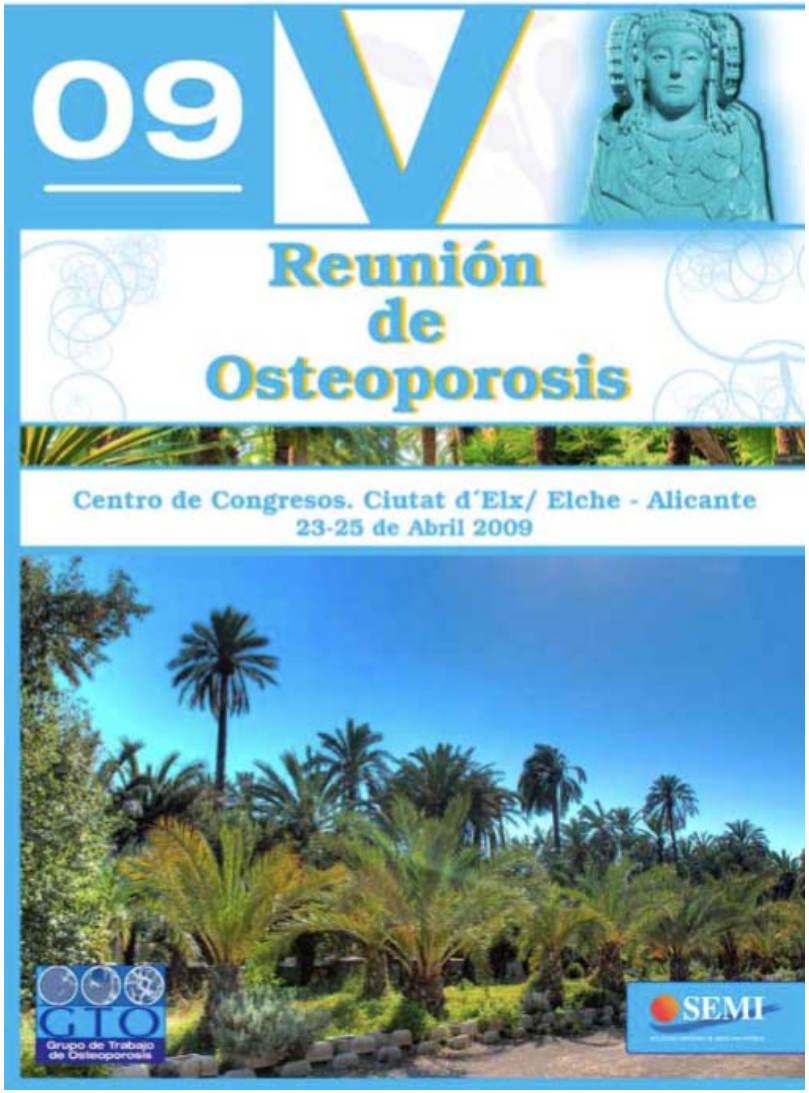
Antirresortivos



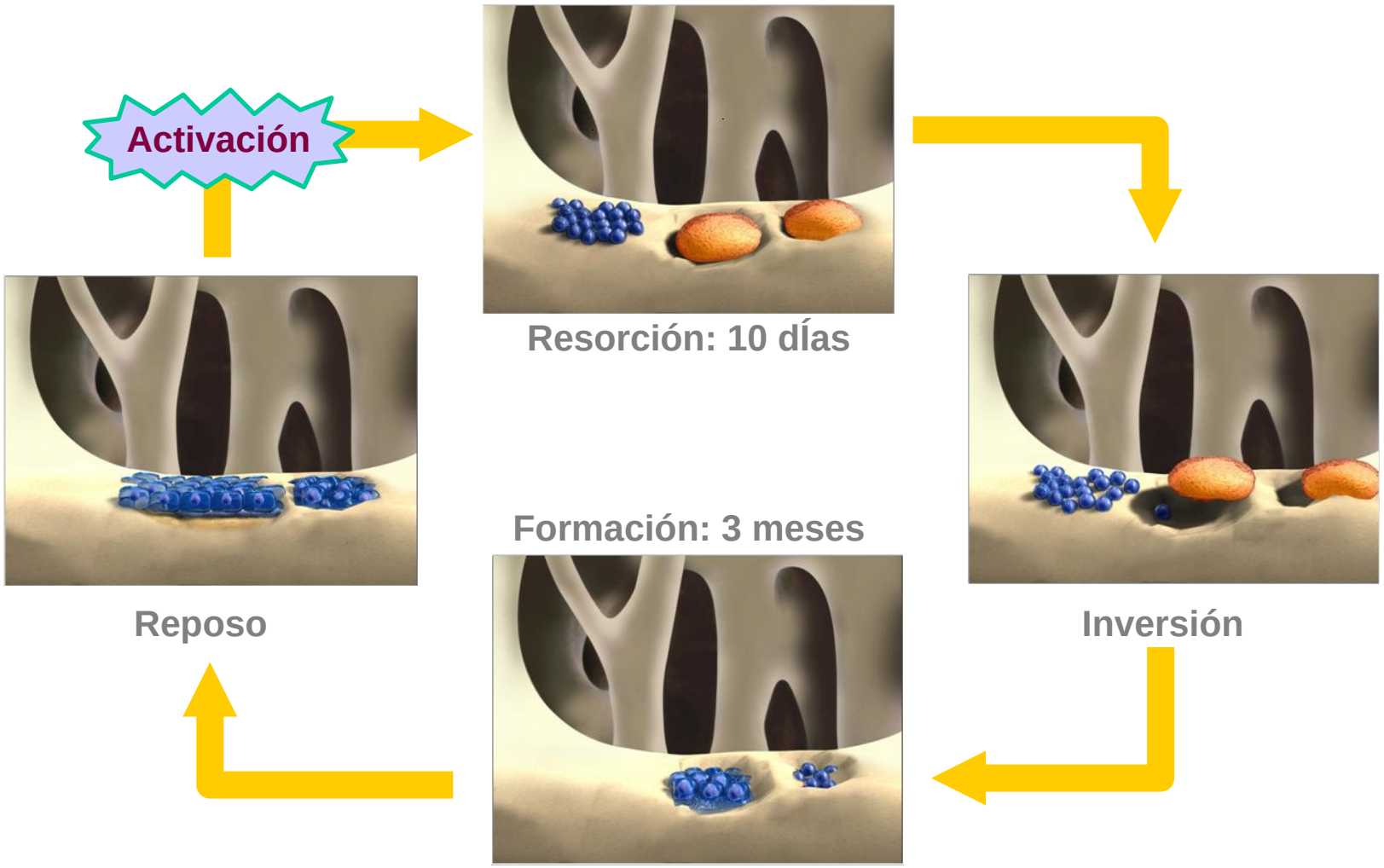
Javier del Pino Montes

Hospital Universitario de Salamanca

Universidad de Salamanca

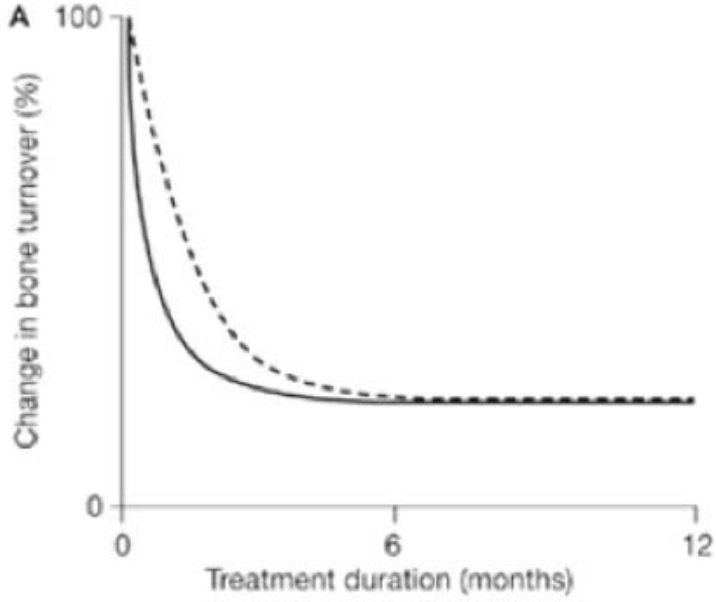
RETICEF

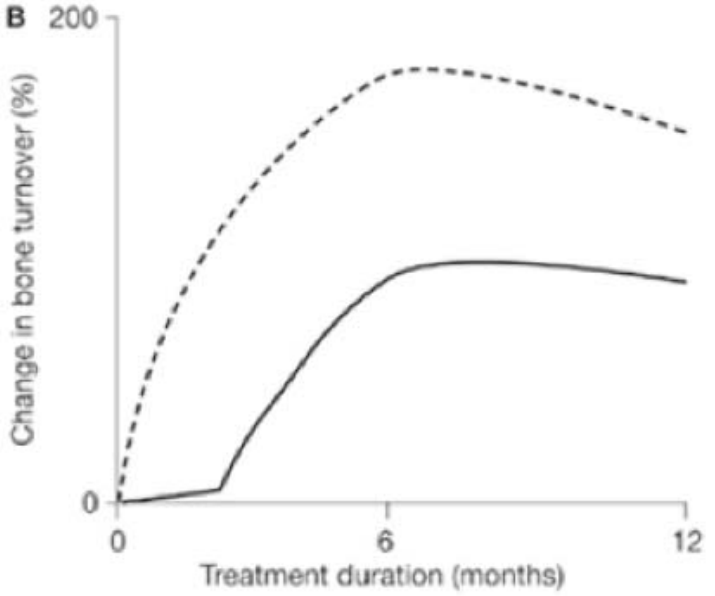
Un esqueleto sano requiere un equilibrio entre la resorción y la formación ósea



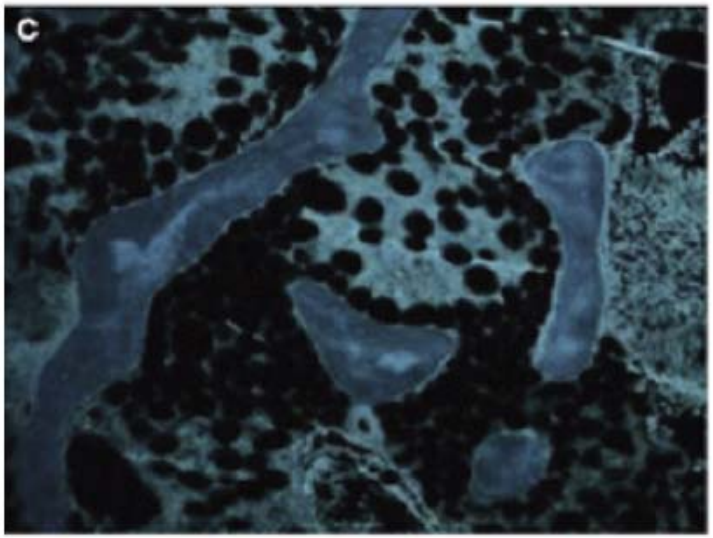
Adaptado de Baron, R. General Principles of Bone Biology. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. Favus MJ (Ed.) 5th Edition. American Society for Bone and Mineral Research, Washington DC, 2003: 1–8

Tratamiento farmacológico de la osteoporosis



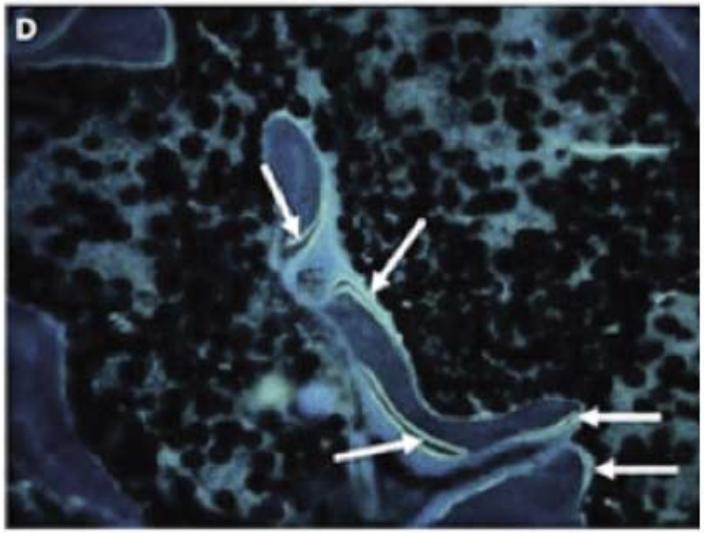


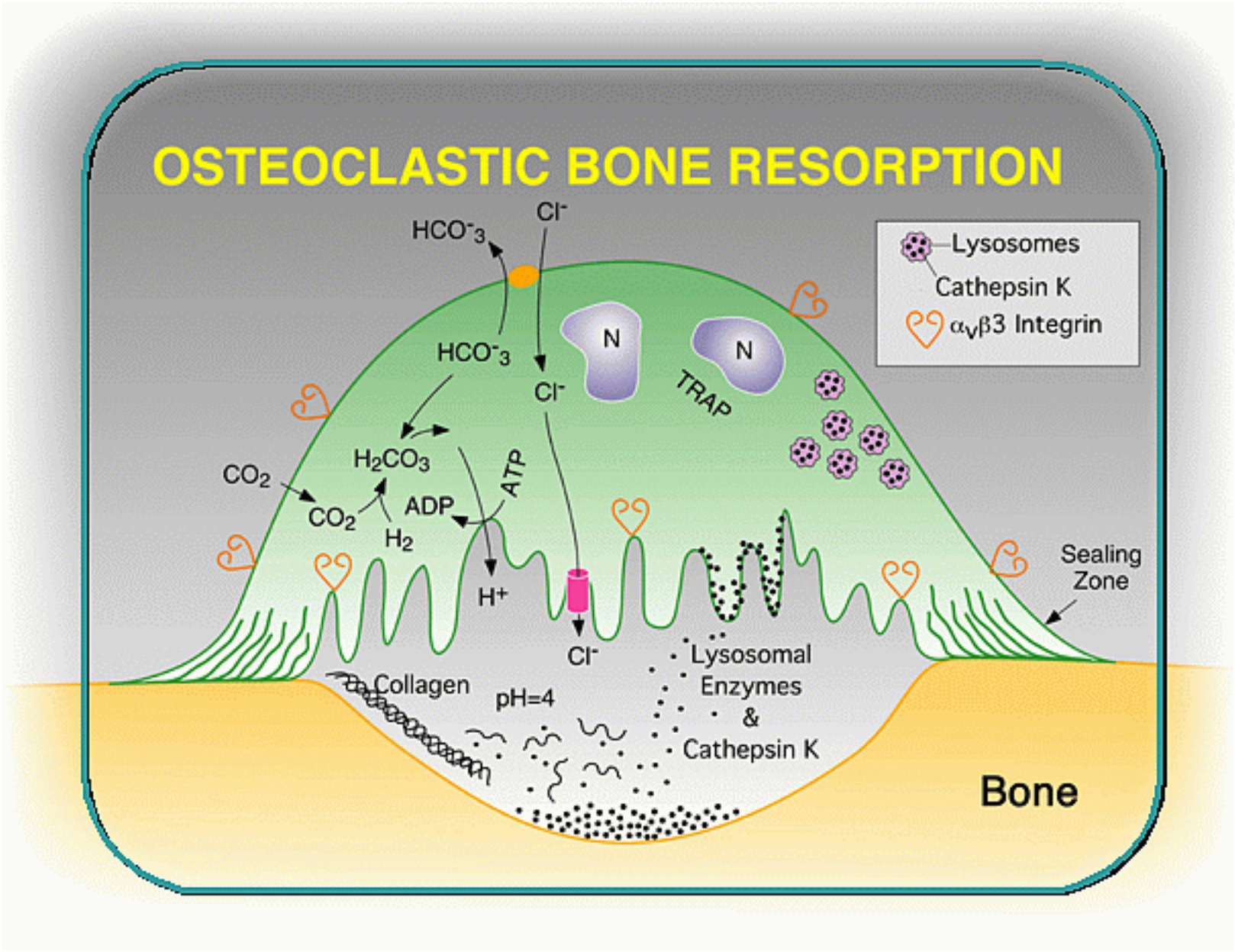
Vit D + Calcio

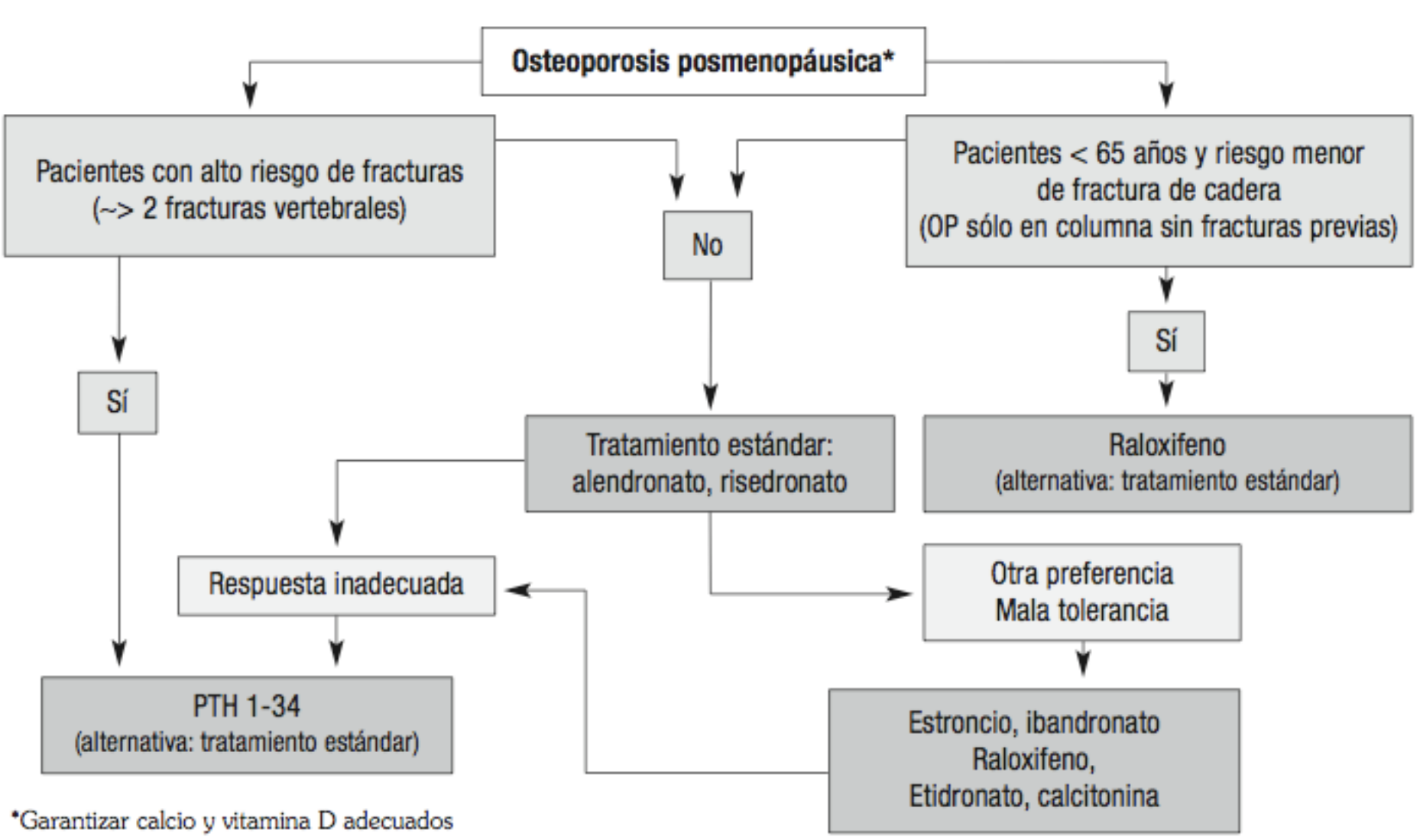


Estroncio

canismo d

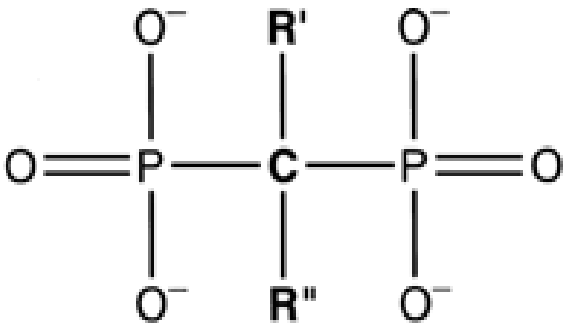


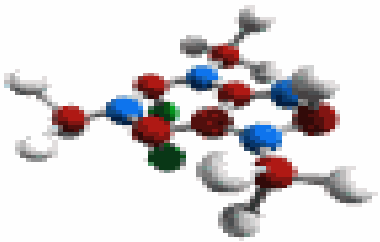

OSTEOCLASTIC BONE RESORPTION
Lysosomes
Cathepsin K
αvβ3 Integrin
HCO-3
Cl-
HCO-3
Cl-
N
N
TRAP
H2CO3
CO2
CO2
ADP
ATP
H2
H+
Cl-
Sealing Zone
Collagen
pH=4
Lysosomal Enzymes & Cathepsin K
Bone



*Garantizar calcio y vitamina D adecuados

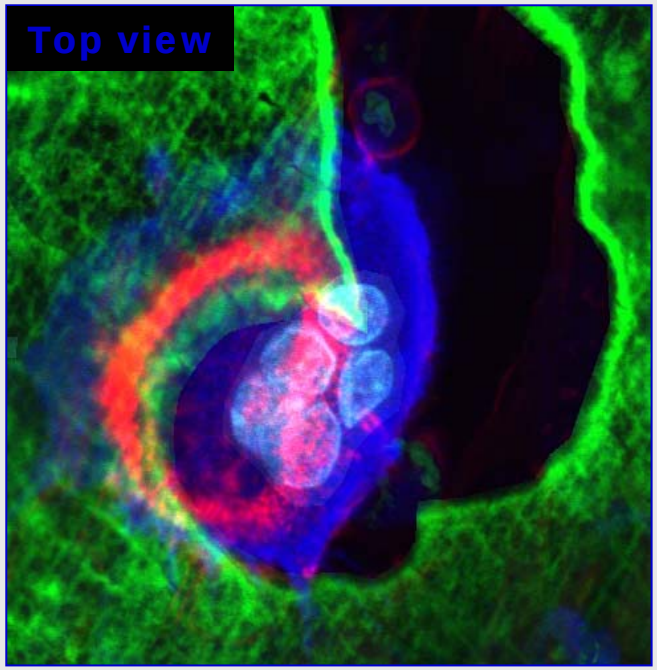
BISFOSFONATOS

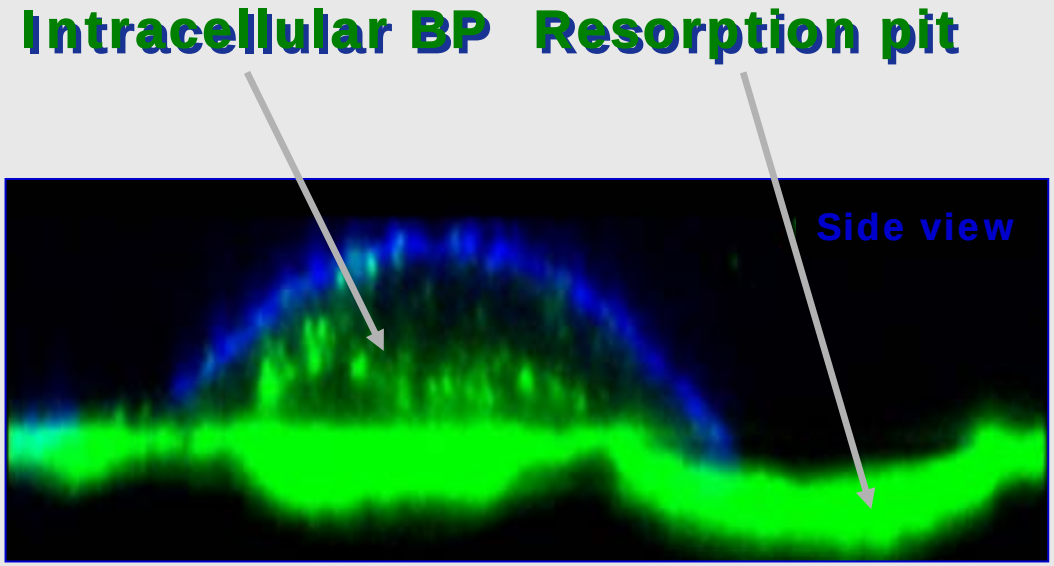




- Inhibición función osteoclástica de forma directa y aumentando la apoptosis del osteoclasto
- Afinidad por el hueso.(20-80%)
- Baja absorción(1-10%).Fuera comidas
- Rápida eliminación por orina.Vida media=20-120 minutos.

Bisphosphonates Are Internalised by Osteoclasts During Bone Resorption

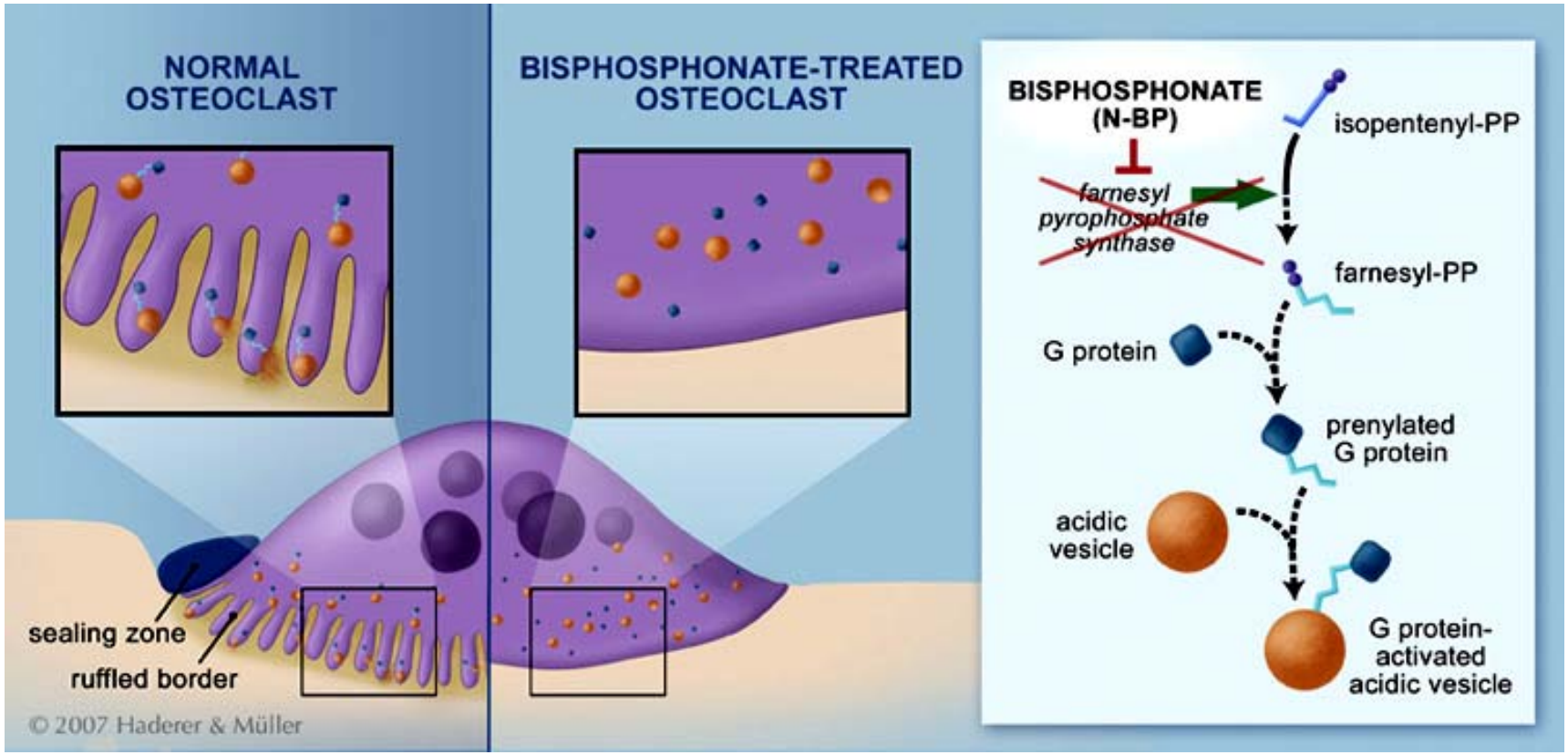




- Bisphosphonate (bone surface)
- Osteoclast membrane and nuclei
- Cytoskeleton

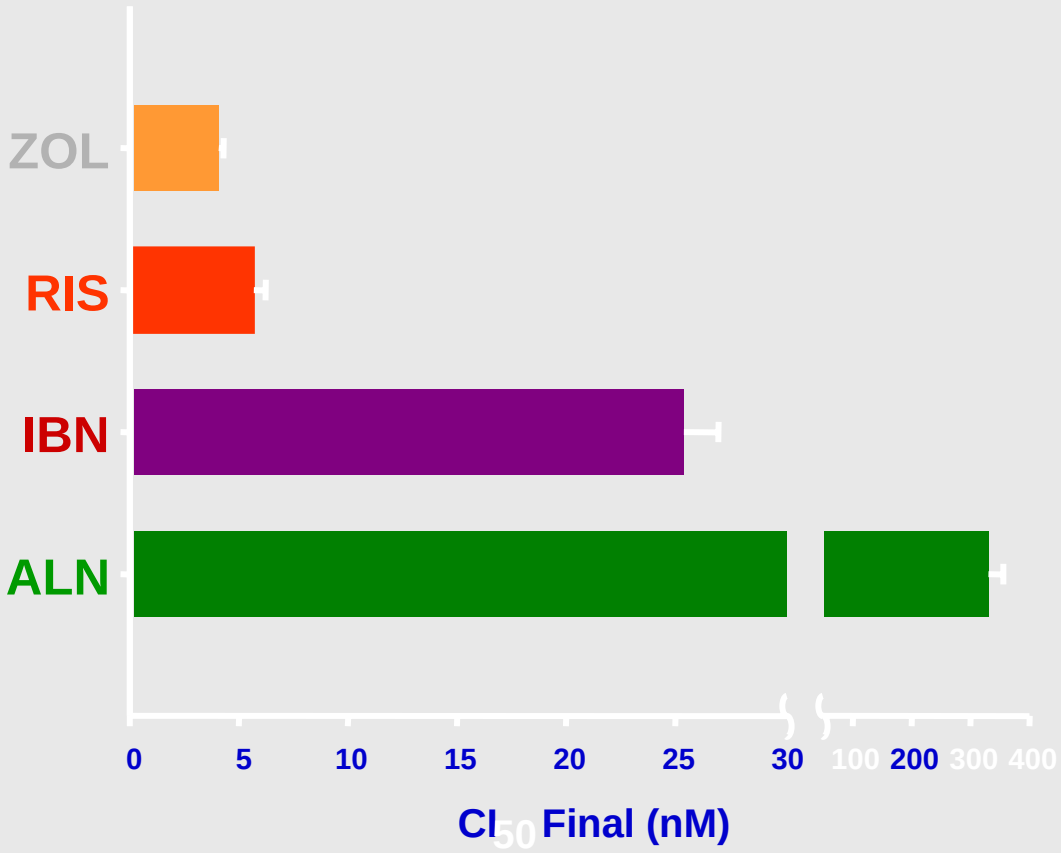
Courtesy of Dr Fraser Coxon, University of Aberdeen

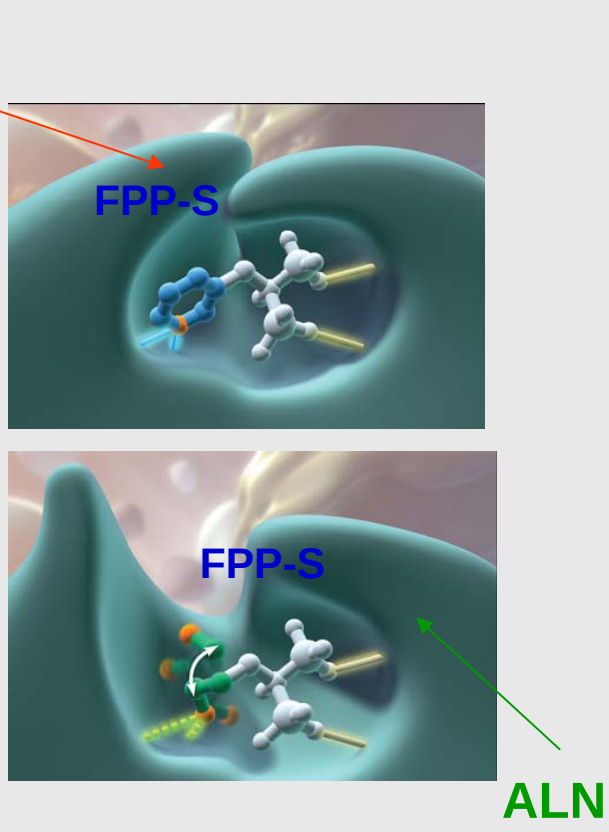
Bisphosphonates Inhibit Bone Resorption by Preventing Formation of the Ruffled Border



Potencia de inhibición de la enzima FPPS (CI_{50})

Cantidad de N-BP necesaria para inhibir el 50% de la actividad enzimática máxima



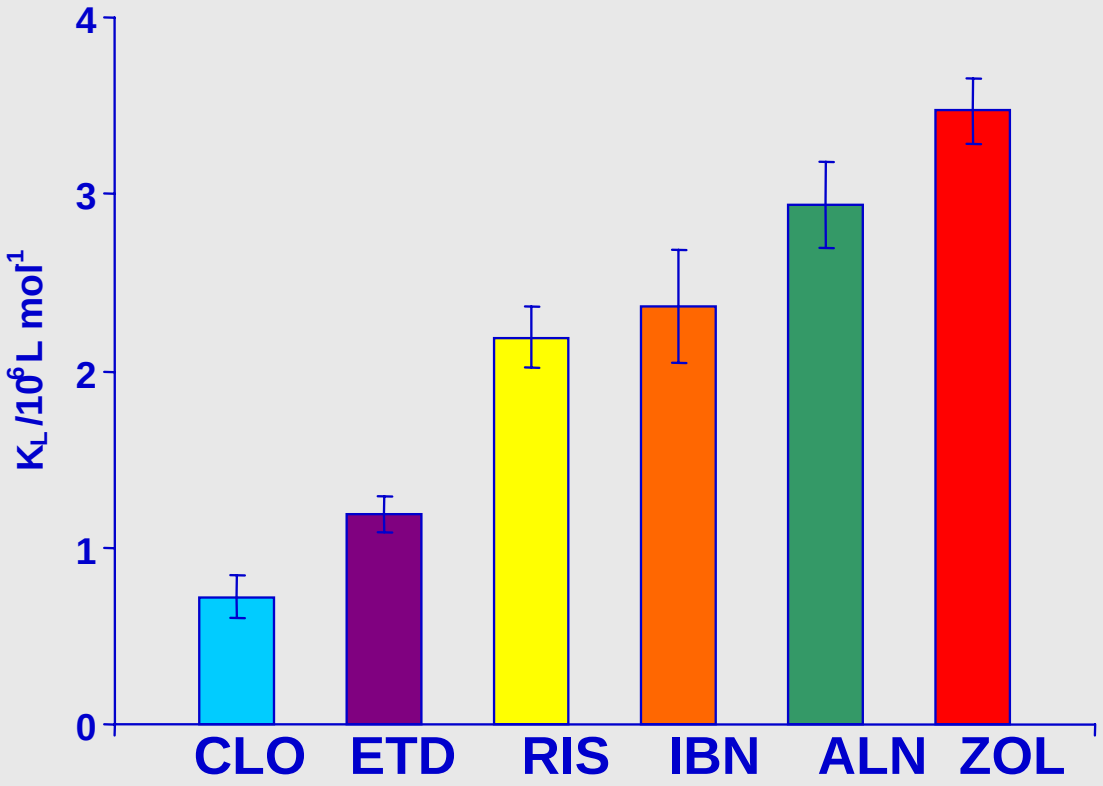


[1] Kavanagh KL, et al. PNAS 2006;103:7829-7834.

[2] Dunford JE, et al. Unpublished data (2006)

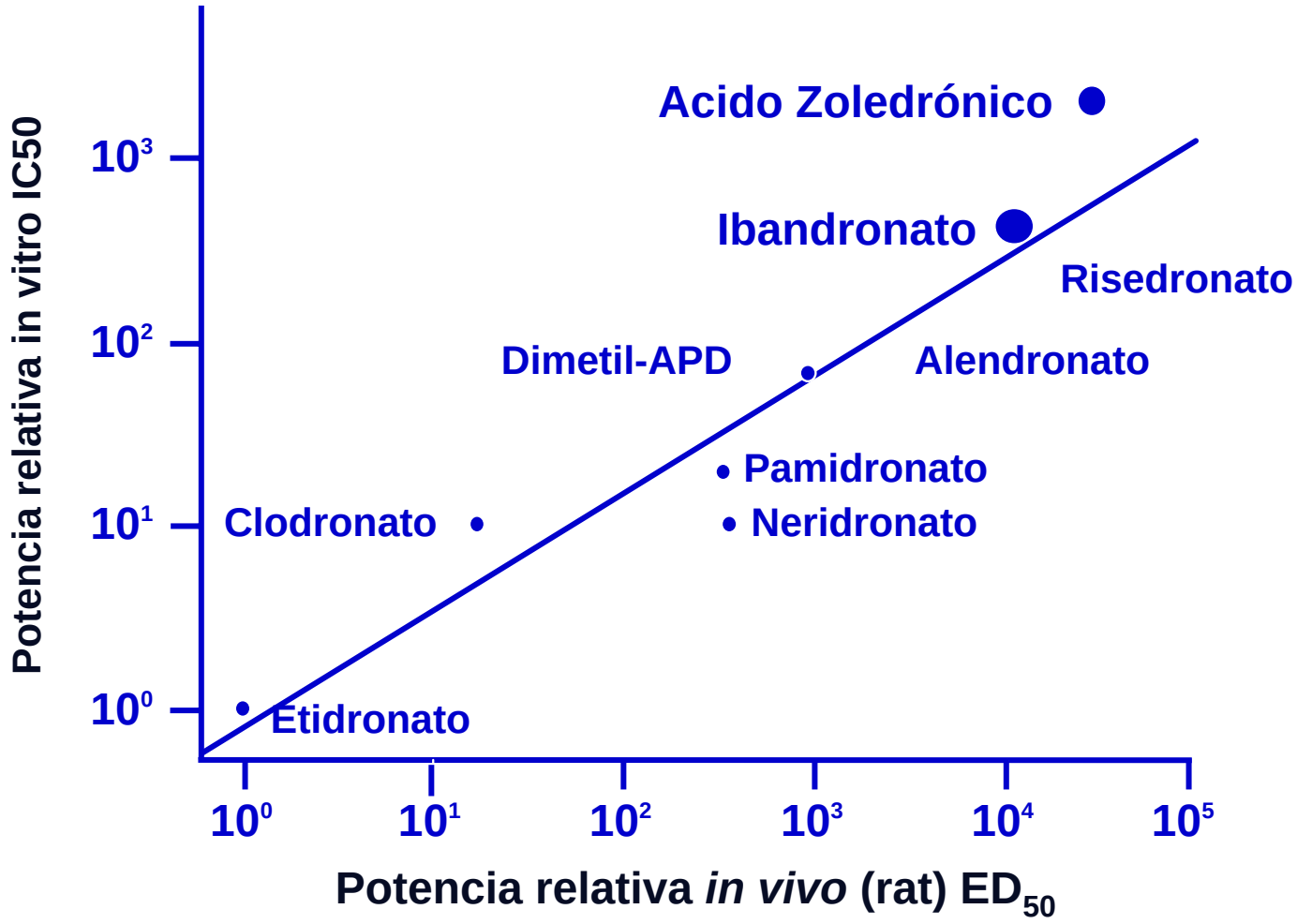
Diferente afinidad de unión al mineral óseo

Constantes de afinidad de adsorción a HAP a pH 7,4



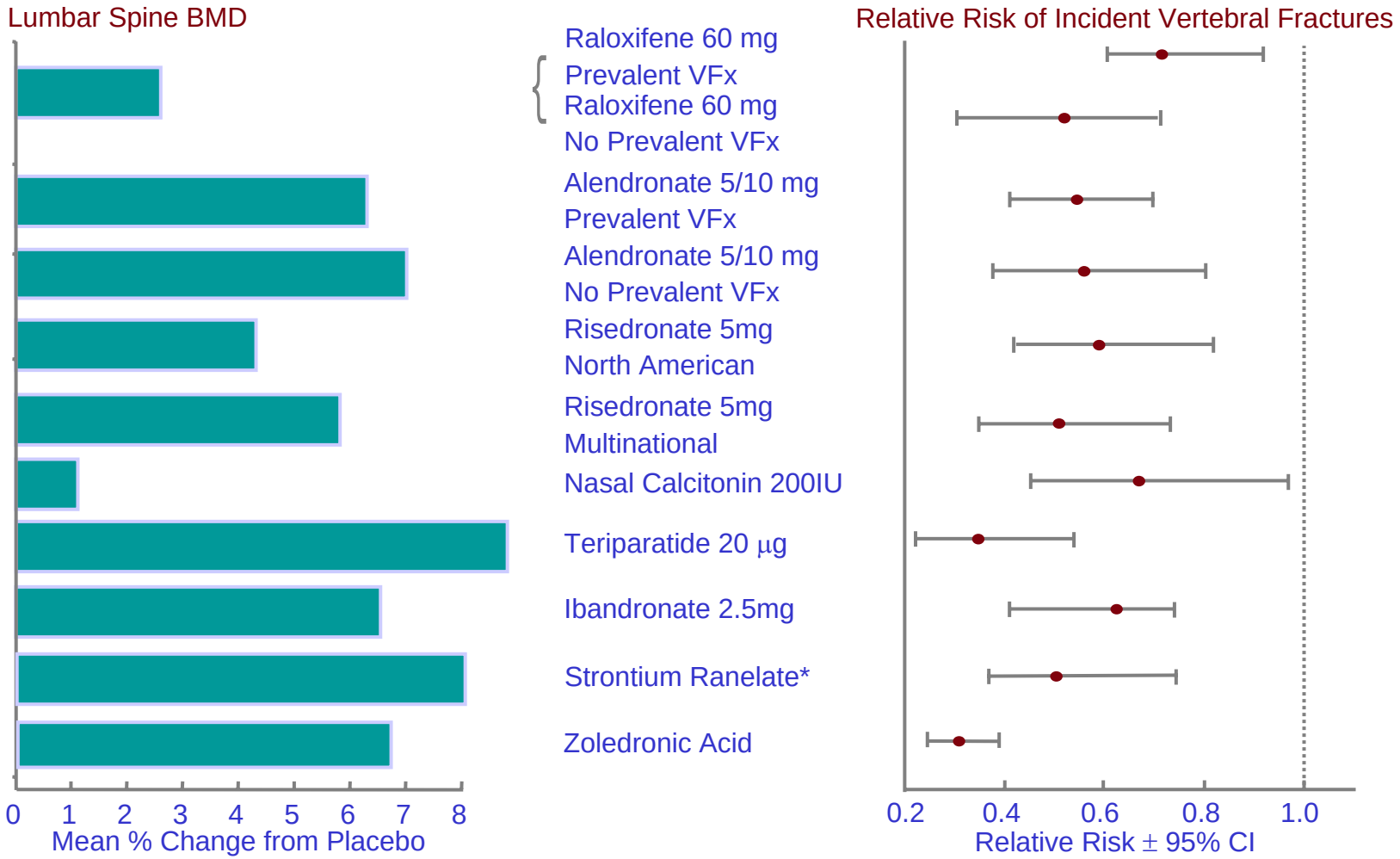
Nancollas GH, et al. Bone 2006;38:617–627

Potencia de los bisfosfonatos



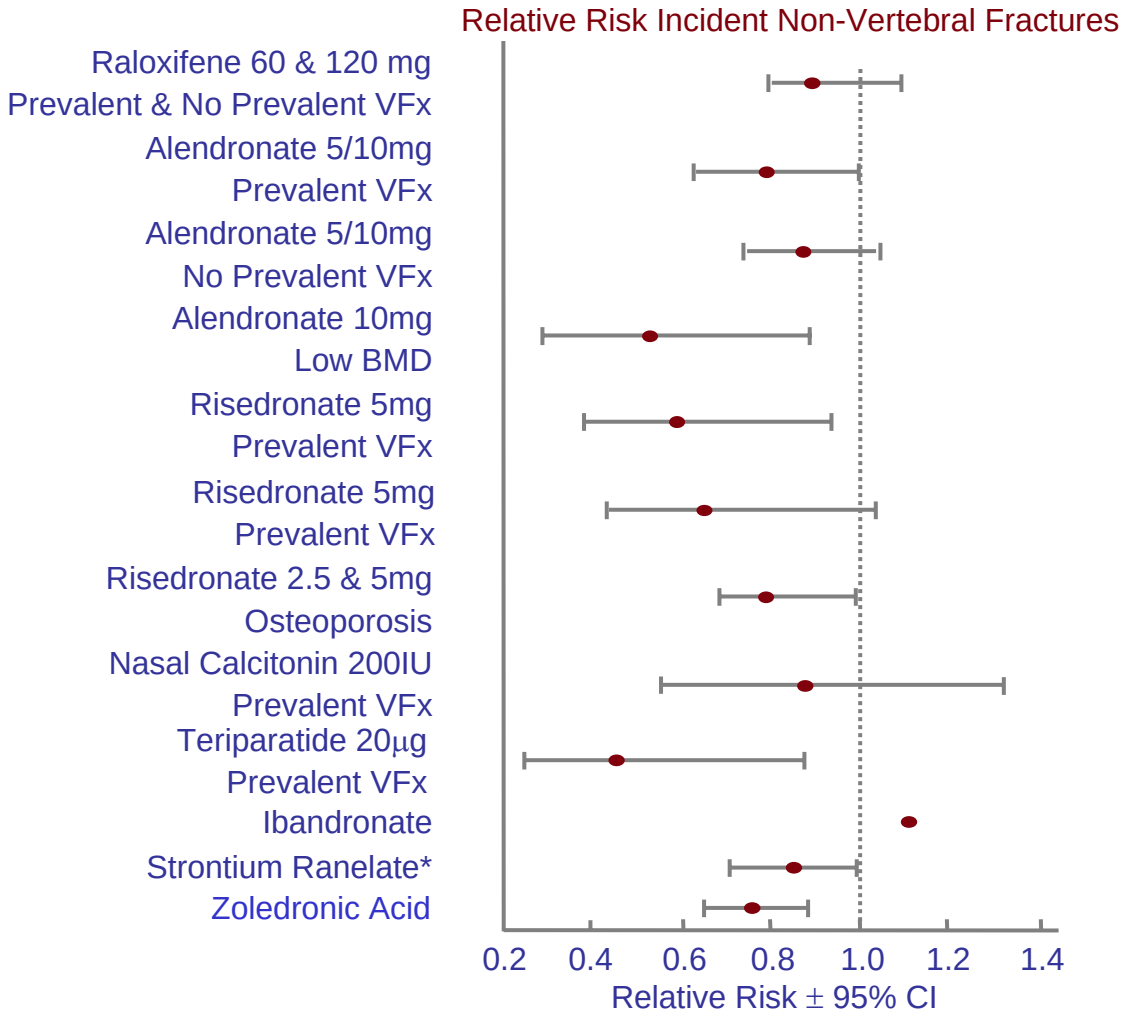
Green J, et al. J Bone Miner Res 1994;9:745–51

Effect of Different Drugs for Osteoporosis on BMD and Vertebral Fracture Risk



Modified from Marcus R, et al. Endocr Rev 2002 23:16-37, with permission, Copyright 2002, The Endocrine Society.

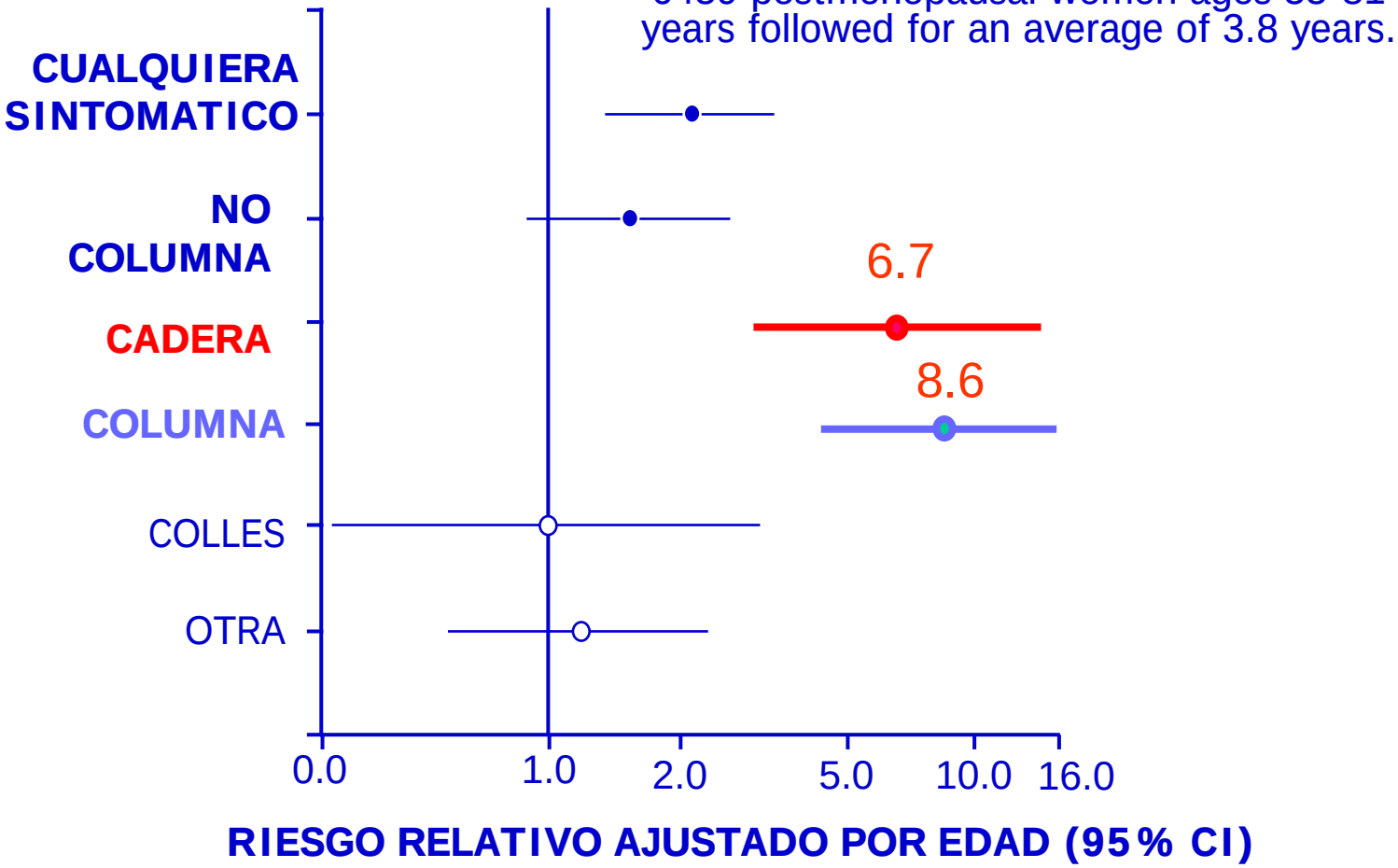
Effect of Different Drugs for Osteoporosis on Non-Vertebral Fracture Risk



Modified from Marcus R, et al. Endocr Rev. 2002 23:16-37, with permission, Copyright 2002, The Endocrine Society.

Riesgo Relativo de Muerte tras Fracturas Clínicas "Fracture Intervention Trial" (FIT)*

*6459 postmenopausal women ages 55-81 years followed for an average of 3.8 years.



Cauley JA et al., *Osteoporos Int*. 2000;11:556-561

The NEW ENGLAND JOURNAL of MEDICINE

Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

Kenneth W. Lyles, M.D., Cathleen S. Colón-Emeric, M.D., M.H.Sc., Jay S. Magaziner, Ph.D., Jonathan D. Adachi, M.D., Carl F. Pieper, D.P.H., Carlos Mautalen, M.D., Lars Hyldstrup, M.D., D.M.Sc., Chris Recknor, M.D., Lars Nordsletten, M.D., Ph.D., Kathy A. Moore, R.N., Catherine Lavecchia, M.S., Jie Zhang, Ph.D., Peter Mesenbrink, Ph.D., Patricia K. Hodgson, B.A., Ken Abrams, M.D., John J. Orloff, M.D., Zebulun Horowitz, M.D., Erik Fink Eriksen, M.D., D.M.Sc., and Steven Boonen, M.D., Ph.D., for the HORIZON Recurrent Fracture Trial*

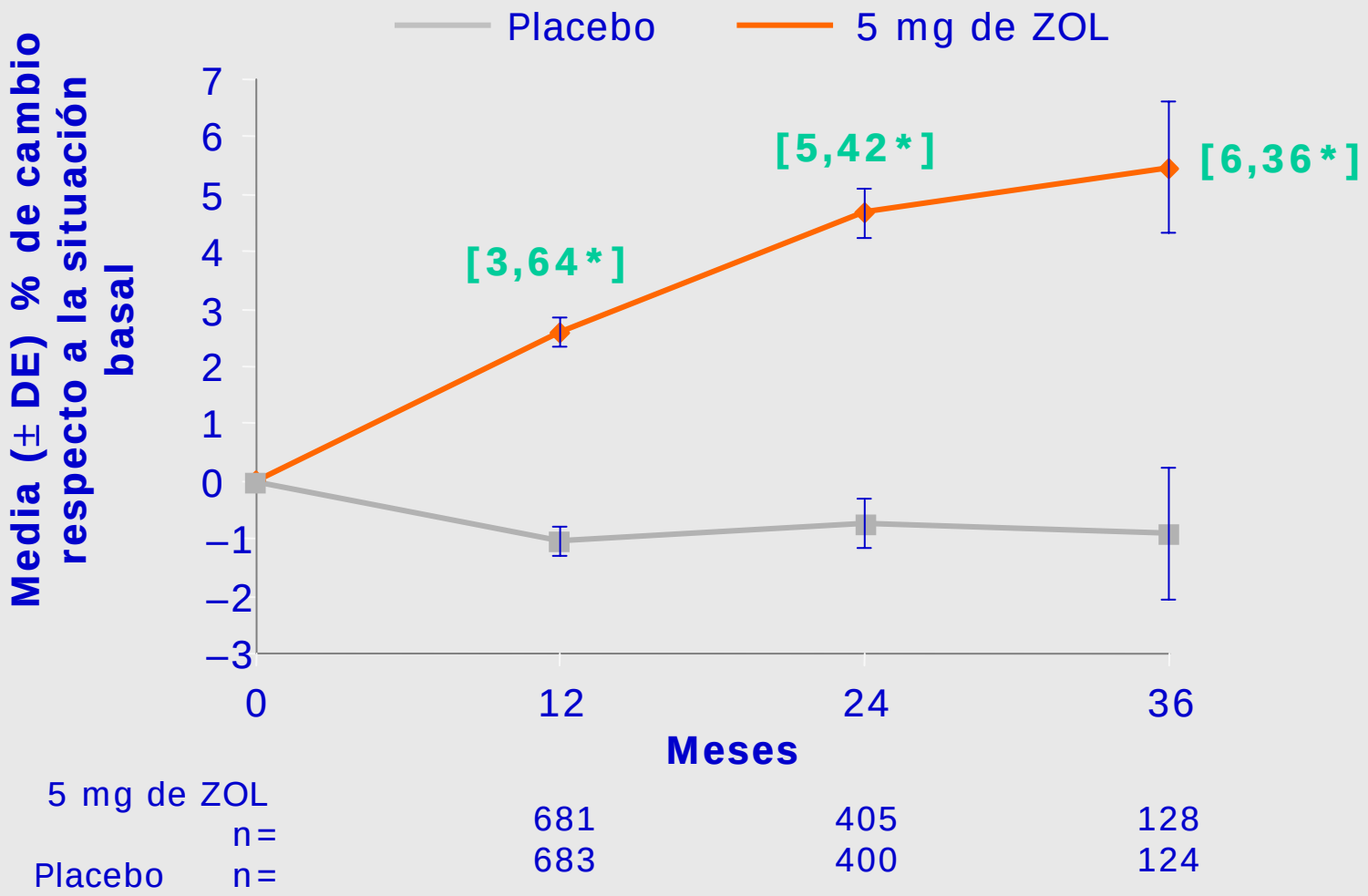
HORIZON-Ensayo Clínico de fracturas recurrentes Generalidades

- **Ensayo clínico randomizado, doble ciego, controlado con placebo**
  - **2.127 hombres y mujeres, en 148 centros médicos, 23 países**

- **Tratamiento**
  - **Perfusión anual de 5 mg de ZOL o de placebo**
  - **Dosis de carga de vitamina D de 50.000 a 125.000 UI**
  - **Suplementos de calcio de 1.000 a 1.500 mg/día; de vitamina D de 800 a 1.200 UI/día**

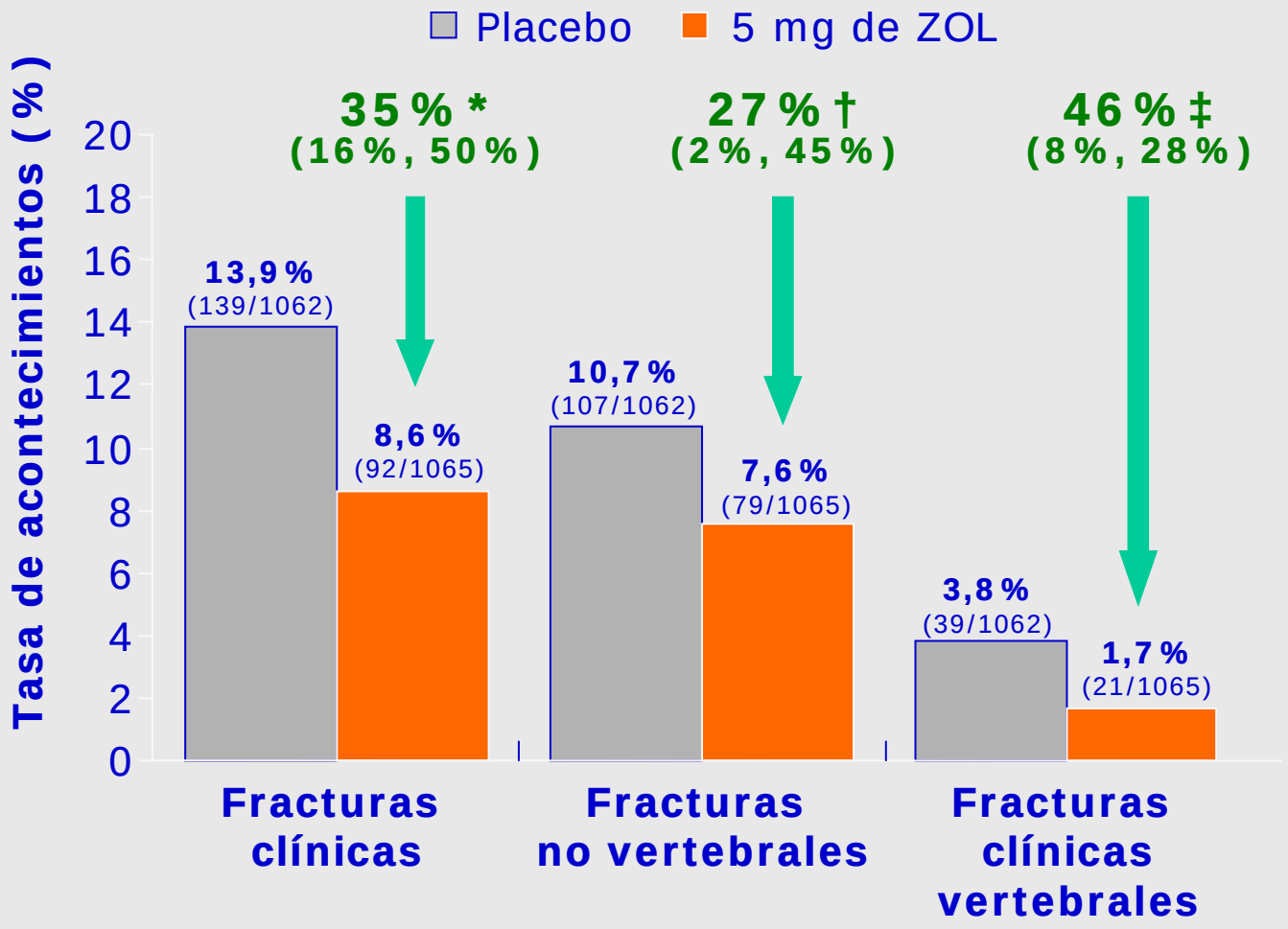
Lyles KW, et al. *N Engl J Med*. 2007. [e-publication 10.1056/NEJMoa074941 at www.nejm.org]

HORIZON-Ensayo Clínico de fracturas recurrentes
Resultados DMO



No incluye el centro 829. Los valores entre paréntesis son la diferencia media de los mínimos cuadrados, ZOL frente a placebo.
**P* < 0,0001; *valor P* calculado a partir del modelo de análisis de la varianza ajustado con respecto al tratamiento y la región.
Lyles KW, et al. *N Engl J Med*. 2007. [e-publication 10.1056/NEJMoa074941 at www.nejm.org]

HORIZON-Ensayo Clínico de fracturas recurrentes
Resultados: Fracturas



*P = 0,0012; †P = 0,0338; ‡P = 0,0210, reducción del riesgo relativo frente a placebo; NS = no significativo.
Los valores situados encima de las barras son tasas de acontecimientos acumulados basados en cálculos de Kaplan-Meier en el mes 12.

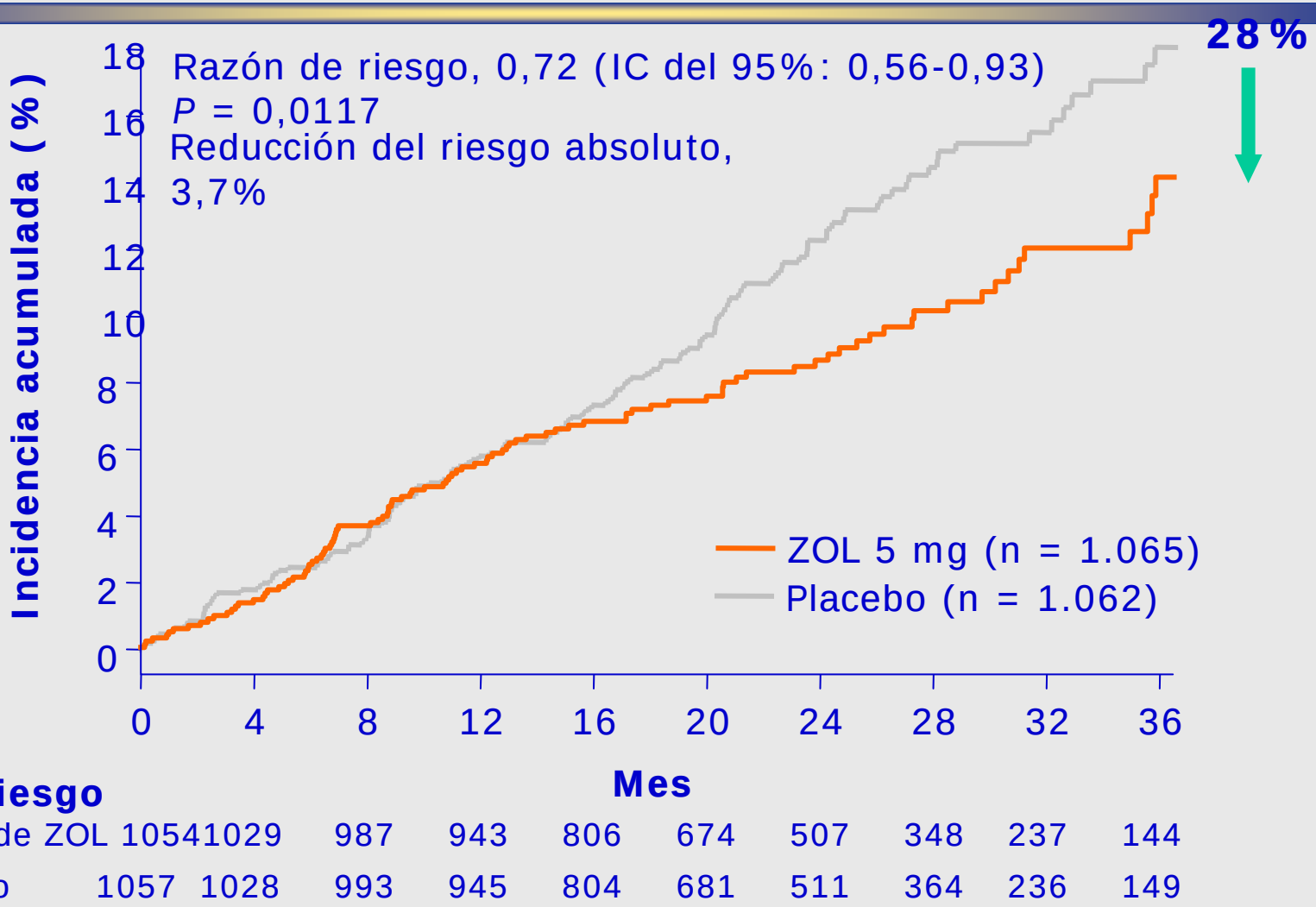
Lyles KW, et al. *N Engl J Med*. 2007. [e-publication 10.1056/NEJMoa074941 at www.nejm.org]

Seguridad: Fallecimientos, AAG, y discontinuaciones por motivos de seguridad

Categoría	5 mg de ZOL (n = 1.054) nº (%)	Placebo (n = 1.057) n º (%)
Fallecimientos	101 (9,6)	141 (13,3)
AAG	404 (38,3)	436 (41,2)
Discontinuaciones		
AAs que causan la discontinuación del fármaco en estudio	56 (5,3)	50 (4,7)
AA que causa la discontinuación del paciente en el estudio	21 (2,0)	18 (1,7)
Anormalidades de laboratorio que causan la discontinuación del paciente en el estudio	3 (0,3)	3 (0,3)

Lyles KW, et al. *N Engl J Med*. 2007. [e-publication 10.1056/NEJMoa074941 at www.nejm.org]

HORIZON-Ensayo Clínico de fracturas recurrentes
Resultados Mortalidad

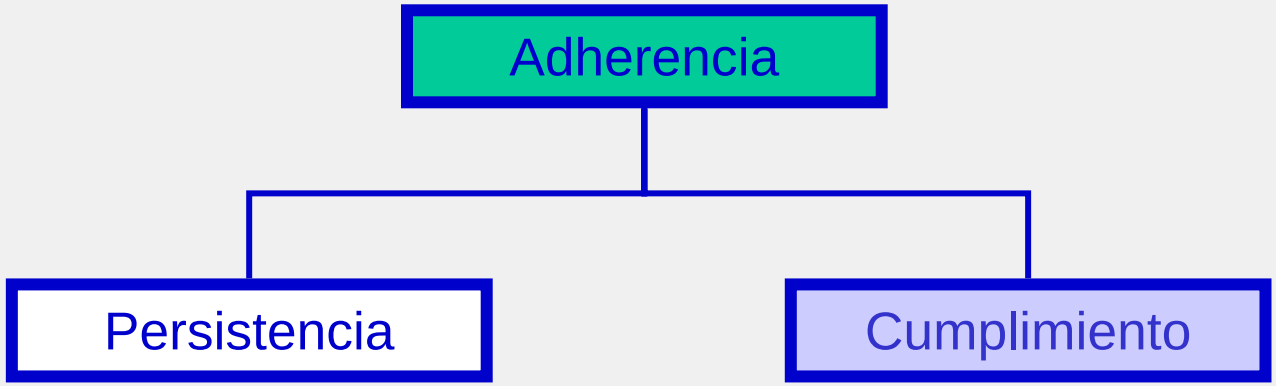


Nº en riesgo

5 mg de ZOL	1054	1029	987	943	806	674	507	348	237	144
Placebo	1057	1028	993	945	804	681	511	364	236	149

Lyles KW, et al. *N Engl J Med*. 2007. [e-publication 10.1056/NEJMoa074941 at www.nejm.org]

Agunos problemas con los bisfosfonatos

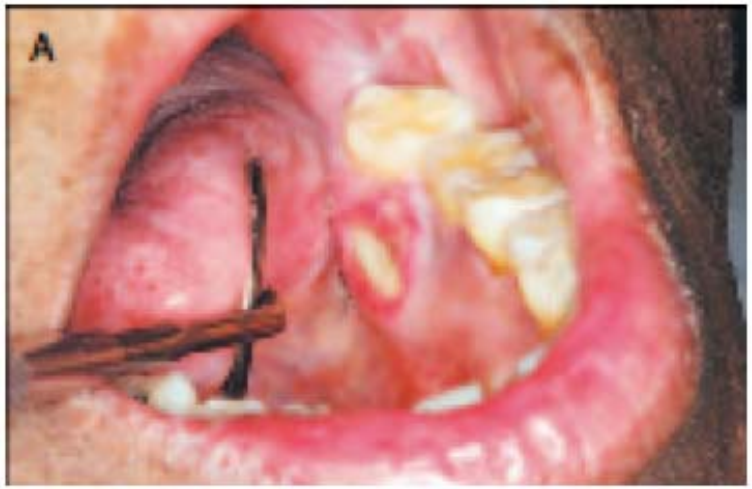


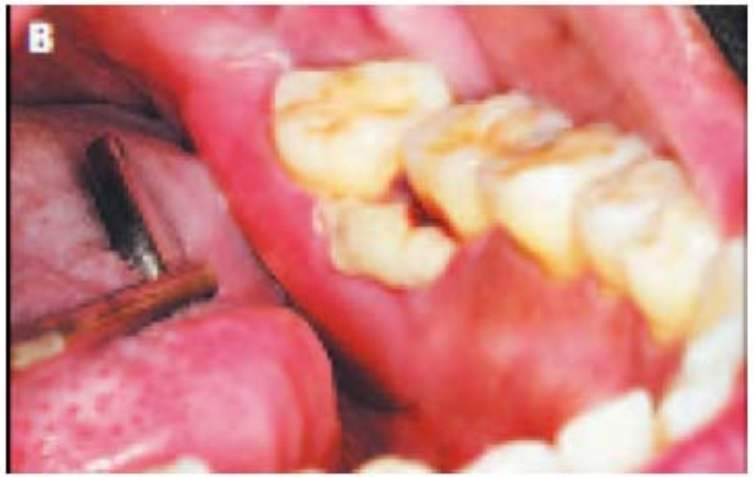
Adapted from: Payer J, et al. *Biomed Pharmacother*. 2007;61:191-193.

Bisfosfonatos
Soluciones a los problemas de adherencia

- Dosis mensuales
- Dosis trimestrales
- Dosis anuales

Osteonecrosis de mandíbula

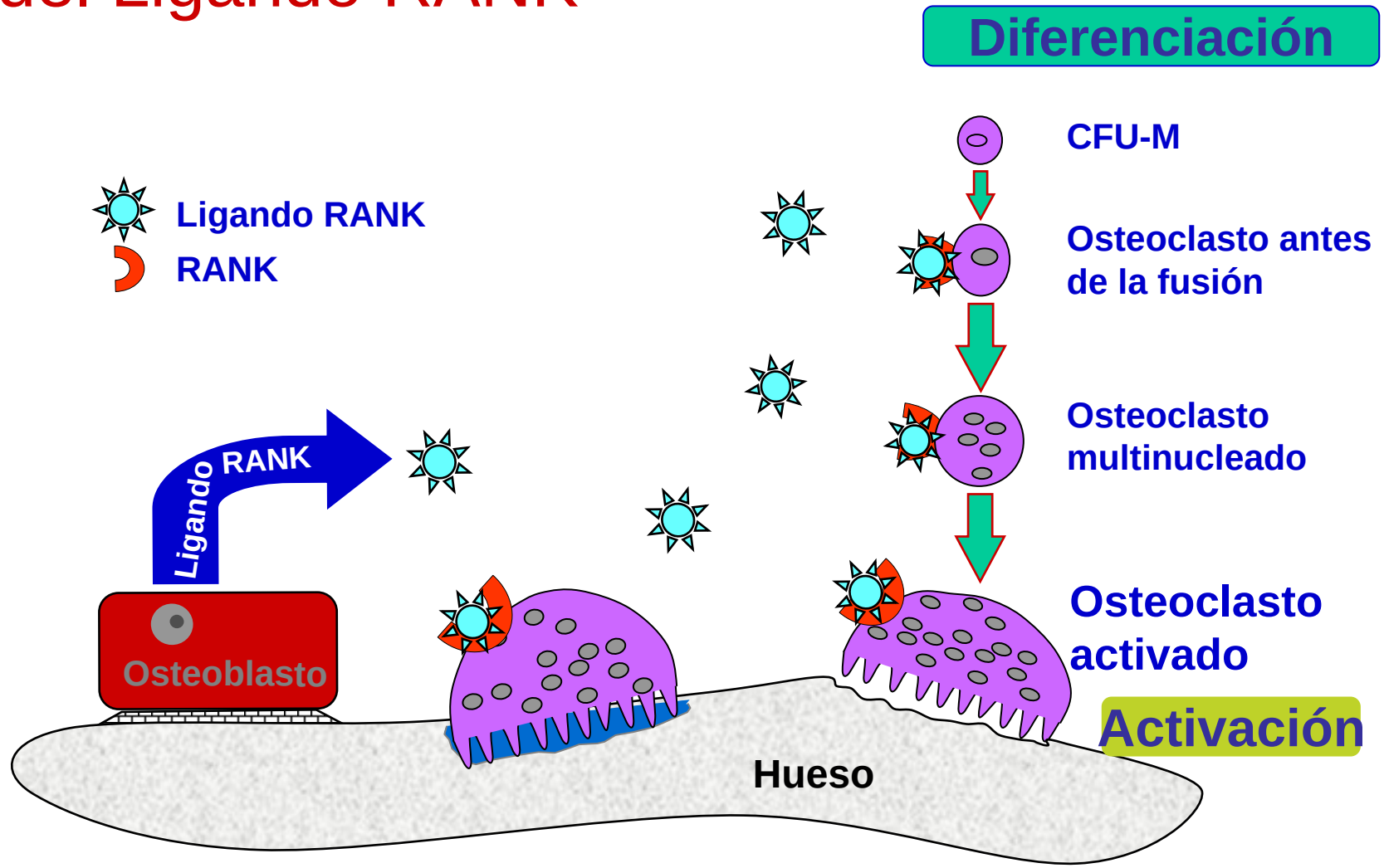




A los 2 meses

Paciente con mieloma y tratamiento con pamidronato

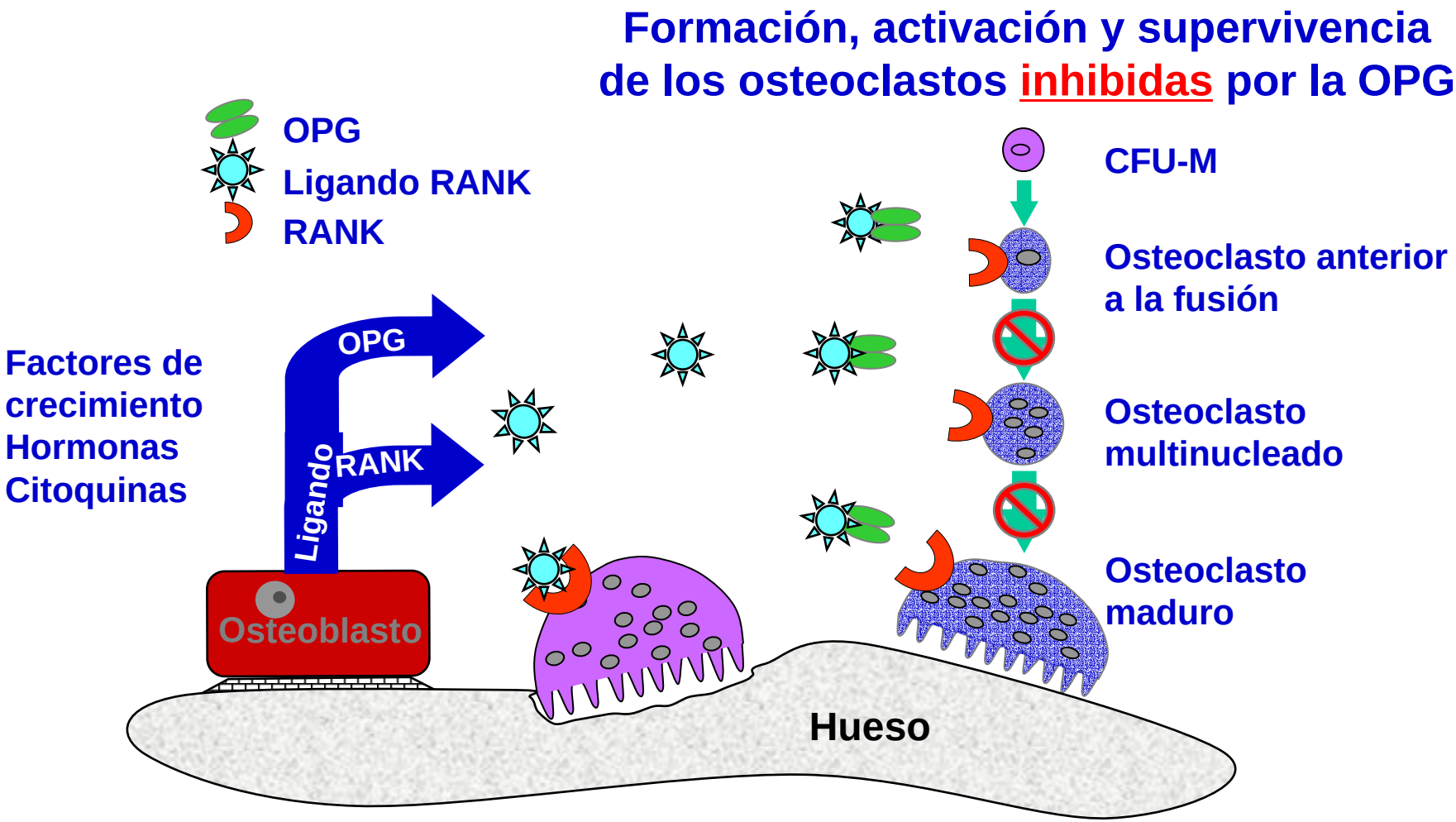
La activación de los osteoclastos depende del Ligando RANK



Adaptado de Boyle WJ *et al.* Nature 2003; 423: 337–342

CFU-M: unidad formadora de colonias de macrófagos

El organismo produce una proteína llamada osteoprotegerina (OPG), que bloquea el Ligando RANK



Adaptado de Boyle WJ *et al.* Nature 2003; 423: 337–342

A Study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis

This study has been completed.

First Received: August 13, 2004 Last Updated: December 3, 2008 History of Changes

Sponsored by:	**Amgen**
Information provided by:	Amgen
ClinicalTrials.gov Identifier:	NCT00089791

Study Type: Interventional
Study Design: Treatment, Randomized, Double Blind (Subject, Investigator), Factorial Assignment

Official Title: A Study to Evaluate **Denosumab** in the Treatment of Postmenopausal Osteoporosis **FREEDOM** (Fracture REduction Evaluation of **Denosumab** in Osteoporosis Every 6 Months)

Primary Outcome Measures:

- Reduction in the number of new vertebral fractures in post menopausal osteoporotic women treated with **denosumab** compared to placebo and to characterize safety and tolerability profile of **denosumab**. [Time Frame: 36 month treatment period] [Designated as safety issue: No]

FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months)

- ECA a 3 años
- 7.868 mujeres
- Edad 60-90 años
- DMO lumbar o total de la cadera T-scores < -2.5 y $\geq$-4.0
- Denosumab 60mg sc cada 6 meses vs placebo, + calcio y vitamina D

FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months)

- Objetivo principal: Fracturas vertebrales
- Objetivos secundarios: Tiempo hasta la primera fractura no vertebral y fractura de cadera.
- También se analizaron las fracturas osteoporóticas mayores (vertebral clínica, cadera, antebrazo y húmero), así como riesgo de fractura a 10 años para fracturas mayores y fracturas de cadera por FRAX

FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months)

Nueva fractura vertebral:

68% (95% CI, 59 - 74%)

(Incidencia acumulada a 3 años: 7.2 vs 2.3%; P<0.0001).

Fractura no vertebral

20% (95% CI [5%, 33%]; 8.0% vs 6.5%, P=0.011)

Fractura de cadera

40% (95% CI [3%, 63%]; 1.2% vs 0.7%, P=0.036).

Fracturas osteoporóticas mayores

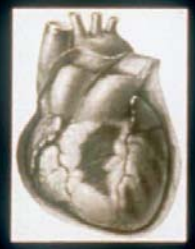
35% (95% CI [22%, 45%]; 8.0% vs 5.3%, P<0.0001).

Moduladores Selectivos de los Receptores Estrogénicos

Agonista

Hueso

Cardiovascular



Antagonista

Mama

Útero

Effects of Arzoxifene on Bone Fractures and Incidence of Breast Cancer

This study is ongoing, but not recruiting participants.

First Received: July 19, 2004 Last Updated: August 20, 2008 History of Changes

Sponsored by:	**Eli Lilly and Company**
Information provided by:	Eli Lilly and Company
ClinicalTrials.gov Identifier:	NCT00088010

Primary Outcome Measures:

- Effects of **arzoxifene** on bone fractures and bone mass [Time Frame: 5 years]
  [Designated as safety issue: No]
- Effects of **arzoxifene** on getting breast cancer [Time Frame: 5 years] [Designated as safety issue: Yes]
- The safety of **arzoxifene** and any side effects [Time Frame: 5 years] [Designated as safety issue: Yes]

Study Evaluating Bazedoxifene Acetate in Osteoporosis

This study is ongoing, but not recruiting participants.

First Received: September 16, 2005 Last Updated: May 6, 2008 History of Changes

Sponsored by:	**Wyeth**
Information provided by:	Wyeth
ClinicalTrials.gov Identifier:	NCT00205777

Para ver esta película, debe disponer de QuickTime™ y de un descompresor .

Primary Outcome Measures:

- Incidence reduction of new vertebral fractures. [Time Frame: 7 years] [Designated as safety issue: No]
- To compare the safety profile fo **bazedoxifene** acetate to placebo. [Time Frame: 7 years] [Designated as safety issue: No]

Secondary Outcome Measures:

- Breast cancer incidence; Clinical vertebral fractures; Worsening vertebral fractures; Nonvertebral fractures; Height changes [Time Frame: 7 years] [Designated as safety issue: Yes]

Postmenopausal Evaluation and Risk-Reduction With Lasofoxifene (PEARL)

This study has been completed.

First Received: August 30, 2005 Last Updated: May 22, 2008 History of Changes

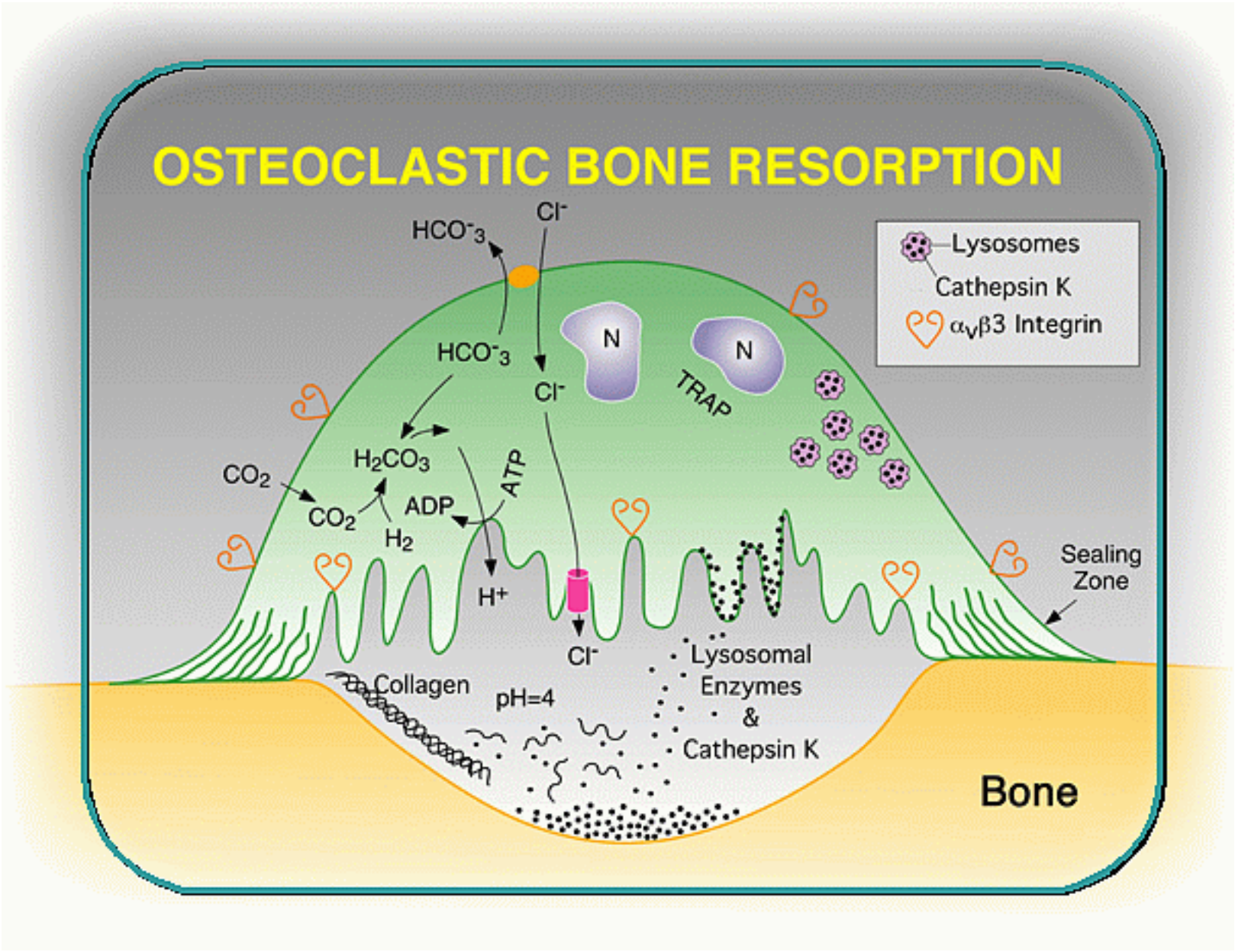
Sponsored by:	**Pfizer**
Information provided by:	Pfizer
ClinicalTrials.gov Identifier:	NCT00141323

Primary Outcome Measures:

- New morphometric vertebral fractures [Time Frame: 3 years] [Designated as safety issue: No]
- New cases of breast cancer [Time Frame: 5 years] [Designated as safety issue: No]
- New non-vertebral fractures [Time Frame: 5 years] [Designated as safety issue: No]

Secondary Outcome Measures:

- All clinical fractures, non-vertebral fractures, BMD, breast cancer, cardiovascular events, and gynecological safety events [Time Frame: 3 years] [Designated as safety issue: Yes]
- All clinical fractures, new morphometric vertebral fractures, BMD, cardiovascular events, and gynecological safety events [Time Frame: 5 years] [Designated as safety issue: Yes]


OSTEOCLASTIC BONE RESORPTION
Lysosomes
Cathepsin K
αvβ3 Integrin
HCO-3
Cl-
HCO-3
Cl-
N
N
TRAP
H2CO3
CO2
CO2
ADP
ATP
H2
H+
Cl-
Sealing Zone
Collagen
pH=4
Lysosomal Enzymes & Cathepsin K
Bone

A Study of MK0822 in Postmenopausal Women With Osteoporosis to Assess Fracture Risk Reduction

This study is currently recruiting participants.
Verified by Merck, April 2009

First Received: September 12, 2007 Last Updated: April 1, 2009 History of Changes

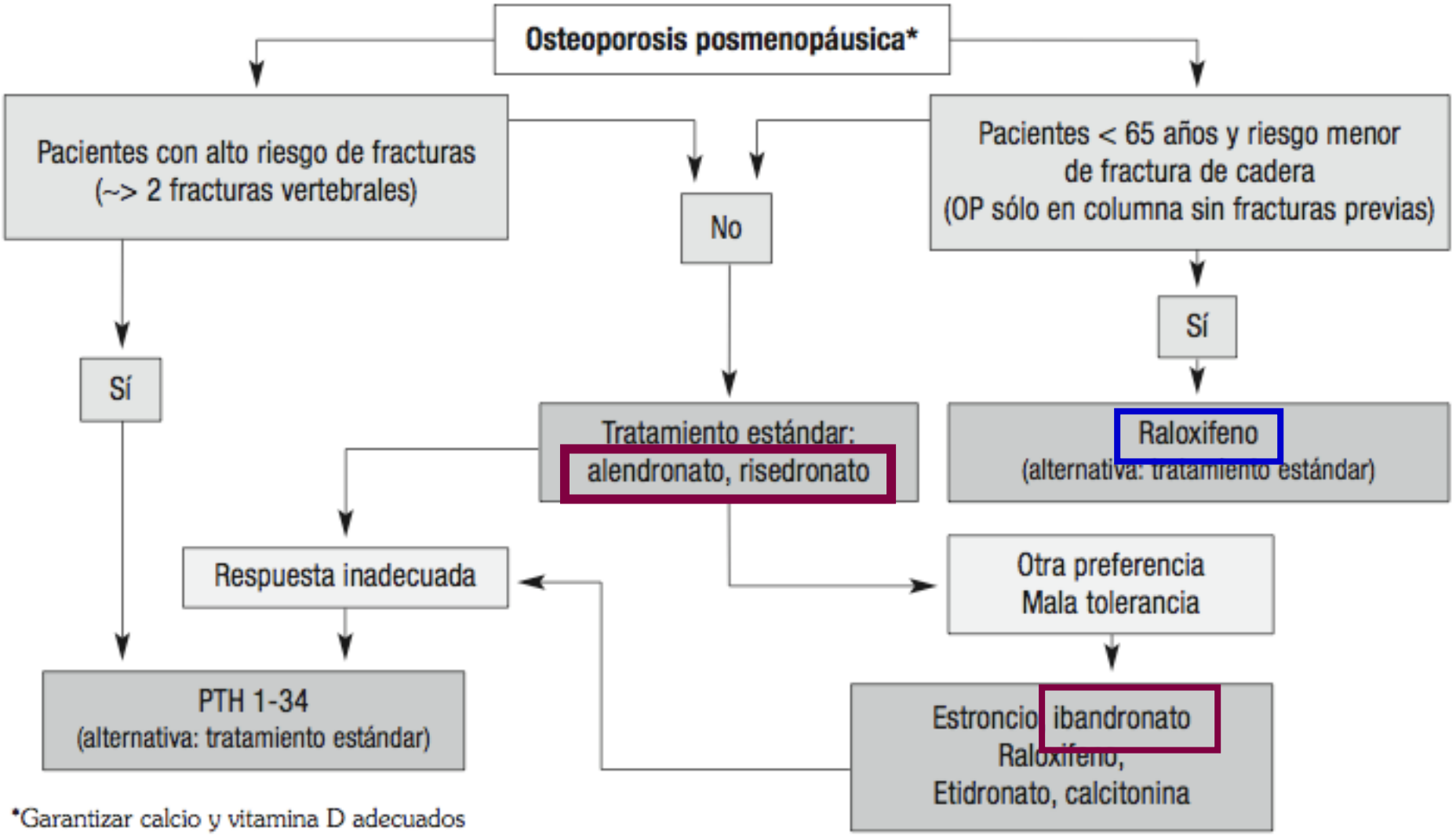
Sponsored by:	**Merck**
Information provided by:	Merck
ClinicalTrials.gov Identifier:	NCT00529373

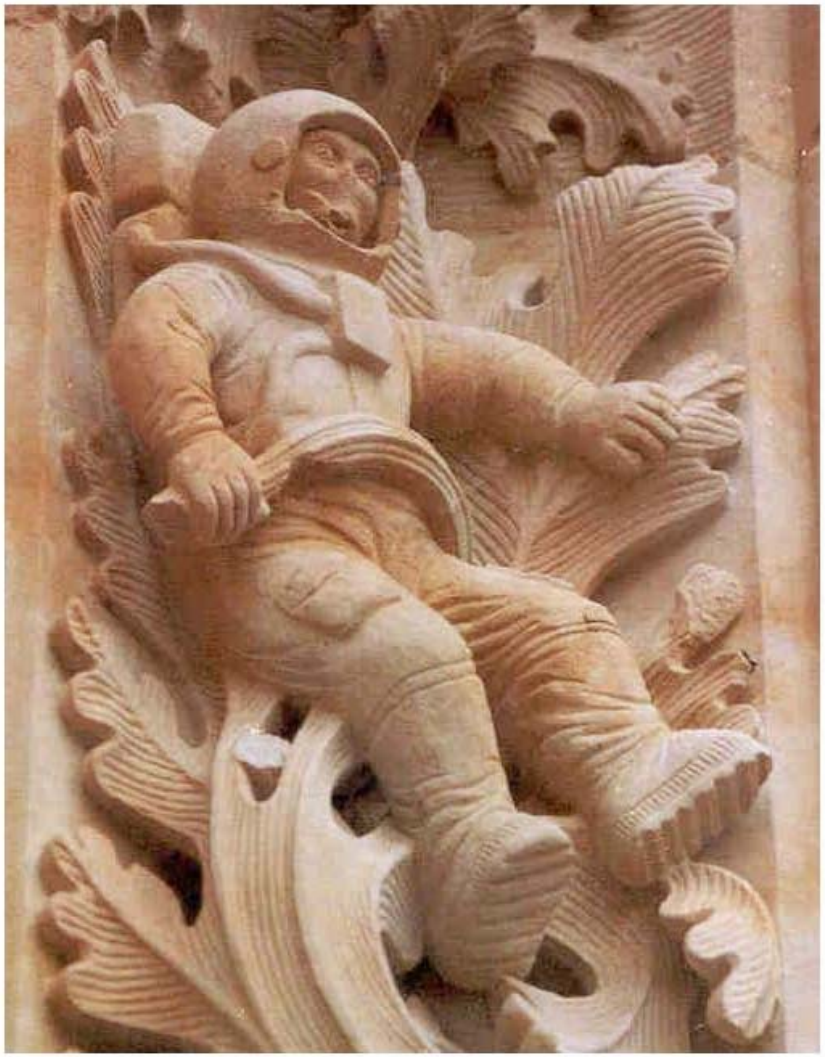
Primary Outcome Measures:

- To determine the incidence of radiographic spine fractures and fractures at other body sites in patients taking MK0822 compared to placebo. [Time Frame: 3 Years] [Designated as safety issue: No]

Secondary Outcome Measures:

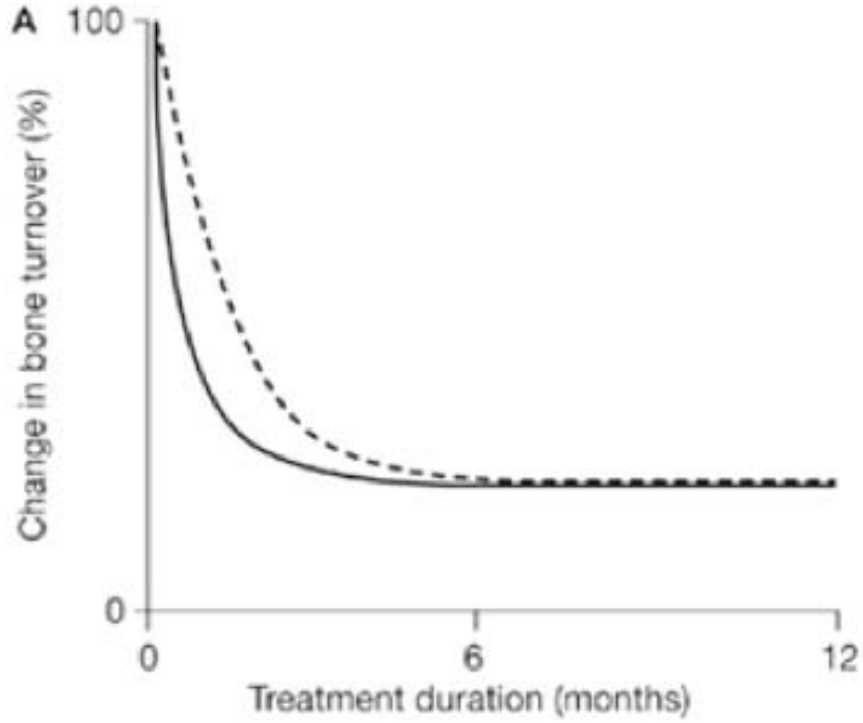
- Changes in Bone Mineral Density (BMD) over the course of the study in patients taking MK0822 compared to placebo. [Time Frame: 3 Years] [Designated as safety issue: No]

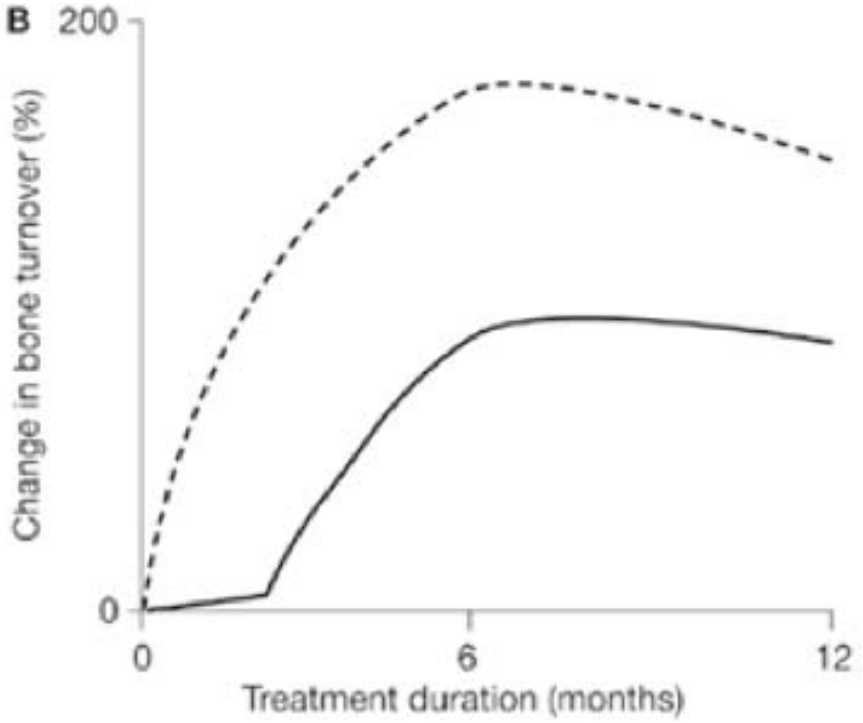

Osteoporosis posmenopáusica*
Pacientes con alto riesgo de fracturas
(~> 2 fracturas vertebrales)
No
Pacientes < 65 años y riesgo menor
de fractura de cadera
(OP sólo en columna sin fracturas previas)
Sí
Sí
Tratamiento estándar:
alendronato, risedronato
Raloxifeno
(alternativa: tratamiento estándar)
Respuesta inadecuada
Otra preferencia
Mala tolerancia
PTH 1-34
(alternativa: tratamiento estándar)
Estroncio ibandronato
Raloxifeno,
Etidronato, calcitonina
*Garantizar calcio y vitamina D adecuados

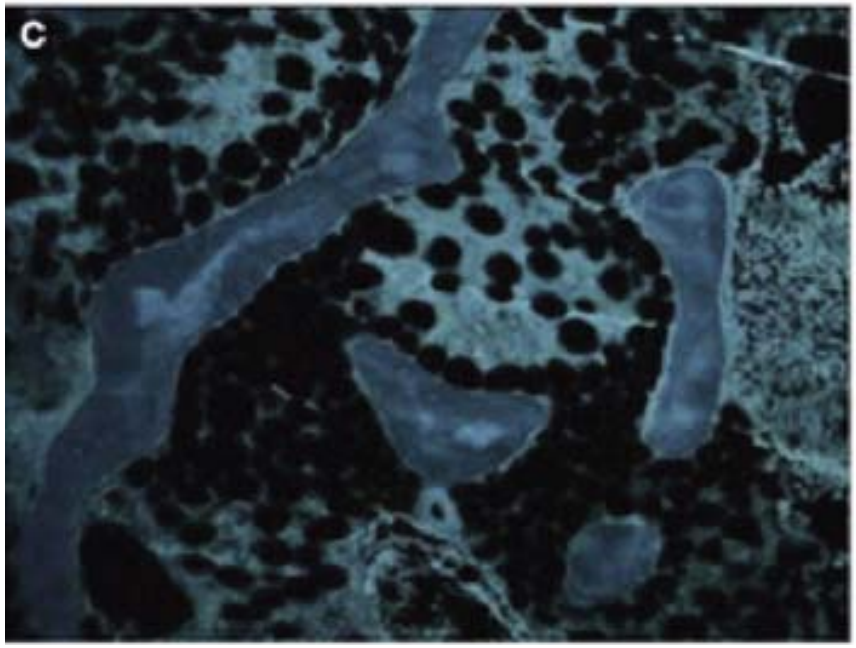


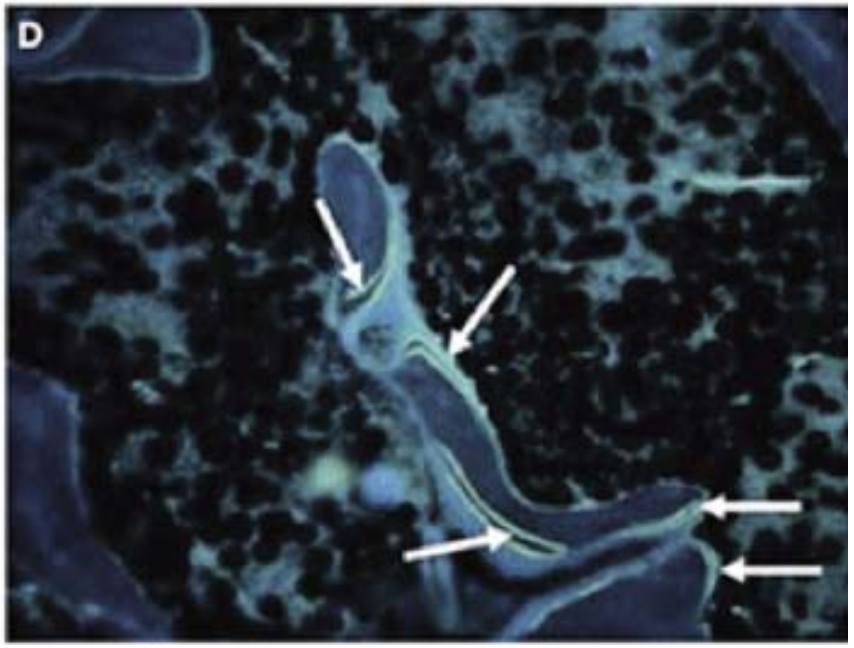
- Bisfosfonatos
  - Acido zoledrónico
- Anti- RANKL
  - Denosumab
- SERM
  - Arzoxifeno
  - Bezadoxifeno
  - Lasofoxifeno
- Inhibidores catepsina K
  - Odanacatib

	Raloxifene 60mg/d	Arzoxifene 20mg/d
Lumbar spine BMD	1.66%	2.75%
Femoral neck BMD	0.46%	1.53%
Total hip BMD	0.82%	1.53%
CTX	-29.8%	-40.6%
PINP	-30.8%	-41.5%

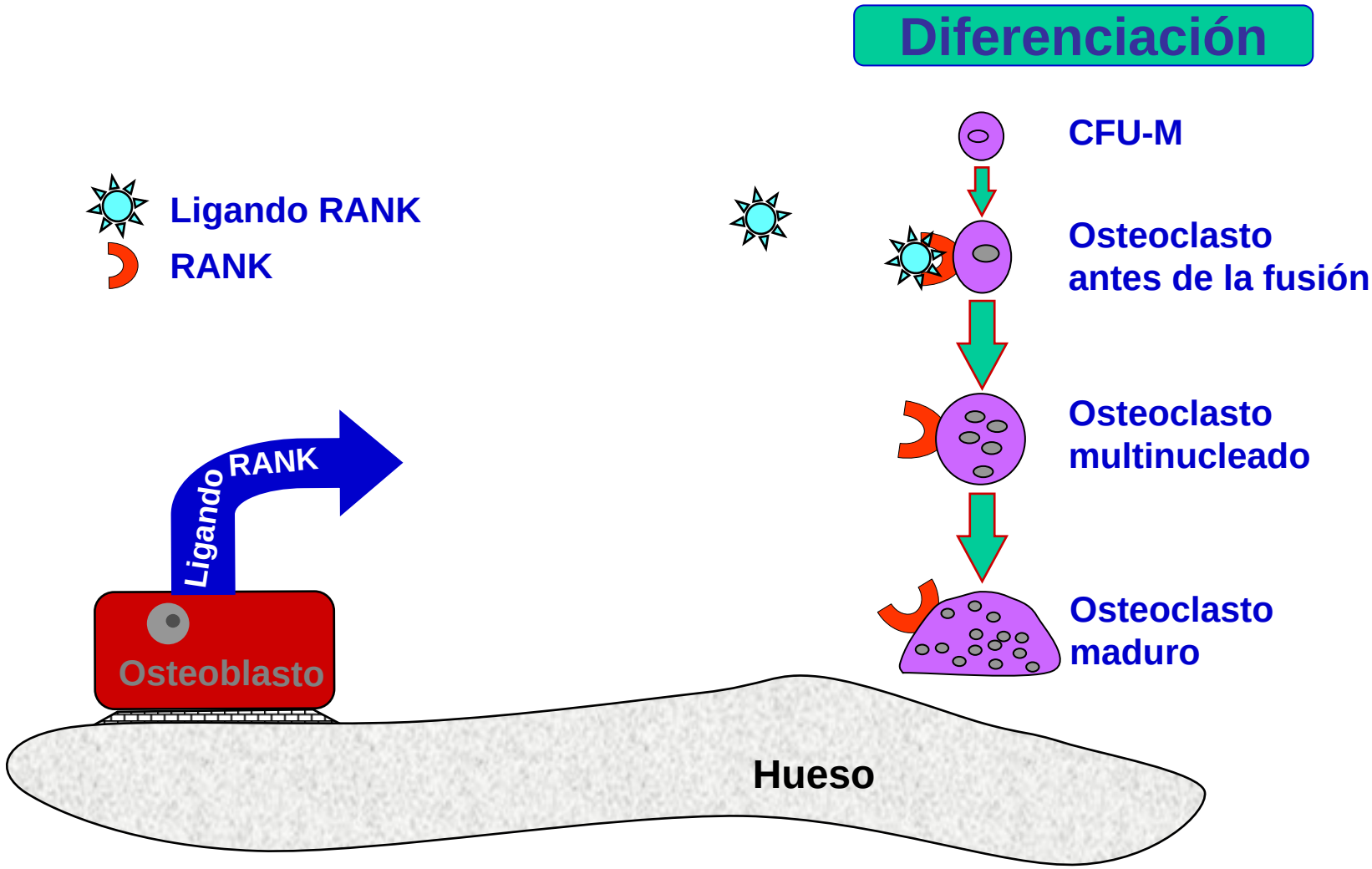

A
100
Change in bone turnover (%)
0
0
6
12
Treatment duration (months)


B
200
Change in bone turnover (%)
0
0
6
12
Treatment duration (months)


C


D

La diferenciación de los precursores de osteoclastos a los osteoclastos maduros depende del Ligando RANK



Adaptado de Boyle WJ *et al.* Nature 2003; 423: 337–342

CFU-M: unidad formadora de colonias de macrófagos