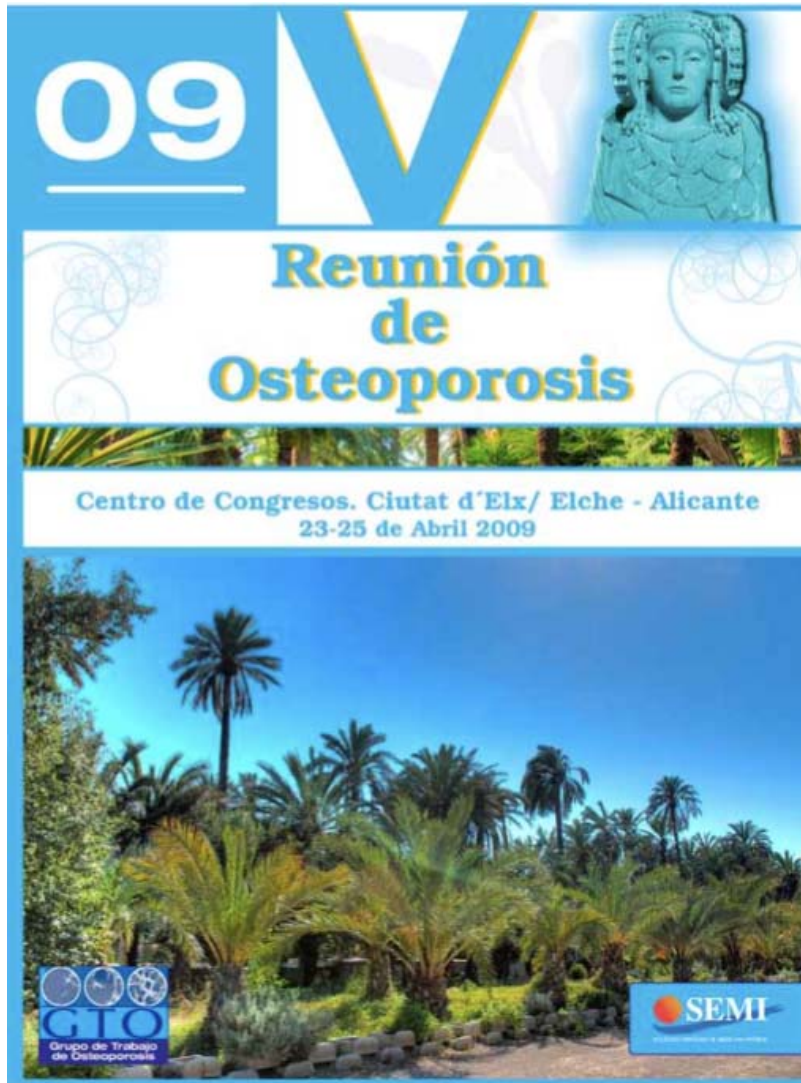


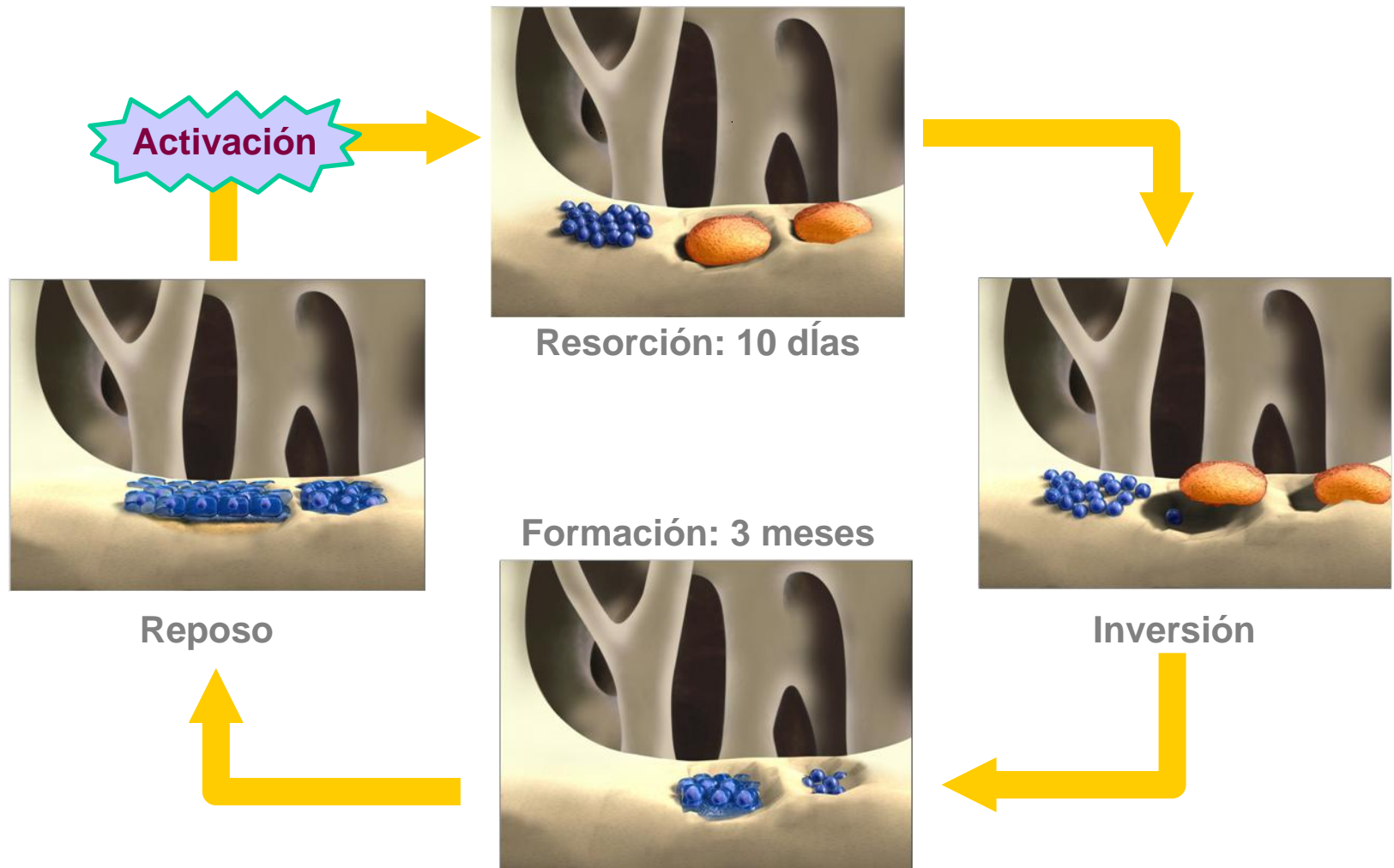
# Antirresortivos



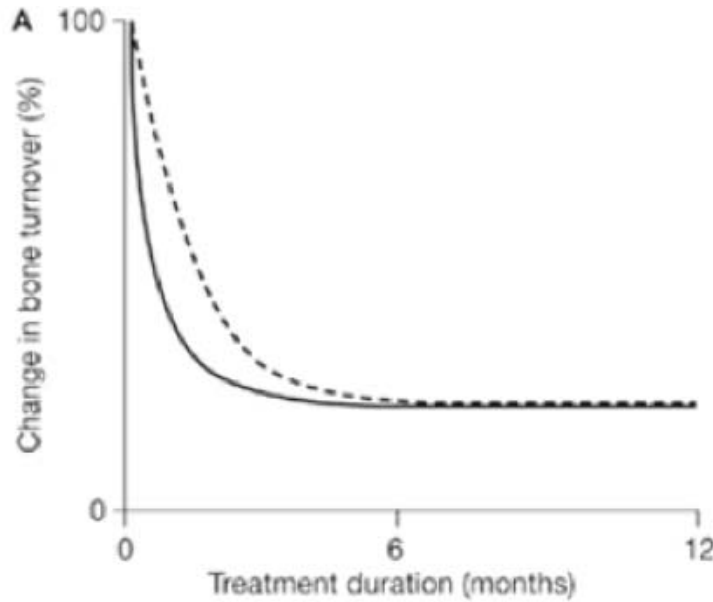
Javier del Pino Montes

Hospital Universitario de  
Salamanca  
Universidad de Salamanca  
RETICEF

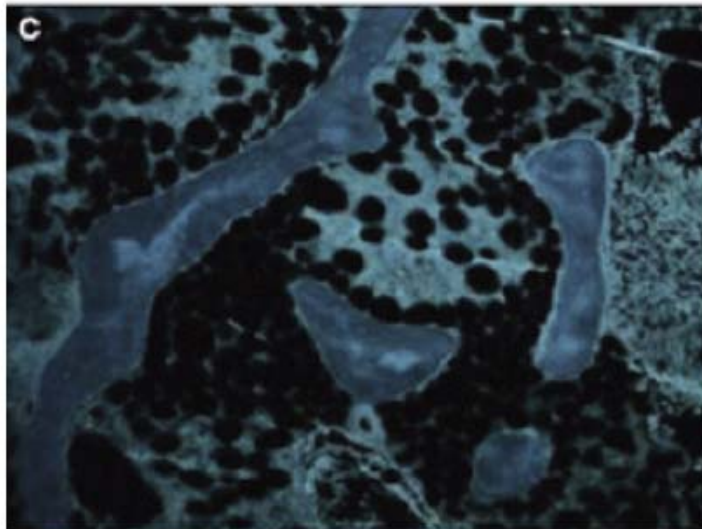
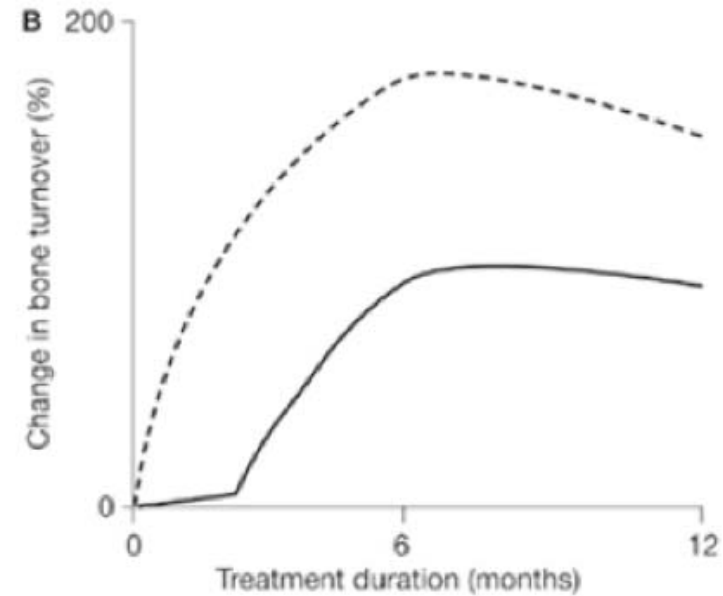
# Un esqueleto sano requiere un equilibrio entre la resorción y la formación ósea



# Tratamiento farmacológico de la osteoporosis

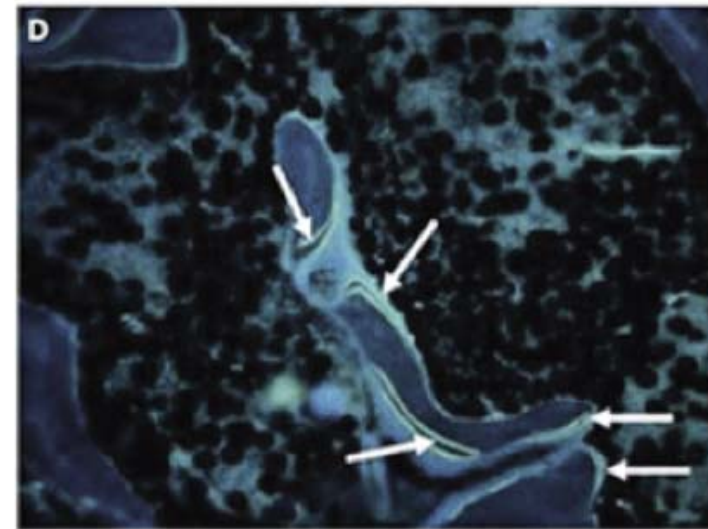


**Vit D + Calcio**

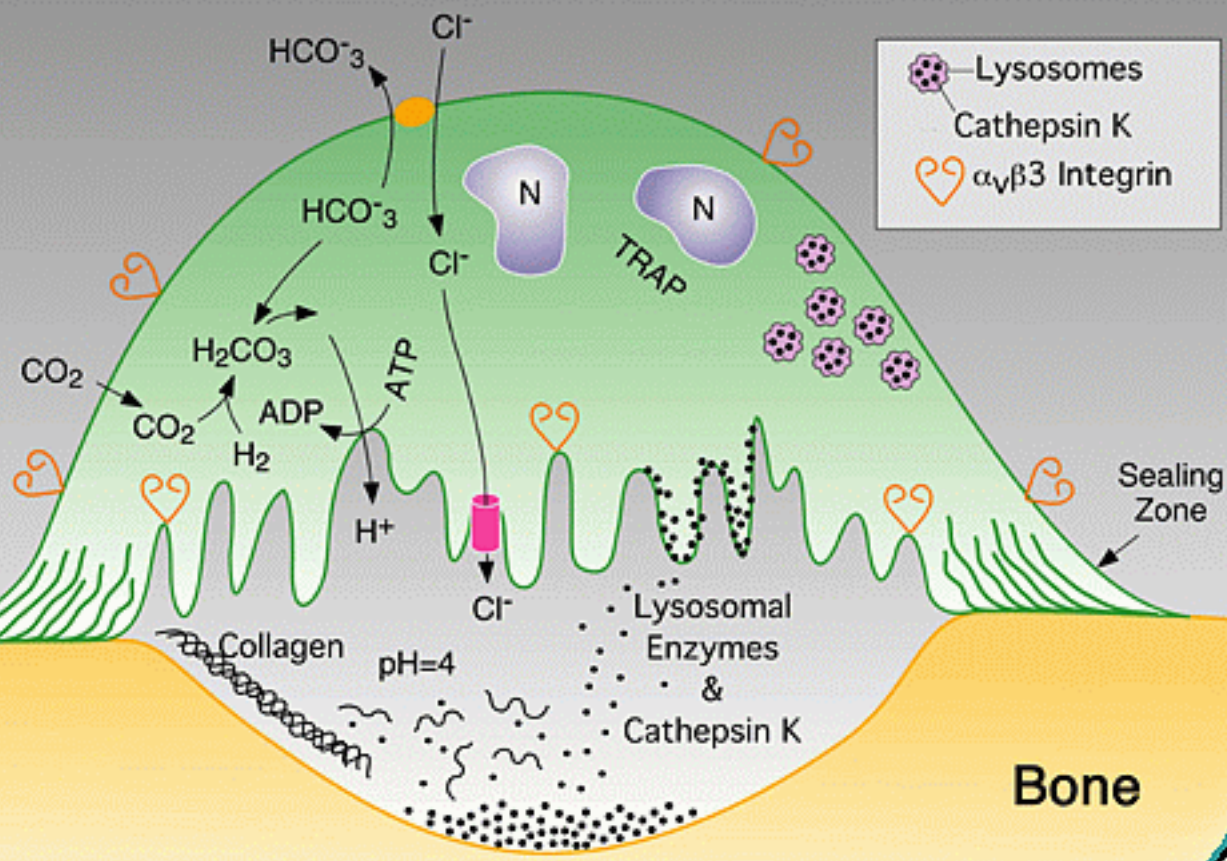


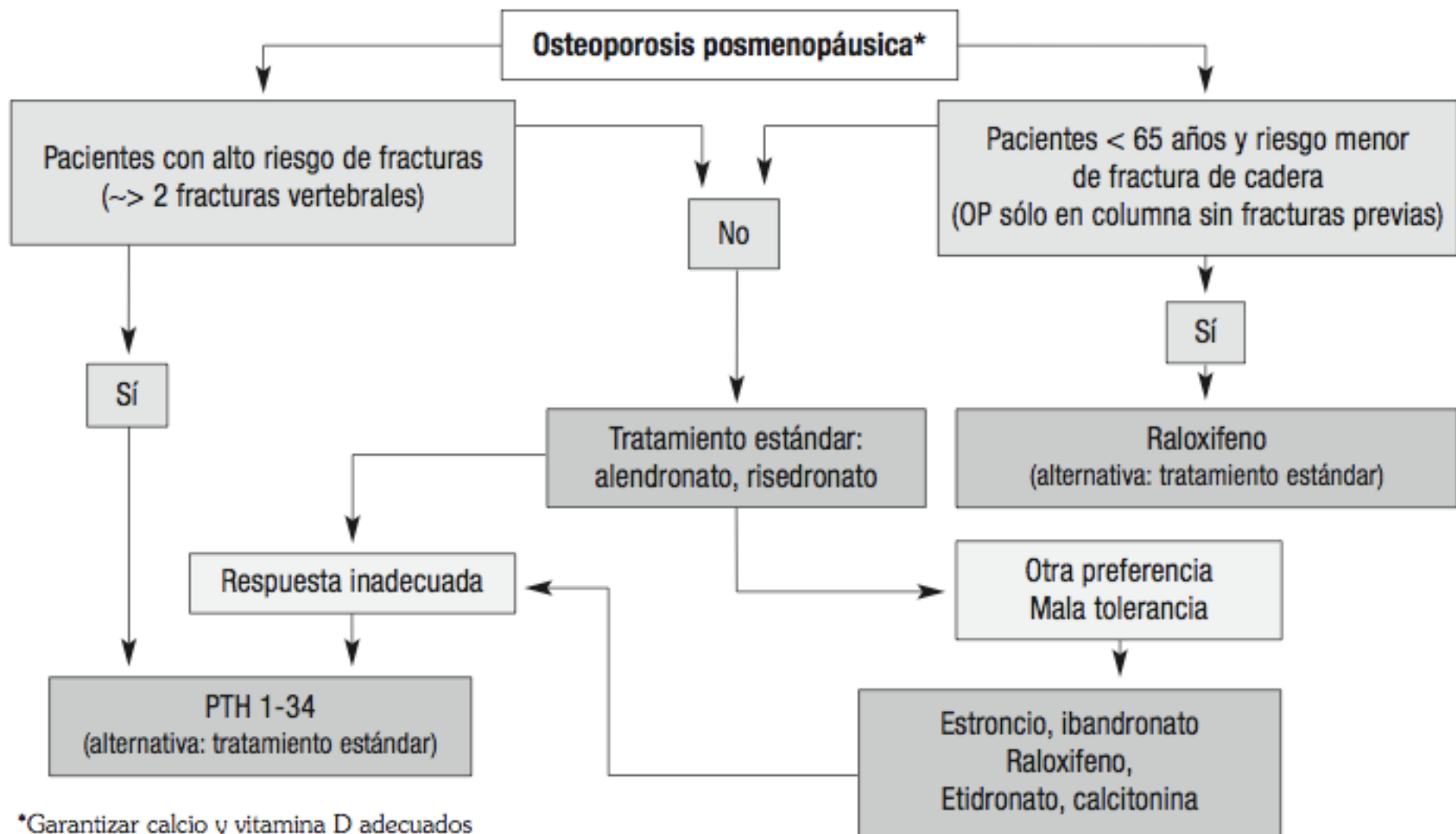
**Estroncio**

**canismo d**



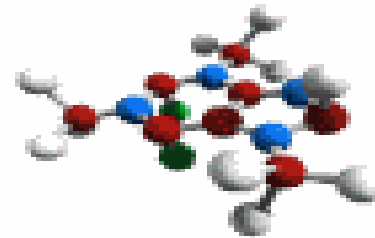
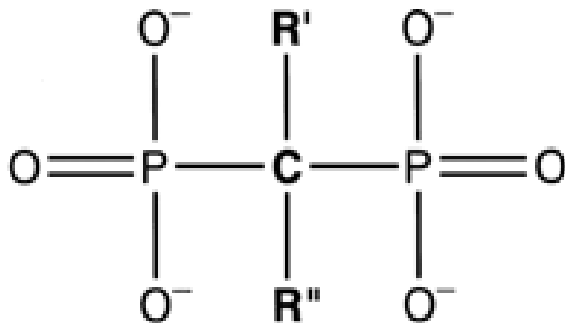
# OSTEOCLASTIC BONE RESORPTION





\*Garantizar calcio y vitamina D adecuados

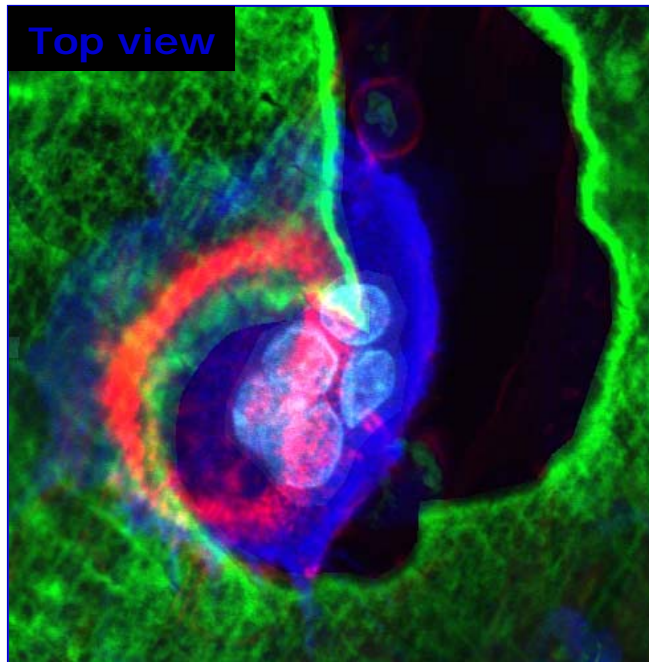
# BISFOSFONATOS



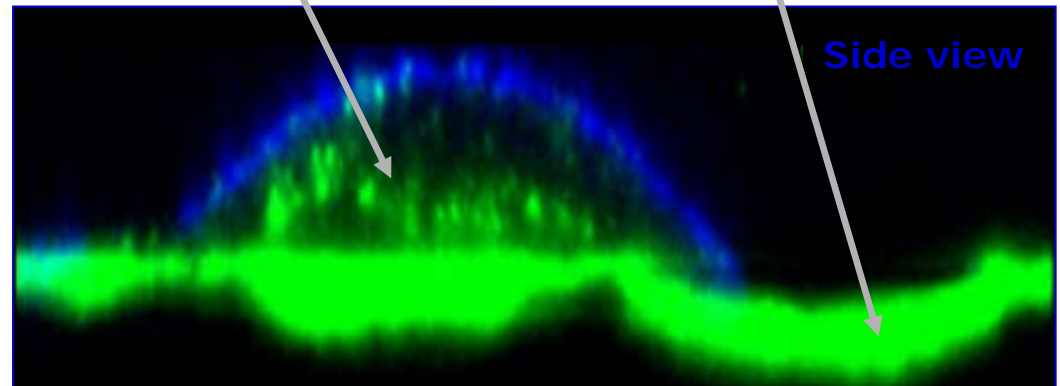
- Inhibición función osteoclástica de forma directa y aumentando la apoptosis del osteoclasto
- Afinidad por el hueso.(20-80%)
- Baja absorción(1-10%).Fuera comidas
- Rápida eliminación por orina.Vida media=20-120 minutos.



# Bisphosphonates Are Internalised by Osteoclasts During Bone Resorption

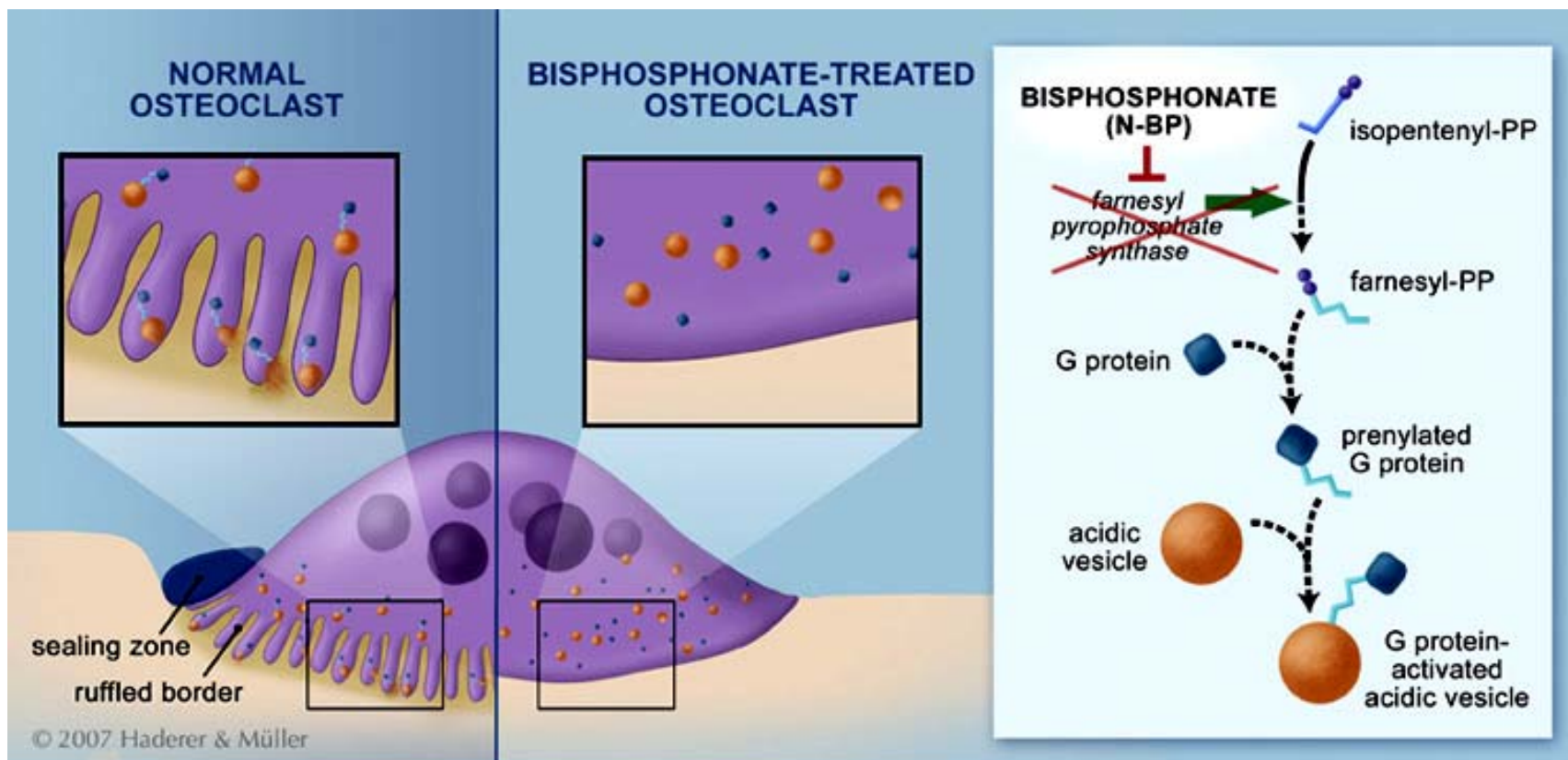


Intracellular BP Resorption pit



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

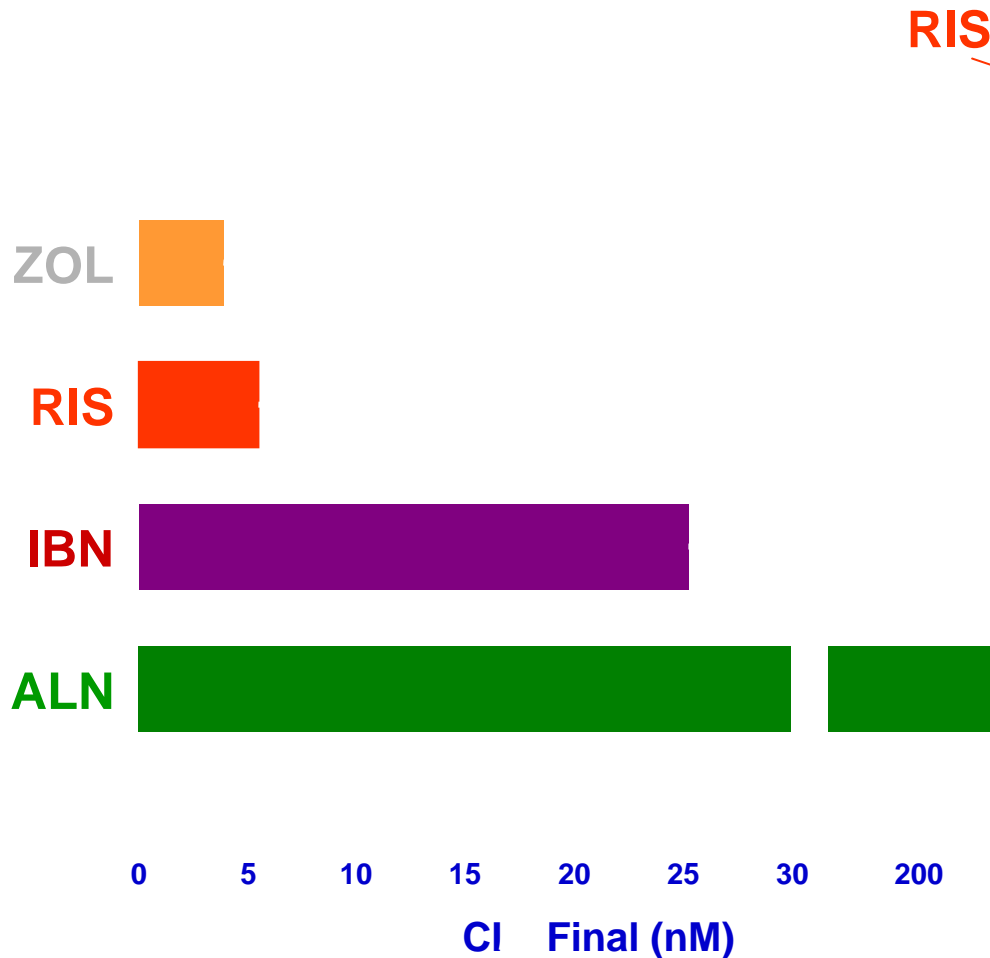
# Bisphosphonates Inhibit Bone Resorption by Preventing Formation of the Ruffled Border



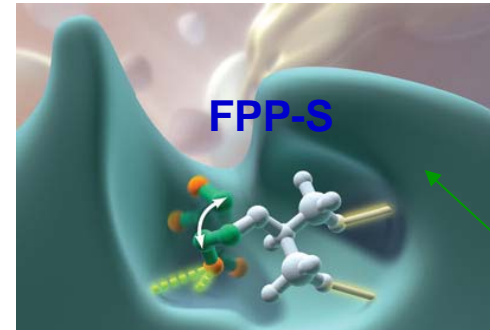
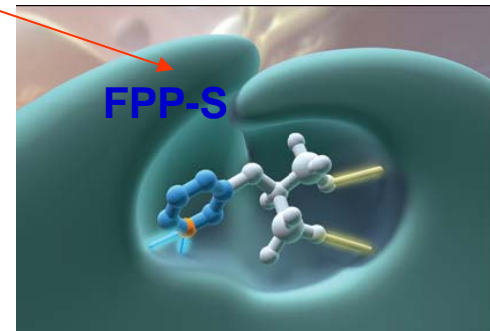


# Potencia de inhibición de la enzima FPPS ( $CI_{50}$ )

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



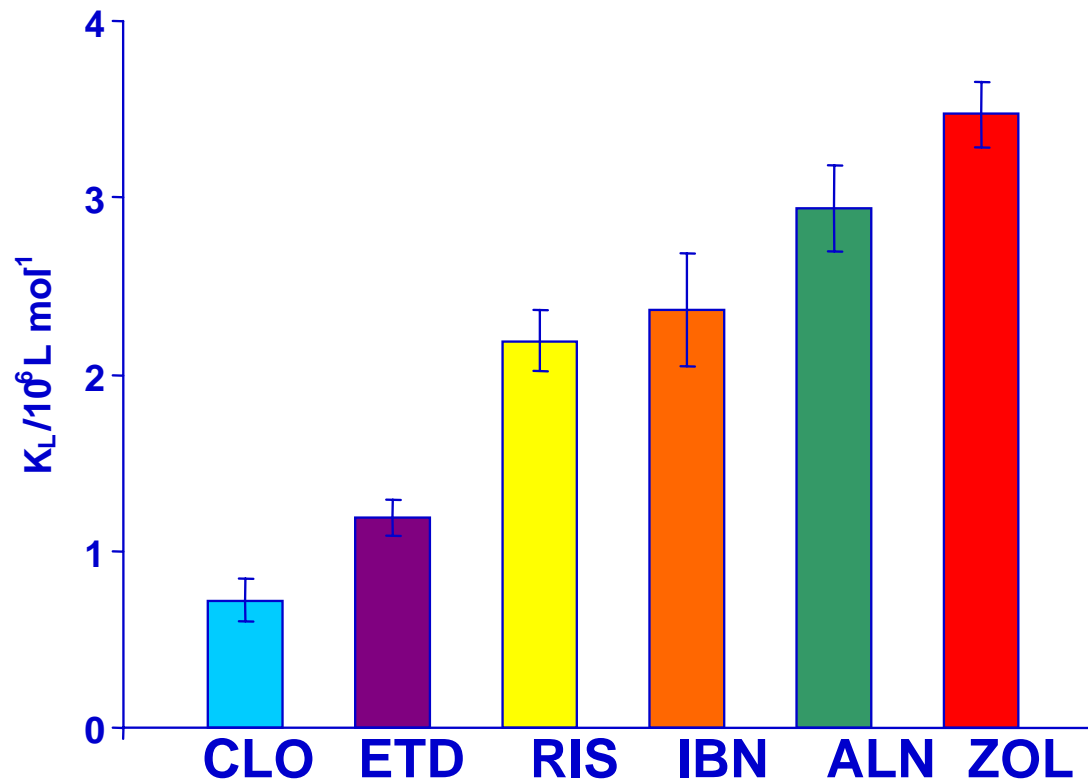
RIS



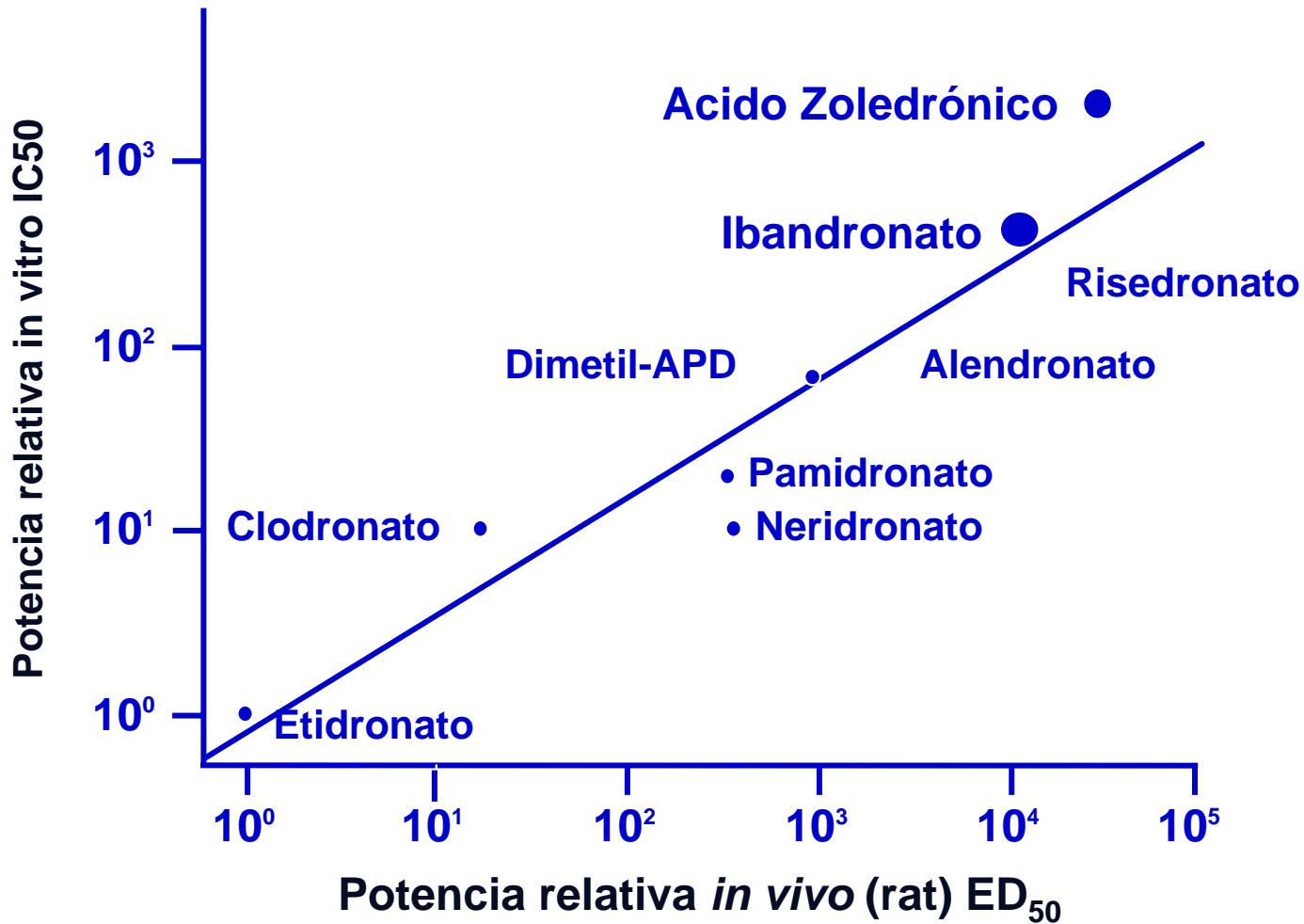
ALN

# Diferente afinidad de unión al mineral óseo

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

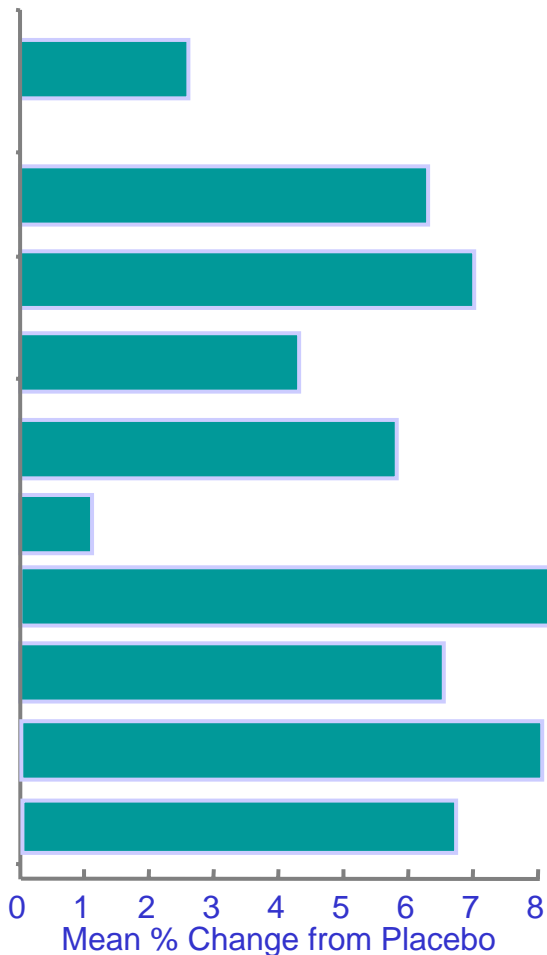


# Potencia de los bisfosfonatos



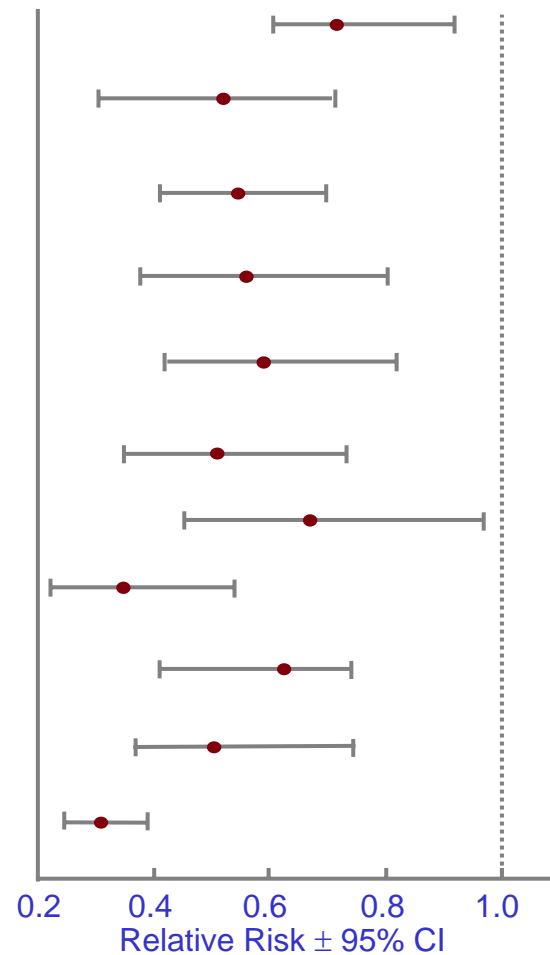
# Effect of Different Drugs for Osteoporosis on BMD and Vertebral Fracture Risk

Lumbar Spine BMD

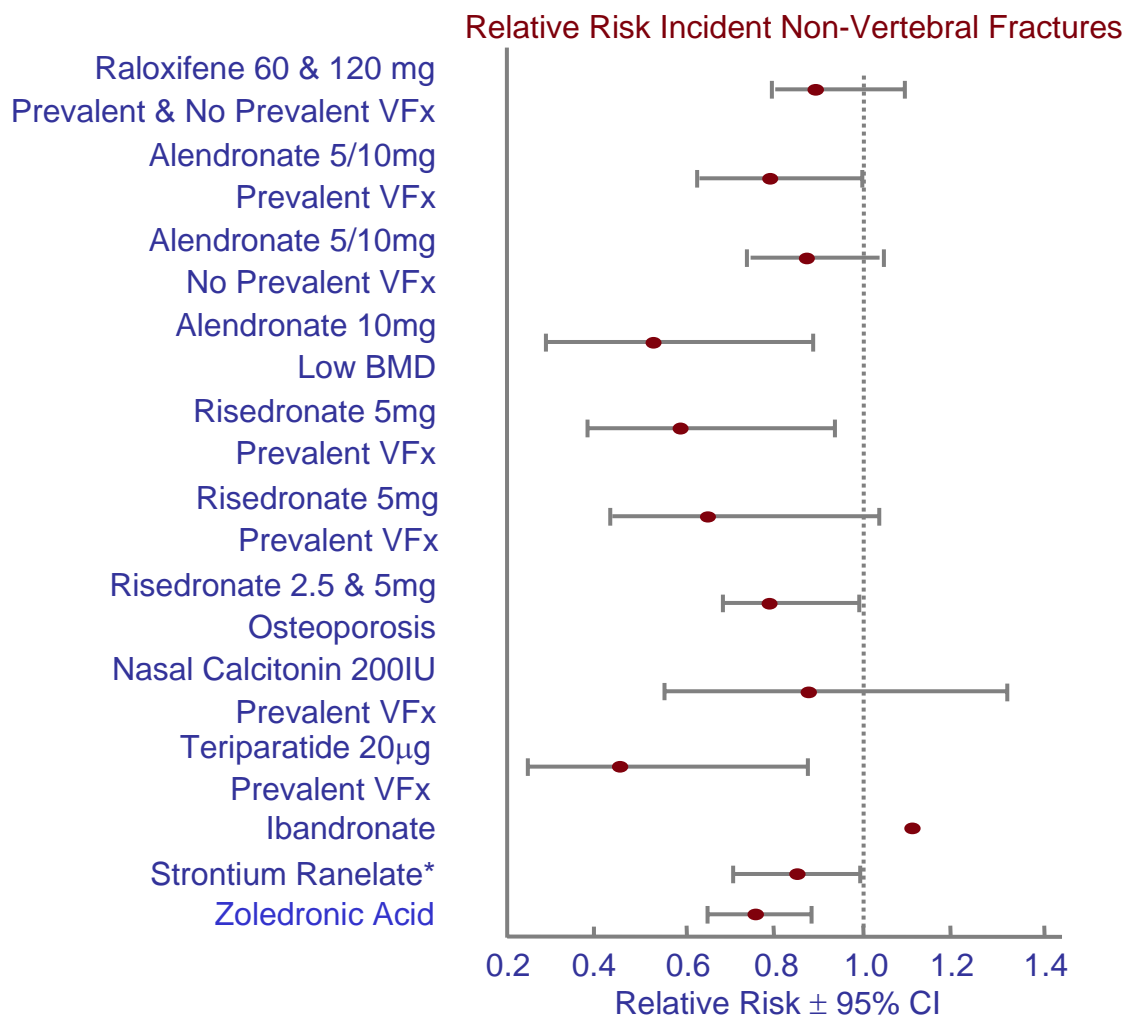


- Raloxifene 60 mg
- Prevalent VFX
- Raloxifene 60 mg
- No Prevalent VFX
- Alendronate 5/10 mg
- Prevalent VFX
- Alendronate 5/10 mg
- No Prevalent VFX
- Risedronate 5mg
- North American
- Risedronate 5mg
- Multinational
- Nasal Calcitonin 200IU
- Teriparatide 20 µg
- Ibandronate 2.5mg
- Strontium Ranelate\*
- Zoledronic Acid

Relative Risk of Incident Vertebral Fractures

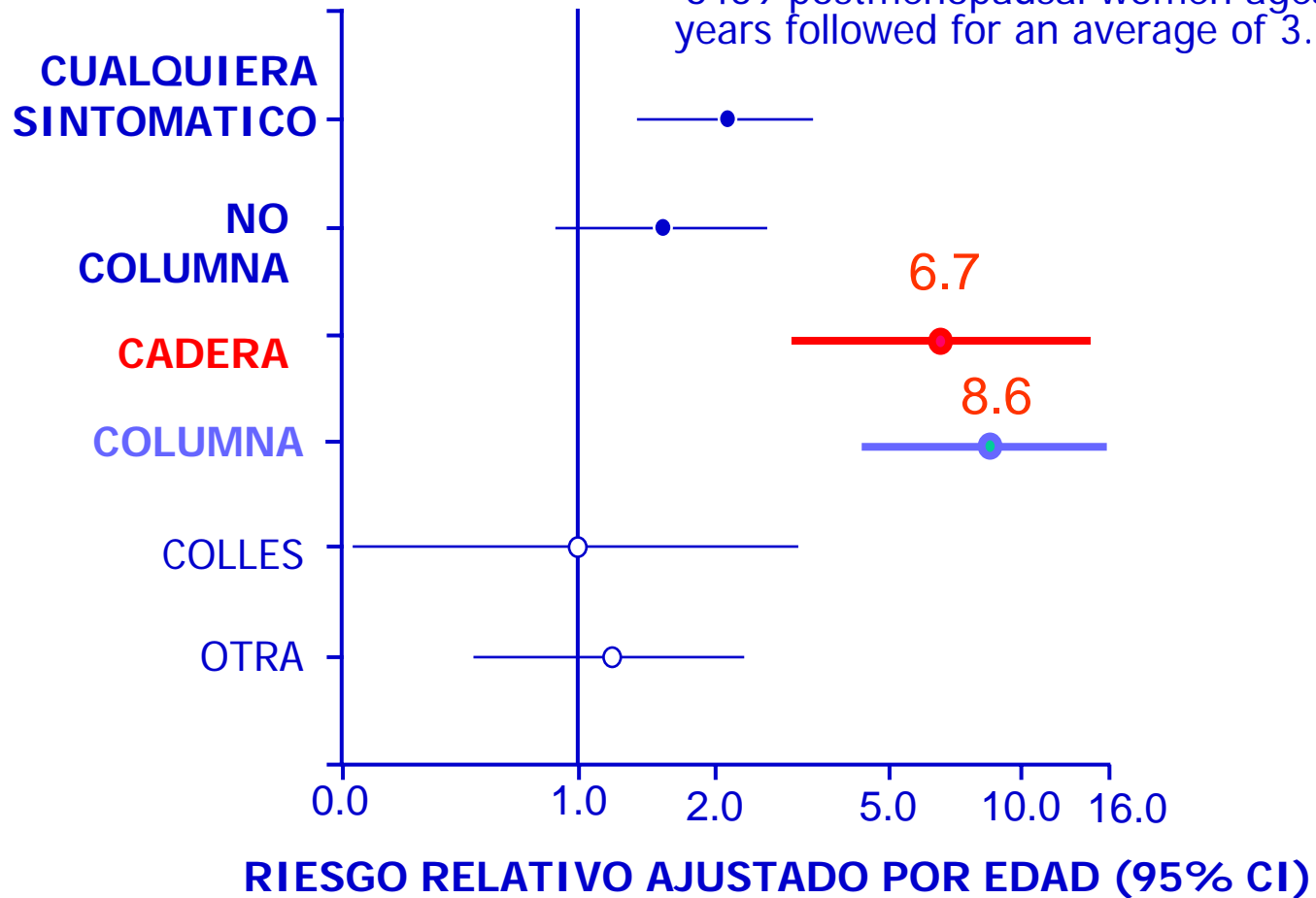


# Effect of Different Drugs for Osteoporosis on Non-Vertebral Fracture Risk



# 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.



# *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**

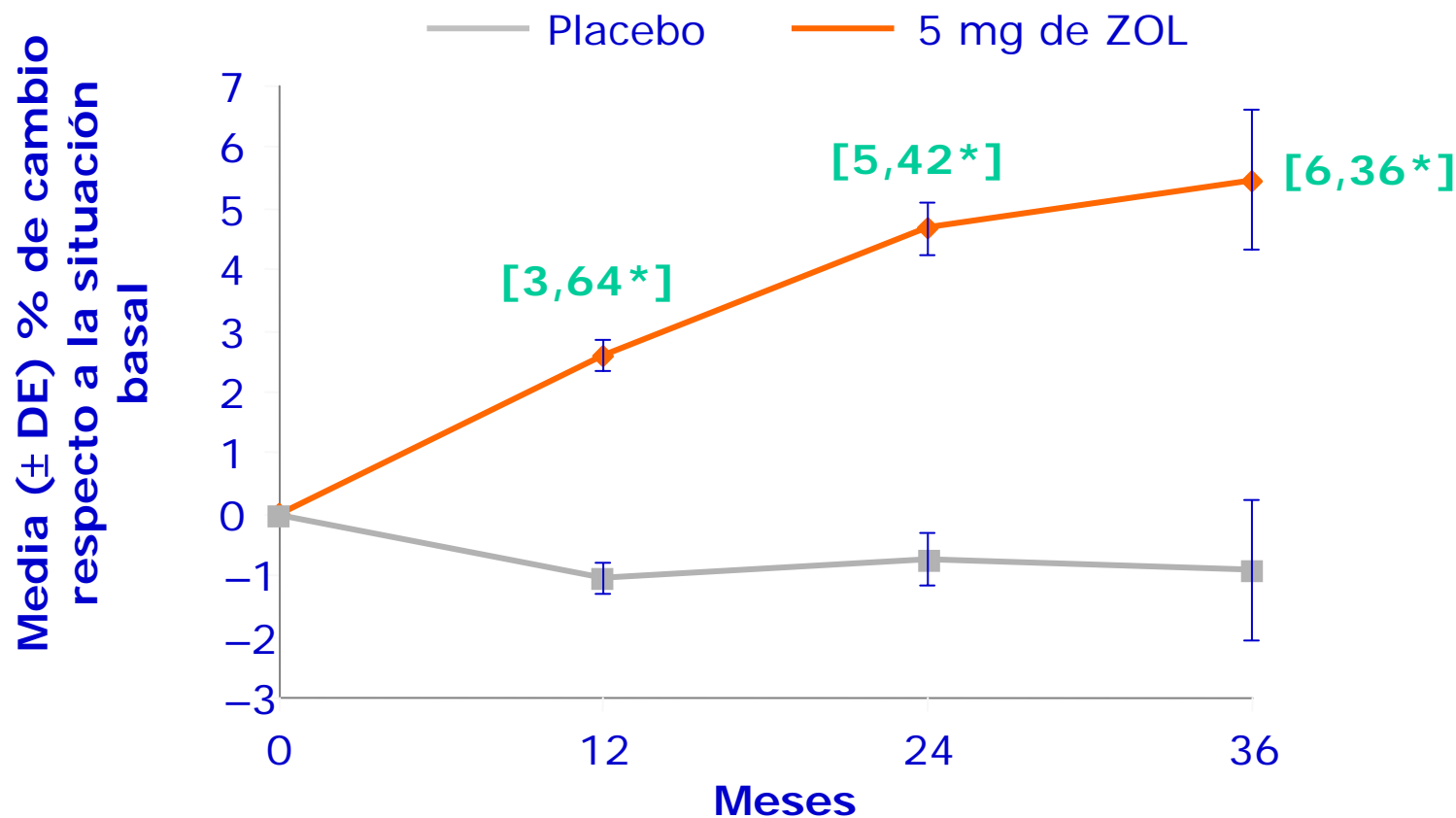
## **Generalidades**

- **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**



# HORIZON-Ensayo Clínico de fracturas recurrentes

## Resultados DMO



5 mg de ZOL	n=	681	405	128
Placebo	n=	683	400	124

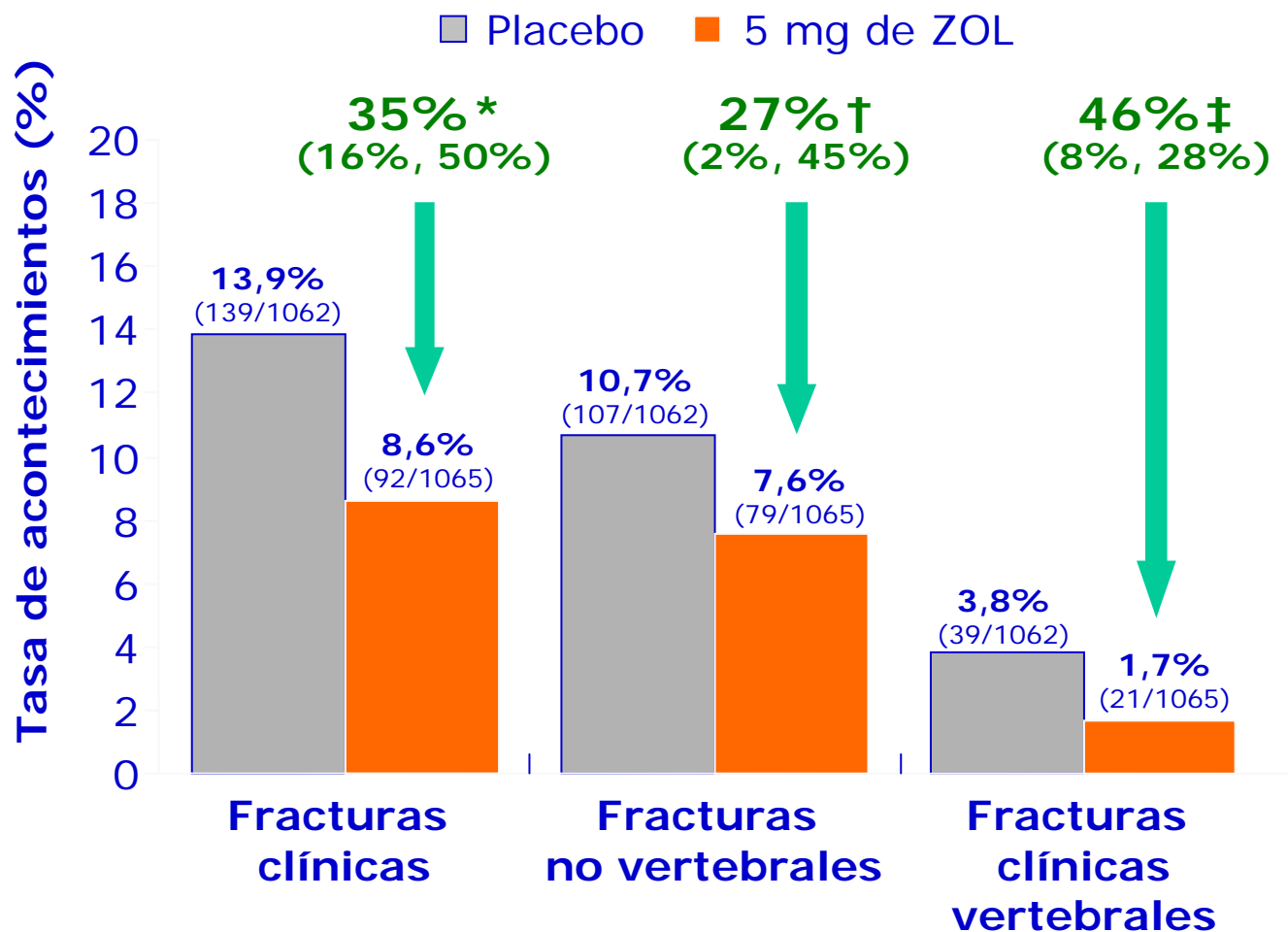
No incluye el centro 829. Los valores entre paréntesis son la diferencia media de los mínimos cuadrados, ZOL frente a placebo.

\* $P < 0,0001$ ; 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](http://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.

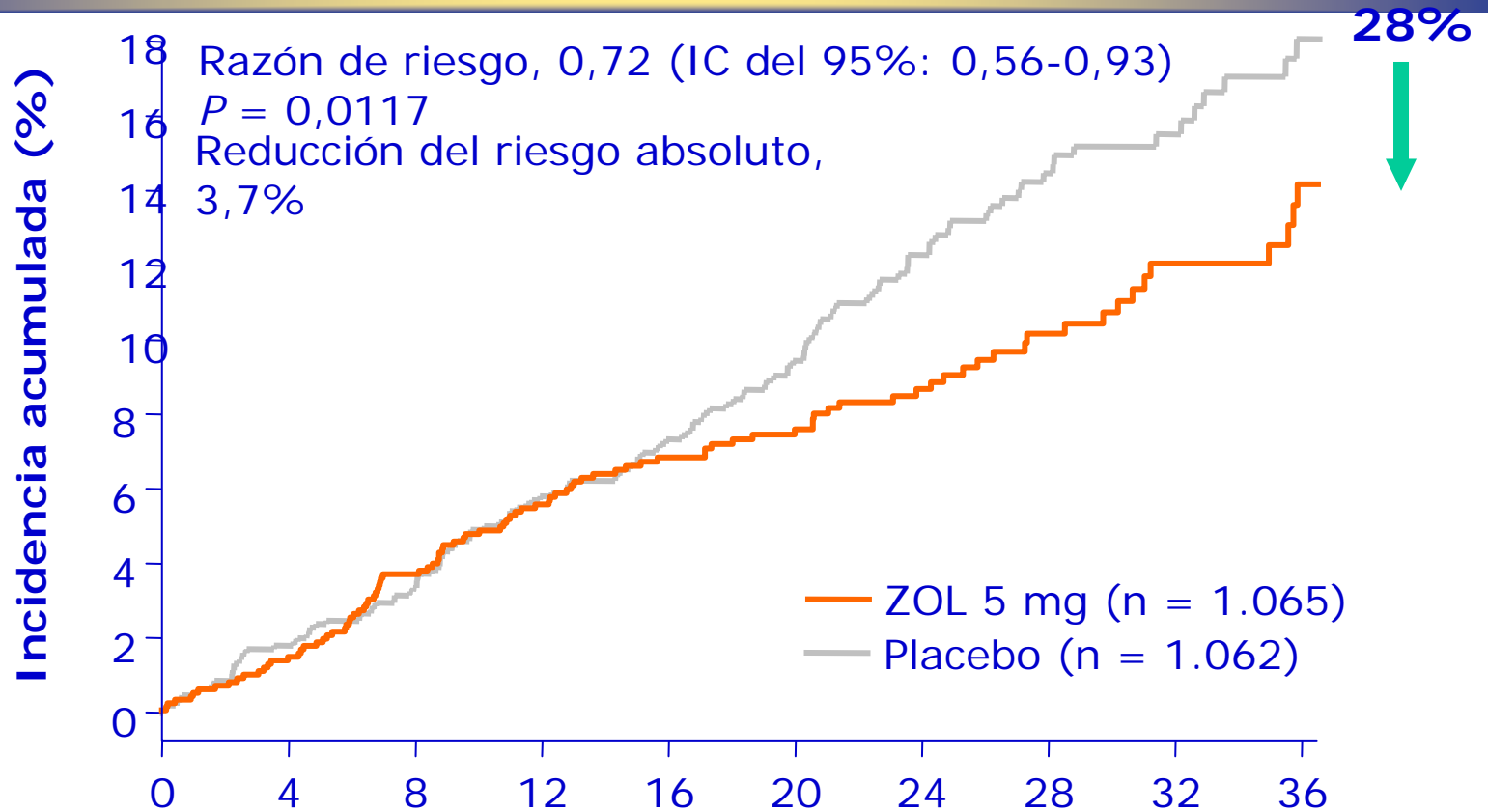
Los valores situados encima de las barras son tasas de acontecimientos acumulados basados en cálculos de Kaplan-Meier en el mes 12. Lyles KW, et al. *N Engl J Med*. 2007. [e-publication 10.1056/NEJMoa074941 at [www.nejm.org](http://www.nejm.org)]

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

Categoría	5 mg de ZOL (n = 1.054) nº (%)	Placebo (n = 1.057) nº (%)
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)

# HORIZON-Ensayo Clínico de fracturas recurrentes

## Resultados Mortalidad

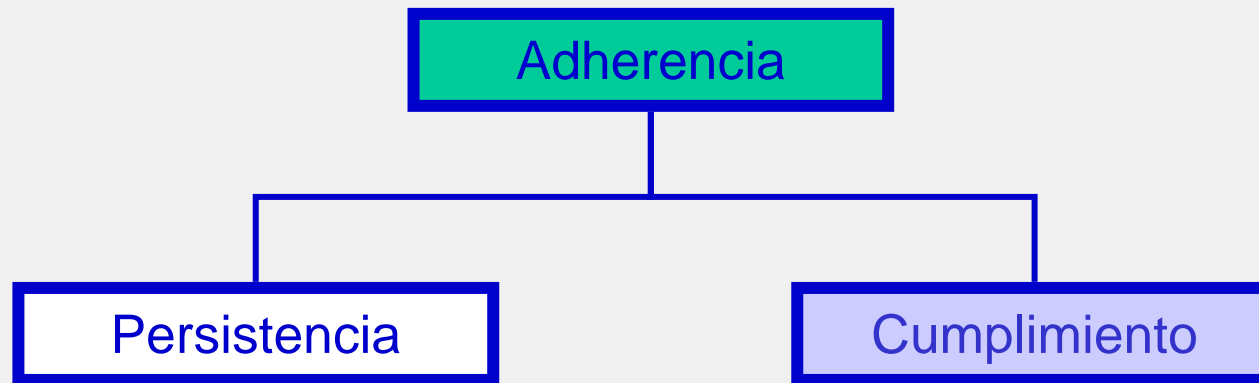


### Nº en riesgo

### Mes

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

# Algunos problemas con los bisfosfonatos



# Bisfosfonatos

## Soluciones a los problemas de adherencia

- Dosis mensuales
- Dosis trimestrales
- Dosis anuales

# Osteonecrosis de mandíbula

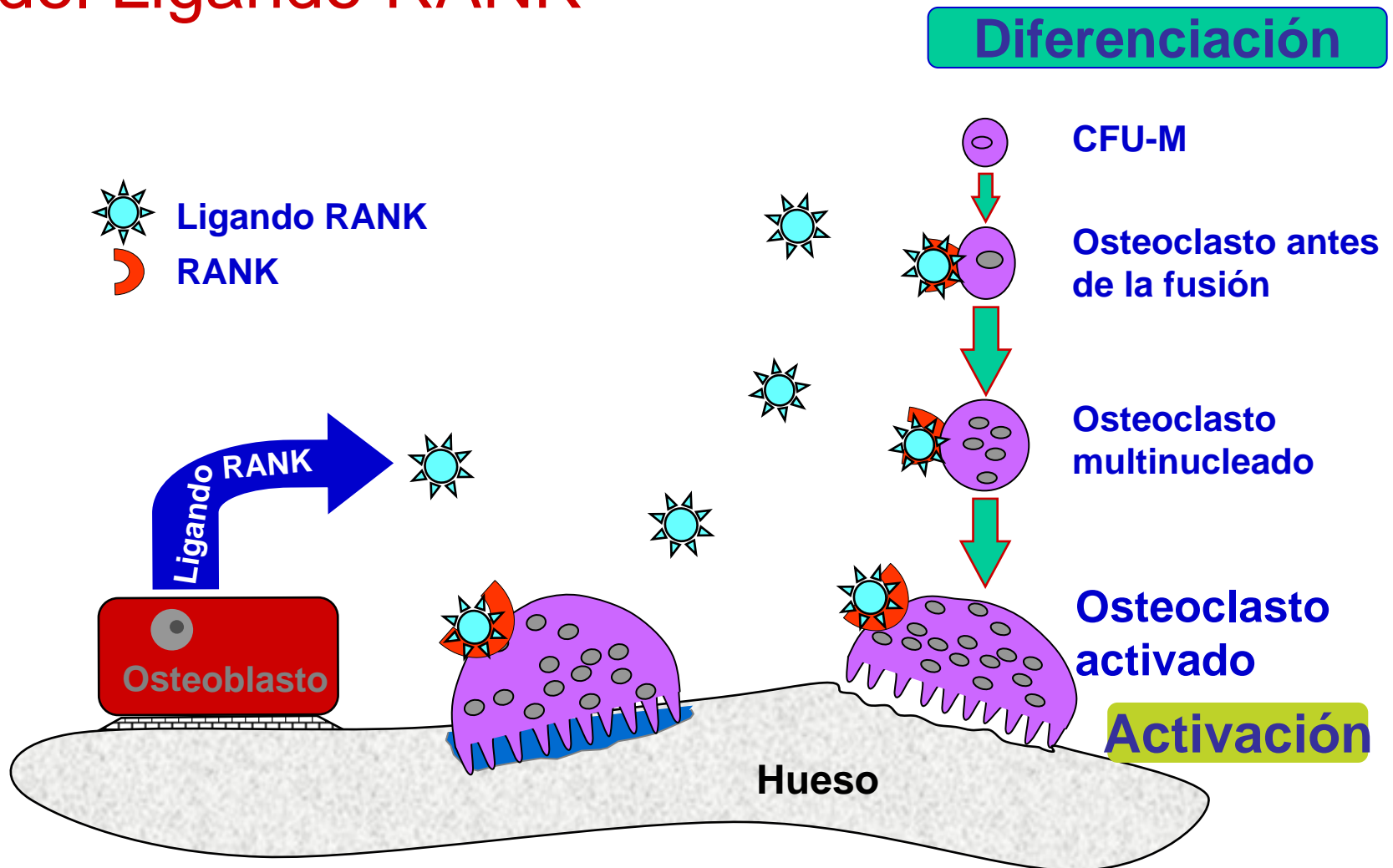


A los 2 meses

Paciente con mieloma y tratamiento con pamidronato

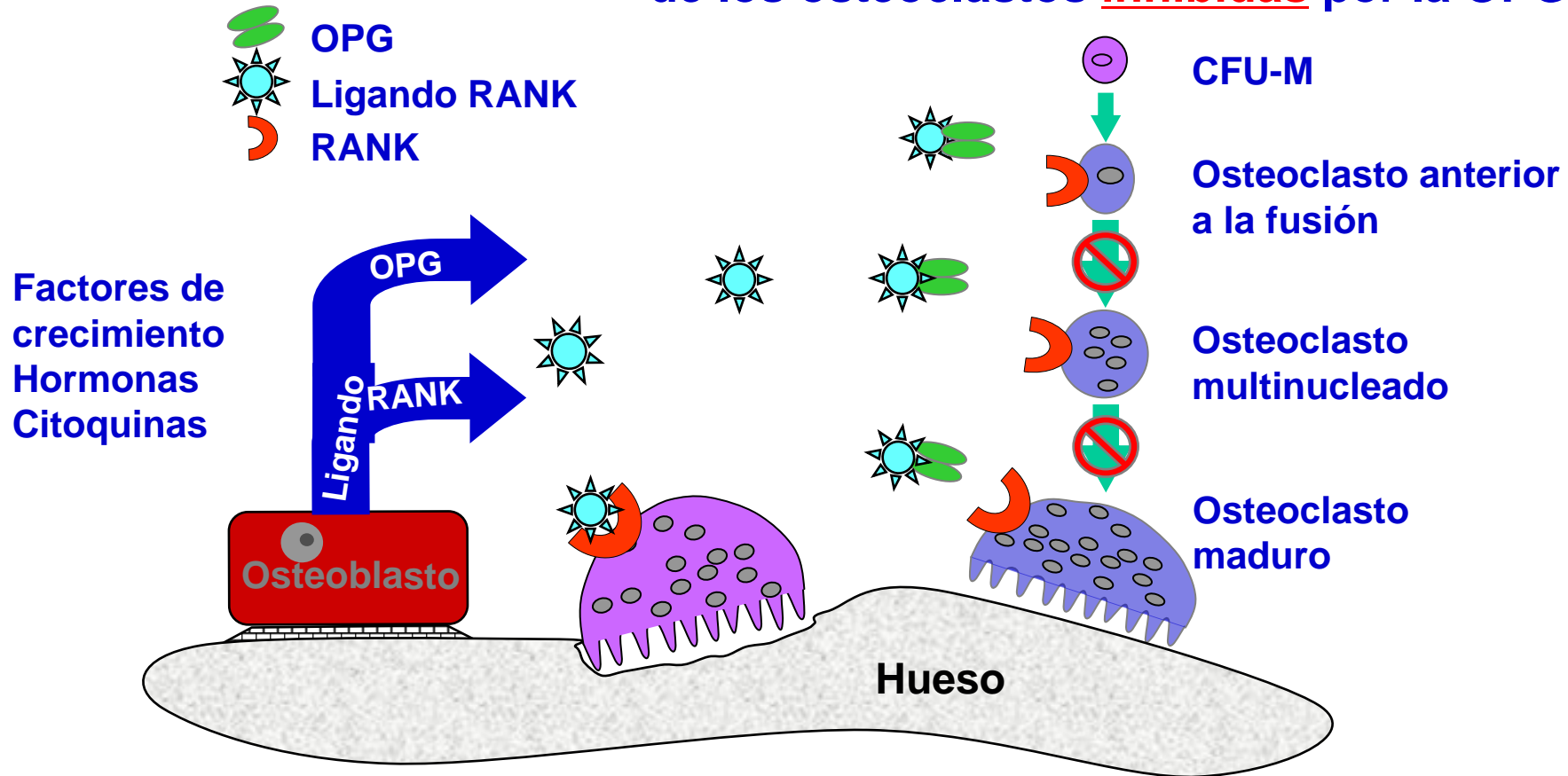


# La activación de los osteoclastos depende del Ligando RANK



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

Formación, activación y supervivencia de los osteoclastos **inhibidas** por la OPG



## 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:	<b>Amgen</b>
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:	<b>Eli Lilly and Company</b>
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:	<b>Wyeth</b>
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](#)

<b>Sponsored by:</b>	<b>Pfizer</b>
<b>Information provided by:</b>	Pfizer
<b>ClinicalTrials.gov Identifier:</b>	NCT00141323

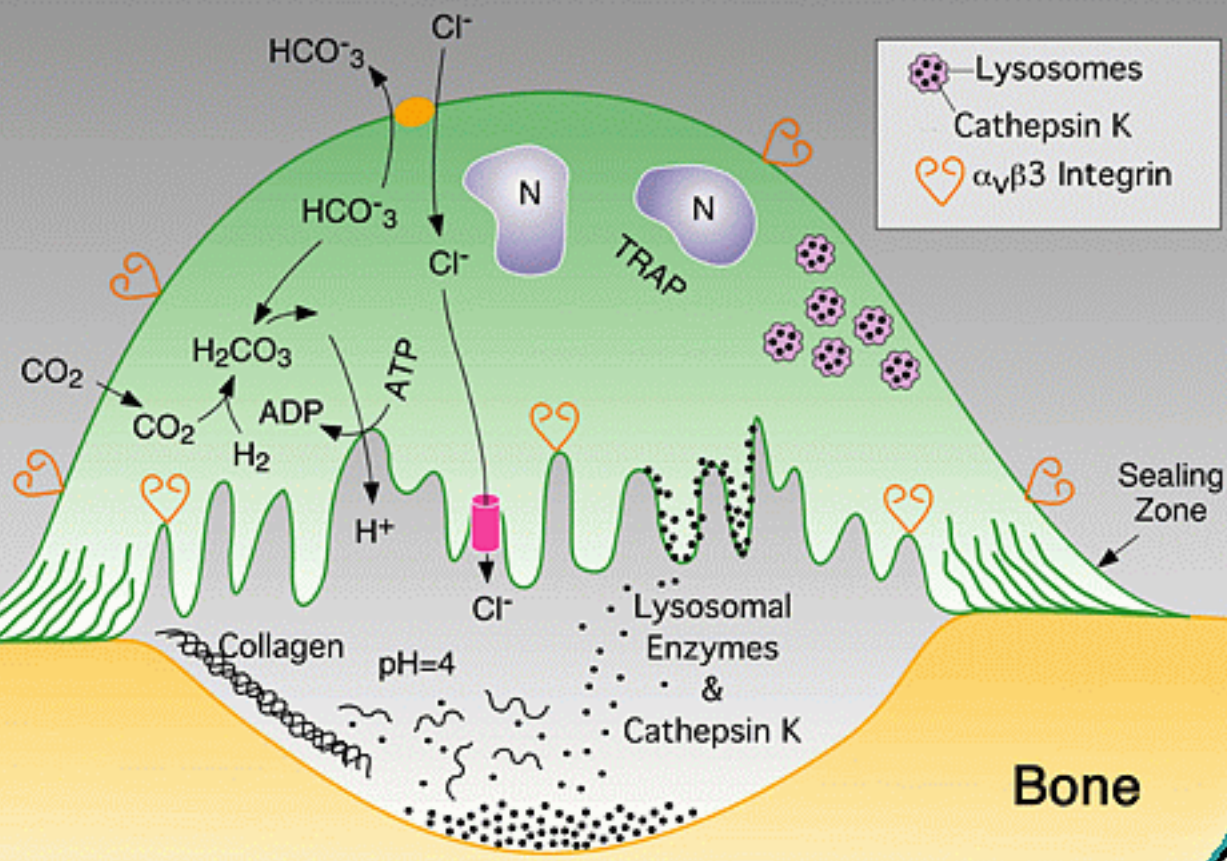
## Primary Outcome Measures:

- 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



## 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](#)

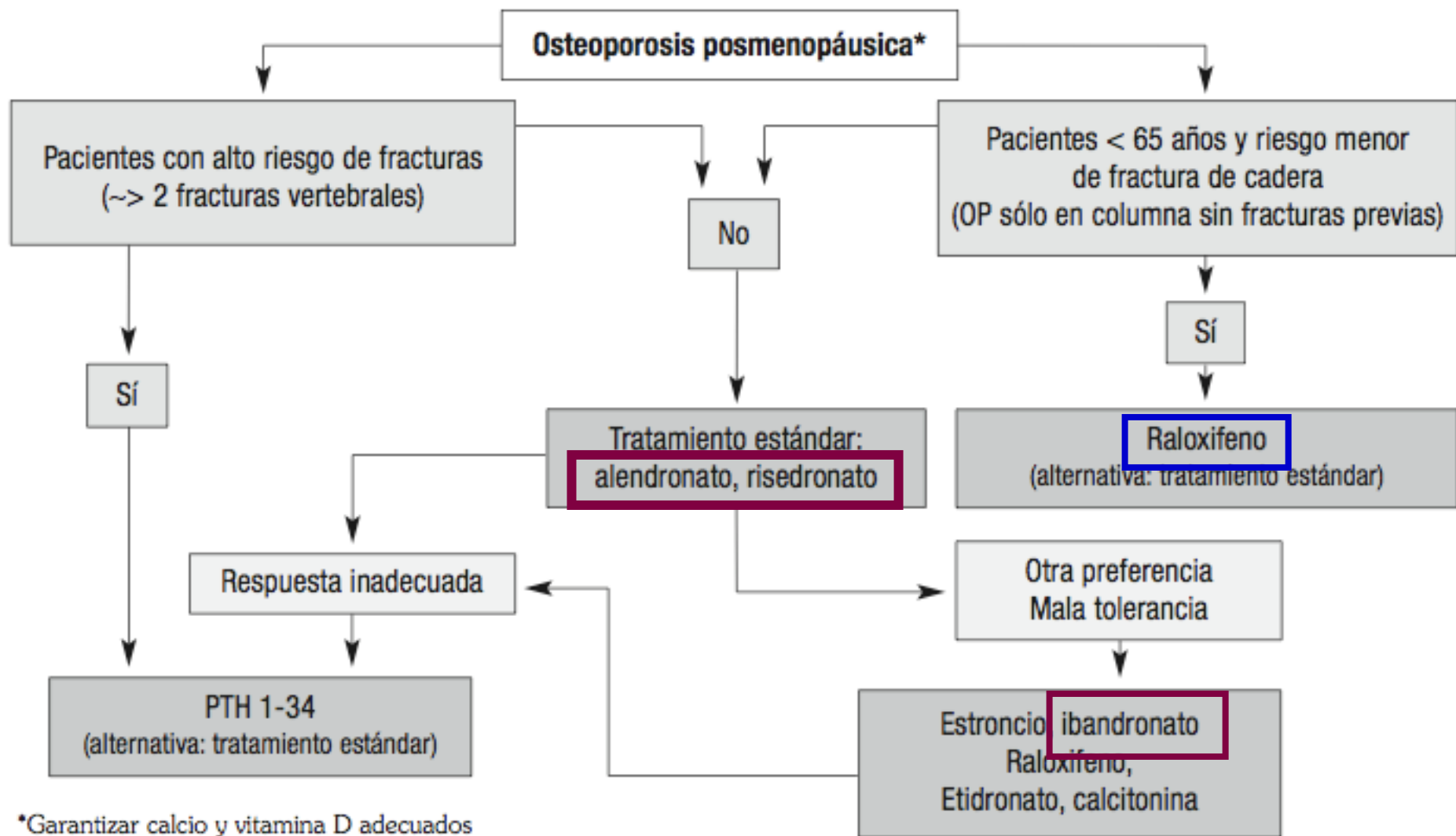
<b>Sponsored by:</b>	<b>Merck</b>
<b>Information provided by:</b>	Merck
<b>ClinicalTrials.gov Identifier:</b>	NCT00529373

### 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 ]



\*Garantizar calcio y vitamina D adecuados

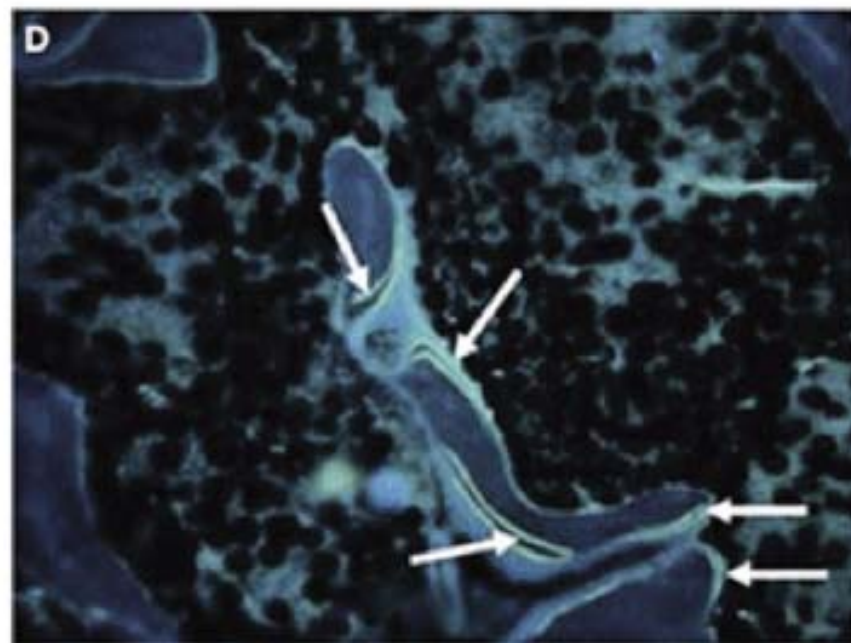
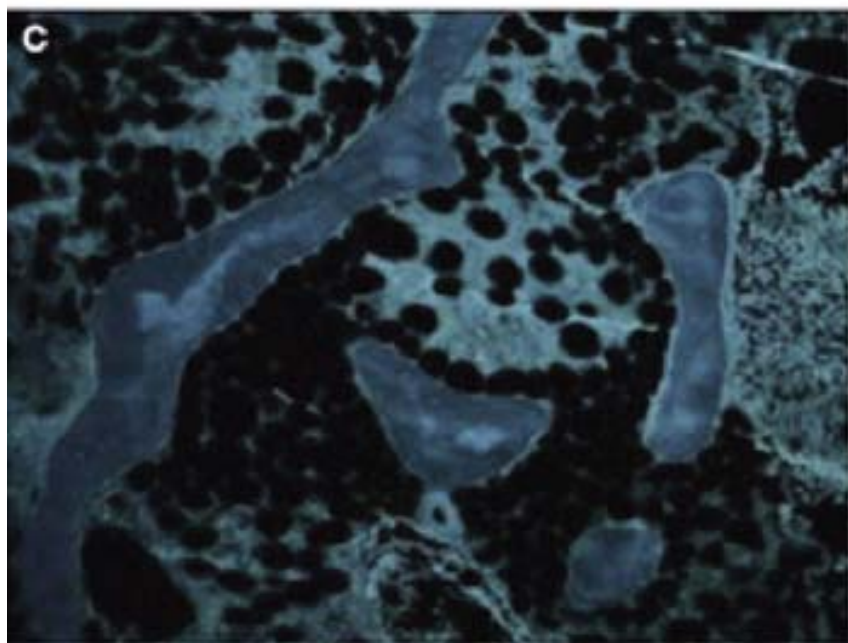
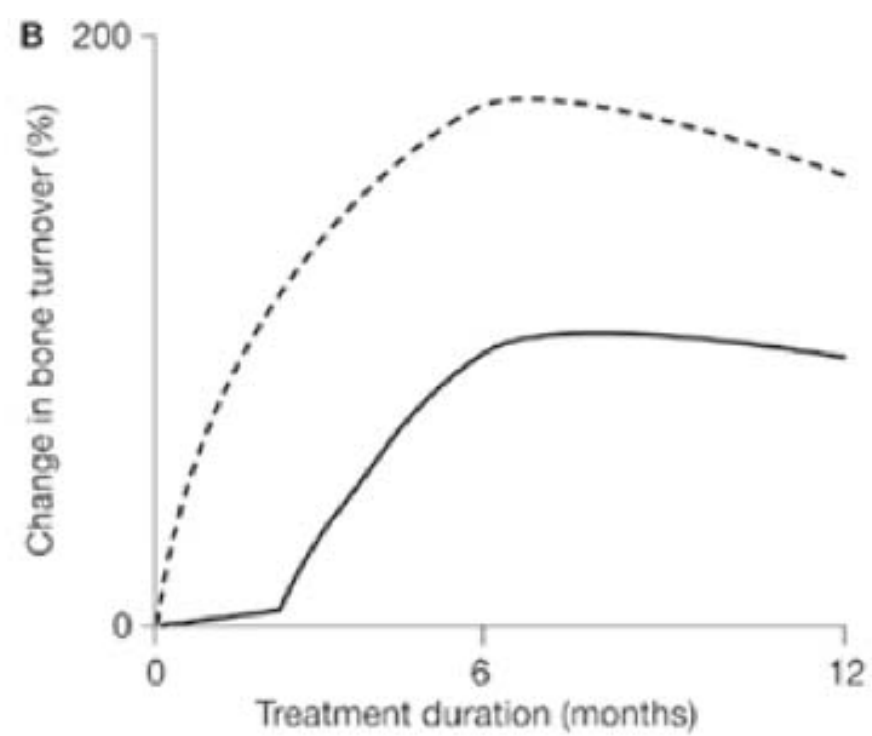
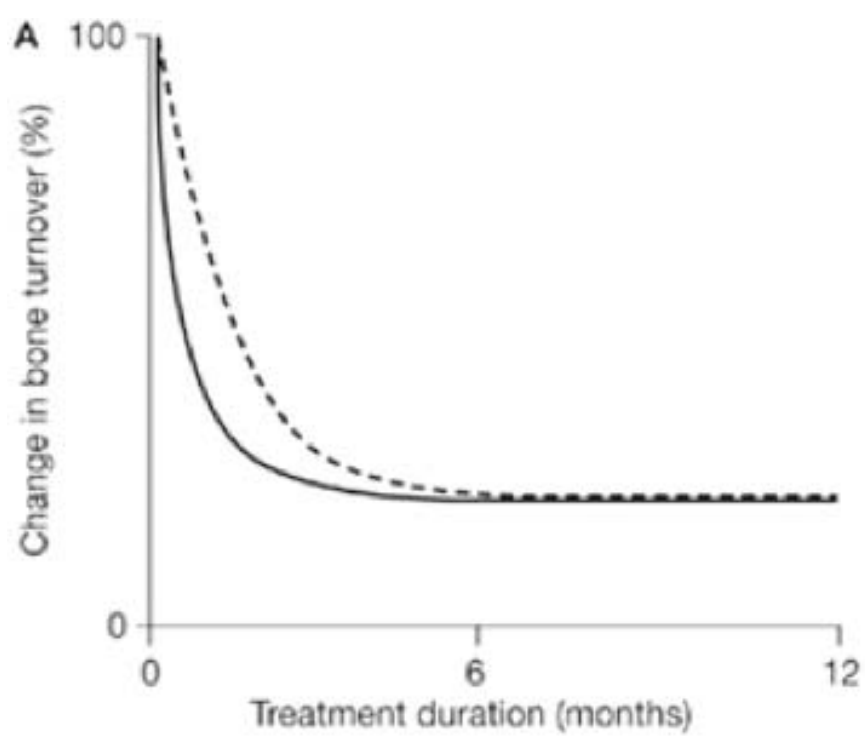


- Bisfosfonatos
  - Acido zoledrónico
- Anti- RANKL
  - Denosumab
- SERM
  - Arzoxifeno
  - Bezadoxifeno
  - Lasofoxifeno
- Inhibidores catepsina K
  - Odanacatib



	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%





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

