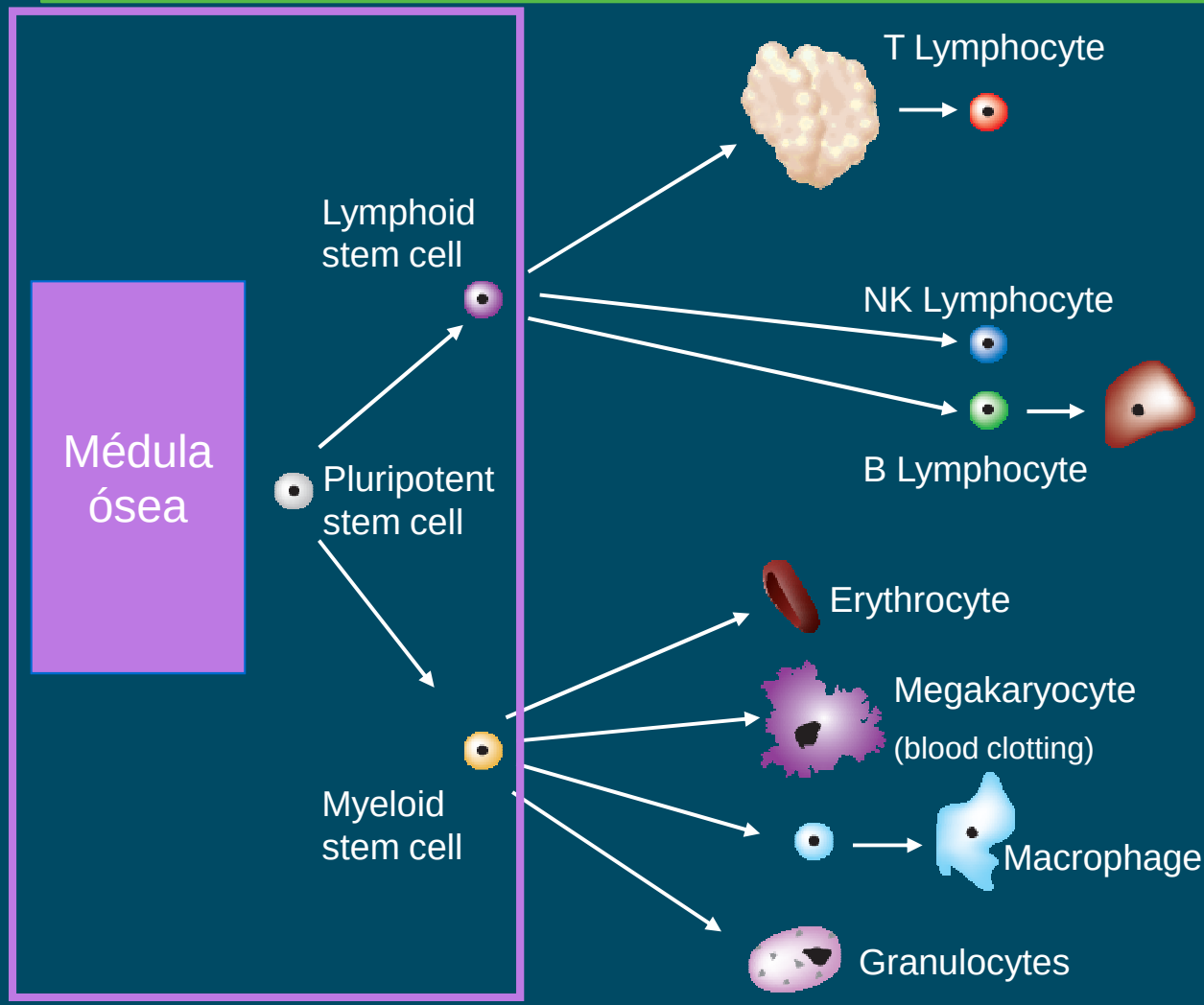
Inhibition of RANK Ligand



CFU-GM = colony-forming unit-granulocyte/macrophage

Adapted from: Boyle WJ, *et al. Nature* 2003;423:337–342.

Los Osteoclastos se originan desde los mismos precursores que las células inmunes

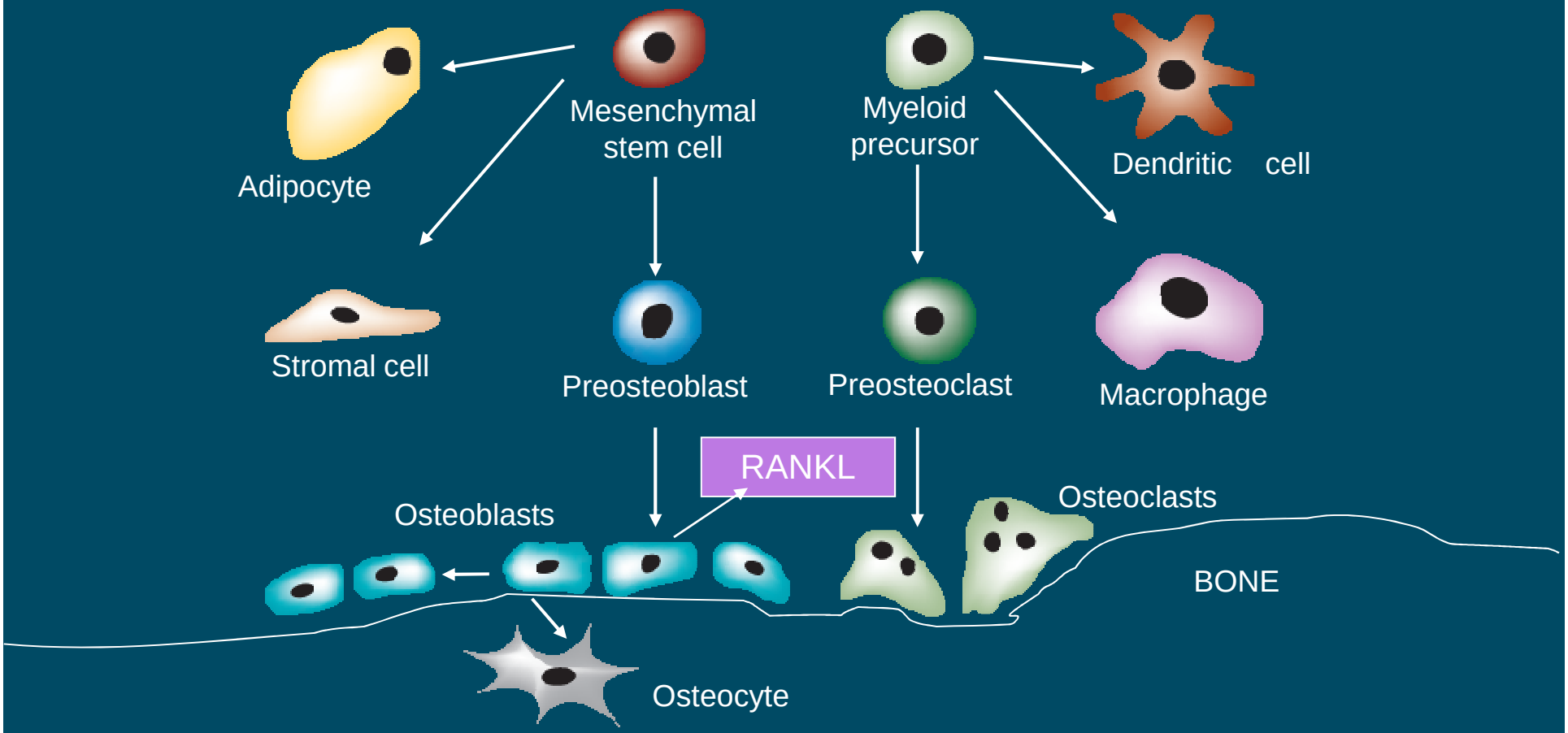


Periphery:
T- and B-cells play major role in adaptive immune responses to provide the body with specific defense against antigens

The myeloid lineage differentiates into several cell types:
Osteoclasts
Dendritic cells
Microglia

Adapted from Yin T, Li L. J. Clin. Invest. 2006; 116:1195-1201.

Los osteoclasos y osteoblastos derivan desde diferentes células precursoras



Walsh MC, et al. Ann. Rev. Immunol. 2006; 24:33-63

RANK/RANK Ligand Expression

RANK

- Osteoclasts and precursors[1]
- Dendritic cells/Langerhans cells[2,]
- Mammary epithelium, upregulated during pregnancy[3]
- Lymph node inducer[4] and thymus epithelial cells during embryogenesis

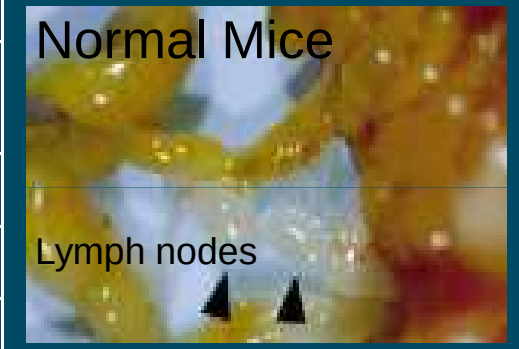
RANK Ligand

- Osteoblasts[5]
- Activated T[6,7] – and B-cells[8]/Keratinocytes[9]
- Mammary epithelium during pregnancy[3]
- Activated synovial fibroblasts[10]
- Cells in the subcapsular sinus of the lymph node[5]

1. Hsu H, et al. PNAS. 1999. 96:3540-3545. 2. Anderson D M et al. Nature. 1997; 390:175-179. 3. Fata J E, et al. Cell. 2000 103:41-50. 4. Kim, D et al. J. Exp. Med. 2000; 192:1467-1478. 5. Lacey D et al. Cell. 1998. 93:165-176. 6. Wong B R J. et al. J. Biol. Chem. 1997a; 272:25190–25194. 7. Kong Y Y Nature. 1999a; 402: 304-309. 8. Kaiwai T et al. Am J. Path. 2006; 169:987-998. 9. Barbaroux J O, et al. J. Immunol. 2008; 181:1103-1108; 10. Takayanagi H, et al. Arth. Rheum. 2000; 43:259-269.

RANKL is involved in development of the immune system during embryogenesis

	RANKL Knock out mice: Complete ablation of RANKL leads to defects in immune system development[1]
Bone	Osteopetrotic; stunted growth
Spleen	Normal architecture; extra-medullary hematopoiesis
Thymus	Decreased cellularity and size
Lymph node	No lymph nodes
Peyer's patch	Normal but small
Lymphocytes	**T cells**: Deficient early intrathymic T cell development (normal T cell numbers); decreased capacity of cytokine production **B cells**: Deficient B lineage development with decreased B cells **Dendritic cells**: Normal DC numbers and function
Teeth	Impaired eruption



Kong et al, Nature 1999b:397:315-323.

RANKL inhibition has no pronounced effects on the immune system development

Genotype	Spleen	Thymus	Lymph node	Peyer's patch	Lymphocytes	Teeth	Bone
RANKL KO Complete ablation of RANKL[2]	Normal architecture Extra-medullory hematopoiesis	Decreased cellularity and size	LN agenesis	Normal but small	Defect in B cell development from pro-B to pre-B transition T cells have a decreased capacity to produce cytokines	Impaired eruption	Osteopetrotic Stunted growth
OPG Tg Life-long RANKL inhibition by OPG over-expression day 15 after gestation[1]		Normal	Normal	Normal	No defects in lymphocyte development and function	Normal	Osteosclerotic Normal growth

RANKL inhibition, but not complete absence, has NO pronounced defects in the development and function of the rodent immune system

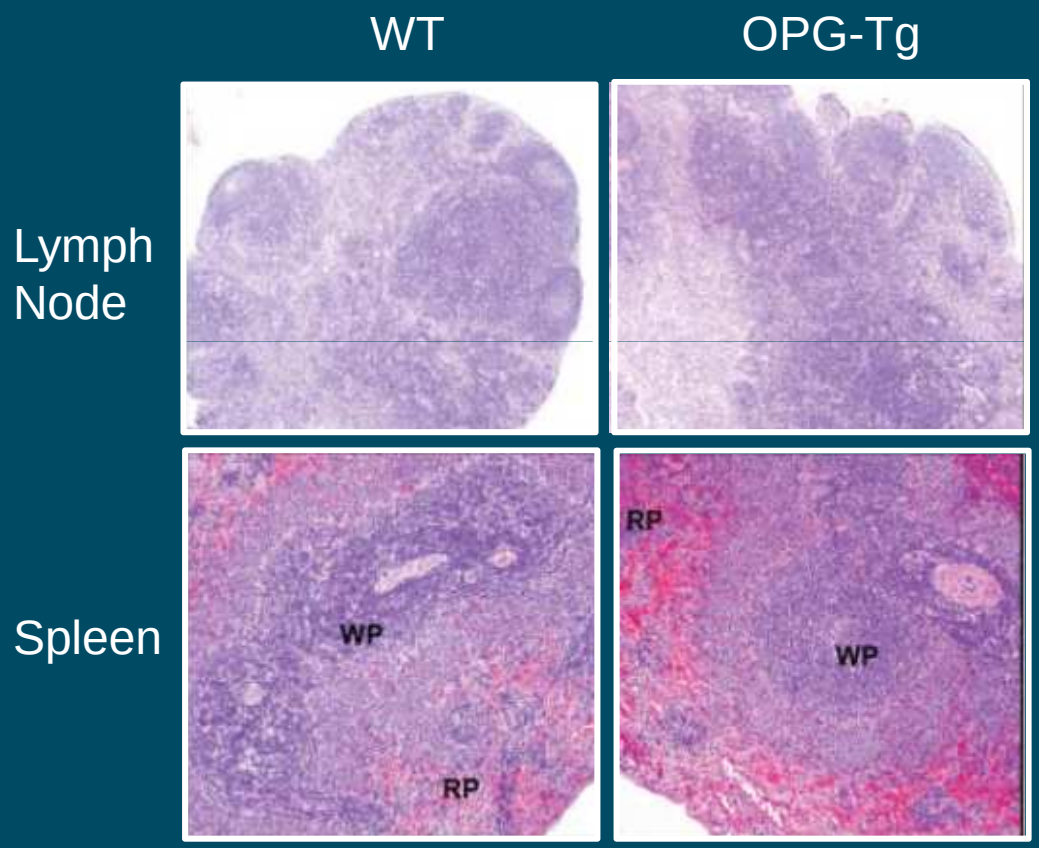
1. Stolina M, et al. J Immunol 2007; 179:7497-7505.; 2 Kong N, et al. 1999b; Nature 397: 315-323. 2.

In preclinical models, RANKL inhibition did not affect immune parameters or altered responses to immune challenges

		Length of RANKL inhibition		
		Short-term (< 3 w, OPG- or RANK-Fc)	**Long-term** (> 1y, dmab)	**Life-long** (OPG-Tg)
Baseline immune parameters	Histologic architecture of **spleen and lymph nodes**[1,2]		**Cyno**	**Mouse, rat**
	Number & percentage of **circulating blood cells**[1,2]		**Cyno**	**Mouse, rat**
	Circulating **Cytokine** levels[1]			**Mouse, rat**
	Circulating **Immunoglobulin** levels [1,3]	**Mouse**		**Mouse, rat**
	T and B cells proliferation in vitro in response to specific antigen[1,3]	**Mouse**		**Mouse, rat**
Immune challenges	Delayed contact hypersensitivity to **oxazolone** in skin[1,3]	**Mouse**		**Mouse**
	Innate immune responses (TNF-alpha & IL6) to **LPS** [1]			**Mouse, rat**
	Humoral reaction to the T cell dependent Ag **KLH** [1-3]	**Mouse**	**Cyno**	**Mouse**
	Humoral reaction to the T cell independent Ag **Pneumovax** [1,3]	**Mouse**		**Mouse**
Infectious disease	**BCG** bacterial infection[3]	**Mouse**		
	Influenza viral infection[4]	**Mouse**		
Auto-immune disease	**Immune-mediated arthritis**[5]	**Rat**		
	Inflammatory bowel disease[6]	**Mouse**		

1. Stolina M, et al. J Immunol. 2007; 179:7497-7505. 2. Stolina M, et al. 35th European Symposium on Calcified Tissues, 2008 (Abstract Tu-P491). 3. Stolina M, et al. Clin Immunol. 2003; 109:347-354. 4. Miller R, et al. J Immunol. 2007;179:266-274. 5. Stolina M, et al. Ann Rheum Dis. 2009; 11:187. 6. Byrne FR, et al. Gut. 2005; 54:78-86.

Normal architecture of spleen and lymph nodes in OPG transgenic rats – a model for RANK Ligand inhibition



- Adult (6-mo-old) OPG-Tg and WT rats exhibit equivalent histologic architecture of mesenteric lymph node and spleen, including evidence of extra-medullary hematopoiesis in the splenic red pulp
- RP = red pulp
- WP = white pulp (leukocyte zone)

Stolina M, et al. J Immunol. 2007; 179:7497-7505.

RANKL inhibition did not affect immune parameters in pre-clinical and clinical studies

- Preclinical evidence to date demonstrates no significant effects of RANK Ligand inhibition on the Immune System
  - Continuous inhibition of RANKL in OPG-Tg mice is not associated with changes in immune responses in the intact immune system[1].
  - The complete lack of RANKL but not RANKL inhibition in animals affects the immune system[2].

- Clinical studies of RANK Ligand inhibition in adults show no significant effects with regards to[3-6]:
  - Mean total white blood cell or differential cell counts
  - Overall lymphocyte counts, T cells (CD3, CD4, CD8 et CD56), B cells (CD20), and NK (Natural Killer)
  - Immunoglobulins production: IgA, IgG, IgM
  - Increased susceptibility to infection

- Patients with mutations in the gene encoding RANKL, did not show immune abnormalities or higher susceptibility to infections[7].

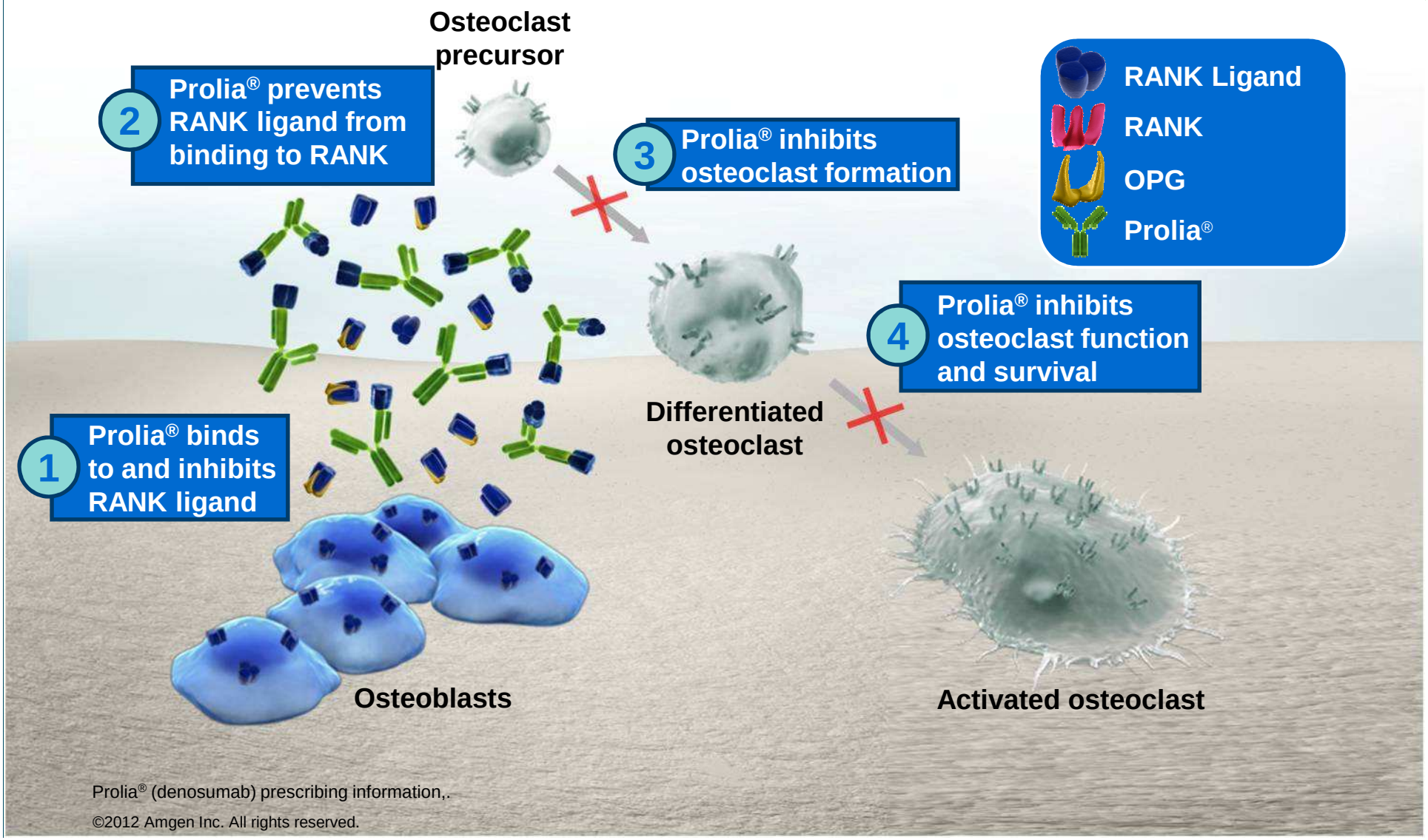
1. Stolina M, et al. J Immunol 2007; 179:7497-7505. 2.Kong N, et al. 1999; Nature 397: 315-323. 3. Bekker PJ, et al. J Bone Miner Res. 2004; 19:1059-1066. 4. McClung MR, et al. N Engl J Med. 2006; 354:821-831. 5. Bone HG, et al. J Clin Endocrinol Metab. 2008; 93:2149-2157. 6. Watts NB et al. Osteoporos Int DOI 10.1007/s00198-011-1755-2. 7. Sobacchi C, et al. Nat Genet. 2007; 39:960-962.

5 Key points to remember

- Normal immune response were observed in preclinical models of RANKL inhibition[1-3].
- Normal white blood cell counts in rodents, cynomolgous monkeys and humans during RANKL inhibition
- Patients with mutations in the RANKL gene did not show immune abnormalities or higher susceptibility to infections[5].

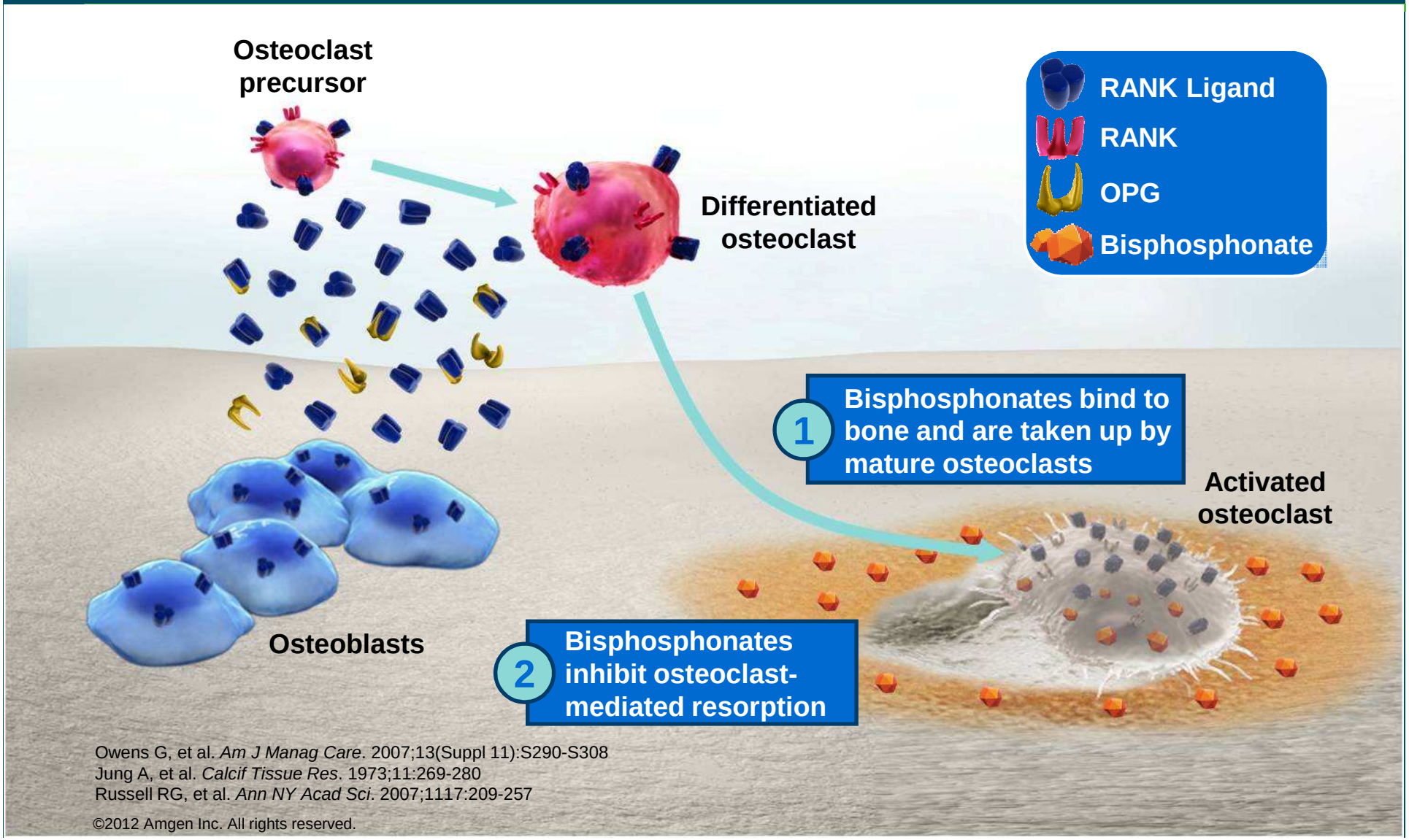
1. Stolina M, et al. J Immunol. 2007;179:7497-505. 2. Stolina M, et al. 35th European Symposium on Calcified Tissues, 2008 (Abstract Tu-P491).
3. Stolina M, et al. Clin Immunol. 2003;109:347-54.. 5.Sobacchi C, et al. Nat Genet. 2007; 39:960-2.

Denosumab, a RANK Ligand Inhibitor, Inhibits Osteoclast Formation, Function, and Survival



Prolia® (denosumab) prescribing information,.

Bisphosphonates Bind to Bone and Inhibit Osteoclasts at the Bone Surface



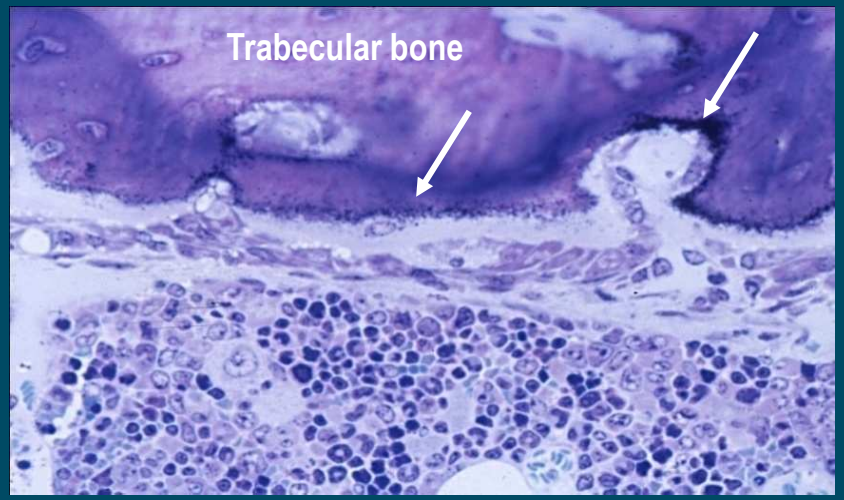
Owens G, et al. *Am J Manag Care*. 2007;13(Suppl 11):S290-S308
Jung A, et al. *Calcif Tissue Res*. 1973;11:269-280
Russell RG, et al. *Ann NY Acad Sci*. 2007;1117:209-257

Bisphosphonates and Denosumab are Distributed Differently

Bisphosphonates are rapidly absorbed to bone surfaces at sites of bone turnover[1-3]

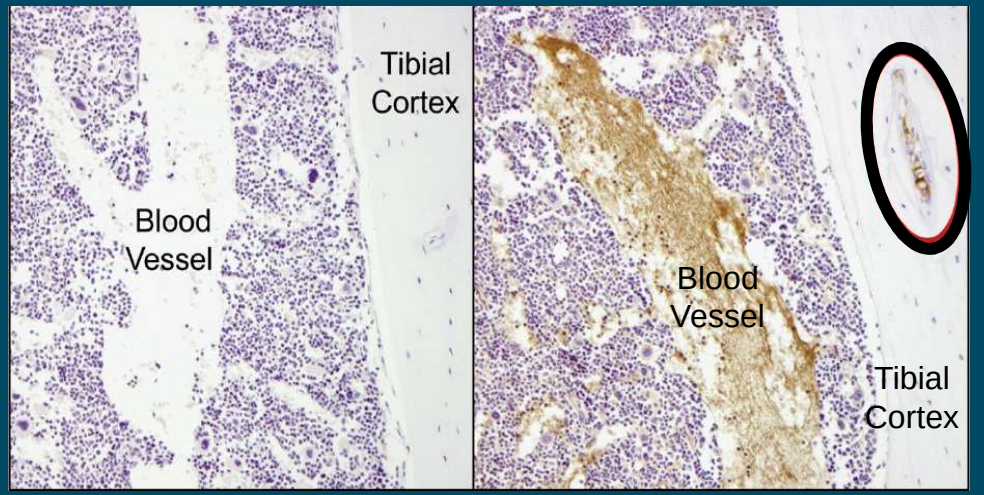
Denosumab circulates in blood and extracellular fluid including bone tissue[1,4]

ALN on bone surfaces at 24 hrs



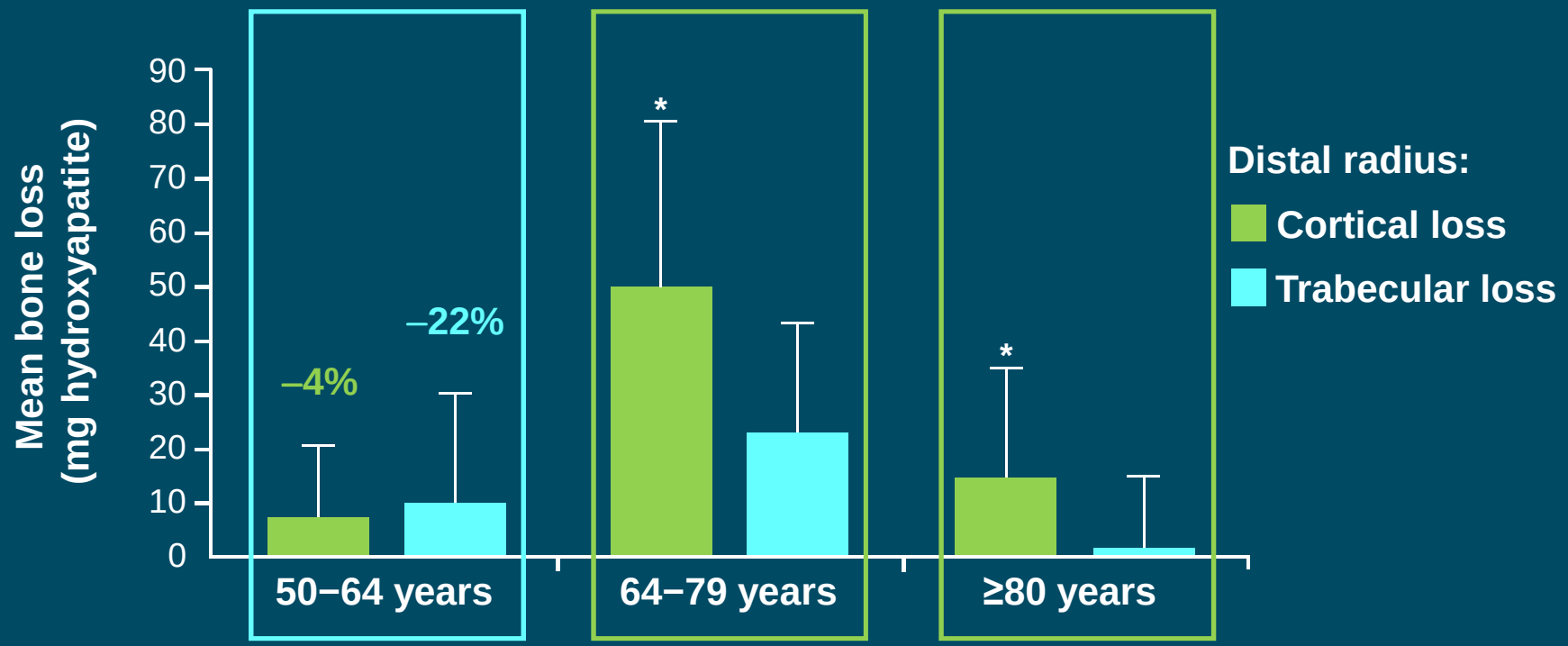
Control

Denosumab



1. Baron R et al, *Bone* 2011;48: 677-692. 2. Kimmel DB *J Dent Res 2007;*86:1022-1033
3. Masarachia P, et al. *Bone* 1996;19:281-290. 4. Kostenuik PJ, et al. *J Bone Miner Res* 2009;24:182-195

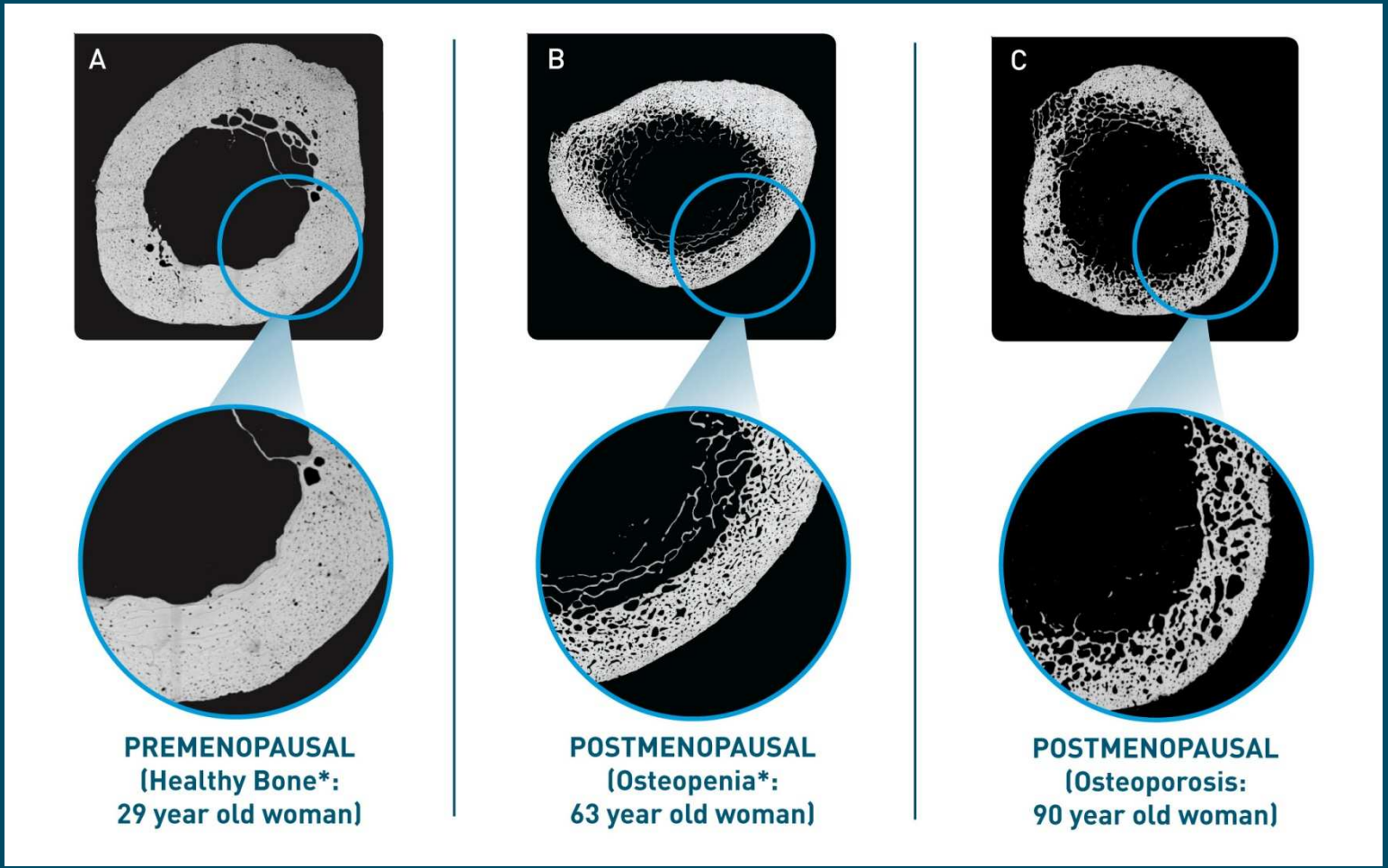
Early After Menopause, Women Lose Primarily Trabecular Bone, Whereas Cortical Bone is Lost Later in Life



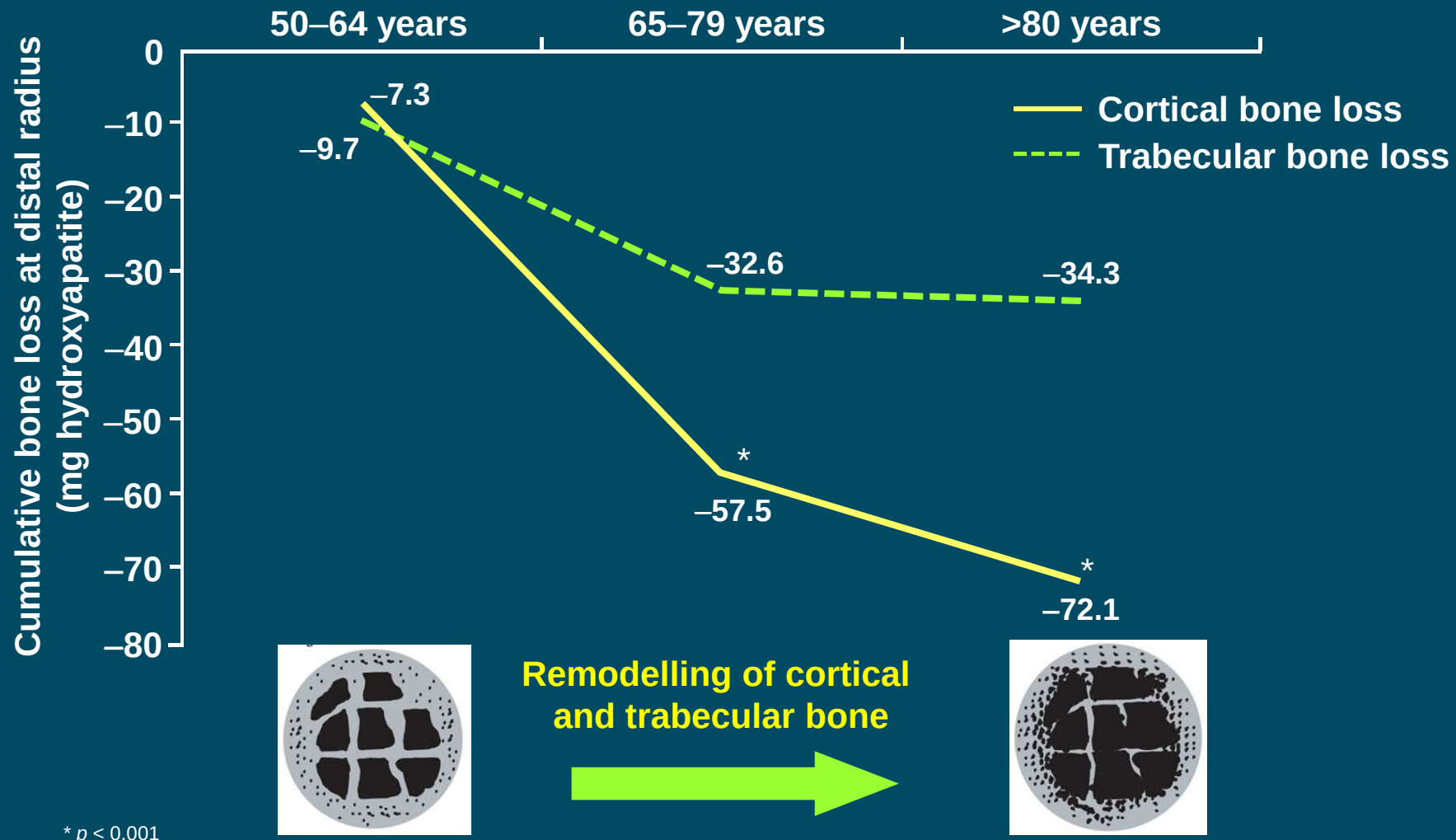
* $p < 0.0001$

Zebaze RM et al. *Lancet* 2010:9727:1729–1736

Pérdida de hueso cortical en la región subtrocantérica



The Majority of Bone Mass Lost over Time is Cortical

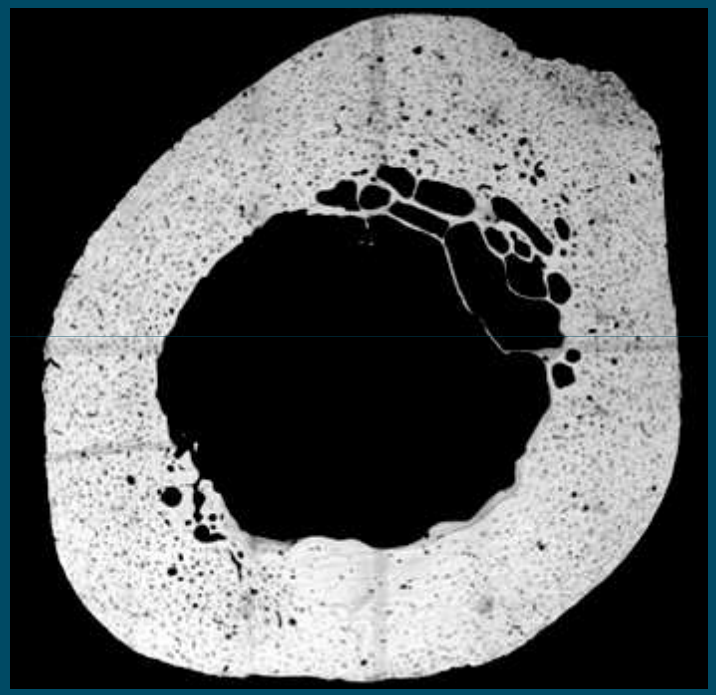


* $p < 0.001$

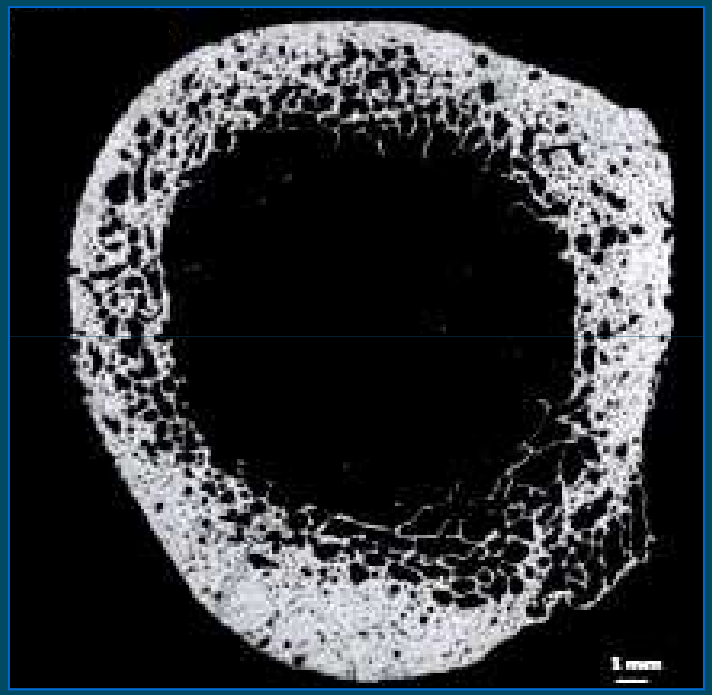
Zebaze RM et al. *Lancet* 2010:9727:1729–1736

Cortical Porosity Increases With Age After Menopause

Cross-sectional images of distal radius



29-year-old woman

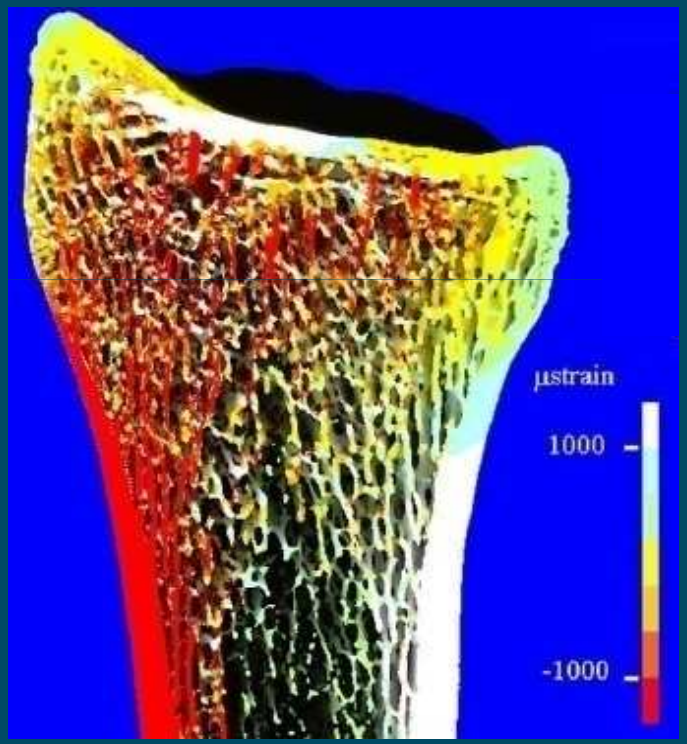


90-year-old woman

Zebaze RM et al. *Lancet* 2010:9727:1729–1736.

Cortical Bone Loss Has More Impact on Bone Strength than Trabecular Bone Loss

Principal strain distribution in the distal radius*



Yellow–red: compressive strain
Blue–green: tensile strain

*Contour plot of the microfinite element calculated principal strain distribution in the distal radius for a distributed load of 1000 Newtons acting normal to the articular surface

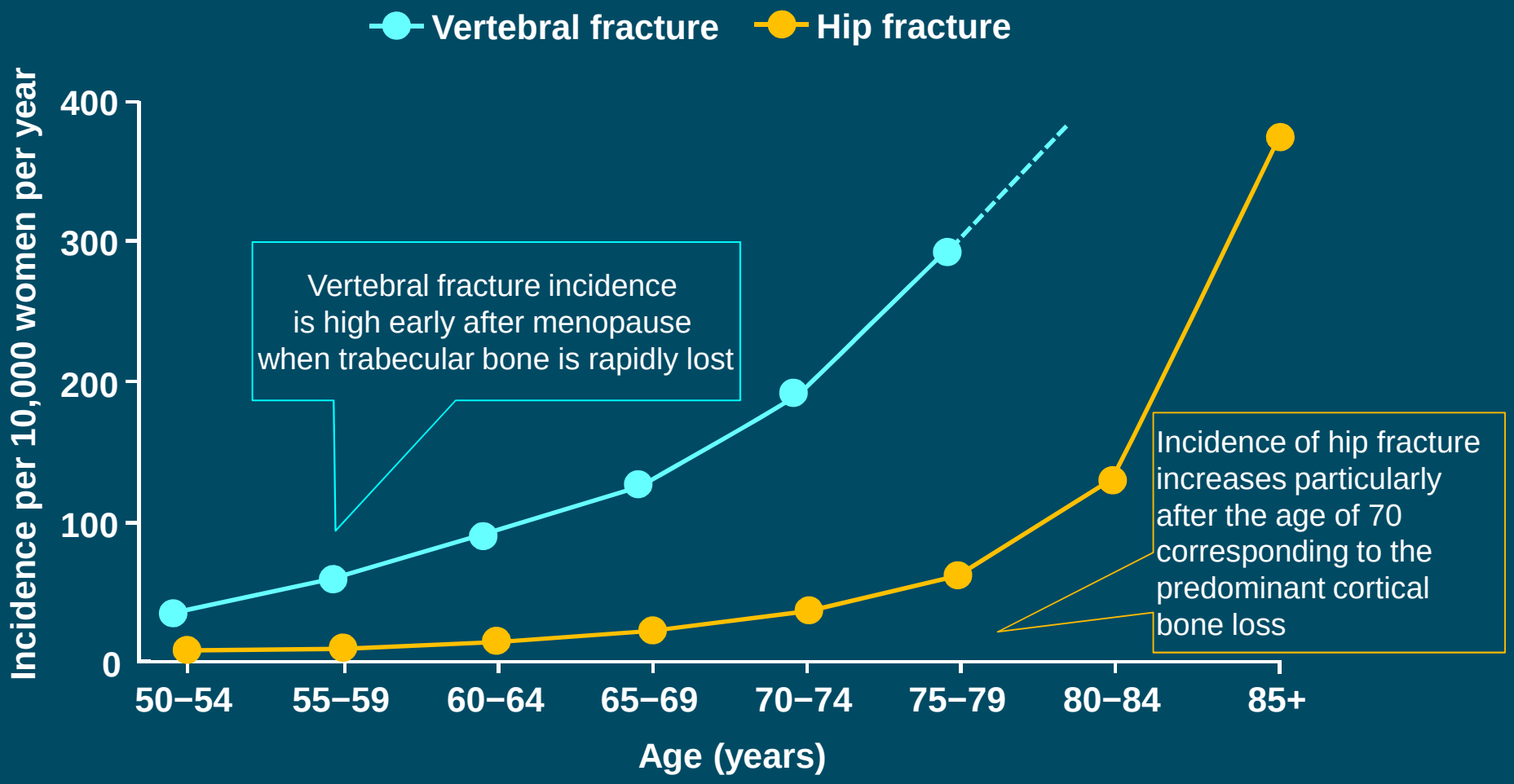
Pistoia W et al. Bone 2003;33(6):937–945

Simulated bone atrophy at the distal radius

Change in bone volume	Mechanism of bone loss	Decrease in strength
–20%	↓ Trabecular number	–11%
–20%	↓ Trabecular thickness	–9%
–20%	↓ Cortical thickness	**–39%**

Bone strength was affected most in the reduced cortical thickness model

Osteoporotic Fracture Incidence Correlates with Progressive Trabecular and Cortical Bone Loss Over Time



Adapted from: Sambrook P & Cooper C. *Lancet* 2006;367:2010-2018

Sin tratamiento previo, con múltiples factores de riesgo de fractura

- **65 años de edad**
- **T-score -3**
- **Actividad física inadecuada**
- **Madre con fx de cadera**

Con una DMO en descenso, a pesar del tratamiento

- 62 años de edad
- Luego de 3 años o más de tratamiento con bifosfonatos
- La evaluación no demuestra causas subyacentes de pérdida de masa ósea

Con intolerancia GI a su medicación actual o mala adherencia

- 65 años de edad
- reporta síntomas GI
- múltiples tratamientos concomitantes

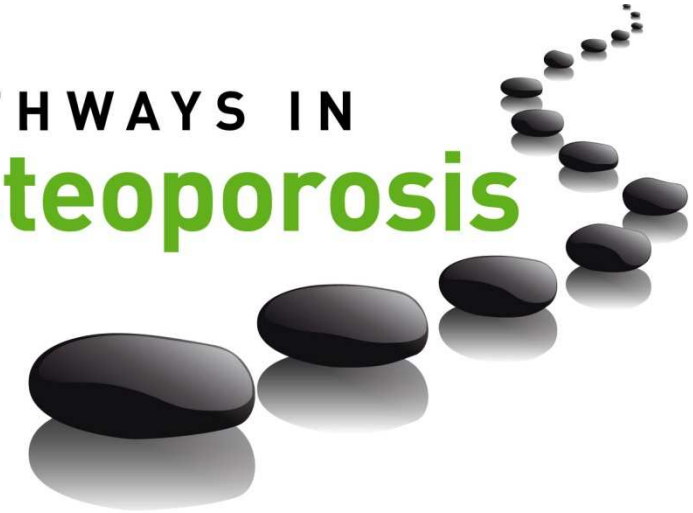
Paciente añosa con o sin disfunción renal

- 79 años de edad
- múltiples tratamientos concomitantes
- con o sin disfunción renal

Sin tratamiento previo, con múltiples factores de riesgo de fractura

- 65 años de edad
- T-score -3
- Actividad física inadecuada
- Madre con fx de cadera

PATHWAYS IN
Osteoporosis



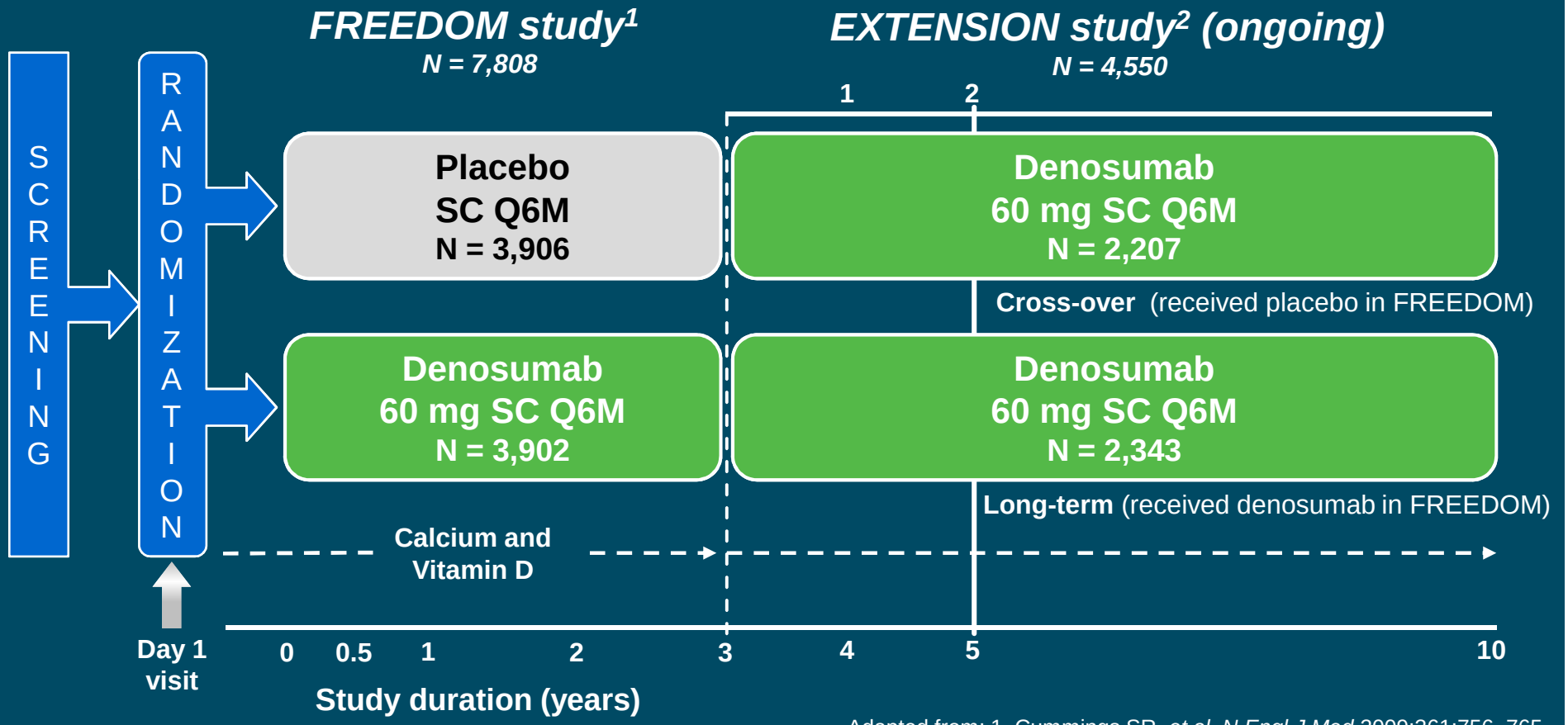
Denosumab Phase III data

FREEDOM

Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months

Phase III FREEDOM and FREEDOM EXTENSION Studies – Study Design

FREEDOM Trial: International multi-center, placebo-controlled study with open-label, single arm extension[1,2]



Adapted from: 1. Cummings SR, *et al. N Engl J Med* 2009;361:756–765.
2. Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

Baseline Demographics and Characteristics Similar Between Treatment Groups

FREEDOM Trial

	Placebo (N = 3,906)	Denosumab 60 mg Q6M (N = 3,902)
Mean age, years (SD)	72.3 (5.2)	72.3 (5.2)
Mean body mass index (SD)	26.0 (4.2)	26.0 (4.1)
Mean 25 (OH) vitamin D level, ng/mL (SD)*	22.9 (11.3)	23.1 (11.7)
Mean lumbar spine T-score (SD)	-2.84 (0.69)	-2.82 (0.70)
Mean total hip T-score (SD)	-1.91 (0.81)	-1.89 (0.81)
Mean femoral neck T-score (SD)	-2.17 (0.71)	-2.15 (0.72)
Prevalent vertebral fracture, N (%)	915 (23.4)	929 (23.8)

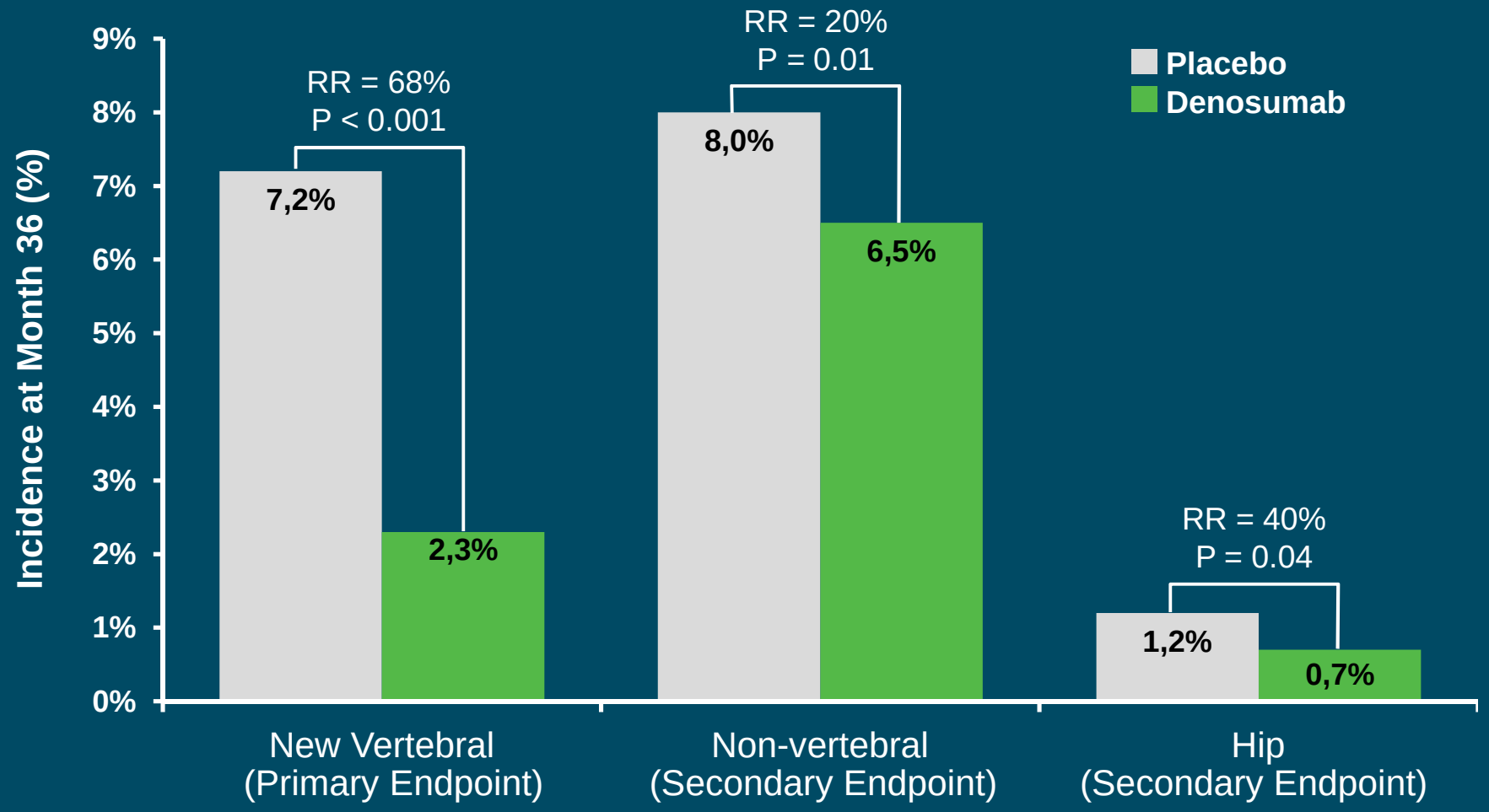
Data depicts patients included in the efficacy analysis, which excludes data from 60 patients at one study center (29 randomized to placebo, 31 randomized to denosumab) because participation of the study center was discontinued due to issues regarding study procedures and data reliability

*Excludes outlier values greater than 200 ng/mL

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

Denosumab Reduced Risk of Vertebral, Non-vertebral and Hip Fractures at 36 Months

FREEDOM Trial

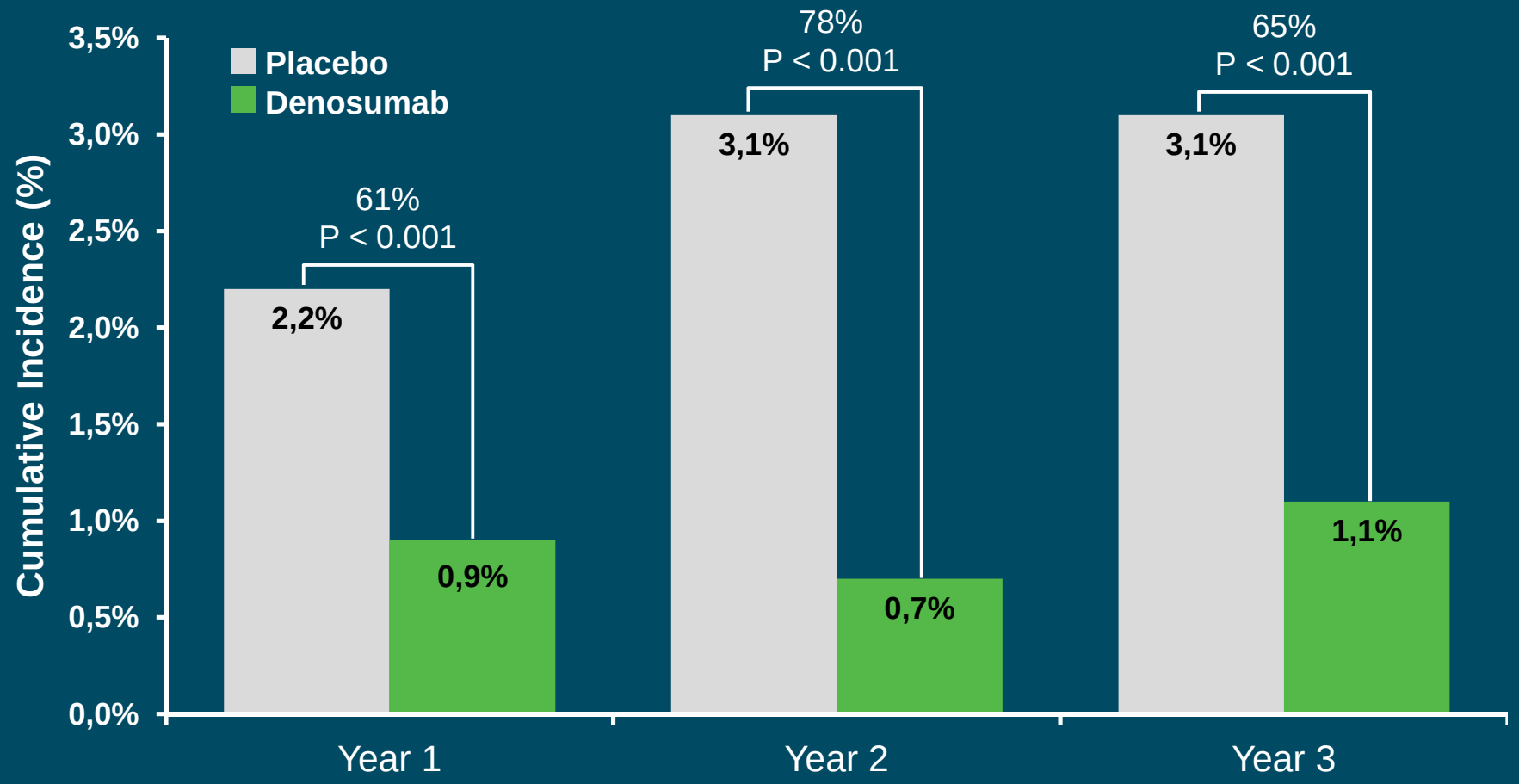


RR = risk reduction

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

Denosumab Reduced Risk of New Vertebral Fractures Each Year of Treatment

FREEDOM Trial

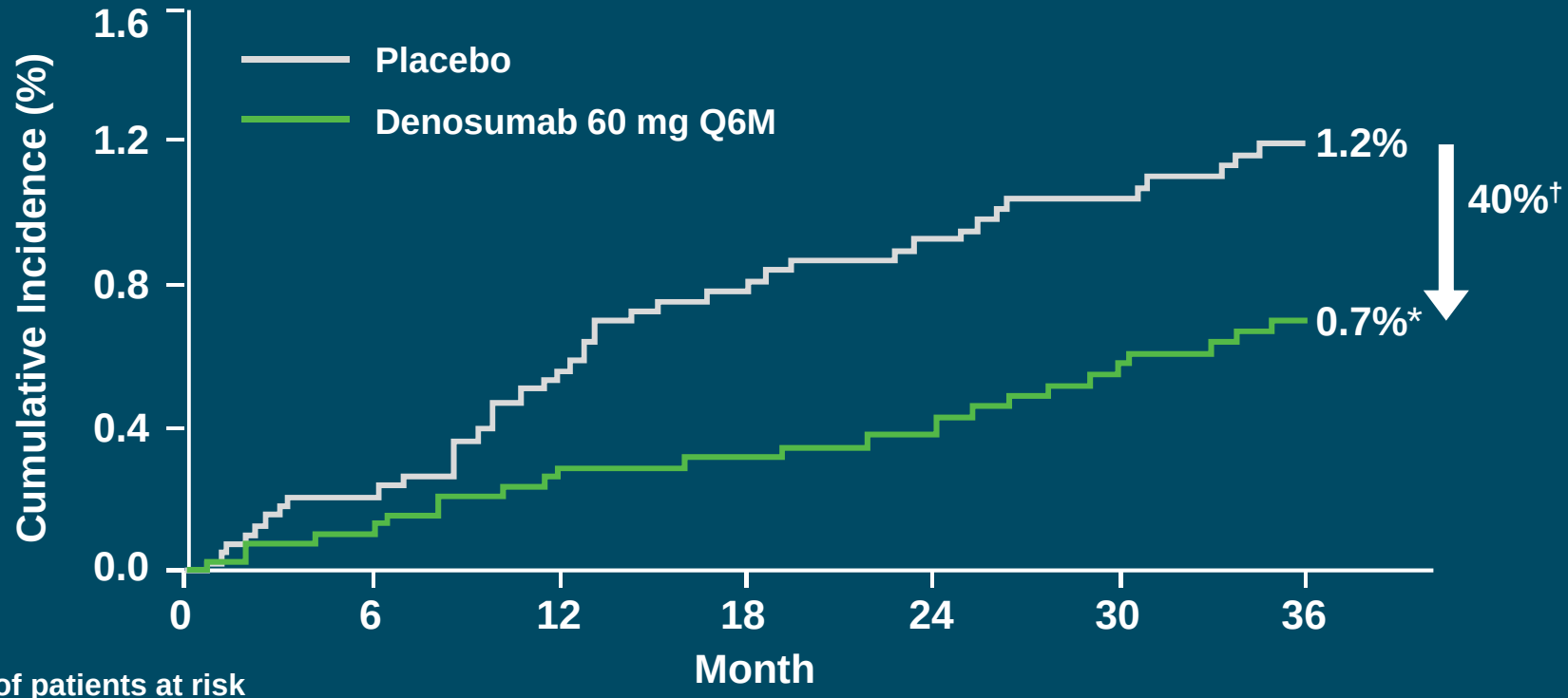


Intent-to-treat, last observation carried forward analysis
The percentage of new vertebral fractures was calculated using the number of patients with a baseline, and at least one post-baseline, spine x-ray evaluation

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

Denosumab Reduced Time to First Hip Fracture by 40% over 36 Months

FREEDOM Trial



Number of patients at risk							
Placebo, N	3,906	3,799	3,672	3,538	3,430	3,311	3,221
Denosumab, N	3,902	3,796	3,676	3,566	3,477	3,397	3,311

†Hip fractures were reduced by 40% (95% CI: 0.37, 0.97)
*P = 0.04

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

Adverse Event Profile of Denosumab Similar to Placebo over 36 Months

FREEDOM Trial

	Placebo (N = 3,876)	Denosumab 60 mg Q6M (N = 3,886)	P value
Adverse events, N (%)			
All adverse events	3,607 (93.1)	3,605 (92.8)	0.91
Serious adverse events	972 (25.1)	1,004 (25.8)	0.61
Deaths	90 (2.3)	70 (1.8)	0.08
Leading to study discontinuation	81 (2.1)	93 (2.4)	0.39
Leading to discontinuing the study drug	202 (5.2)	192 (4.9)	0.55

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

Adverse Events over 36 Months

FREEDOM Trial

	Placebo (N = 3,876)	Denosumab 60 mg Q6M (N = 3,886)
Adverse events, N (%)		
Infection	2,108 (54.4)	2,055 (52.9)
Malignancy	166 (4.3)	187 (4.8)
Injection-site reaction	26 (0.7)	33 (0.8)
Hypocalcemia	3 (0.1)	0 (0)
Delayed fracture healing	4 (0.1)	2 (0.05)
Femoral shaft fracture	3 (0.1)	0 (0)
Humerus non-union fracture	1 (0.03)	0 (0)
Osteonecrosis of the jaw	0 (0)	0 (0)
Adverse events occurring with ≥ 2% incidence and P ≤ 0.05, N (%)		
Eczema	65 (1.7)	118 (3.0)
Fall*	219 (5.7)	175 (4.5)
Flatulence	53 (1.4)	84 (2.2)

*Excludes falls occurring on the same day as a fracture

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

Serious Adverse Events over 36 Months

FREEDOM Trial

	Placebo (N = 3,876)	Denosumab 60 mg Q6M (N = 3,886)	P value
Serious adverse events, N (%)			
Malignancy	125 (3.2)	144 (3.7)	0.28
Infection	133 (3.4)	159 (4.1)	0.14
Cardiovascular events	178 (4.6)	186 (4.8)	0.74
Stroke	54 (1.4)	56 (1.4)	0.89
Coronary heart disease	39 (1.0)	47 (1.2)	0.41
Peripheral vascular disease	30 (0.8)	31 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Serious adverse events occurring with ≥ 0.1% incidence and P ≤ 0.01, N (%)			
Cellulitis (includes erysipelas)	1 (<0.1)	12 (0.3)	0.002
Concussion	11 (0.3)	1 (<0.1)	0.004

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

En tratamiento con Bifosfonatos

- 62 años de edad
- Con una DMO en descenso, o luego de 3 años o más de tratamiento con bifosfonatos

PATHWAYS IN
Osteoporosis

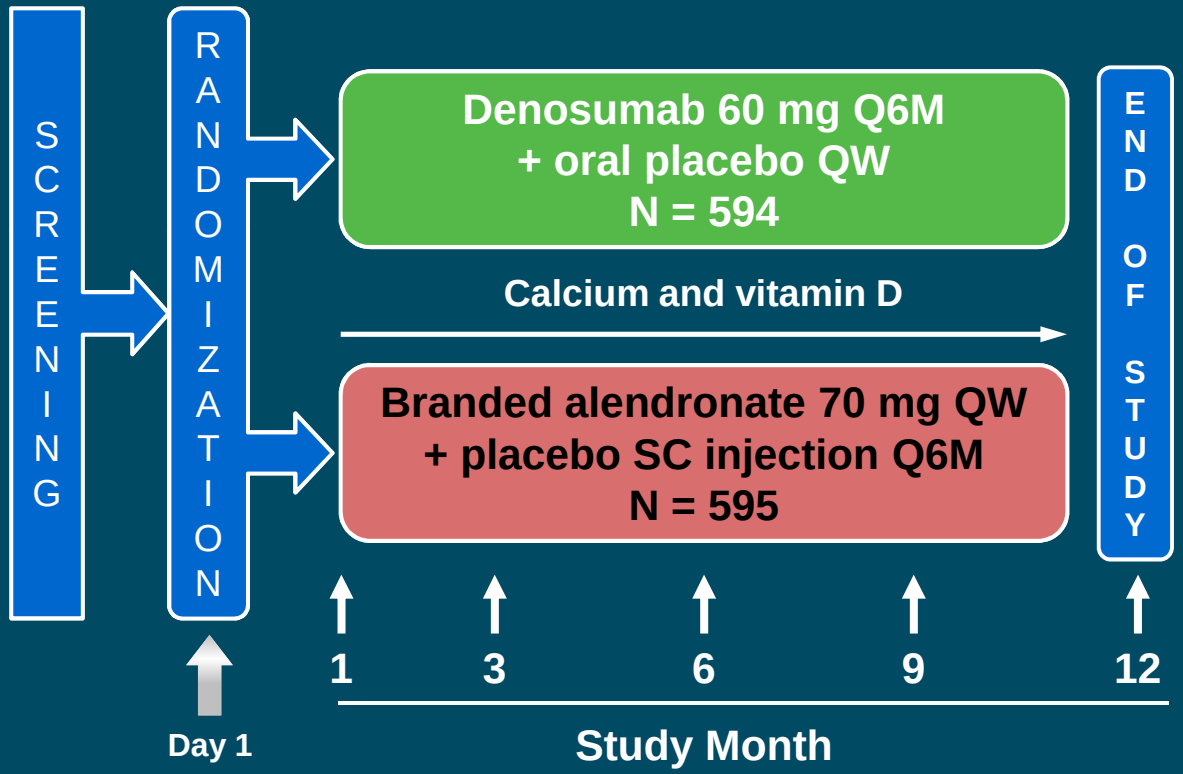
Denosumab Phase III data

DECIDE – Phase III Initiation Study

Determining Efficacy: Comparison of Initiating Denosumab vs AlEndronate

Study Design

DECIDE Study: Multicenter, double-blind, double-dummy, active-controlled study



Study population

- 1,189 postmenopausal women
- T-score ≤ -2.0 at lumbar spine or total hip

Primary endpoint

- Change in BMD at total hip at month 12

Secondary endpoints

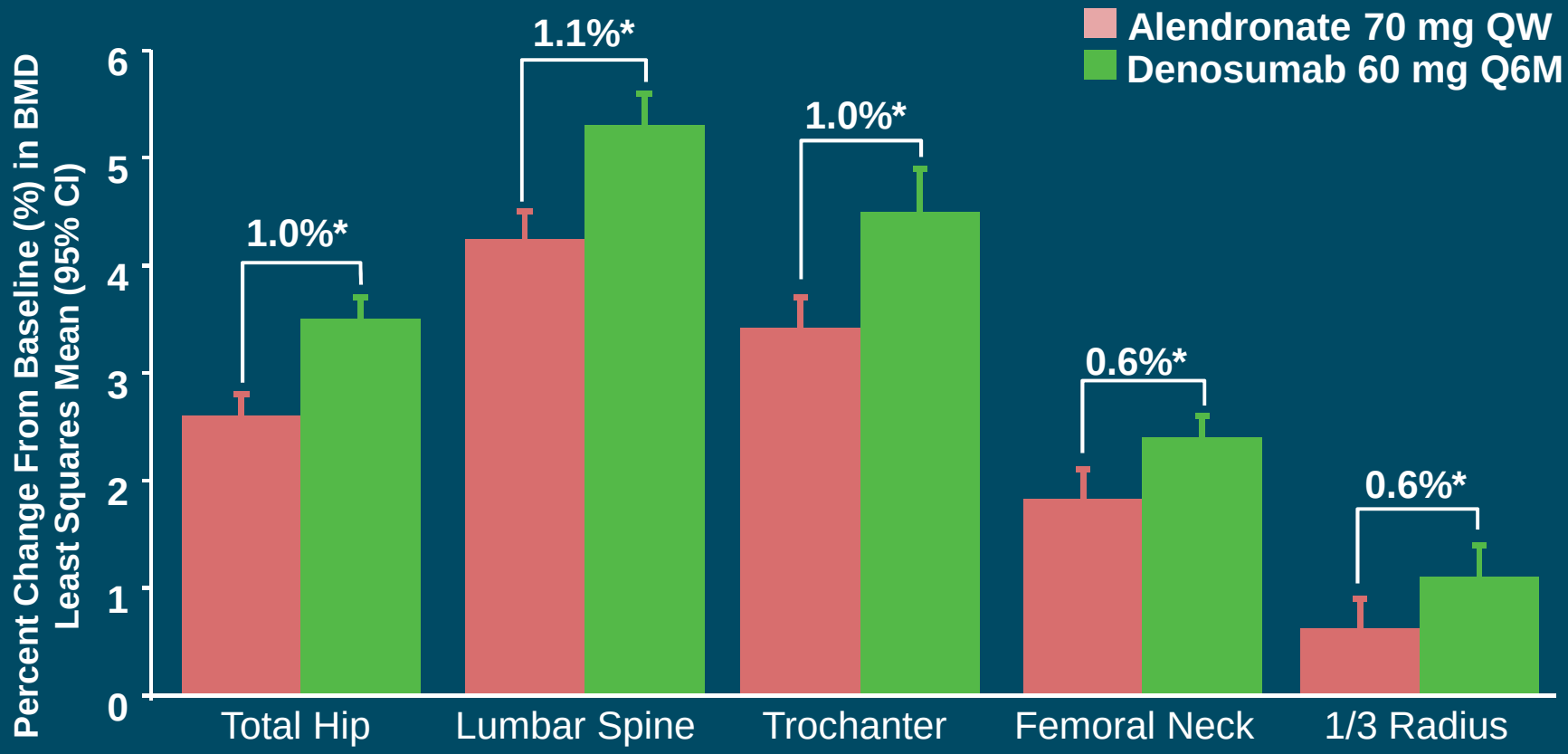
- Change in BMD at lumbar spine, femoral neck, trochanter, and 1/3 radius at month 12

Q6M = once every 6 months; QW = once weekly; SC = subcutaneous

Adapted from: Brown JP, *et al. J Bone Miner Res* 2009;24:153–161.

Denosumab Increased BMD vs Alendronate at All Measured Skeletal Sites

DECIDE Study

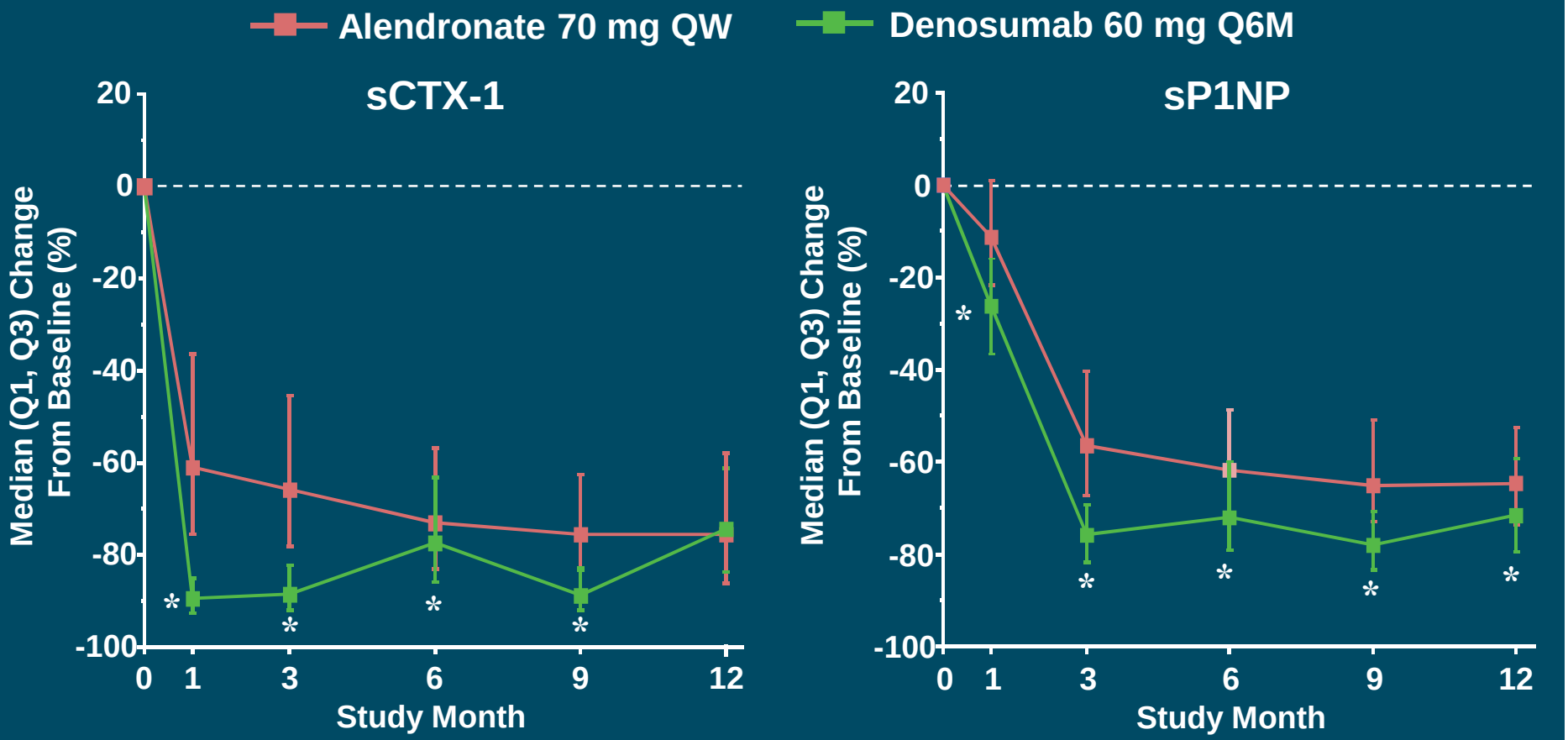


*P ≤ 0.0001

Adapted from: Brown JP, *et al. J Bone Miner Res* 2009;24:153–161.

Greater Decreases in Bone Turnover Markers with Denosumab vs Alendronate

DECIDE Study



*P ≤ 0.0001

Adapted from: Brown JP, *et al. J Bone Miner Res* 2009;24:153–161.

PATHWAYS IN Osteoporosis

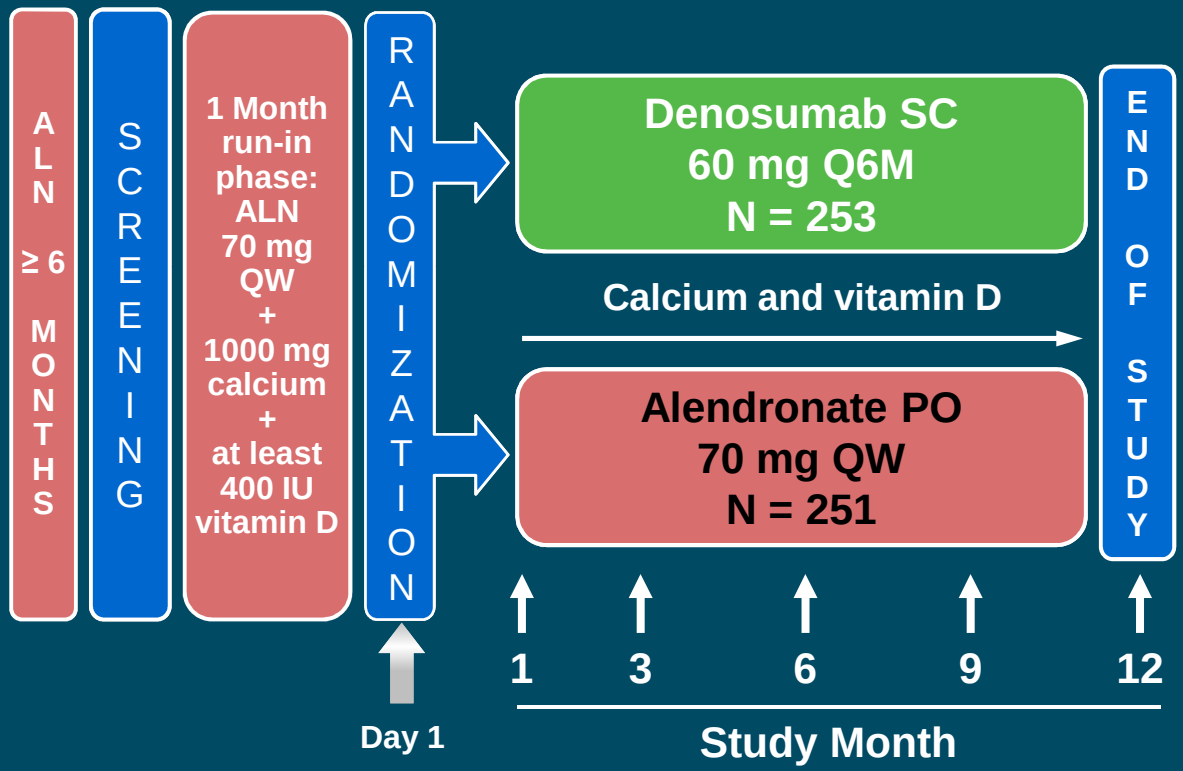
Denosumab Phase III data

STAND – Phase III Transition Study

Study of Transitioning from AleNdronate to Denosumab

Study Design

STAND Study



Study population

- 504 postmenopausal women previously treated with alendronate 70 mg QW or equivalent for ≥ 6 months
- T-score ≤ –2.0 and ≥ –4.0 at lumbar spine or total hip

Primary endpoint

- Change in BMD at total hip at month 12

Secondary endpoints

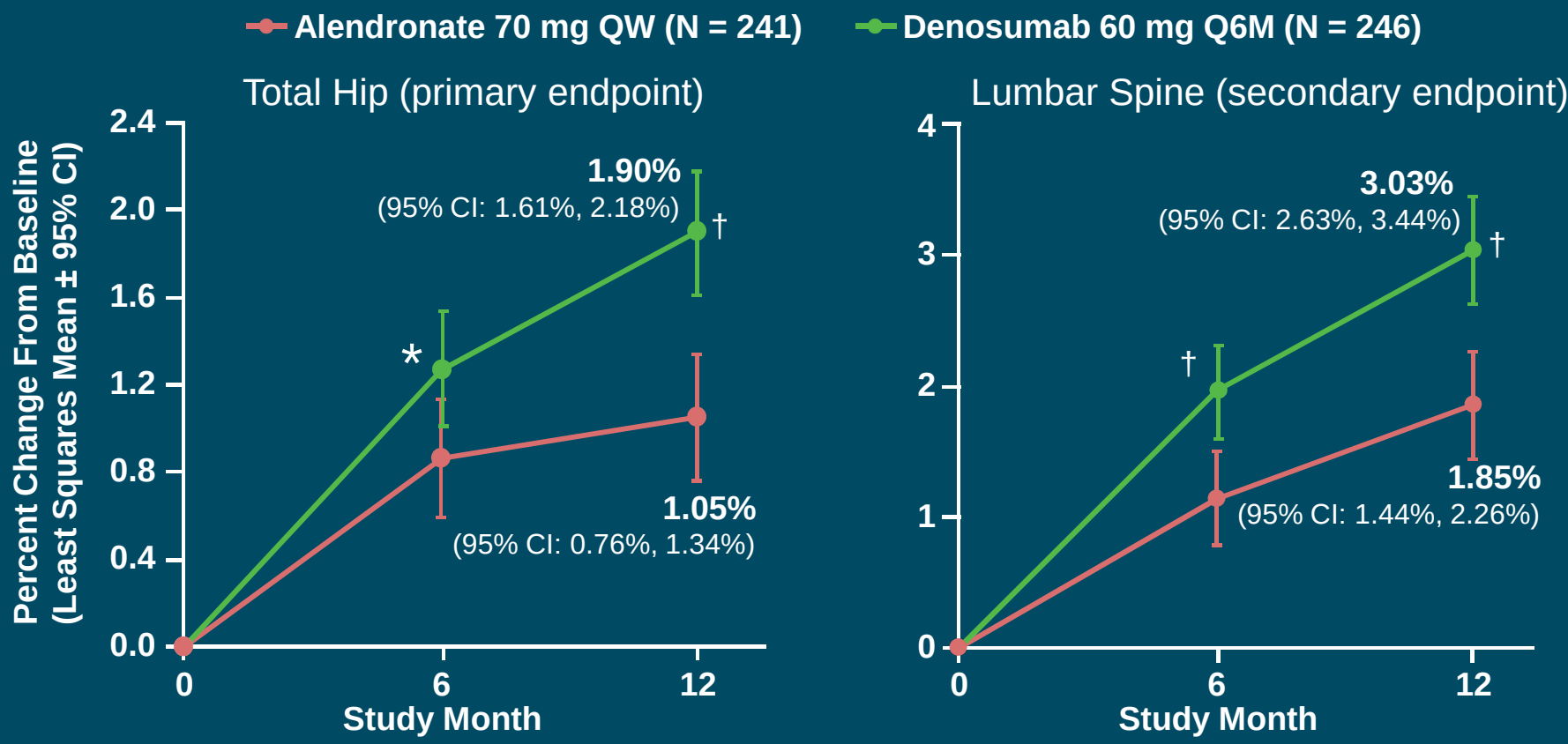
- Change in lumbar spine BMD at month 12
- Change in serum CTX-I at month 3

ALN = alendronate; QW = once weekly; SC = subcutaneously; Q6M = once every 6 months; PO = orally

Adapted from: Kendler DL, *et al. J Bone Miner Res* 2010;25:72–81.

Transition to Denosumab Increased Total Hip and Lumbar Spine BMD Over Continued Treatment with Alendronate

STAND Study

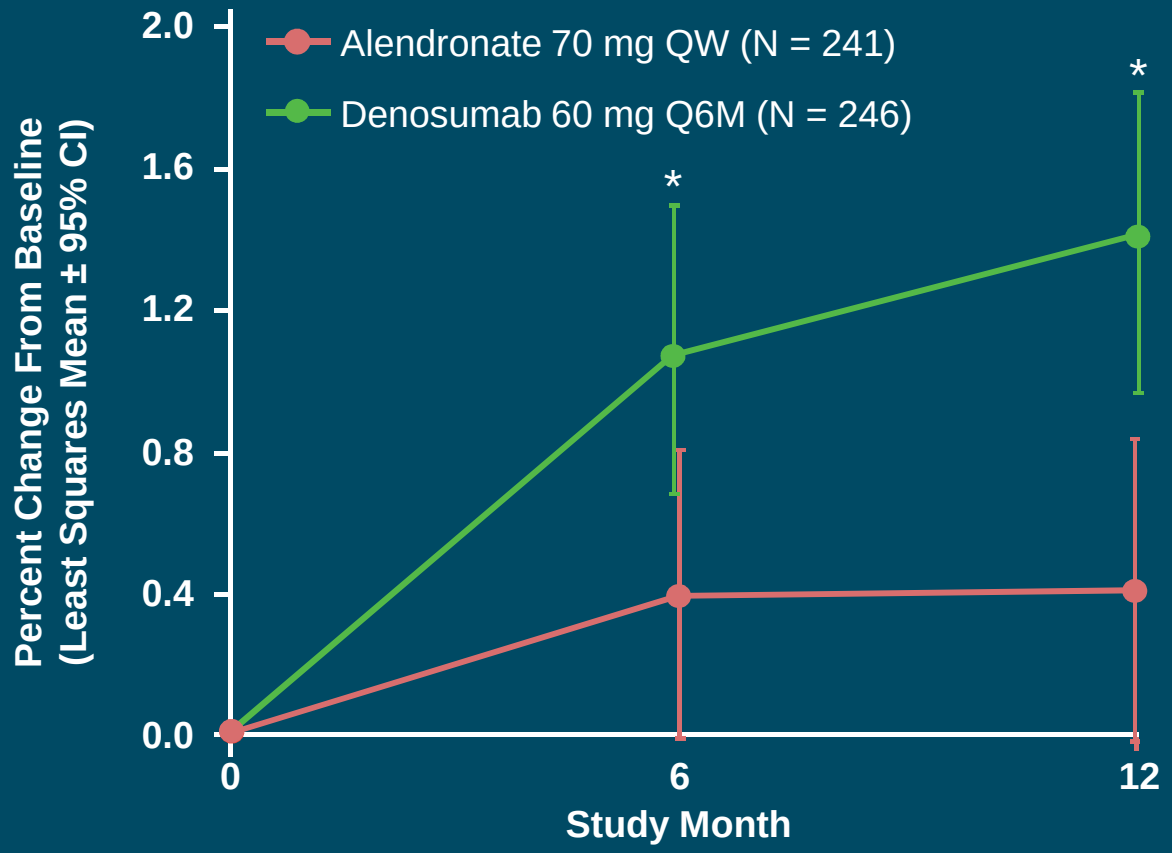


N = number of patients who have a baseline and ≥ 1 post-baseline evaluation
*P < 0.05; †P < 0.01

Adapted from: Kendler DL, *et al. J Bone Miner Res* 2010;25:72–81.
Kendler DL, et al. Poster presented at IOF World Congress on Osteoporosis, Bangkok, Thailand; December 3–7 2008.

Transition to Denosumab Increased Femoral Neck BMD Over Continued Treatment with Alendronate

STAND Study

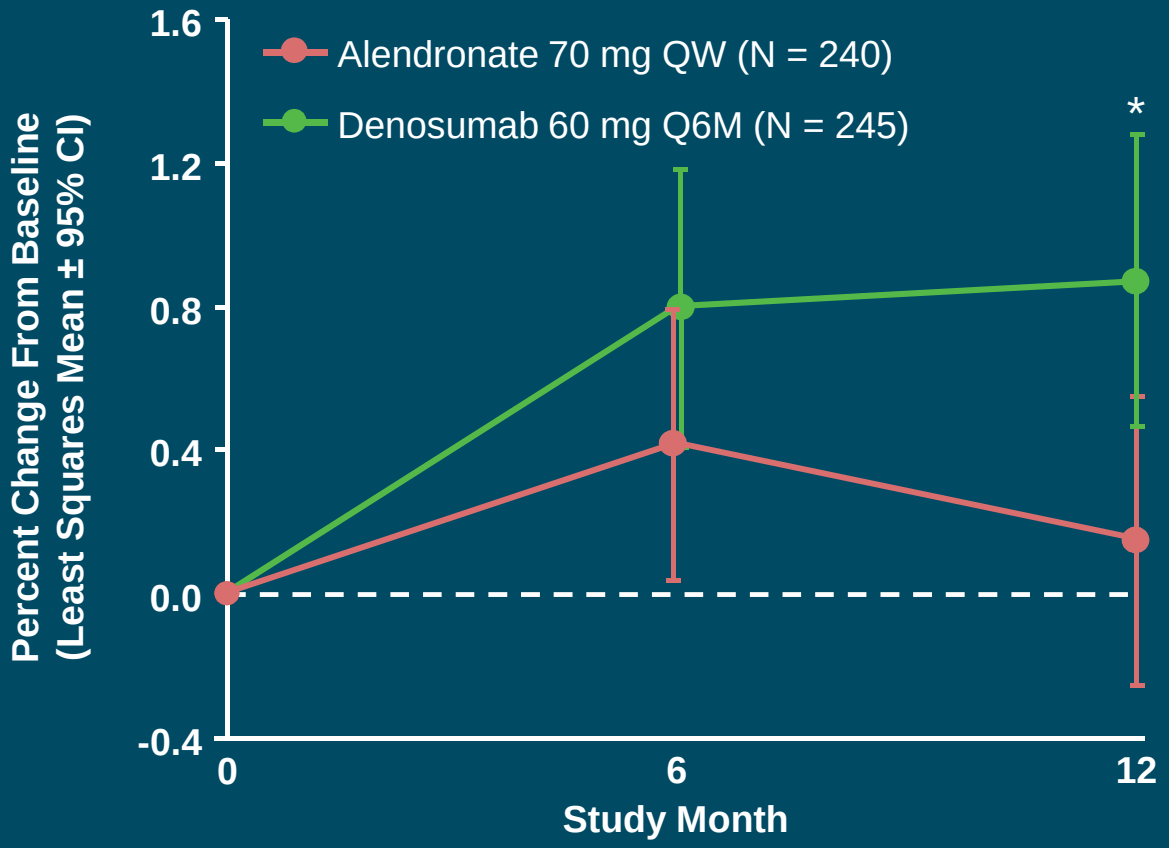


N = number of patients who have a baseline and ≥ 1 post-baseline evaluation
*P < 0.01

Adapted from: Kendler DL, *et al. J Bone Miner Res* 2010;25:72–81.
Kendler DL, et al. Poster presented at IOF World Congress on Osteoporosis, Bangkok, Thailand; December 3–7 2008.

Transition to Denosumab Increased 1/3 Radius BMD Over Continued Treatment with Alendronate

STAND Study

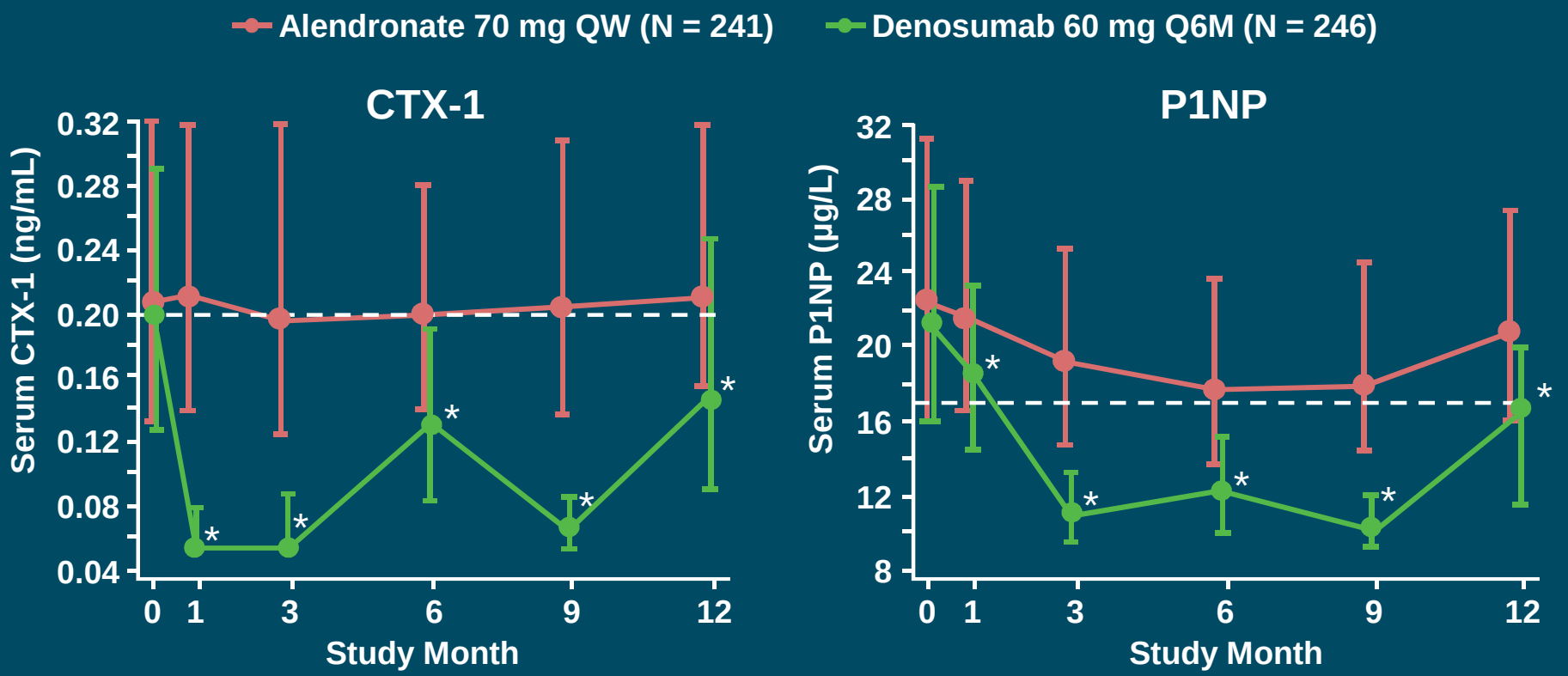


N = number of patients who have a baseline and ≥ 1 post-baseline evaluation
*P < 0.025

Adapted from: Kendler DL, *et al. J Bone Miner Res* 2010;25:72–81.
Kendler DL, et al. Poster presented at IOF World Congress on Osteoporosis, Bangkok, Thailand; December 3–7 2008.

Transition to Denosumab Decreased Bone Turnover Markers Over Continued Treatment with Alendronate

STAND Study



Dotted line is lower limit of premenopausal reference range
Values are medians; error bars represent the interquartile range; analysis carried out in the observed data set; missing values were not imputed
*P < 0.0001

Adapted from: Kendler DL, *et al. J Bone Miner Res* 2010;25:72–81.
Kendler DL, et al. Poster presented at IOF World Congress on Osteoporosis, Bangkok, Thailand; December 3–7 2008.

PATHWAYS IN
Osteoporosis

Denosumab Phase III data

TTR - TTI

Transition To Risedronate

Transition To Ibandronate

OBSTETRICS & GYNECOLOGY, JUNE 2013

Denosumab Compared With Ibandronate in Postmenopausal Women Previously Treated With Bisphosphonate Therapy

A Randomized Open-Label Trial

Chris Recknor, MD, Edward Czerwinski, MD, Henry G. Bone, MD, Sydney L. Bonnick, MD, Neil Binkley, MD, Santiago Palacios, MD, Alfred Moffett, MD, Suresh Siddhanti, PhD, Irene Ferreira, PhD, Prayashi Ghelani, BSc, MSc, Rachel B. Wagman, MD, Jesse W. Hall, MD, Michael A. Bolognese, MD, and Claude-Laurent Benhamou, MD

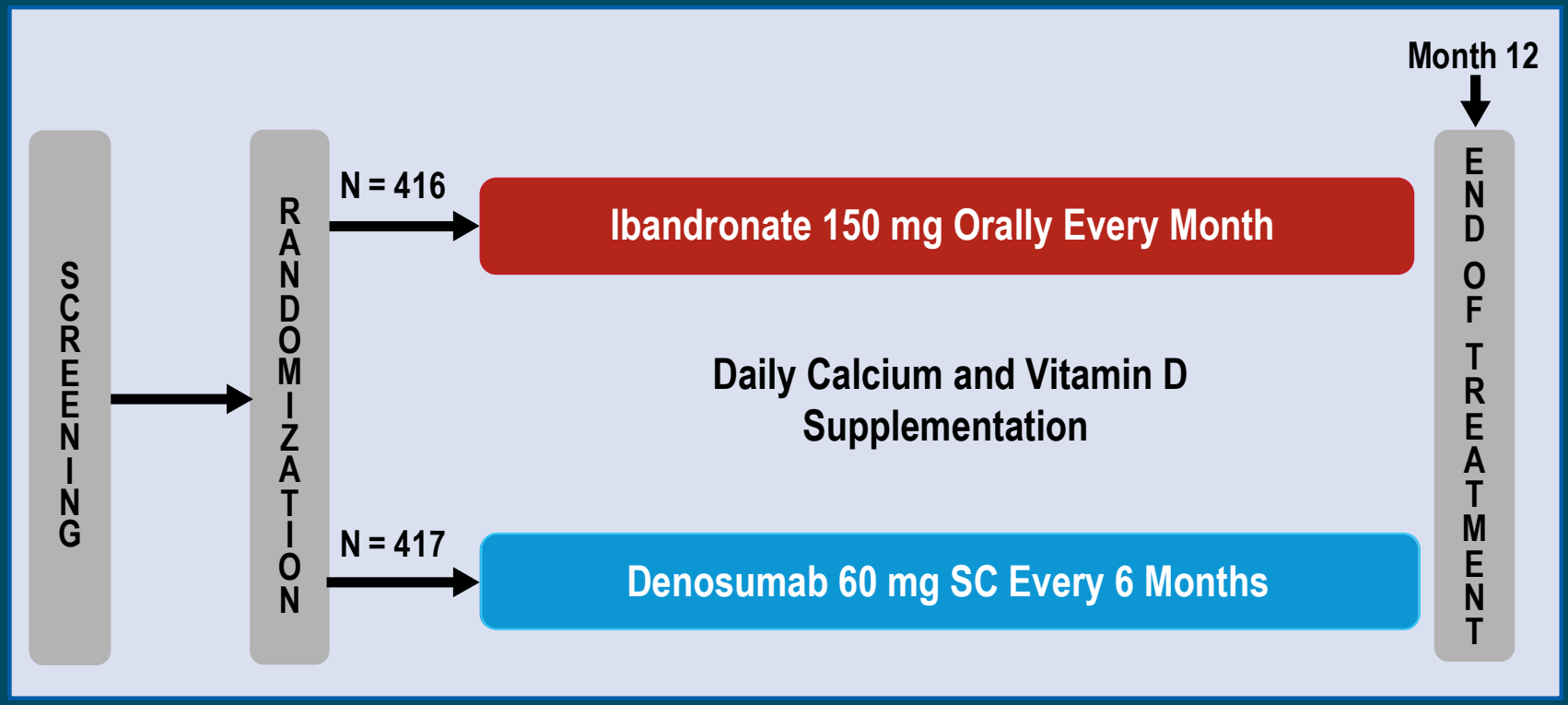
From the United Osteoporosis Centers, Gainesville, Georgia; Medical College Jagiellonian University, Krakow, Poland; Michigan Bone and Mineral Clinic, Detroit, Michigan; the Clinical Research Center of North Texas, Denton, Texas; the University of Wisconsin–Madison Osteoporosis Clinical Center and Research Program, Madison, Wisconsin; the Palacios Institute of Woman's Health, Madrid, Spain; OB-GYN Associates of Mid Florida, PA, Leesburg, Florida; Amgen Inc, Thousand Oaks, California; Amgen Ltd, Cambridge, United Kingdom; Ovatech Solutions Ltd, London, United Kingdom; The Bethesda Health Research Center, Bethesda, Maryland; and Institut National de la Santé et de la Recherche Médicale (INSERM) U658, CHR d'Orléans, Orléans, France.

Funding support Sponsored by Amgen Inc, Thousand Oaks, California.

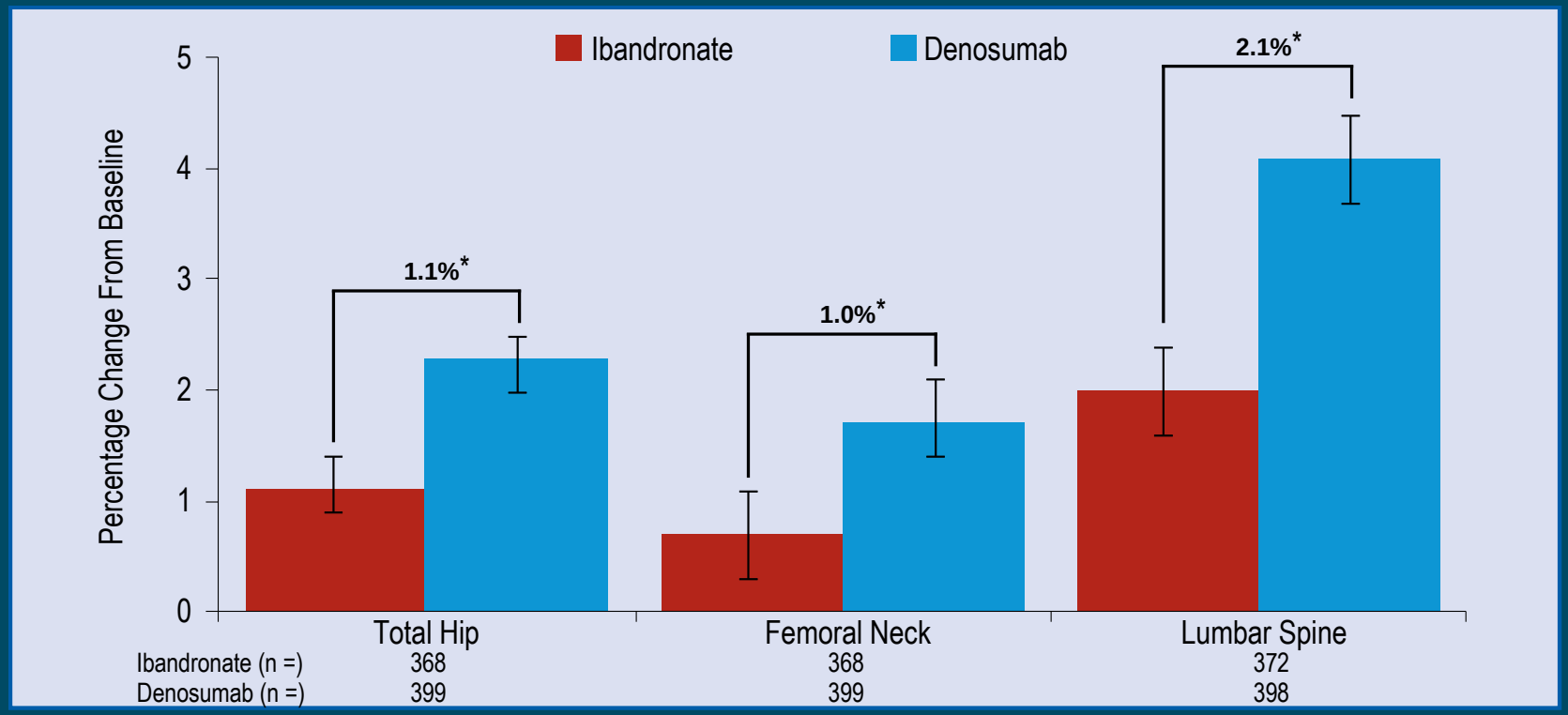
OBJECTIVE: To compare the efficacy and safety of denosumab to ibandronate in postmenopausal women with low bone mineral density (BMD) previously treated with a bisphosphonate.

METHODS: In a randomized, open-label study, postmenopausal women received 60 mg denosumab subcutaneously every 6 months (n=417) or 150 mg ibandronate orally every month (n=416) for 12 months. End points included percentage change from baseline in total hip, femoral neck, and lumbar spine BMD at

METHODS: Figure 1. Study Design



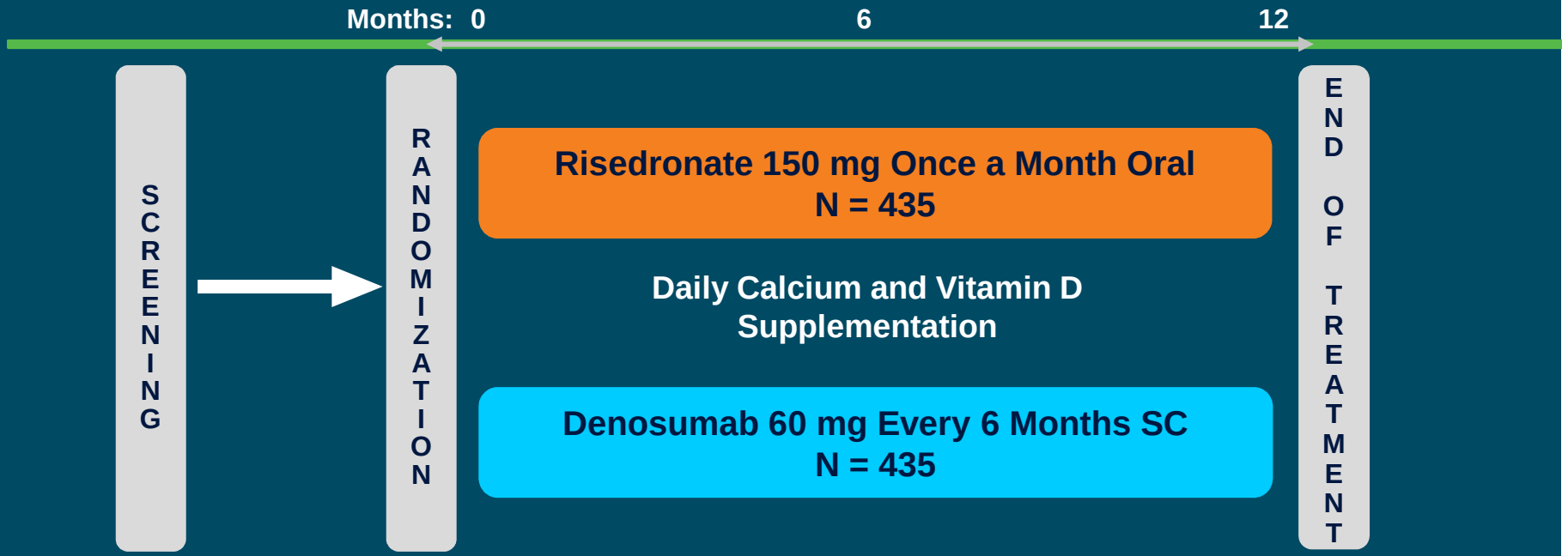
Cambio porcentual en la DMO de denosumbab vs ibandronato



Values are least squares means and 95% confidence intervals from ANCOVA. *$P < 0.0001$ vs ibandronate. n = number of subjects included in analysis. Results based on observed data; results based on the primary imputation method or any other pre-specified sensitivity methods were similar.

Transition to Risedronate (TTR) Study Design

International (EU, AUS, CAN), multicenter, randomized, open-label, parallel-group study



Key Study Entry Criteria

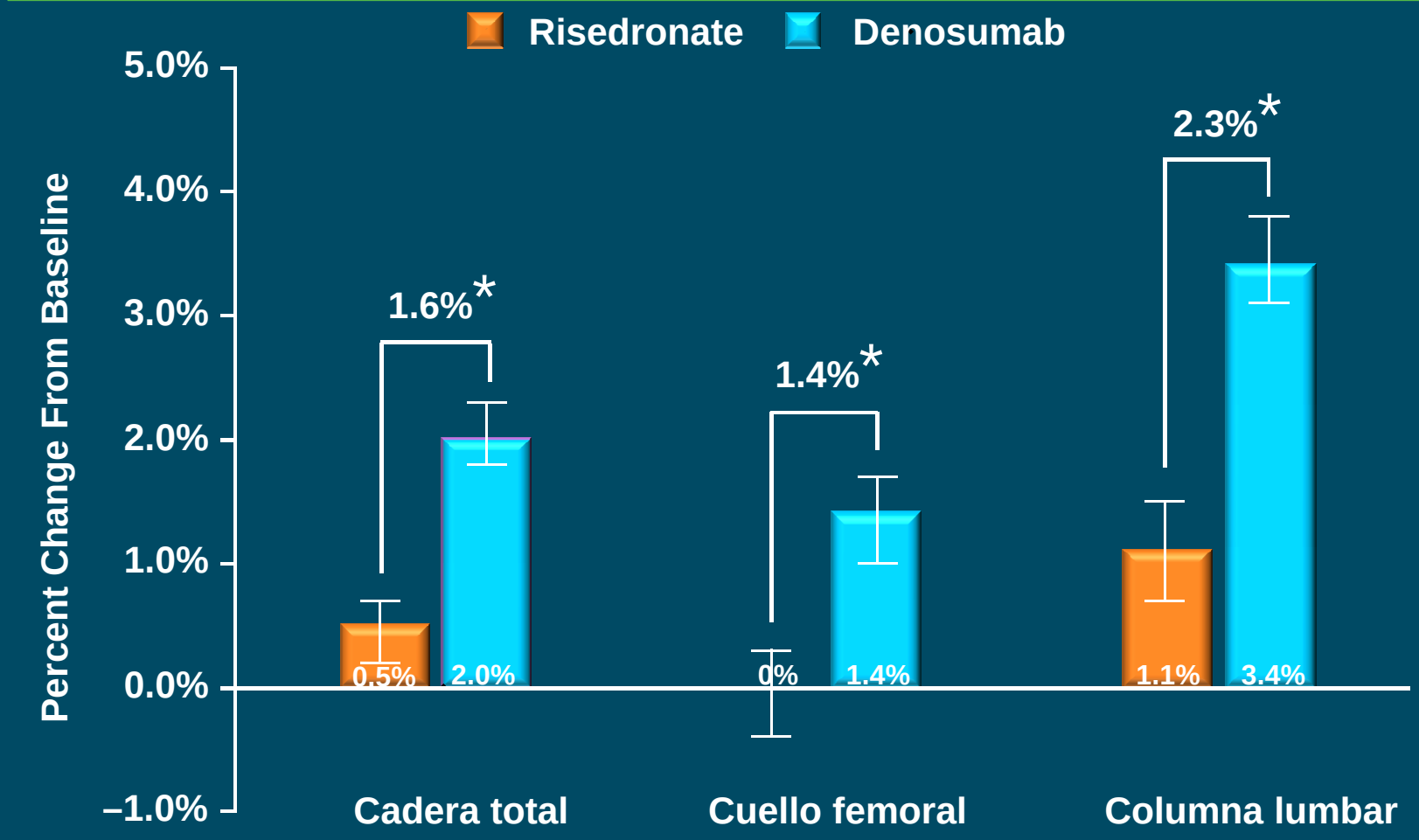
- Postmenopausal women aged ≥ 55 years
- Previously received alendronate but have:
  - Stopped taking alendronate or
  - Insufficient adherence (OS-MMAS < 6)
- Have received their first prescription of daily or weekly alendronate ≥ 1 month prior to screening

Endpoints

- Percent change from baseline in total hip BMD at 12 months (primary)
- Percent change from baseline in femoral neck and lumbar spine BMD at month 12
- Percent change from baseline in serum β-CTX at month 1 and 6 (subset)
- Incidence of adverse/serious adverse events

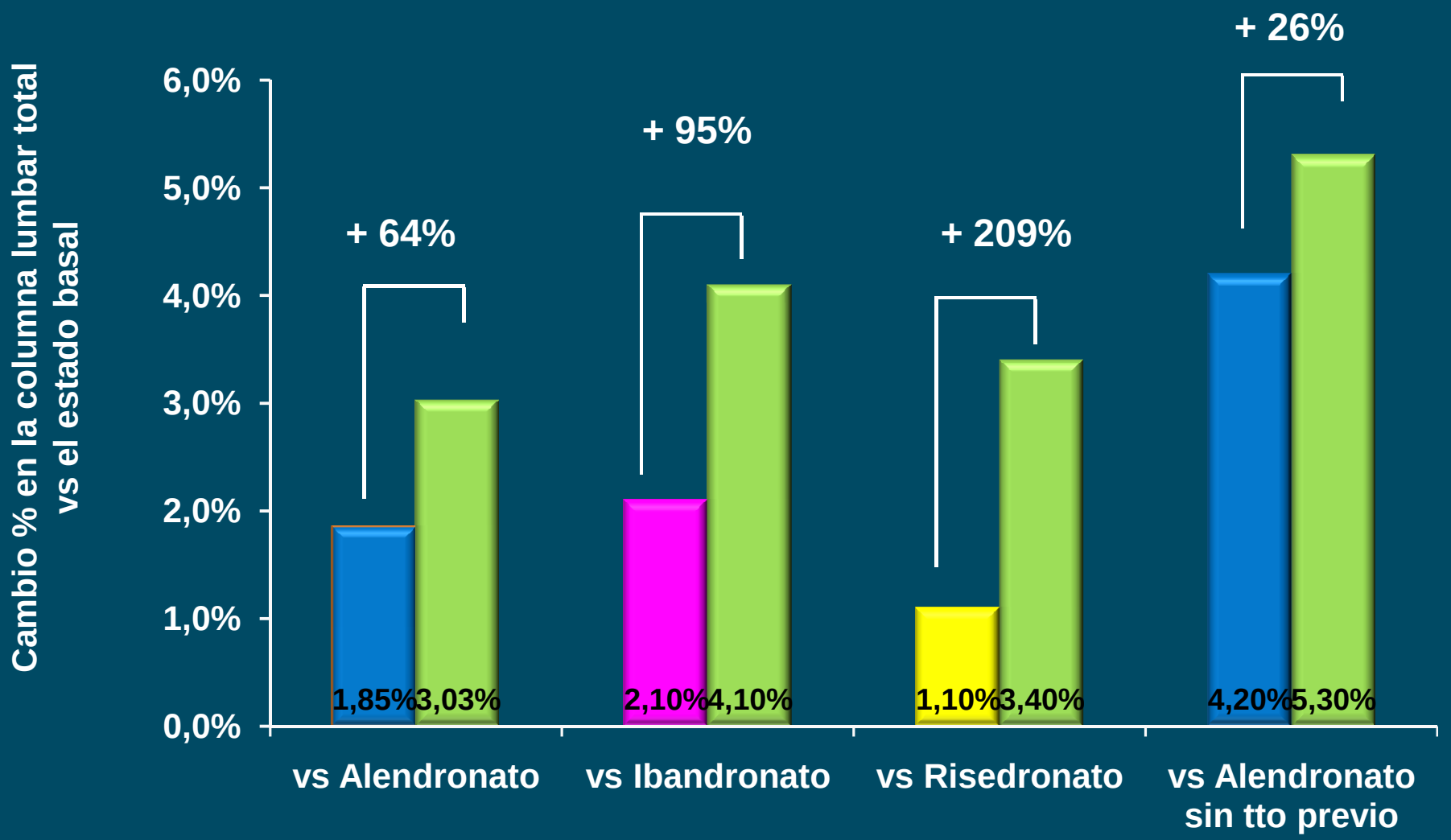
OS-MMAS = Osteoporosis Specific Morisky Medication Adherence Scale. SC = subcutaneous.

Efecto del Denosumab y el risedronato en la DMO a los 12 meses

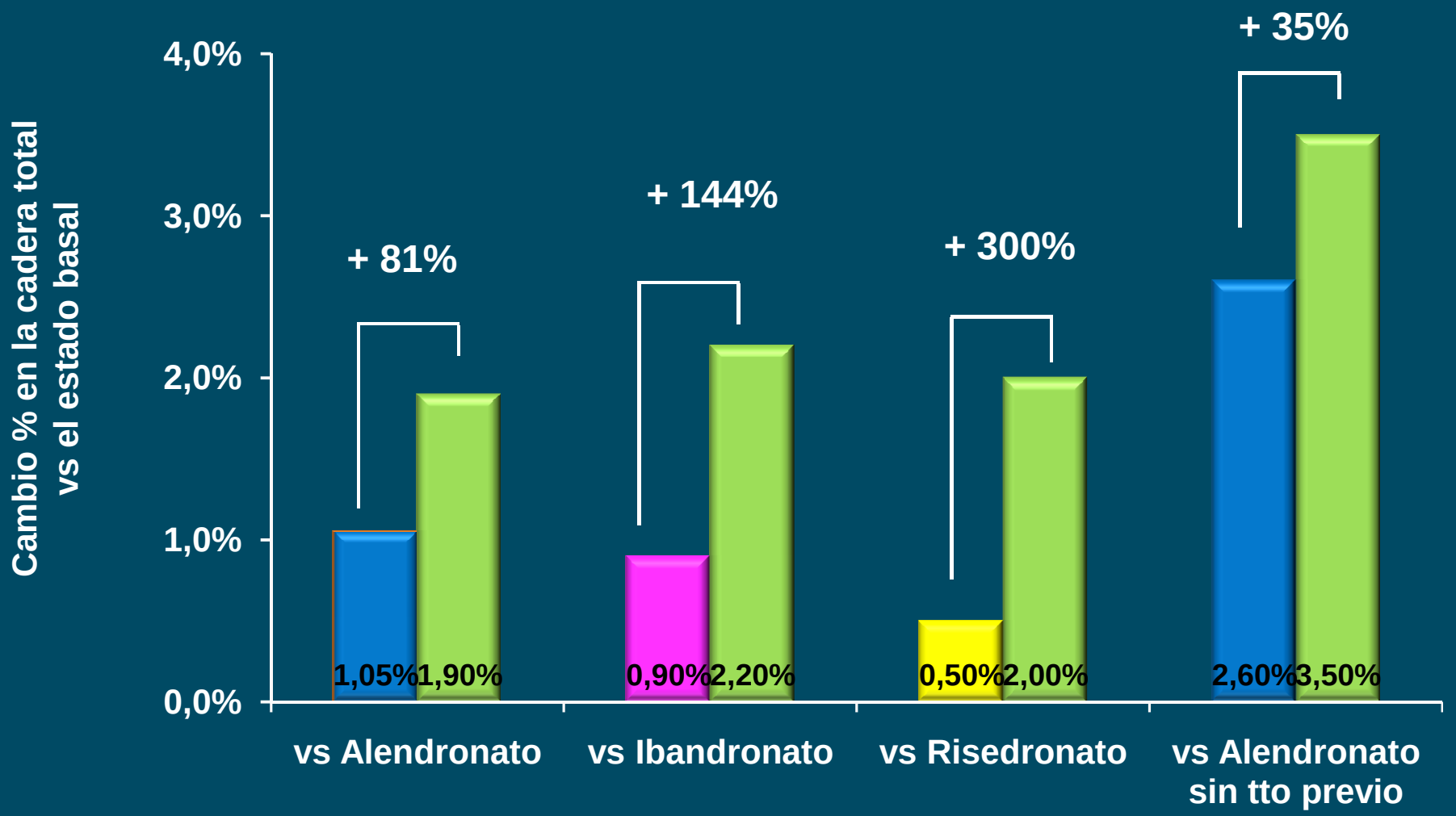


Data are least-squares means and 95% confidence intervals. *$p < 0.0001$ denosumab vs risedronate.
Prespecified analyses included imputed data.

Resultados de denosumab vs bifosfonatos: Columna lumbar



Resultados de denosumab vs bifosfonatos – Cadera total



Con intolerancia GI a su medicación actual o mala adherencia

- 65 años de edad
- reporta síntomas GI
- múltiples tratamientos concomitantes

PATHWAYS IN
Osteoporosis

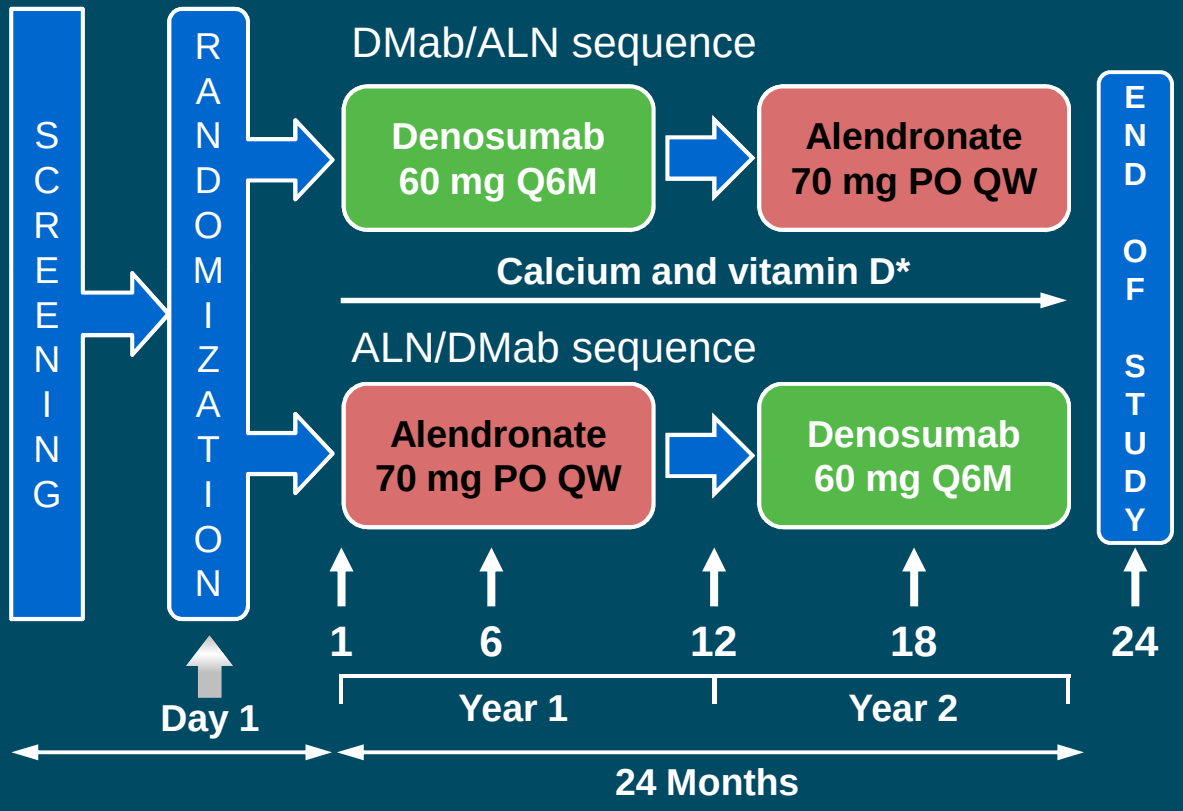
Denosumab Phase III data

DAPS

Denosumab Adherence and Preference Study

Study Design

DAPS Study: Open-label, randomized, cross-over study



Study population

- Postmenopausal women ≥ 55 years
- BMD T-scores ≤ -2.0 to ≥ -4.0 at the spine, hip, or femoral neck

Objectives

- To evaluate adherence (including compliance and persistence)
- To also evaluate patient treatment beliefs, preference, satisfaction, and bother

Primary endpoint

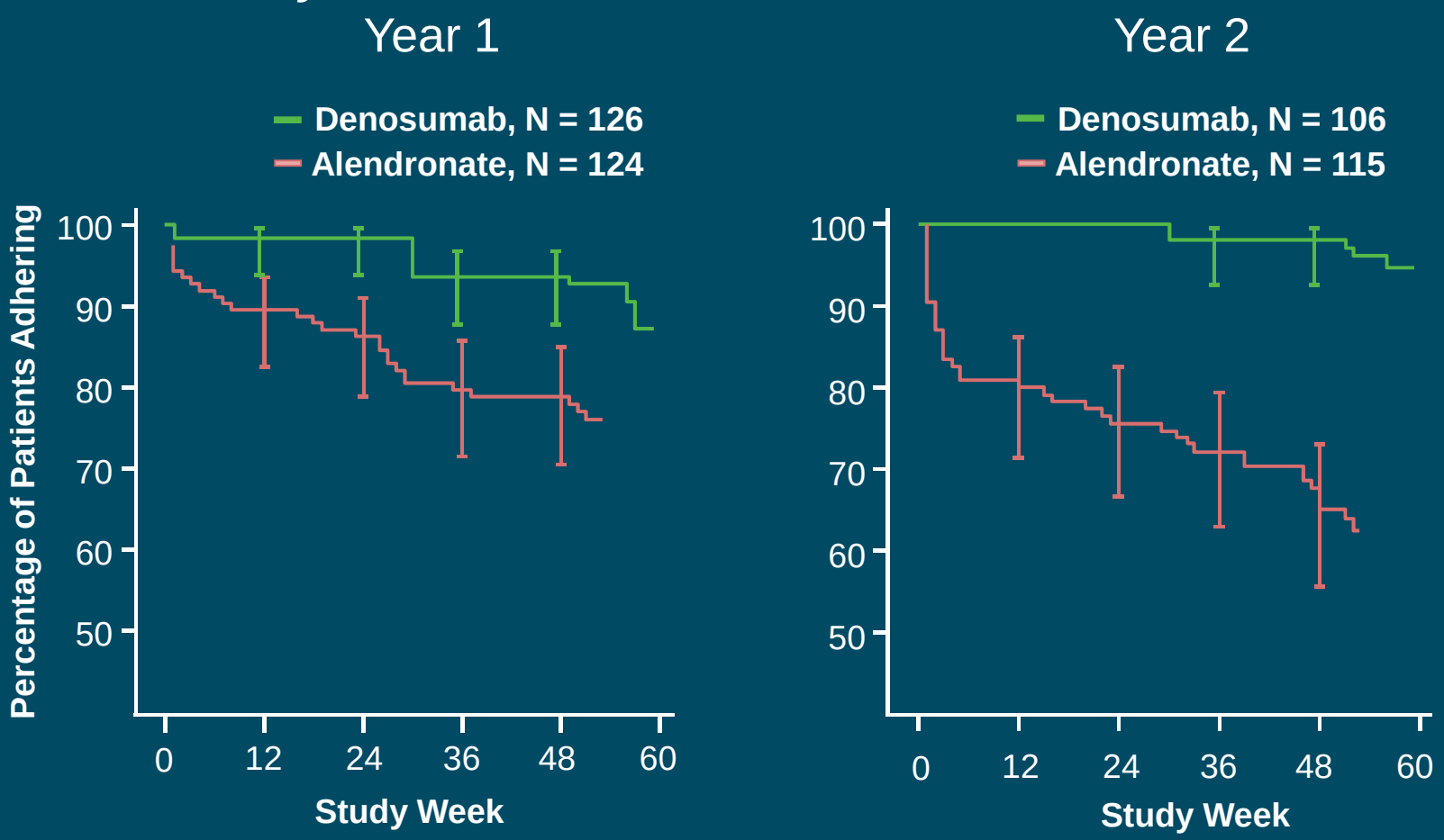
- Adherence during the first year

*All subjects were instructed to take daily supplements of ≥ 1000 mg calcium and ≥ 400 IU vitamin D
DMab = denosumab; ALN = alendronate

Adapted from: Freemantle N, *et al. Osteoporosis Int* 2012;23:317–326.

Time to Treatment Non-adherence Shorter with Alendronate than Denosumab and More Pronounced After Cross-over

DAPS Study

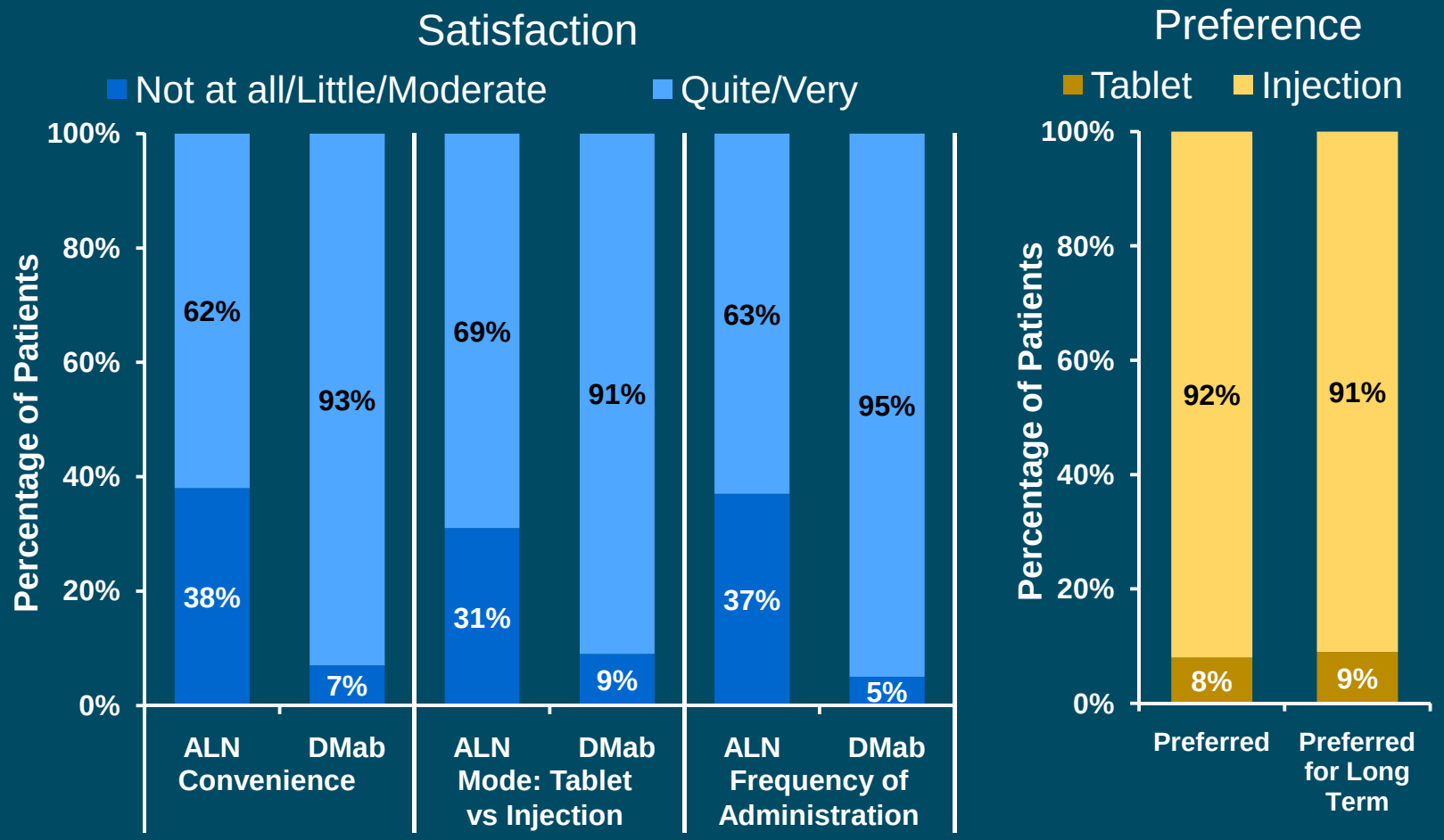


For each treatment group, time points with > 95% cumulated subjects were excluded

Adapted from: Freemantle N, *et al. Osteoporosis Int* 2012;23:317–326.

Greater Patient Satisfaction with Denosumab than Alendronate

DAPS Study

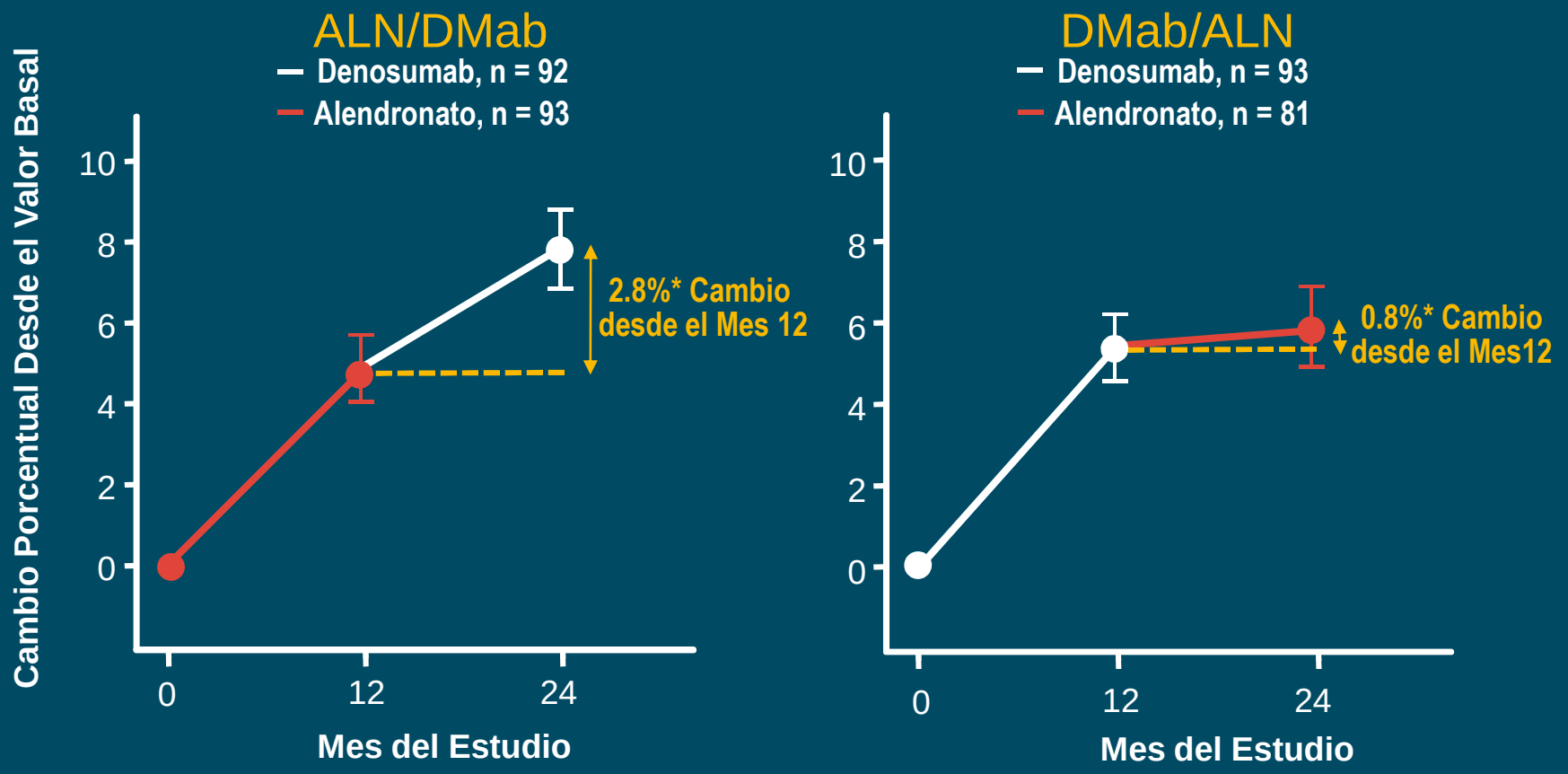


P < 0.001 vs alendronate
Preference was assessed only in Year 2

Adapted from: Freemantle N, *et al. Osteoporosis Int* 2012;23:317–326.

Cambio Porcentual de la DMO en la Columna Lumbar

Estudio DAPS



- Los análisis de la DMO fueron exploratorios y no tenían el poder para estudiar una diferencia cierta [1]

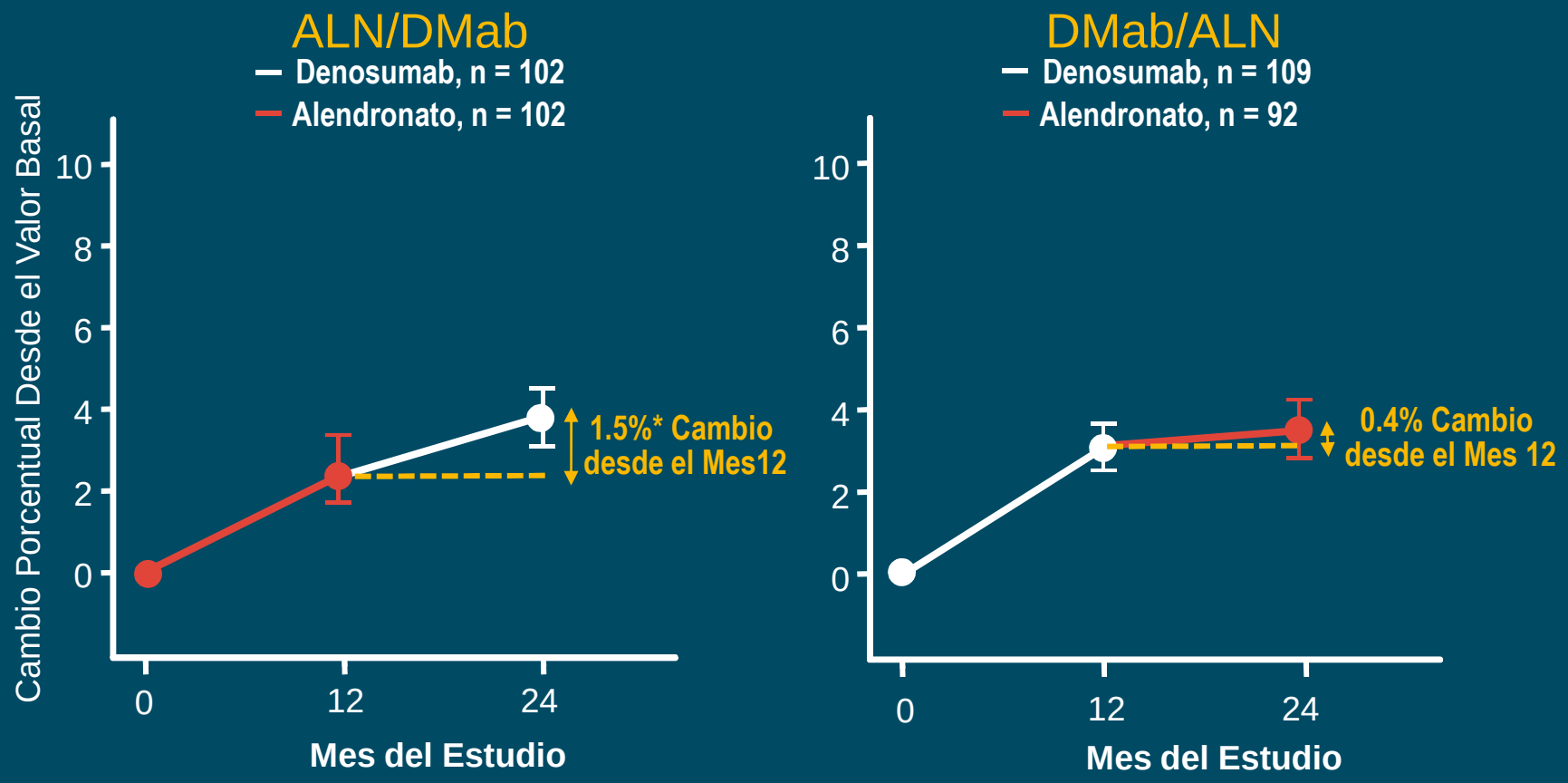
Para cada período de tratamiento fue utilizado un modelo ANCOVA para calcular el cambio porcentual desde el Mes 12 hasta el Mes 24 (indicado en amarillo). El valor l del período basal de la variable tratamiento, tipo de aparato, el valor del período basal por interacción del tipo de aparato fue ajustado por separado y estratificado por centro y por fractura osteoporótica previa.

*Diferencia estadísticamente significativa

McClung MR, *et al*. Presentado en: La Sociedad Internacional para la Densitometría Clínica; Abril 6-9, 2011, Miami, FL. Poster 116.

Cambio Porcentual de la DMO en la Cadera Total

Estudio DAPS



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*Diferencia estadísticamente significativa

McClung MR, et al. Presentado en: La Sociedad Internacional para la Densitometría Clínica; Abril 6-9, 2011, Miami, FL. Poster 116.

Paciente añosa con o sin disfunción renal

- 79 años de edad
- múltiples tratamientos concomitantes
- con o sin disfunción renal

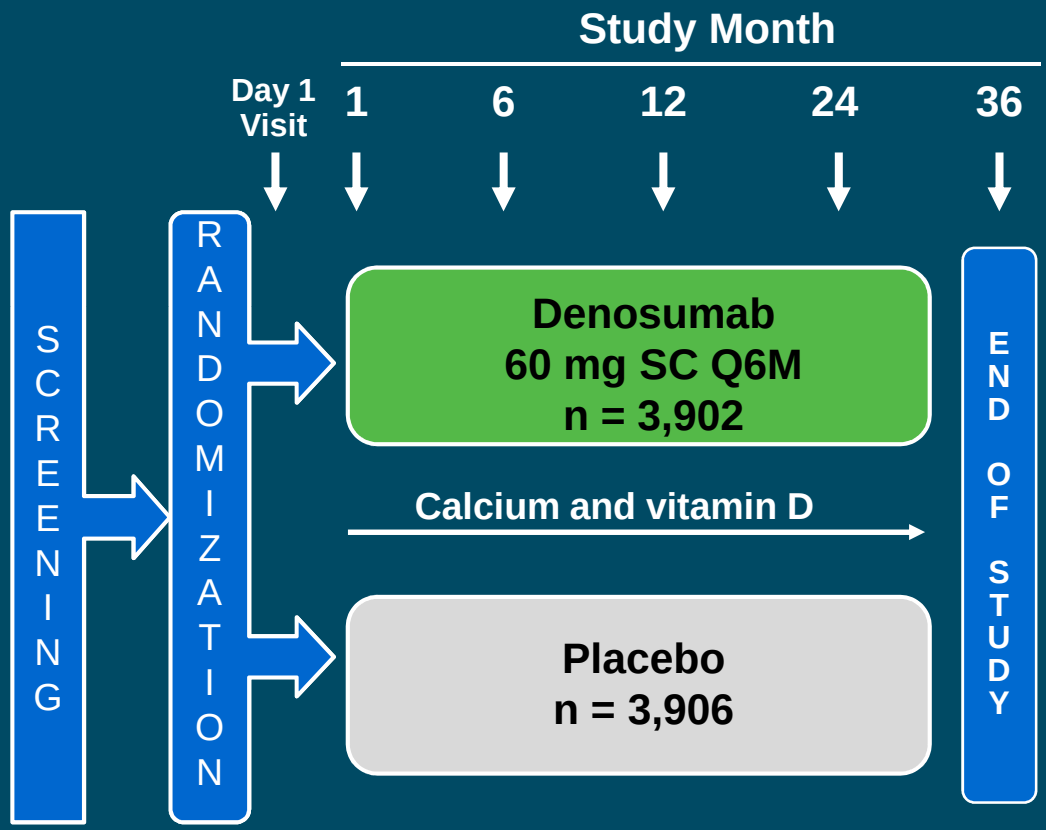
PATHWAYS IN
Osteoporosis

Denosumab Phase III data

FREEDOM Higher Risk Sub-analysis

Study Design

FREEDOM Trial – Higher Risk Sub-analysis



Study population

- 7,808 postmenopausal women
- T-score < –2.5 at the lumbar spine or total hip and not < –4.0 at either site

Objective of this analysis

- Assess the effect of denosumab treatment on fracture risk in high-risk subsets of the Pivotal Phase III Trial population
  - New vertebral fractures
  - Hip fractures

- **International, placebo-controlled study**

SC = subcutaneously; Q6M = once every 6 months

Cummings SR, *et al. N Engl J Med* 2009;361:756–765.
Boonen S, *et al. J Clin Endocrin Metab*. 2011;96:1727–1736.

Definition of Higher Risk Subjects Used in Subgroup Analyses

FREEDOM Trial – Higher Risk Sub-analysis

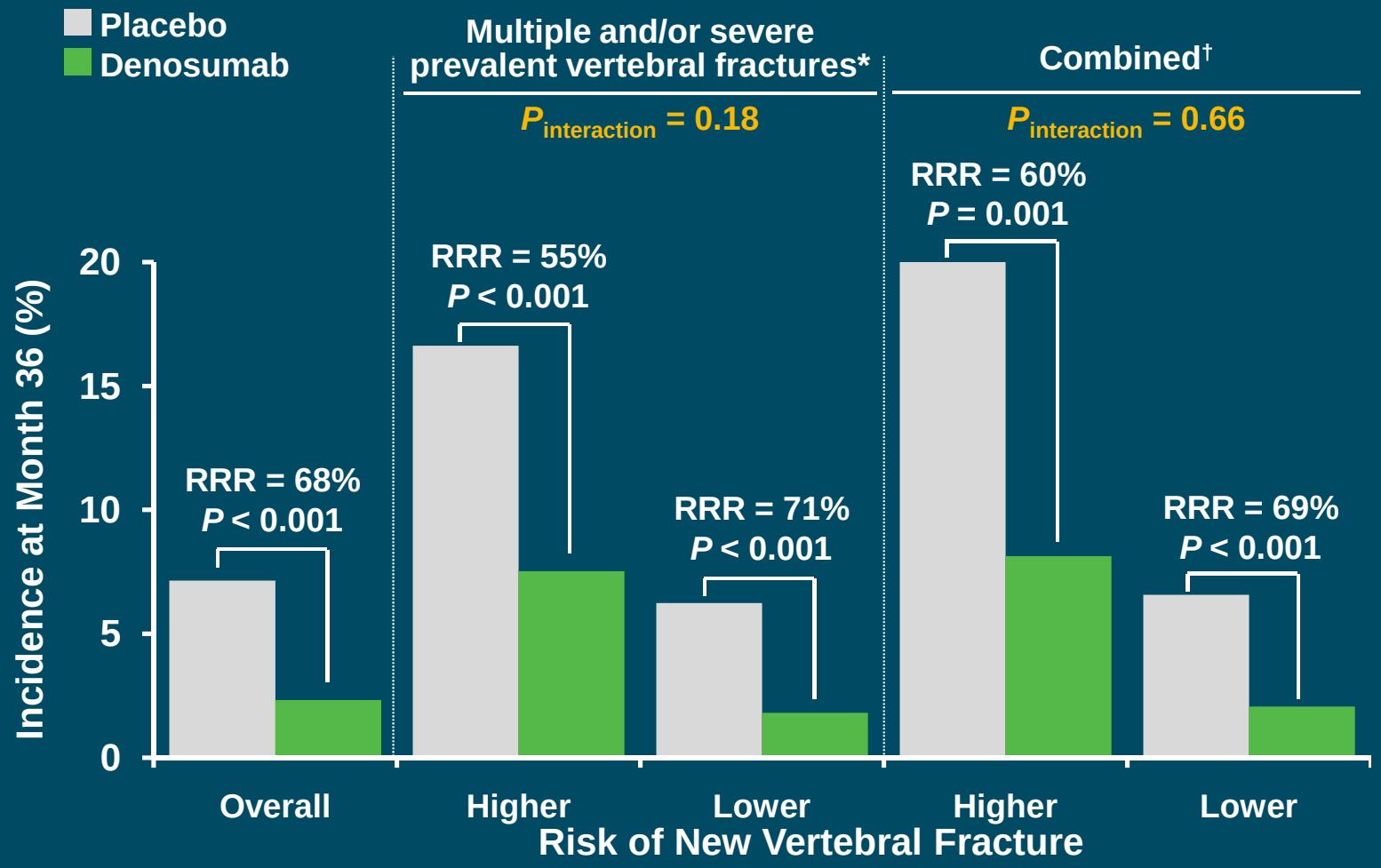
Outcome	Higher Risk Sub-analyses*
New Vertebral Fracture	*Any of the following:* • ≥ 2 preexisting vertebral fractures with any degree of deformity *or* ≥ 1 prevalent vertebral fracture with moderate or severe deformity, *or* both • Femoral neck BMD T-score ≤ –2.5 • Multiple and/or moderate or severe vertebral deformities with a femoral neck BMD T-score ≤ –2.5
Hip Fracture	*Any of the following:* • ≥ 75 years old • Femoral neck BMD T-score ≤ –2.5 • ≥ 75 years old and a femoral neck BMD T-score ≤ –2.5

*All analyses were done post hoc except for new vertebral fractures in women with a femoral neck BMD T-score ≤ –2.5

BMD = bone mineral density

Boonen S, *et al. J Clin Endocrin Metab*. 2011;96:1727–1736.

The Effect of Denosumab on New Vertebral Fractures in Higher Risk Populations

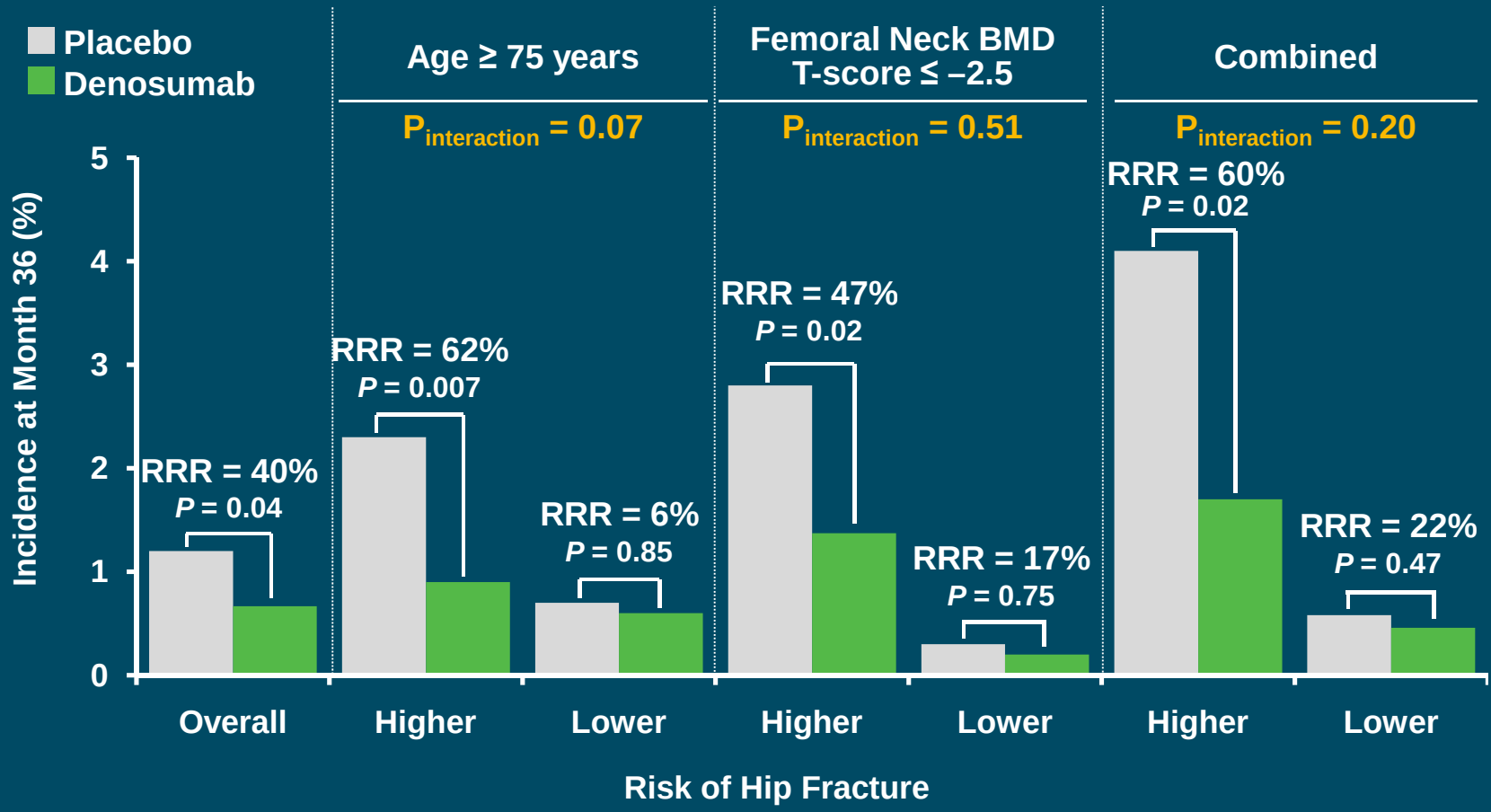


*≥ 2 preexisting vertebral fractures with any degree of deformity or ≥ 1 prevalent vertebral fracture with moderate or severe deformity, or both

†Multiple and/or moderate or severe vertebral deformities with a femoral neck BMD T-score ≤ –2.5

Adapted from: Boonen S, et al. *J Clin Endocrin Metab*. 2011;96:1727–1736.

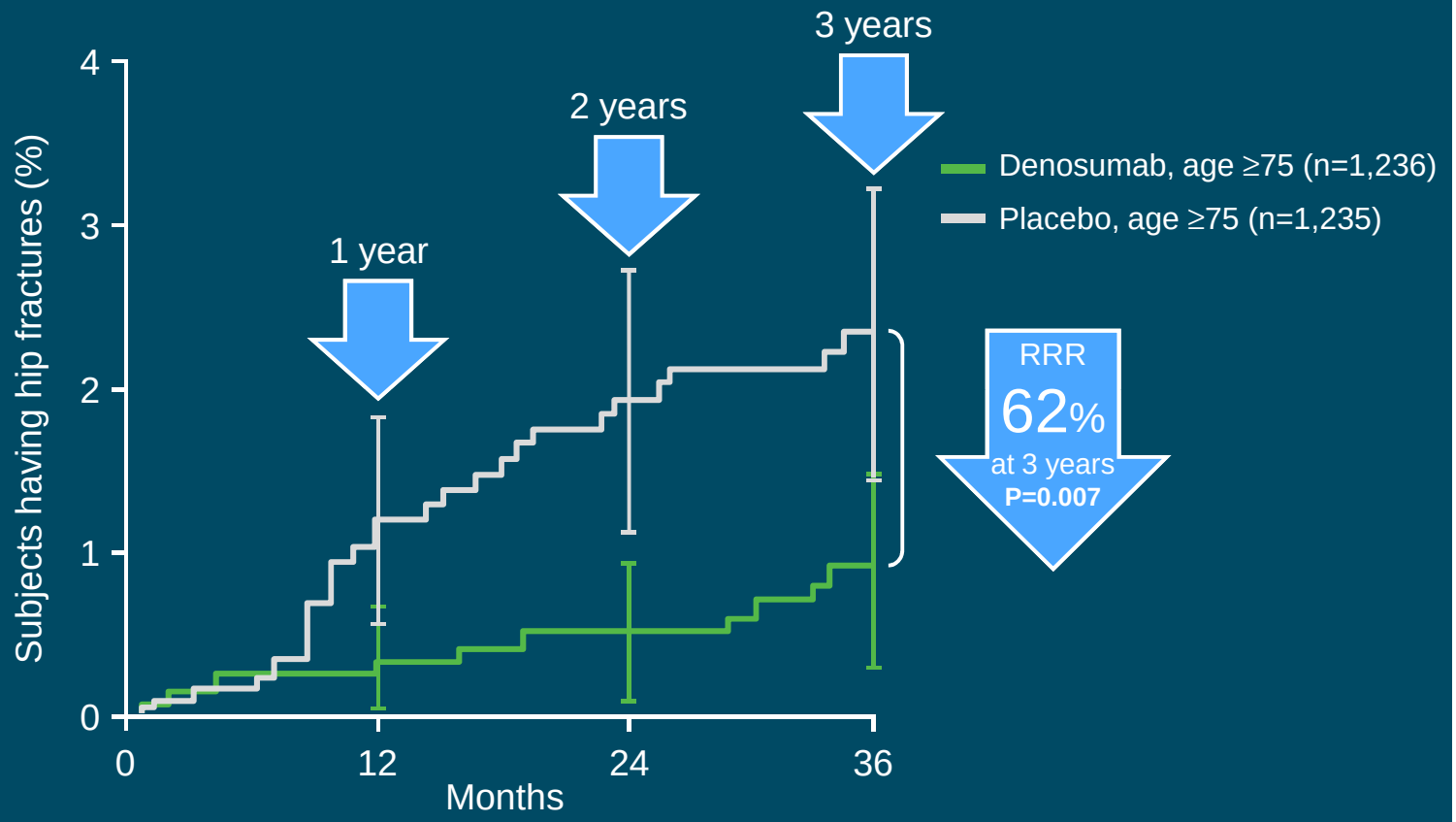
The Effect of Denosumab on New Hip Fractures in Higher Risk Populations



FN = femoral neck

Boonen S, *et al. J Clin Endocrin Metab*. 2011;96:1727–1736.

Denosumab Reduces Hip Fractures by 62%* in Patients Aged ≥75 Years (in a Post Hoc Analysis)[1]



- This early onset of action at the hip has not been documented with any other antiresorptive drug[1–6]

Absolute risk reduction for denosumab vs placebo was 1.4% for hip fractures[1]

*Denosumab provided a hip fracture risk reduction of 6% (P=0.85) in patients 60 to 74 years and 62% (P=0.007) in patients 75 to 90 years. Age P interaction value =0.07. Patients with femoral neck T-scores of ≤ −2.5[1]

1. Boonen S, *et al. J Clin Endocrinol Metab* 2011;96:1727–1736.
2. Boonen S, *et al. J Am Geriatr Soc* 2010;58:292–299.
3. Harris ST, *et al. JAMA* 1999;282:1344–1352.
4. McClung MR, *et al. N Engl J Med* 2001;344:333–340.
5. Seeman E, *et al. Bone* 2010;46:1038-1042.

PATHWAYS IN Osteoporosis

Denosumab Phase III data

FREEDOM EXTENSION

Baseline Characteristics

Phase III: FREEDOM and FREEDOM EXTENSION Studies

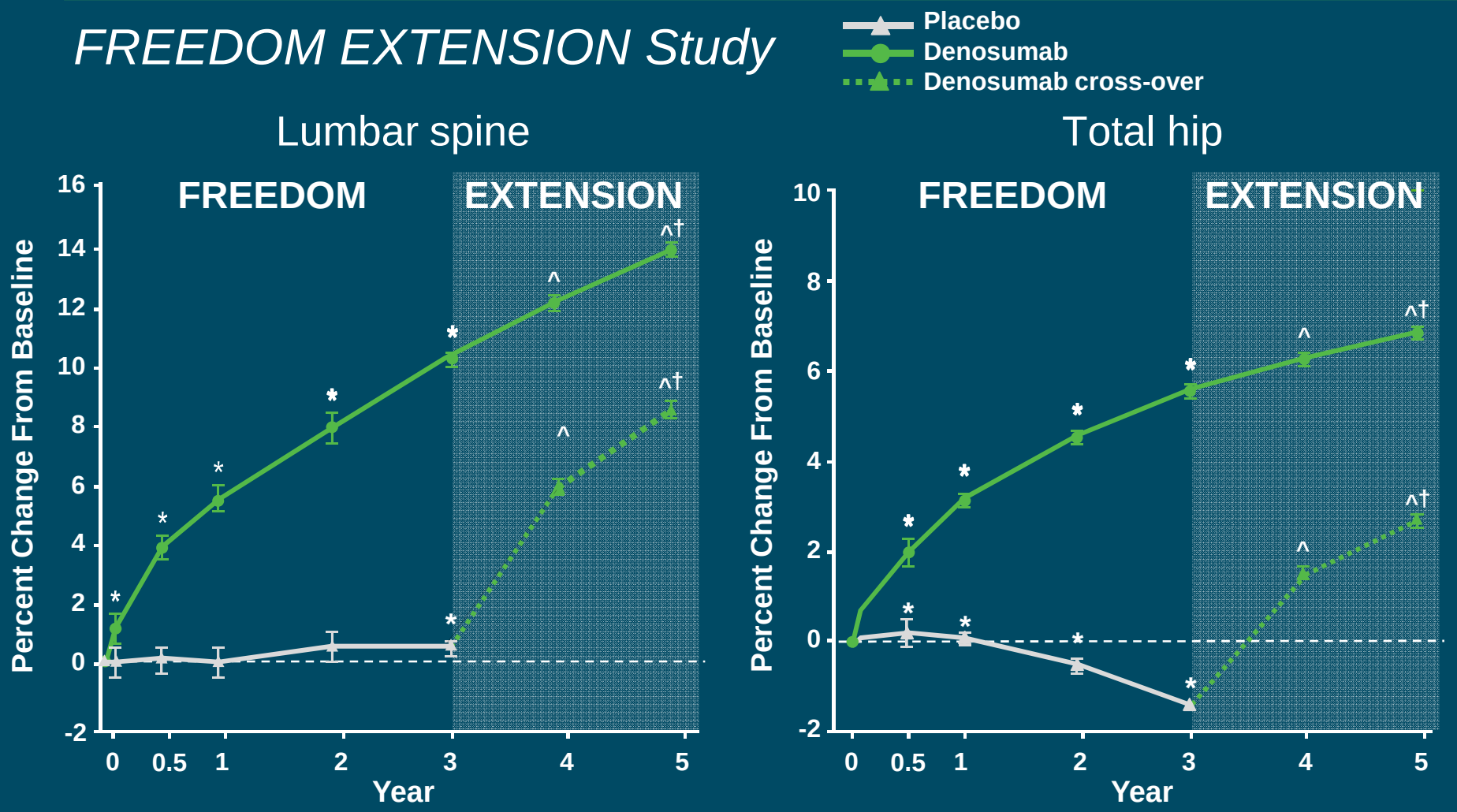
	Long-term denosumab treatment EXTENSION subjects N = 2,343		Cross-over denosumab treatment EXTENSION subjects N = 2,207	
	FREEDOM Baseline	EXTENSION Baseline	FREEDOM Baseline	EXTENSION Baseline
Age, years	71.9 (5.0)	74.9 (5.0)	71.8 (5.1)	74.8 (5.1)
Age groups, % ≥ 65 years ≥ 75 years	 94.3% 28.3%	 97.9% 53.7%	 93.7% 28.3%	 97.4% 52.2%
Prevalent vertebral fractures, %	23.9%	24.5%	22.0%	25.0%
LS BMD T-score	-2.83 (0.67)	-2.14 (0.80)	-2.84 (0.68)	-2.81 (0.75)
TH BMD T-score	-1.85 (0.79)	-1.50 (0.79)	-1.85 (0.79)	-1.93 (0.80)
CTX* ng/mL, median	0.524	0.183	0.554	0.568
P1NP* µg/L, median	46.7	17.5	54.2	48.8

LS = lumbar spine; TH = total hip
Data are mean (SD) unless otherwise noted
•Includes data from 65 subjects (long-term) and 36 subjects (cross-over)

Adapted from: Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

Continuation of Denosumab Treatment Increases Lumbar Spine and Total Hip BMD Year on Year

FREEDOM EXTENSION Study

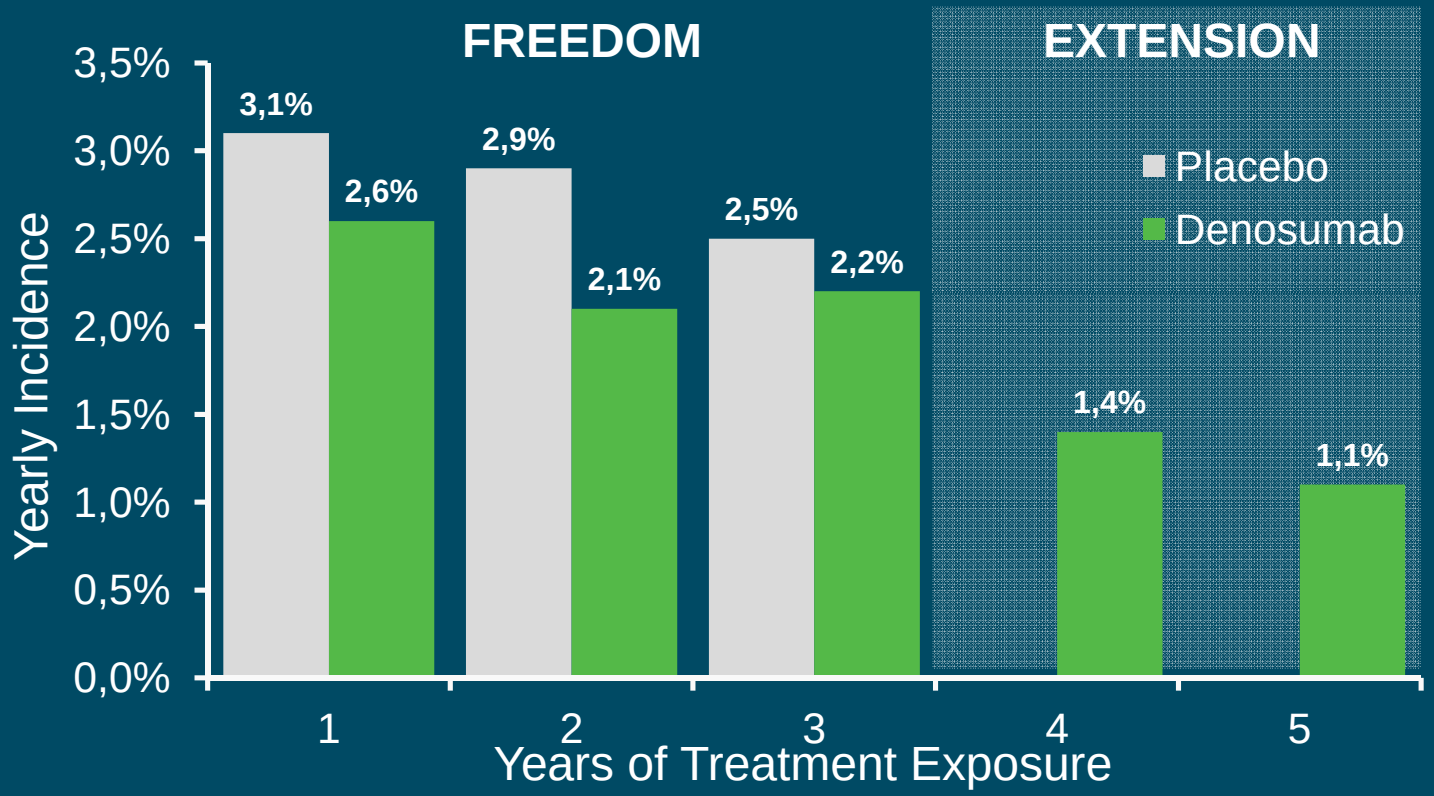


LS mean (95% CI)
*p < 0.05 vs FREEDOM baseline; ^p < 0.05 vs FREEDOM and EXTENSION baseline; †p < 0.05 vs year 4

Adapted from: Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

Continuation of Denosumab Maintains a Low Incidence of Non-vertebral Fractures

FREEDOM EXTENSION Study

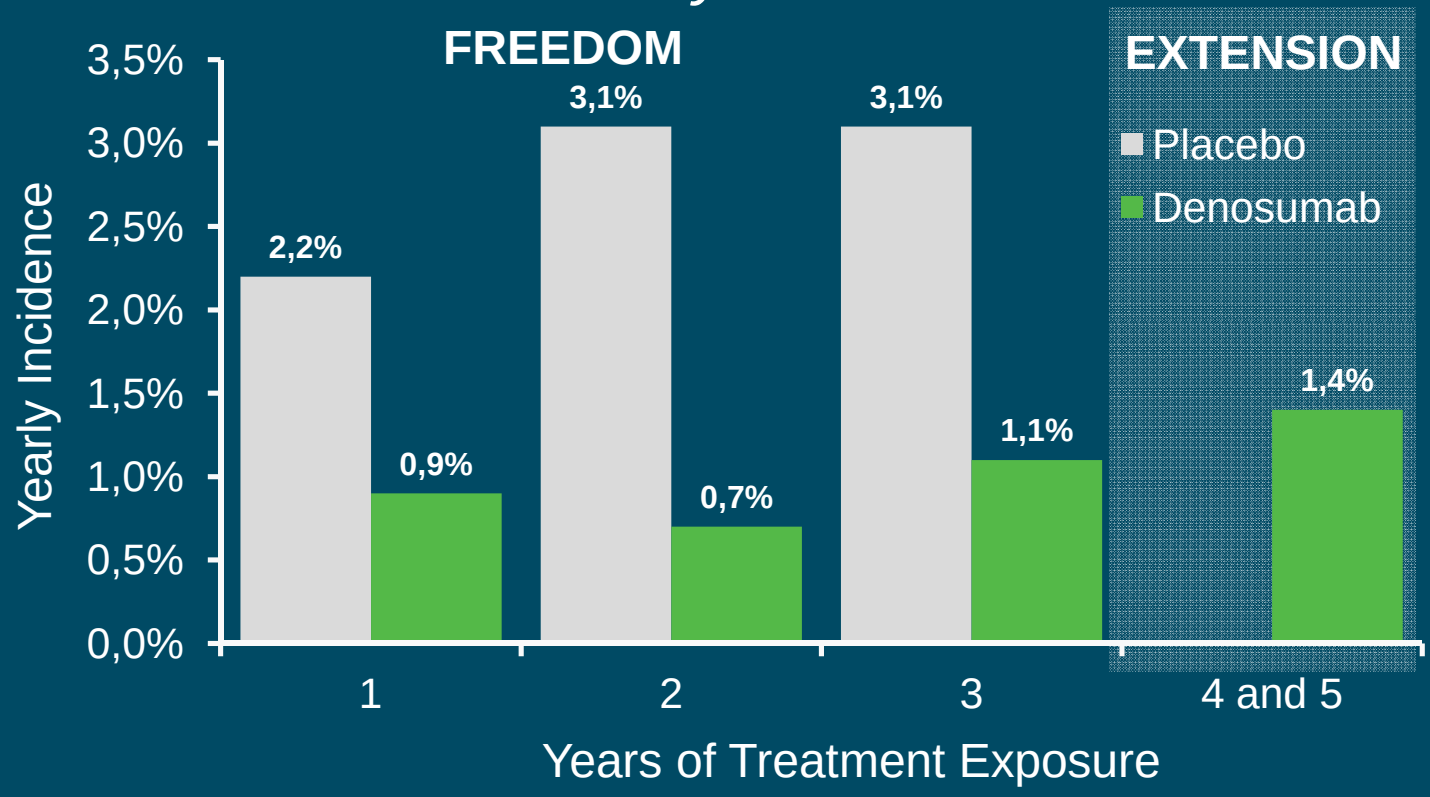


No. subjects with ≥ 1 fracture	**116**	**98**	**103**	**75**	**83**	**73**	**32**	**25**
No. subjects at beginning of each period	**3,906**	**3,902**	**3,688**	**3,682**	**3,454**	**3,487**	**2,343**	**2,242**

Adapted from: Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

Continuation of Denosumab Maintains a Low Incidence of New Vertebral Fractures

FREEDOM EXTENSION Study



No. subjects with ≥ 1 fracture	**82**	**32**	**107**	**24**	**98**	**35**	**59 (2-year total)**
No. subjects at beginning of each period	**3,691**	**3,702**	**3,400**	**3,453**	**3,186**	**3,247**	**2,100**

Adapted from: Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

Tolerability Profile of Denosumab During Years 4 and 5 is Similar to Years 1–3

FREEDOM EXTENSION Study: Exposure-adjusted Subject Incidence of Adverse Events (rates per 100 patient-years)

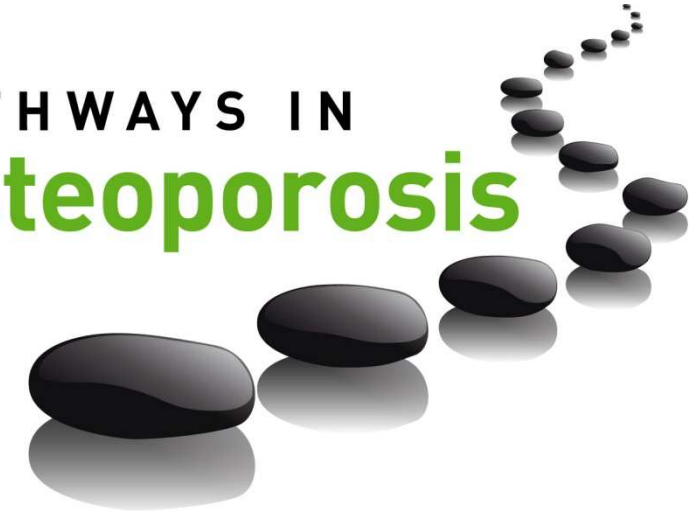
	FREEDOM Years 1–3		EXTENSION Long-term Years 4–5	EXTENSION Cross-over Years 1–2
	Placebo N = 3,883	Denosumab N = 3,879	Denosumab N = 2,343	Denosumab N = 2,206
All AEs	156.1	154.3	113.2	111.4
Infections	30.7	29.3	25.1	27.4
Eczema	0.6	1.1	1.1	0.9
Hypocalcemia	< 0.1	0.0	< 0.1	0.1
Serious AEs	10.4	10.6	10.8	11.1
Infections	1.3	1.5	1.2	1.5
Cellulitis or Erysipelas	< 0.1	0.1	< 0.1	< 0.1
Fatal adverse events	0.8	0.6	0.6	0.8

- **ONJ:** There were four adjudicated cases of ONJ in the extension study: Two cases in the cross-over and two cases in the continued denosumab group
- **Atypical fracture:** two cases of atypical femoral fractures have been reported from the FREEDOM Extension trial 20060289

ONJ = osteonecrosis of the jaw

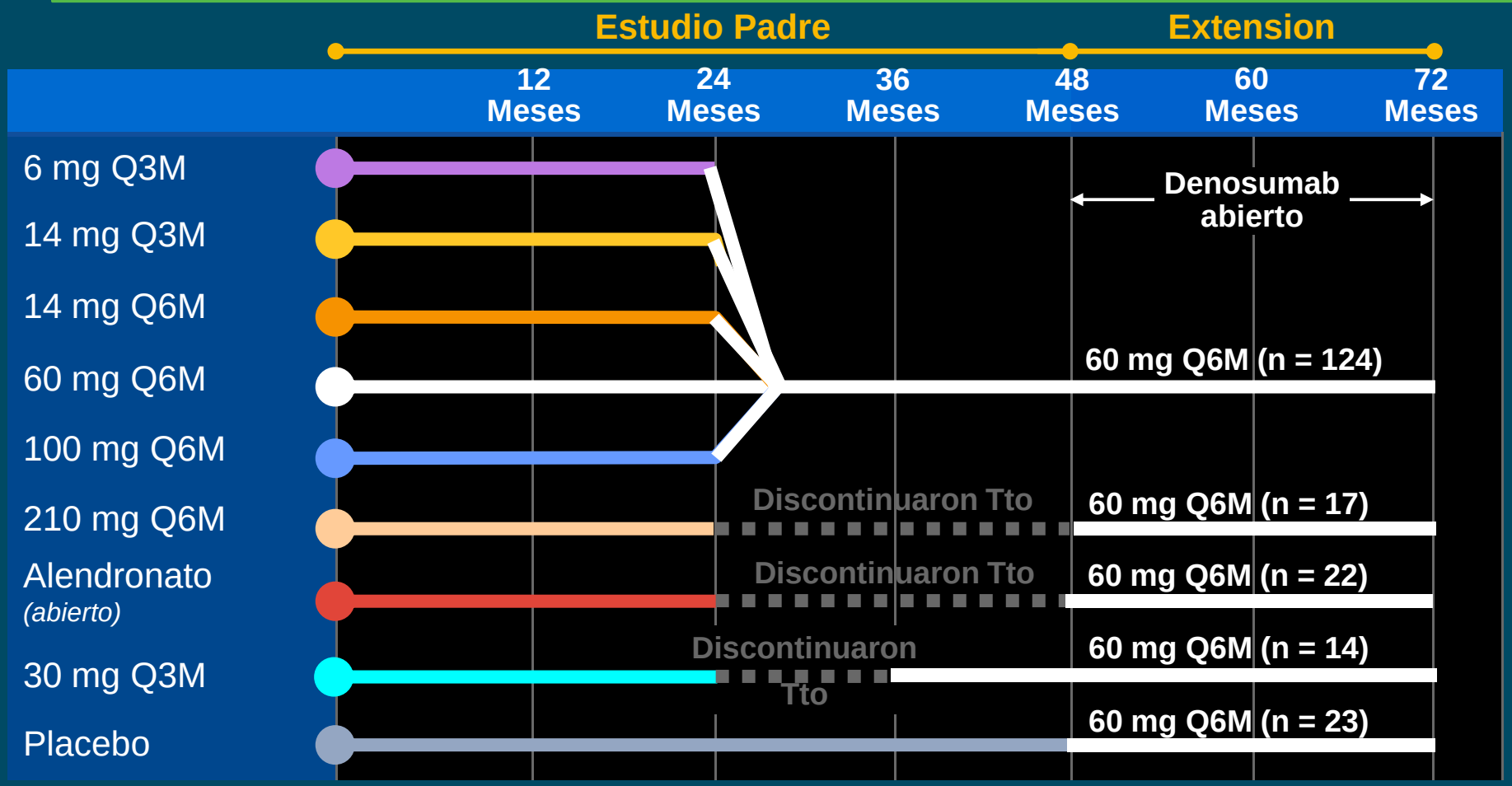
Adapted from: Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

PATHWAYS IN
Osteoporosis



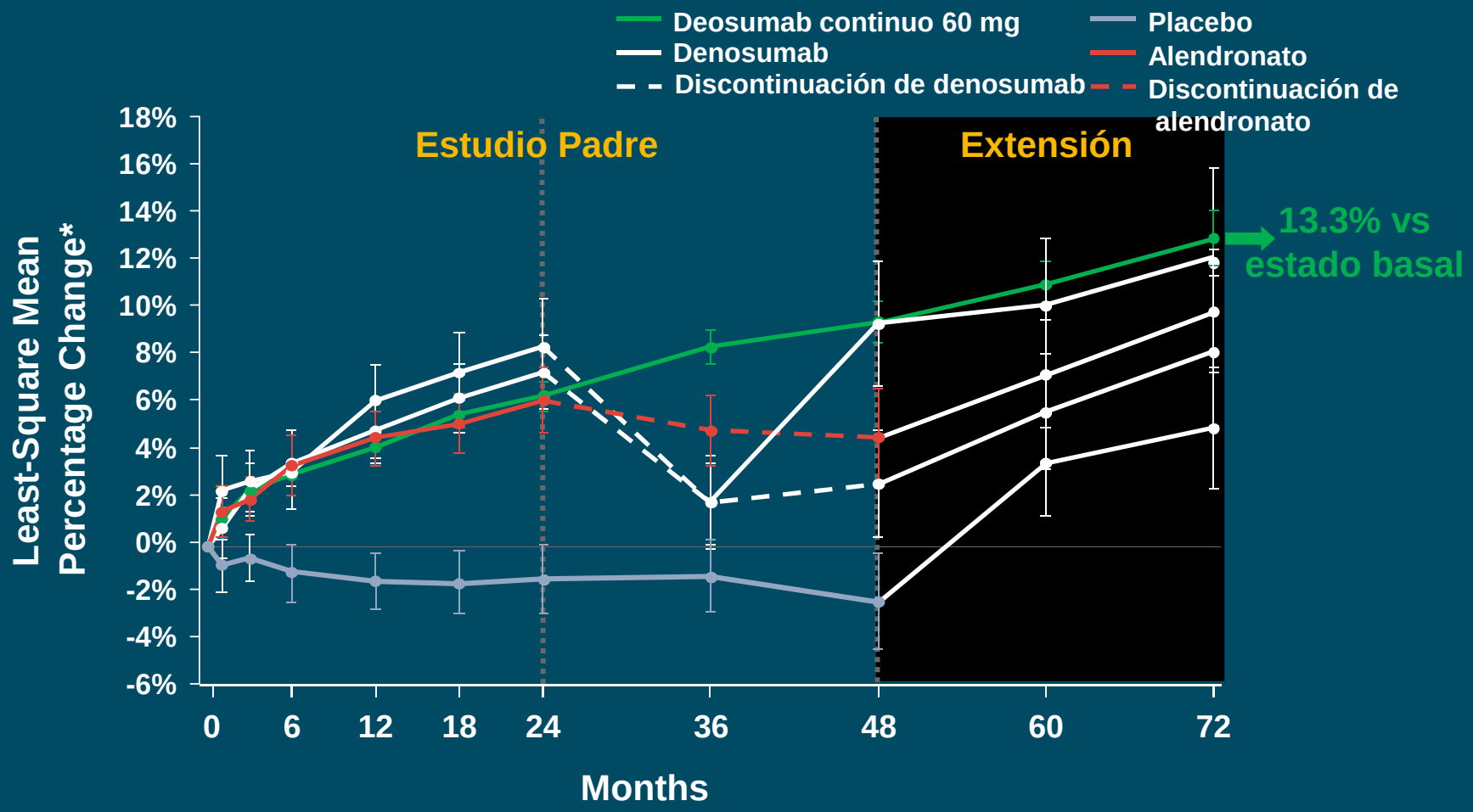
Denosumab Phase II data

Diseño del Estudio: Asignación de tratamiento a lo largo de 6 años *Estudio de Fase 2 - extensión*



Adaptado de Miller PD, et al. *Bone*. 2008;43:222-229.
McClung MR, et al. *N Engl J Med*. 2006;354:821-831.
Miller P, et al. *J Bone Miner Res.* 2009;24(Suppl 1). http://www.asbmr.org. Accessed September 17, 2009. Abstract A09001486 and oral presentation.

Efecto de 6 años de denosumab en la DMO de columna lumbar *Fase 2 – Extension*

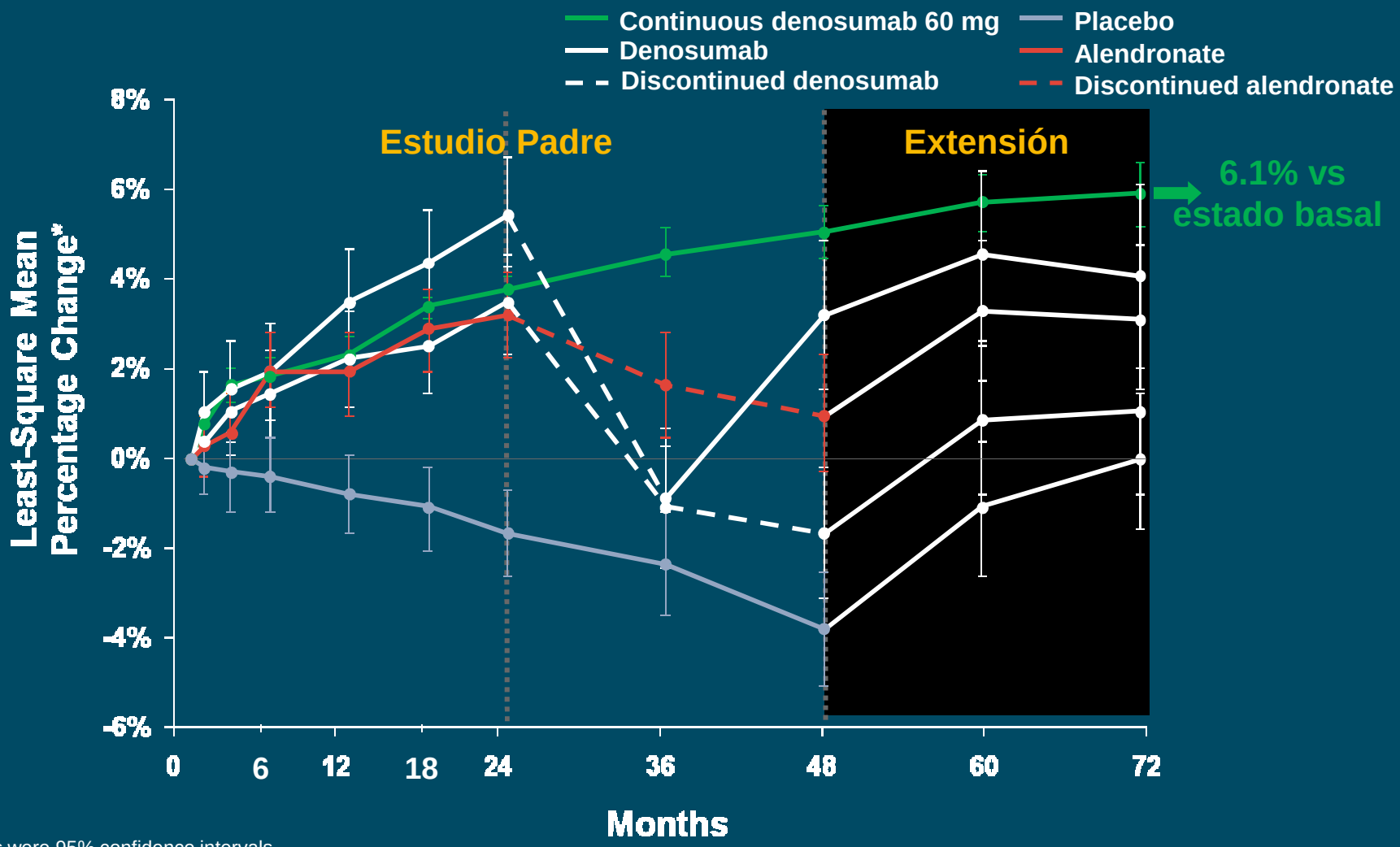


BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy. Head-to-head fracture studies have not been conducted.

*Error bars were 95% confidence intervals

Adapted from: Miller P, et al. *J Bone Miner Res.* 2009;24(Suppl 1). http://www.asbmr.org. Accessed September 17, 2009. Abstract A09001486 and oral presentation.

Efecto de 6 años de denosumab en la DMO de cadera total *Fase 2 – Extension*

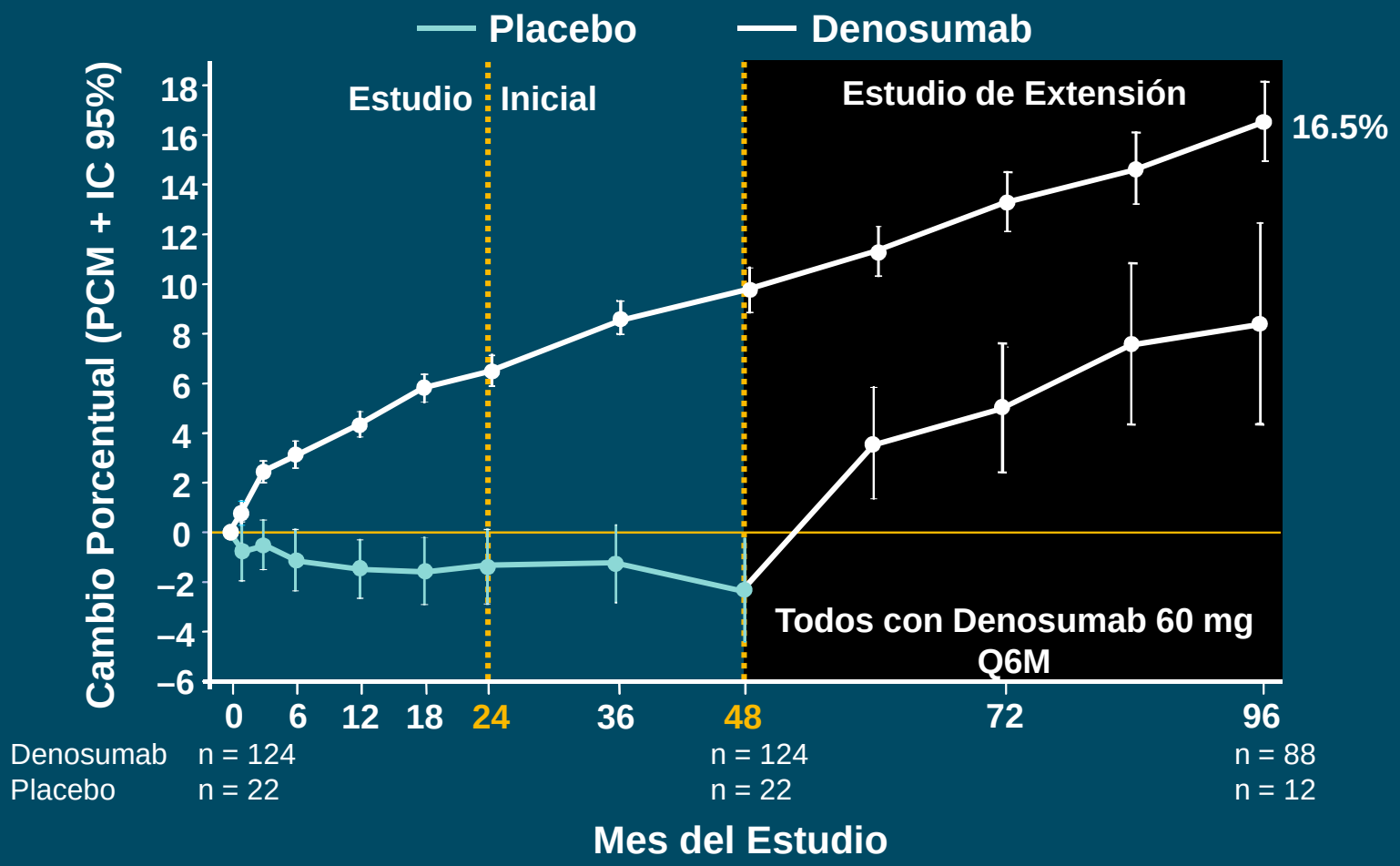


*Error bars were 95% confidence intervals

Adapted from: Miller P, et al. *J Bone Miner Res.* 2009;24(Suppl 1). http://www.asbmr.org. Accessed September 17, 2009. Abstract A09001486 and oral presentation.

con Denosumab Sobre la DMO de la Columna Lumbar

Fase 2 – Estudio de Extensión

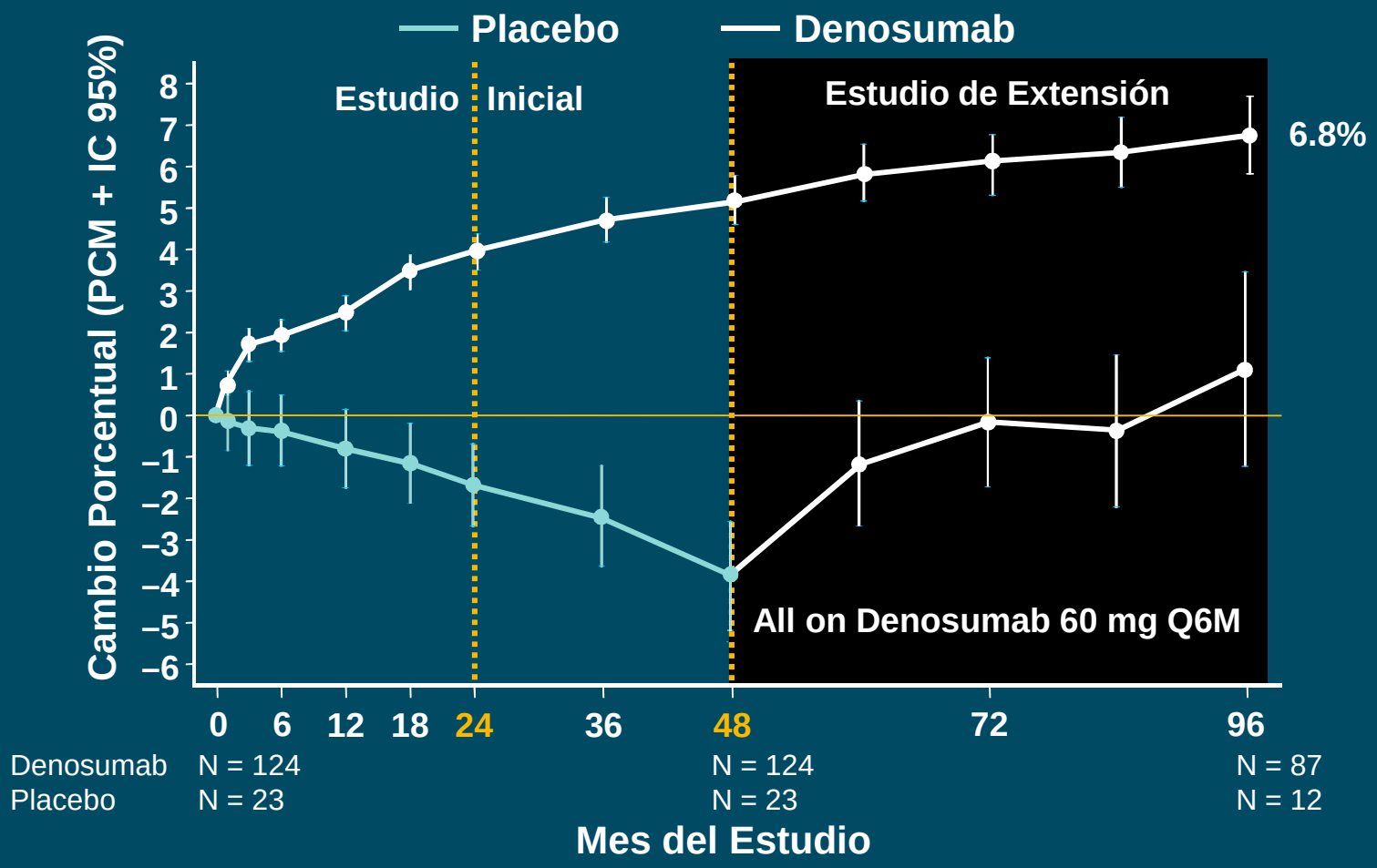


DMO= densidad mineral ósea; PCM = promedio cuadrados mínimos; I C= intervalo de confianza

Adaptado de: McClung MR, et al. Presentado en la: Reunión Anual de la Sociedad Americana para la Investigación Ósea y Mineral; Septiembre 17, 2011; San Diego, CA.

con Denosumab Sobre la DMO de la Cadera Total

Fase 2 – Estudio de Extensión



Adaptado de: McClung MR, et al. Presentado en la: Reunión Anual de la Sociedad Americana para la Investigación Ósea y Mineral; Septiembre 17, 2011; San Diego, CA.

Síntesis de la evidencia

- Denosumab tiene un modo de acción antiresortiva diferente, dirigido al ligando RANK
  - Trabaja tanto en hueso cortical y trabecular
- Denosumab reduce el riesgo de fractura en la cadera y en otros sitios importantes
- Denosumab incrementa en mayor medida la DMO que los BF
- Permite una mejor adherencia al tratamiento
- Denosumab es bien tolerado