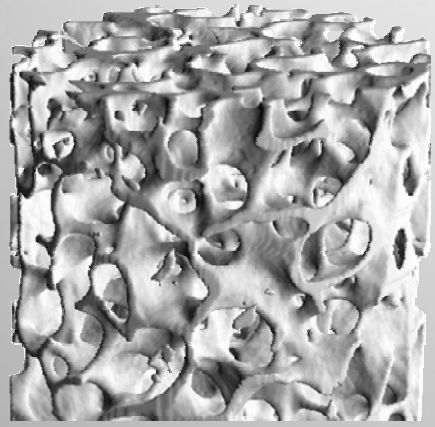
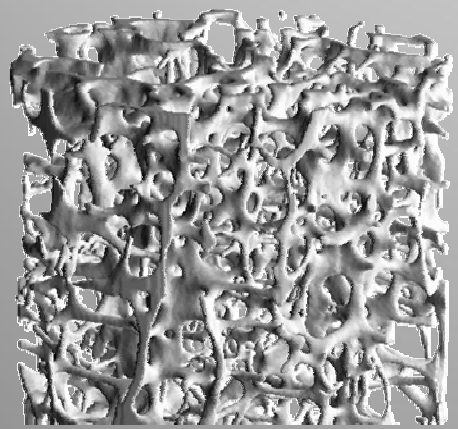
ODANACATIB

José Luis Pérez Castrillón
Hospital Río Hortega
Valladolid

Definición de Osteoporosis



Normal Bone

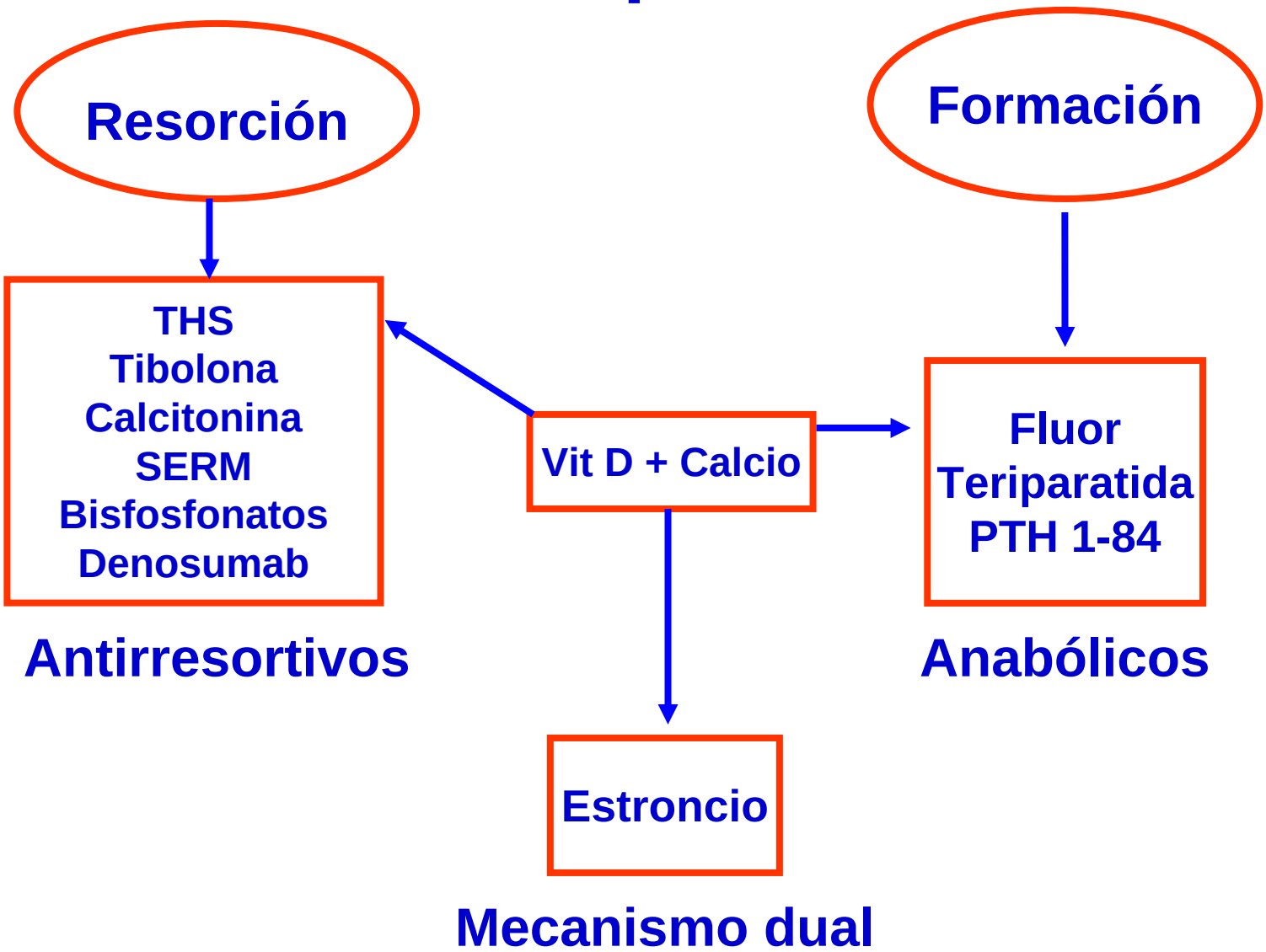


Osteoporotic Bone

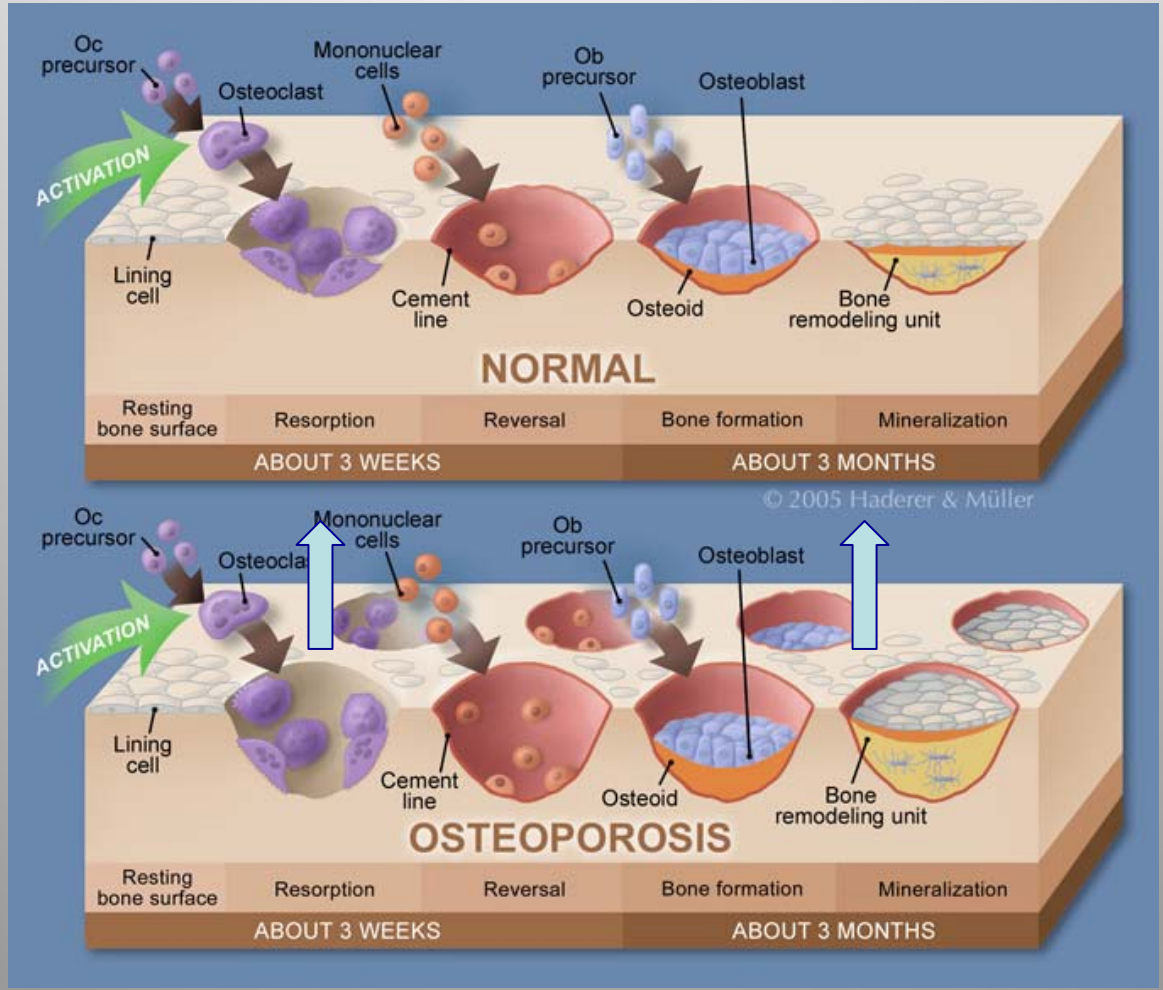
- Alteración esquelética caracterizada por una resistencia ósea comprometida que predispone a un incremento del riesgo de fractura.
- La resistencia ósea refleja la integración de dos hechos claves : densidad ósea y calidad ósea.

Images courtesy of Ralph Müller

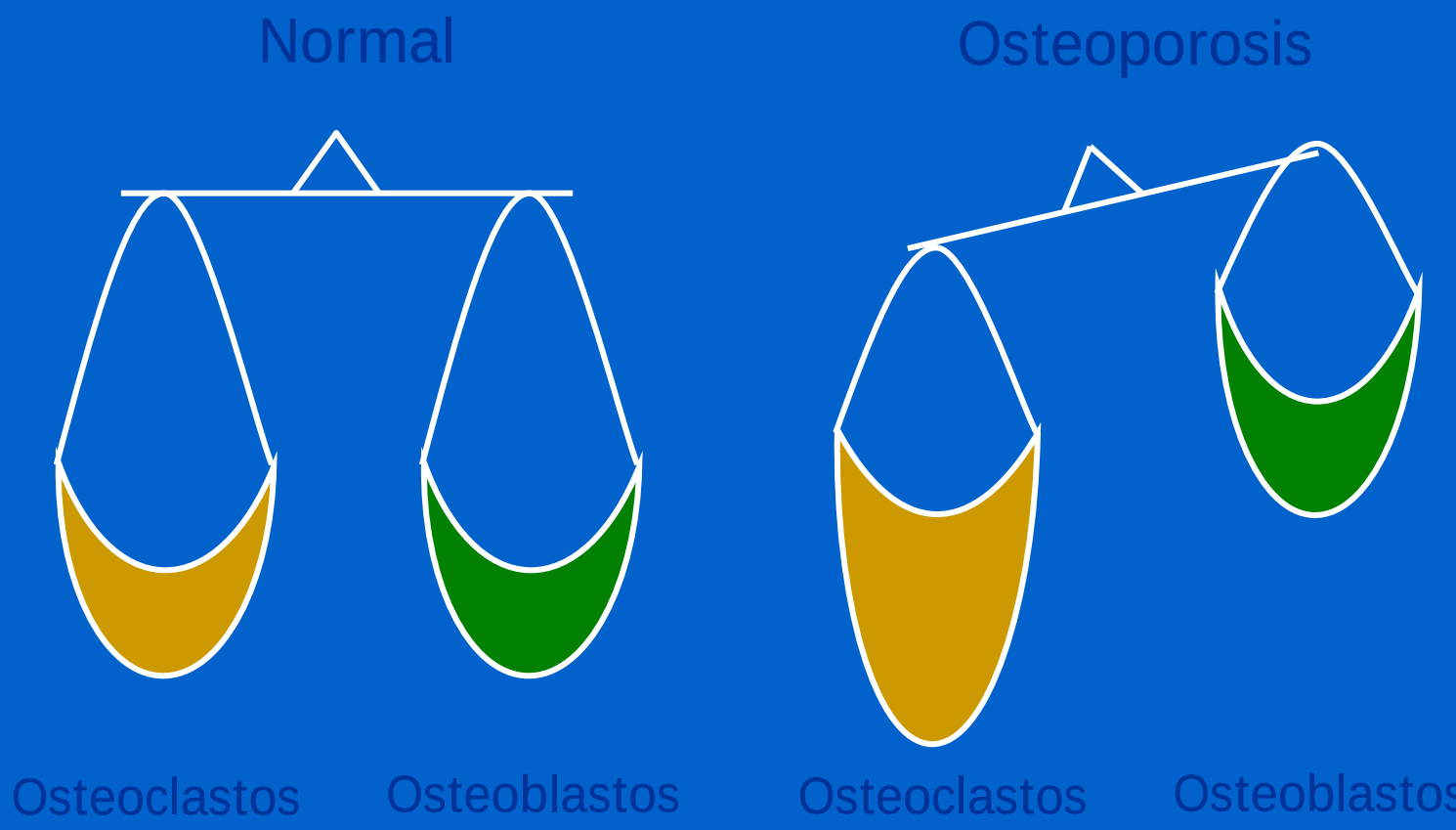
Tratamiento farmacológico de la osteoporosis

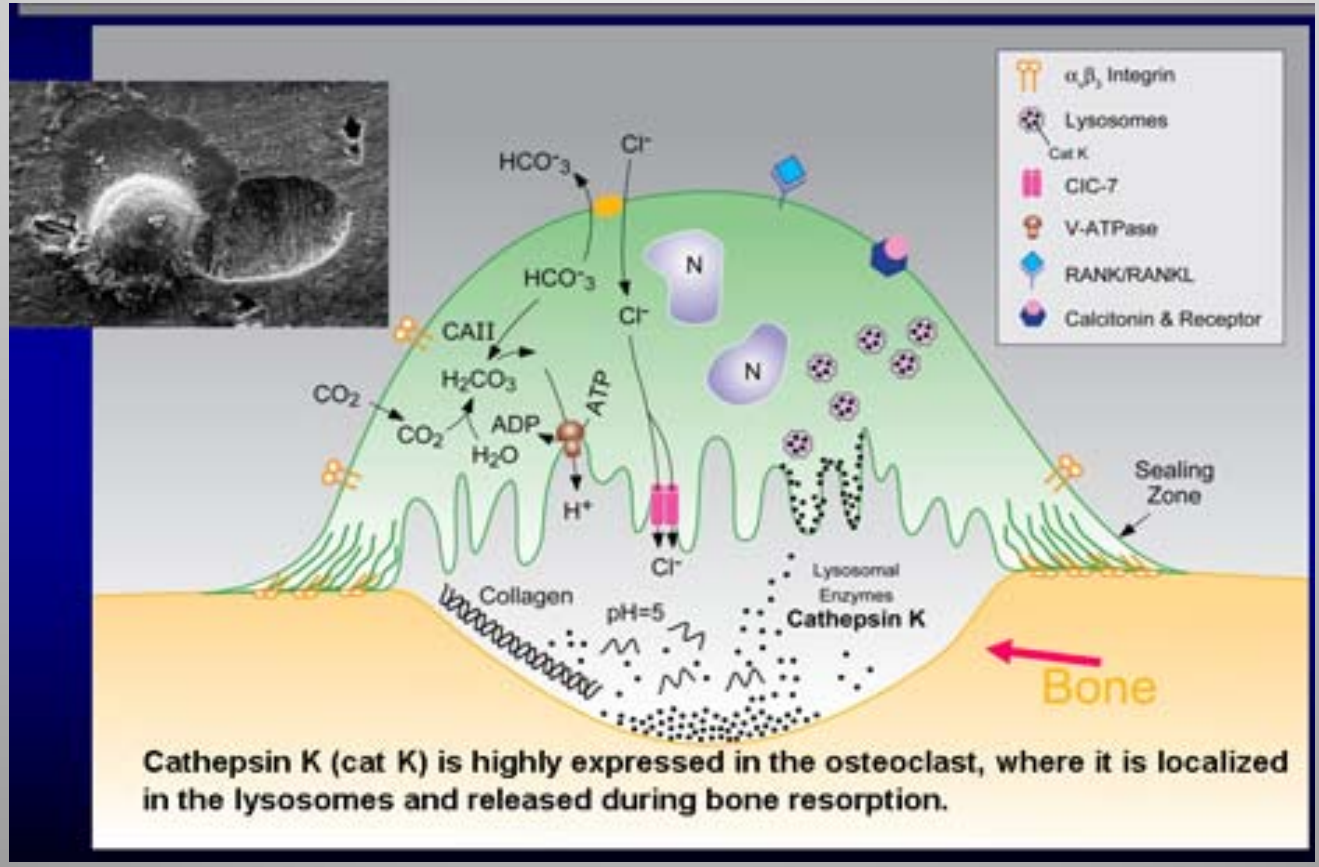


EL REMODELADO ÓSEO ESTÁ INCREMENTADO EN OSTEOPOROSIS



La osteoporosis es una enfermedad de desequilibrio metabólico entre la formación y la destrucción óseas, que provoca una pérdida de masa ósea y deterioro de su microarquitectura. Esto induce una pérdida de resistencia esquelética





Cathepsin K (cat K) is highly expressed in the osteoclast, where it is localized in the lysosomes and released during bone resorption.

CATEPSINAS HUMANAS

Existen 11 tipos diferentes de catepsinas expresadas en el genoma humano

- **Se localizan en lisosomas y son secretados de forma pericelular**

- **Son proteasas , mas eficaces a pH ácido**

- **Expresion ubicua: B,C.F,H,L,O,Z**
- **Expresión restringida K,S,W,V**

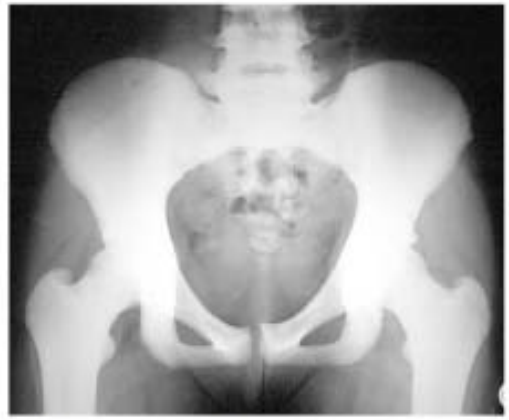
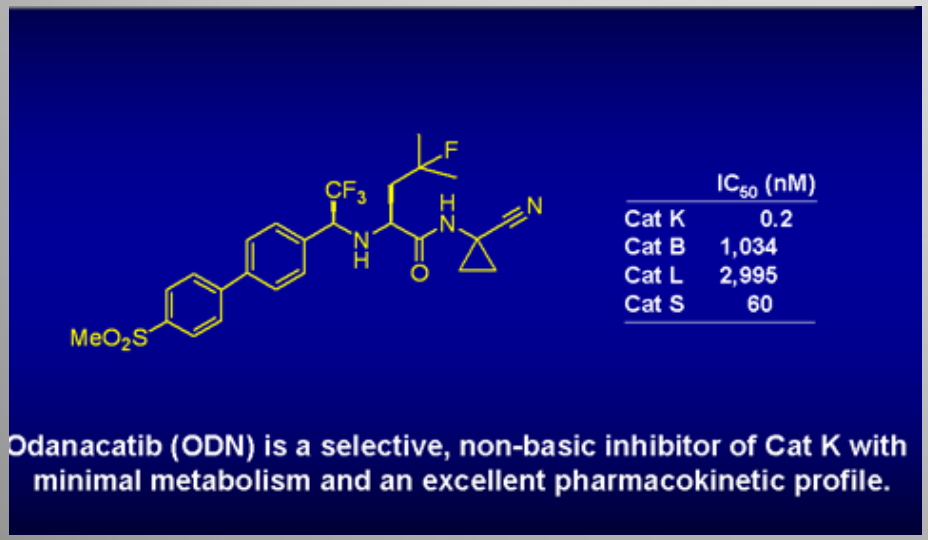
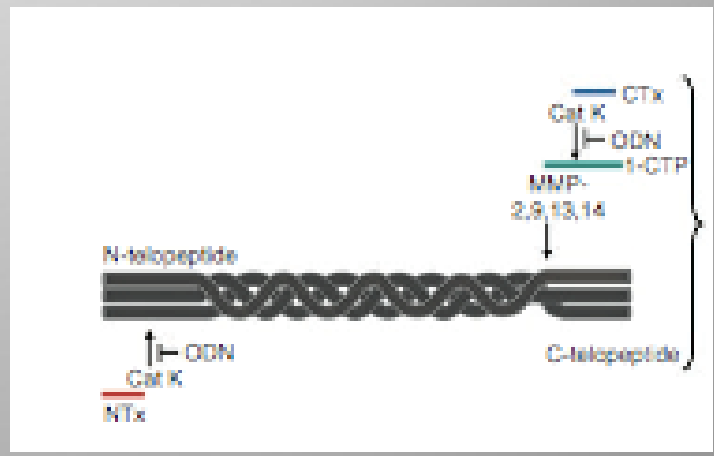


Figure 3. Pelvic and spinal x-ray: generalized increase of the bone density with more cortical and trabecular bone. Homogeneous osteosclerosis.

Picnodisostosis es una displasia ósea osteoescleerotica que cursa con talla baja, acreosteolisis en falanges distales y deformidades craneales.Está asociada a una mutación del gen de la catepsina K

ODANACATIB

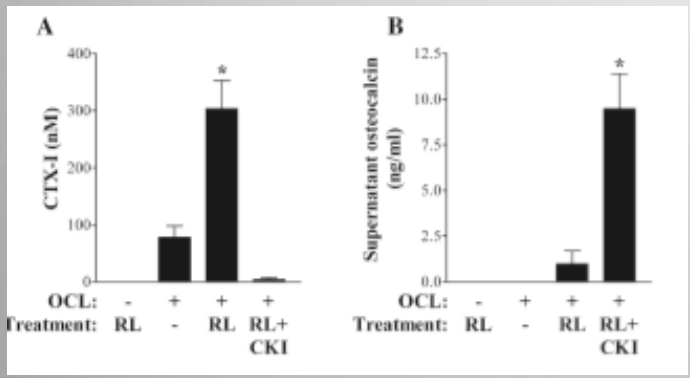

F
CF3
H
N
N
H
O
N
MeO2S
IC50 (nM)
Cat K 0.2
Cat B 1,034
Cat L 2,995
Cat S 60
Odanacatib (ODN) is a selective, non-basic inhibitor of Cat K with minimal metabolism and an excellent pharmacokinetic profile.


CTx
Cat K
ODN
t-CTP
MMP-
2,9,13,14
N-telopeptide
ODN
Cat K
NTx
C-telopeptide

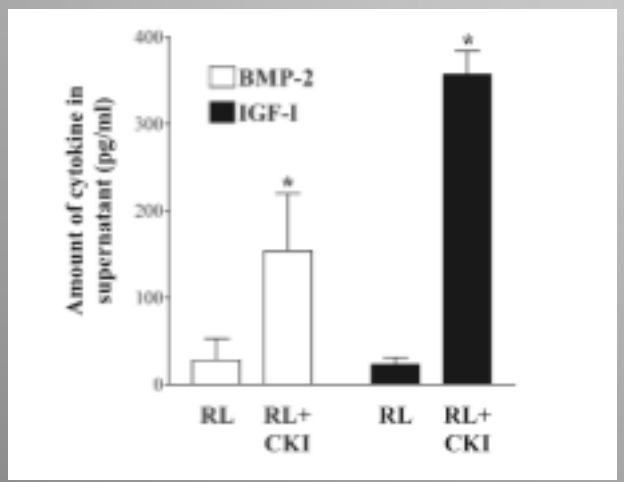
ELSEVIER
Bone 42 (2008) 200–211
BONE
www.elsevier.com/locate/bone

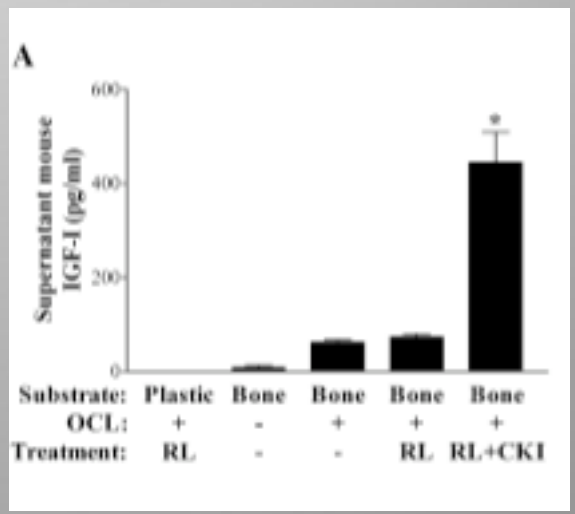
Cathepsin K inhibitors prevent matrix-derived growth factor degradation by human osteoclasts

Karen Fuller [a], Kevin M. Lawrence [a], Jade L. Ross [a], Urszula B. Grabowska [b], Masahiro Shiroo [b], Bertil Samuelsson [b], Timothy J. Chambers [a,*]



El inhibidor de la catepsina aumenta en el sobrenadantel las concentraciones de IGF-1 y BMP2





Bone 44 (2009) 199–207

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Bone density, strength, and formation in adult cathepsin K (−/−) mice

B. Pennypacker [a,*], M. Shea [b], Q. Liu [b], P. Masarachia [a], P. Saftig [c], S. Rodan [d], G. Rodan [†], D. Kimmel [a]

[a] Department of Molecular Endocrinology and Bone Biology, Merck Research Laboratories, WP26A-1000 West Point, PA 19486, USA
[b] Oregon Health Sciences University, Portland, OR, USA
[c] Christian-Albrechts Universität, Kiel, Germany
[d] Department of Biochemistry, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, USA

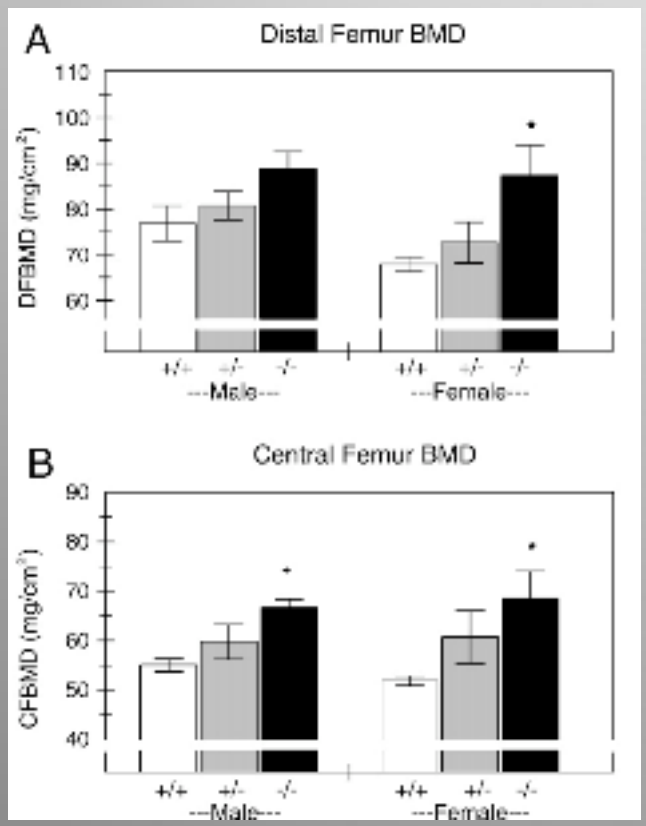


Table 2
Trabecular bone volume and microarchitecture (distal femur)

Sex	Genotype	Bone volume (BV/TV, %)	Trabecular thickness (Tb.Th, μm)	Trabecular number (Tb.N, #/mm)
M	Wild-type	12.4±1.6	38.1±3.2	3.16±1.2
M	+/−	16.6±3.0	44.8±4.7	3.60±3.1
M	(−/−)	21.1±1.8*	53.4±2.5*	3.95±2.5
F	Wild-type	5.2±0.7	26.9±1.5	1.84±1.0
F	+/−	14.2±3.5*	40.0±5.1*	3.22±1.7*
F	(−/−)	29.4±4.6*	66.1±5.2*	4.35±1.9*
	Genotype effect	<0.0001	<0.0001	<0.0001
	Gender effect	0.3262	0.0253	0.0025
	Interaction	0.0143	0.0038	0.0077

Mean±SEM. *Significantly different from WT of same gender (*P<0.05).

Los ratones Knockout tenían mayor masa ósea y mejor calidad ósea que los ratones no manipulados

DESARROLLO CLÍNICO DE UN FÁRMACO

- ESTUDIOS PRECLÍNICOS
- ESTUDIOS FASE I
- ESTUDIOS FASE II
- ESTUDIOS FASE III
- ESTUDIOS FASE IV

ESTUDIO FASE I

Clinical Pharmacology & Therapeutics (2009); **86**, 2, 175–182 doi:10.1038/clpt.2009.60

Effect of the Cathepsin K Inhibitor Odanacatib on Bone Resorption Biomarkers in Healthy Postmenopausal Women: Two Double-Blind, Randomized, Placebo-Controlled Phase I Studies

S A Stoch[1], S Zajic[1], J Stone[1], D L Miller[1], K Van Dyck[1], M J Gutierrez[2], M De Decker[3], L Liu[1], Q Liu[1], B B Scott[1], D Panebianco[1], B Jin[1], L T Duong[1], K Gottesdiener[1] and J A Wagner[1]

- **Estudio doble ciego, randomizado, comparado con placebo**
- **Mujeres sanas postmenopausicas:**
  < 75 años en dosis semanal (n: 49)
  < 70 años en dosis diaria (n: 30)
- **Dosis semanal: 5,25,50,100 mg**
- **Dosis diaria: 0,5, 2,5, 10 mg**
- **Duración estudio 21 dias**
- **No se administró calcio ni vitamina D**

Clinical Pharmacology & Therapeutics (2009); **86**, 2, 175–182 doi:10.1038/clpt.2009.60

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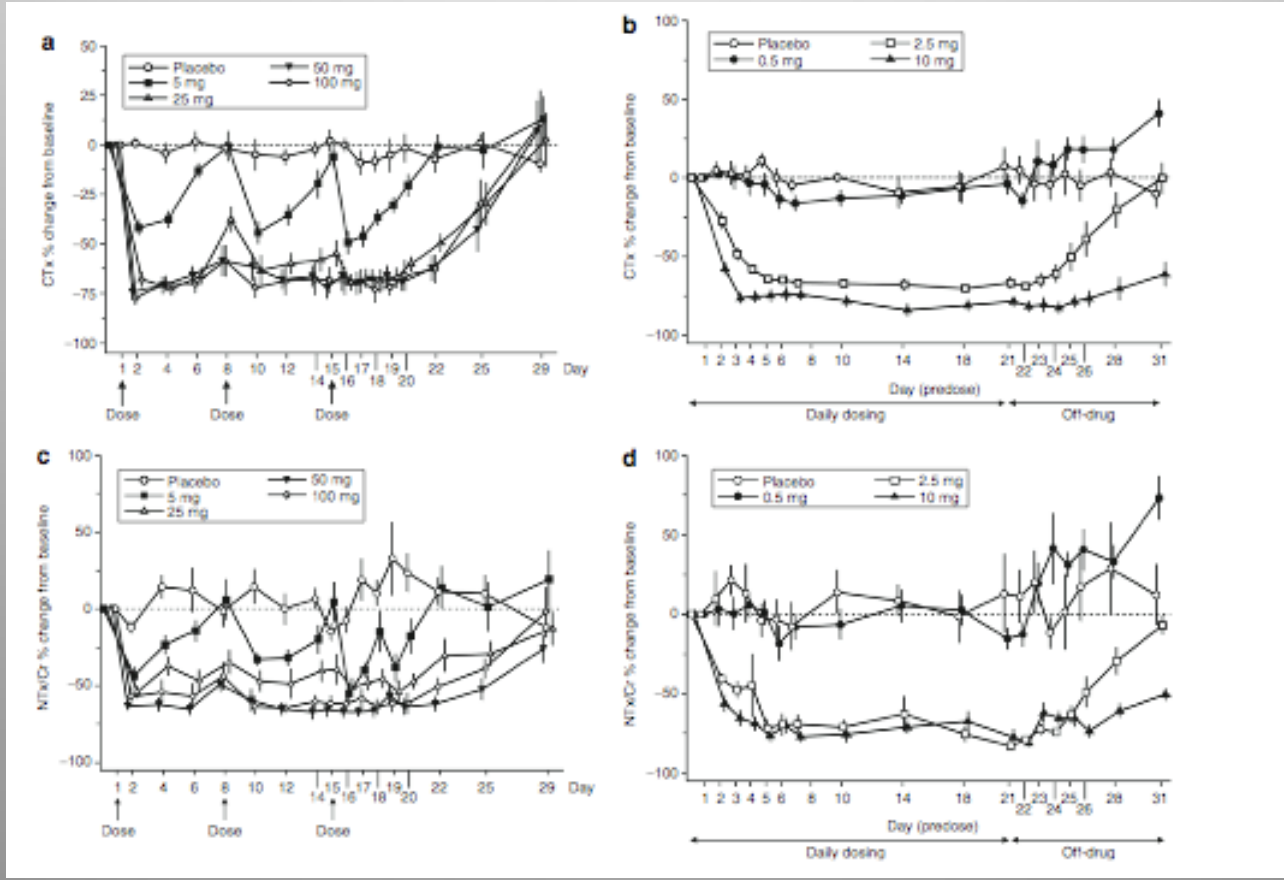
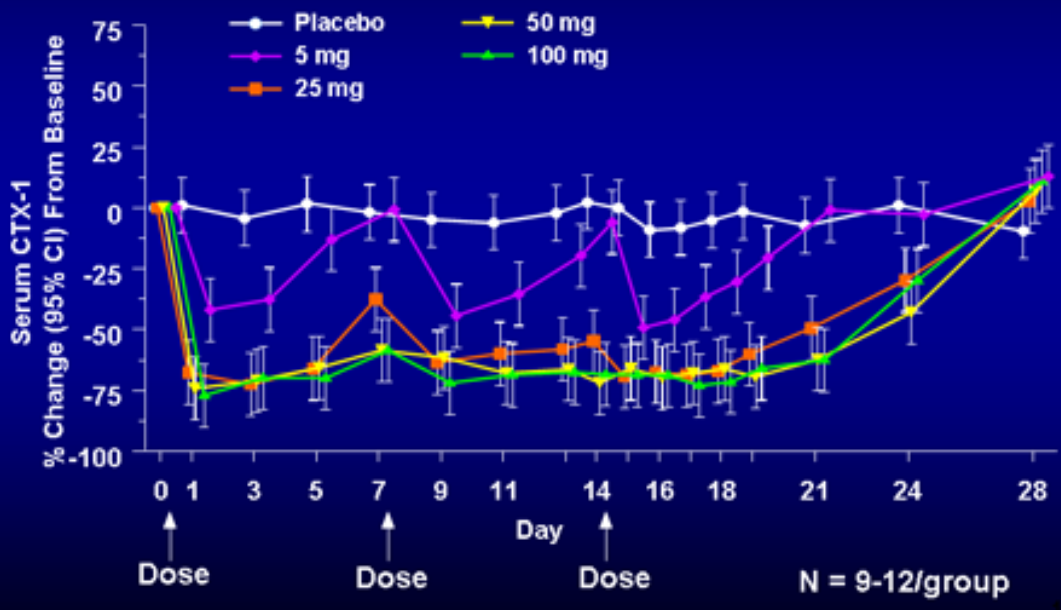


Phase I: ODN and Bone Resorption After 3 Weeks of Once-weekly Dosing



ESTUDIO FASE II

CLINICAL TRIALS

JBMR

Odanacatib, a Cathepsin-K Inhibitor for Osteoporosis: A Two-Year Study in Postmenopausal Women With Low Bone Density

Henry G Bone,[1] Michael R McClung,[2] Christian Roux,[3] Robert R Recker,[4] John A Eisman,[5] Nadia Verbruggen,[6] Carolyn M Hustad,[7] Carolyn DaSilva,[7] Arthur C Santora,[7] and B Avery Ince[7]

Journal of Bone and Mineral Research, Vol. 25, No. 5, May 2010, pp 937–947

ESTUDIO FASE II

- Estudio doble ciego, randomizado, comparado con placebo
- Mujeres postmenopausicas (> 5 años de la última regla) con DMO entre -2 y -3.5 en cualquier localización
- N : 399 pacientes, completaron el estudio 331 (83.6 %). Se incluyeron en la extensión 320 de las que completaron los 24 meses 270 (70 %)
- Dosis semanal: 3,10,25,50 mg
- Duración estudio 12 meses con extension programada de 24
- Se administró calcio (500mg/dia) y vitamina D (5600 UI/semana)

CLINICAL TRIALS

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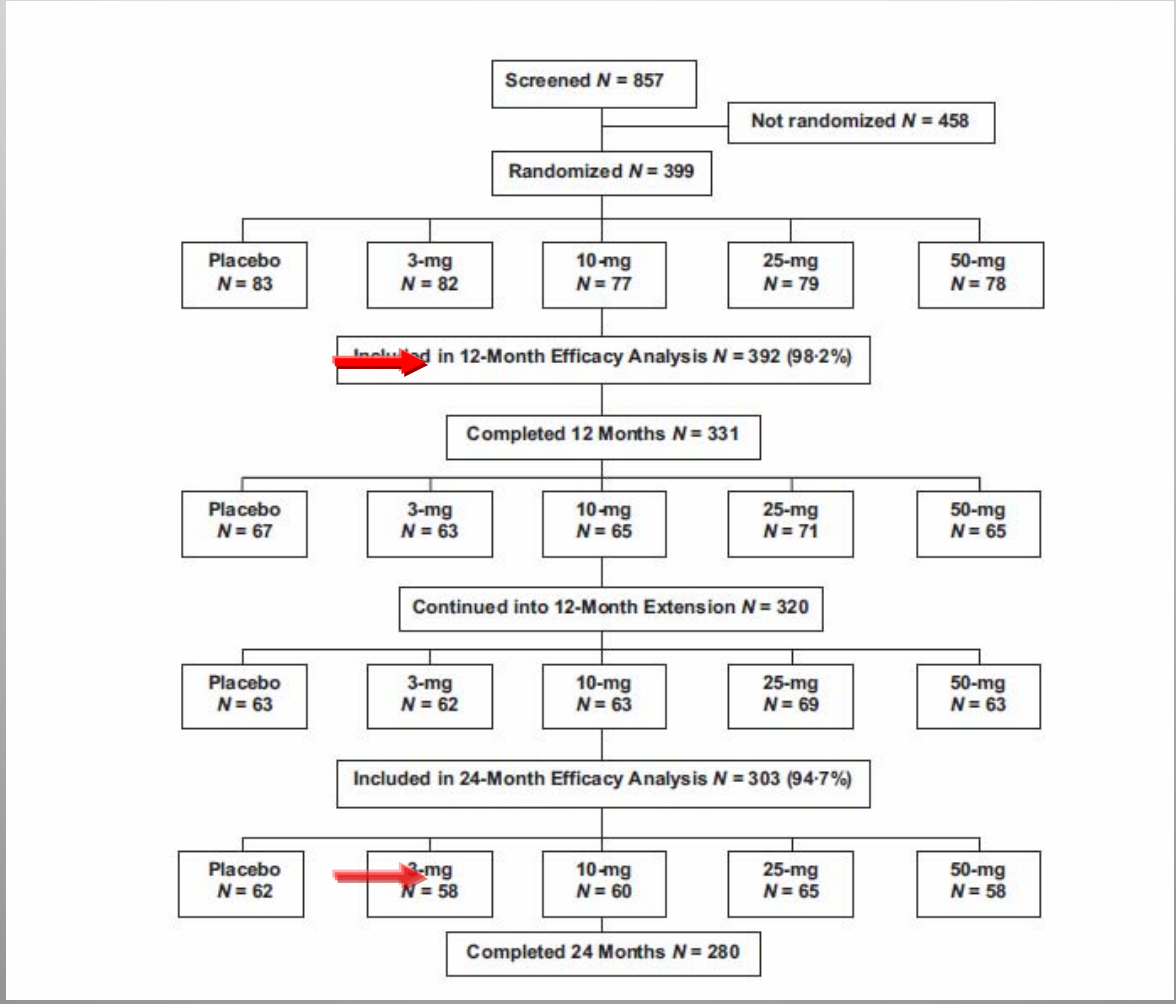

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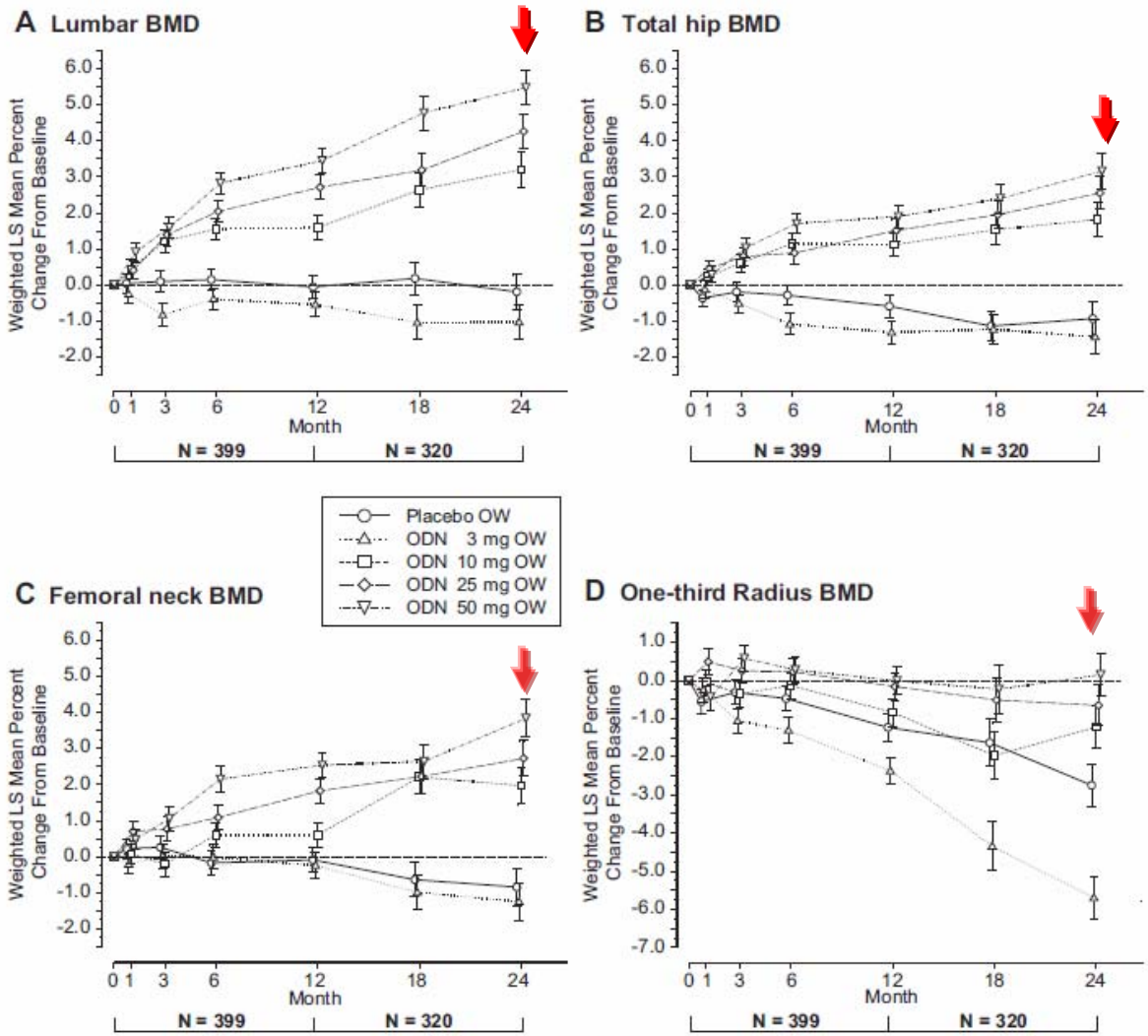

No data are being carried forward from the base study to the extension period.

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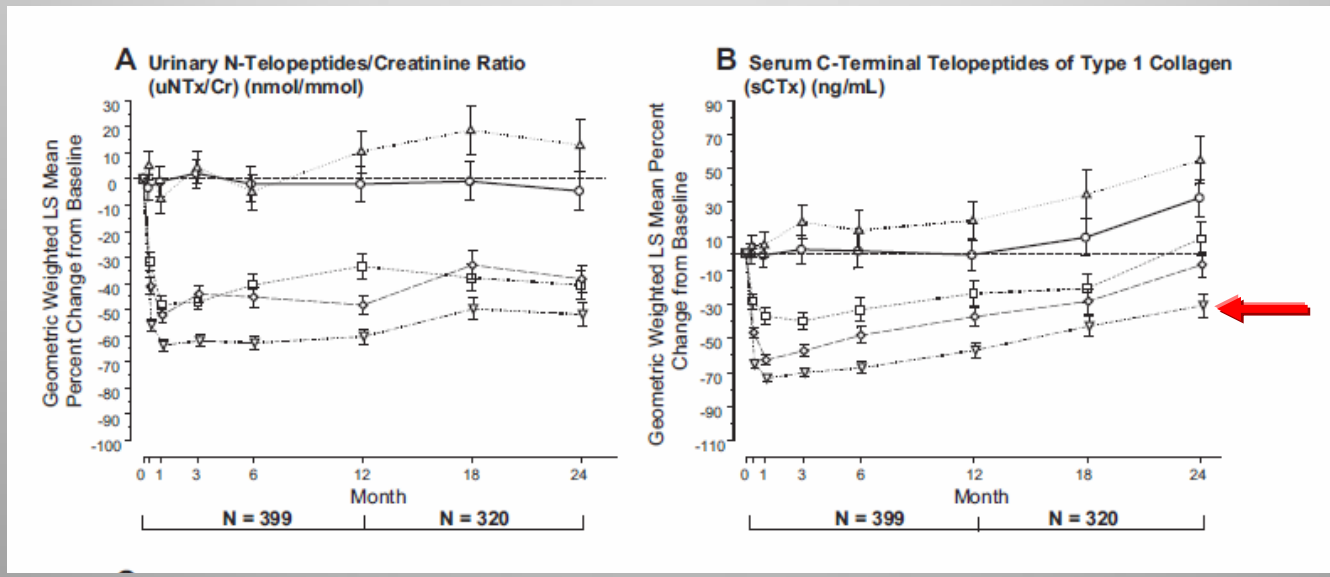

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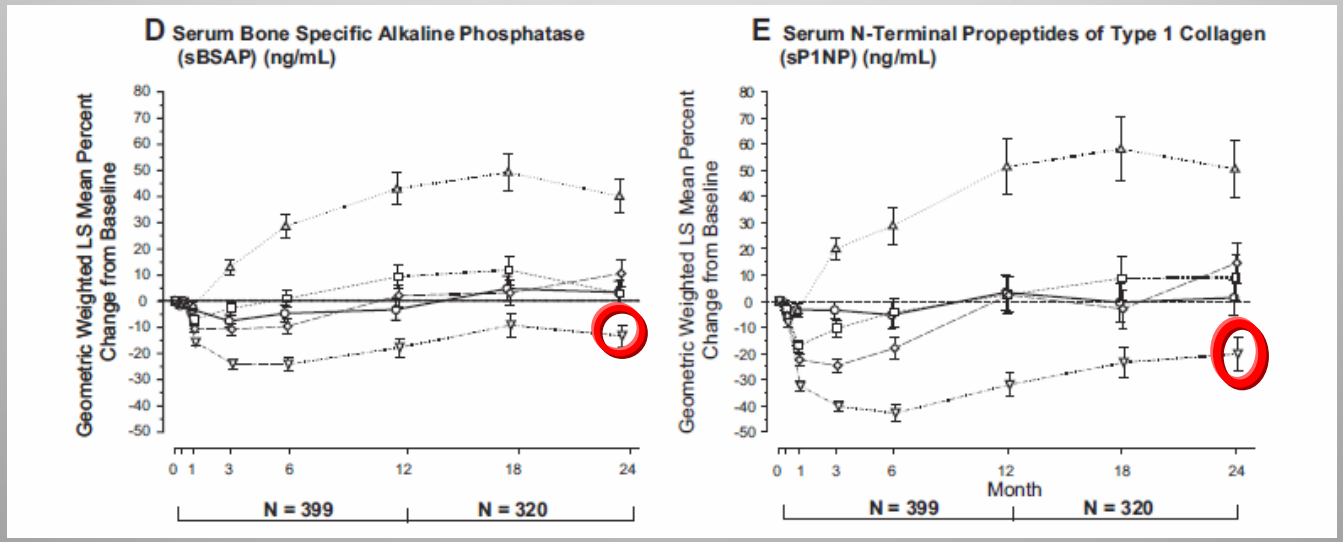

EFECTOS ADVERSOS

	Placebo	OD (3 mg)	OD (10 mg)	OD (25 mg)	OD (50 mg)
EA clínicos	77 (92.8 %)	76 (92.7 %)	73 (94.8 %)	72 (91.1 %)	72 (92.3 %
EA serios	8 (9.6 %)	12(14.6 %)	10 (13 %)	9 (11.4 %)	14 (13.9%)
EA cutáneos	19 (22.9 %)	18 (22 %)	16 (20.8 %)	20 (25.3 %)	19 (24.4 %)
Abandono por EA	11 (13.3 %	13 (15.9 %)	13 (19.9 %)	6 (7.6 %)	13 (16.7 %)
Abandono por EA Cutaneos	2 (2.4 %)	3 (3.7 %)	2 (2.6 %)	0	4 (5.1 %)

ORIGINAL ARTICLE

JBMR

Odanacatib in the Treatment of Postmenopausal Women With Low Bone Mineral Density: Three-Year Continued Therapy and Resolution of Effect

John A Eisman,[1] Henry G Bone,[2] David J Hosking,[3] Michael R McClung,[4] Ian R Reid,[5] Rene Rizzoli,[6] Heinrich Resch,[7] Nadia Verbruggen,[8] Carolyn M Hustad,[9] Carolyn DaSilva,[9] Romana Petrovic,[8] Arthur C Santora,[9] B Avery Ince,[9] and Antonio Lombardi[9]

Journal of Bone and Mineral Research, Vol. 26, No. 2, February 2011, pp 242–251

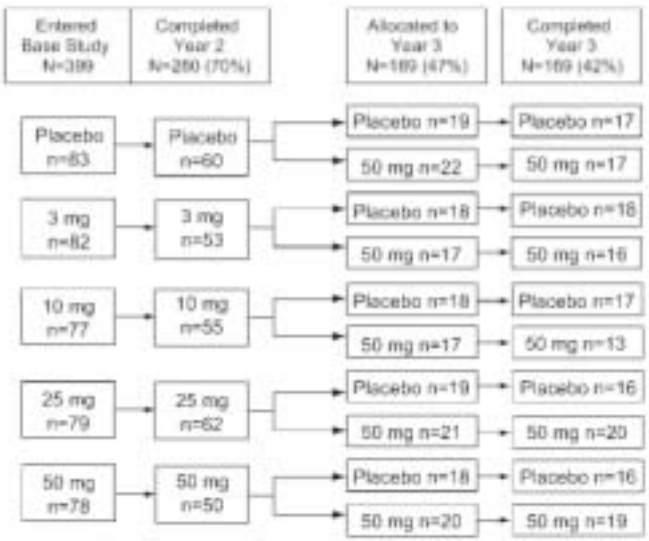

Fig. 1. Patient randomization in extension study.

Table 1. Baseline Patient Characteristics of Women in Year 3 Extension

	Placebo (*N* = 92)		ODN 50 mg (*N* = 97)	
	n	%	*n*	%
Age (years)[a]				
<65	50	54.3	56	57.7
≥65	42	45.7	41	42.3
Mean (SD)	63.8 (8.2)		64.2 (6.9)	
Race				
Asian	1	1.1	0	
Black	1	1.1	0	
White	65	70.7	73	75.3
All others	25	27.2	24	24.7
Years since last menses				
Mean (SD)	16.7 (9.6)		18.4 (9.0)	
Age at last menses				
Mean (SD), years	47.1 (6.9)		45.8 (6.7)	
T-scores (mean ± SD)				
Lumbar spine	−2.2 ± 0.8		−2.2 ± 0.7	
Total hip	−1.5 ± 0.7		−1.4 ± 0.8	
Femoral neck	−1.8 ± 0.7		−1.8 ± 0.7	
Trochanter	−1.3 ± 0.7		−1.1 ± 0.8	

SD = Standard deviation.
[a]Age at baseline of base study.

ORIGINAL ARTICLE

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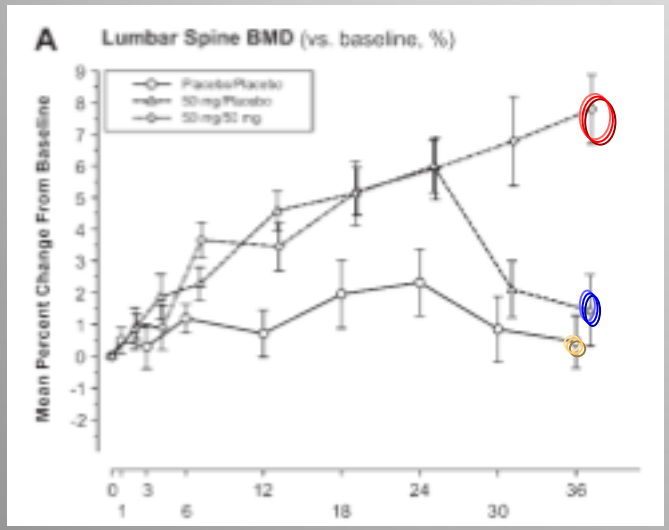

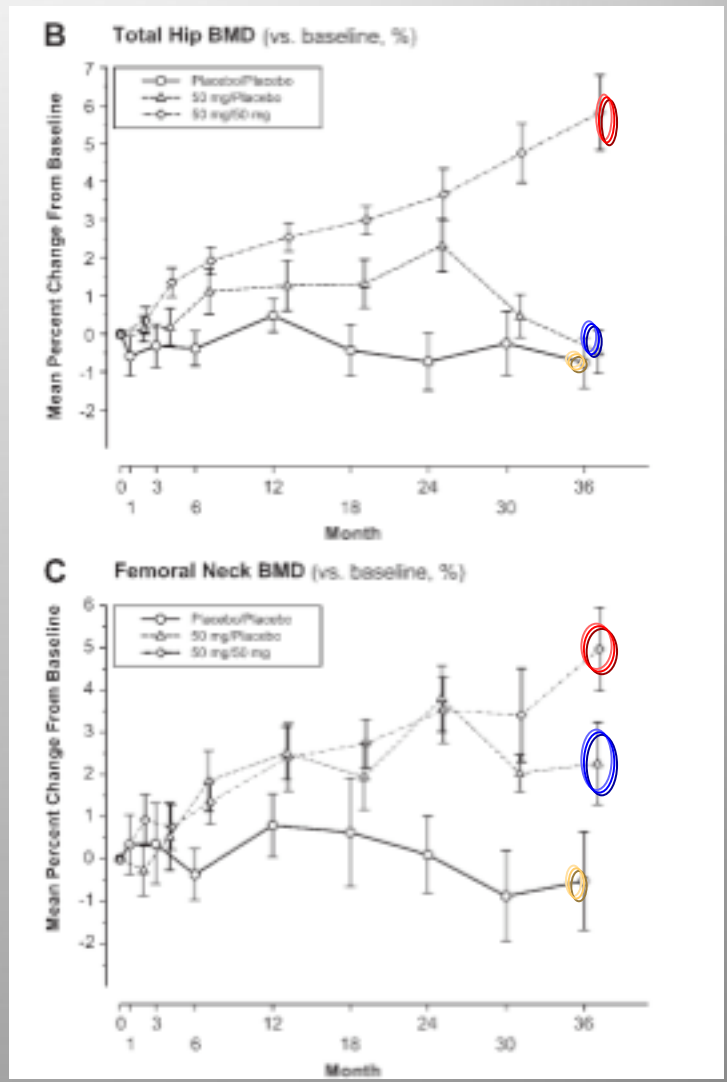

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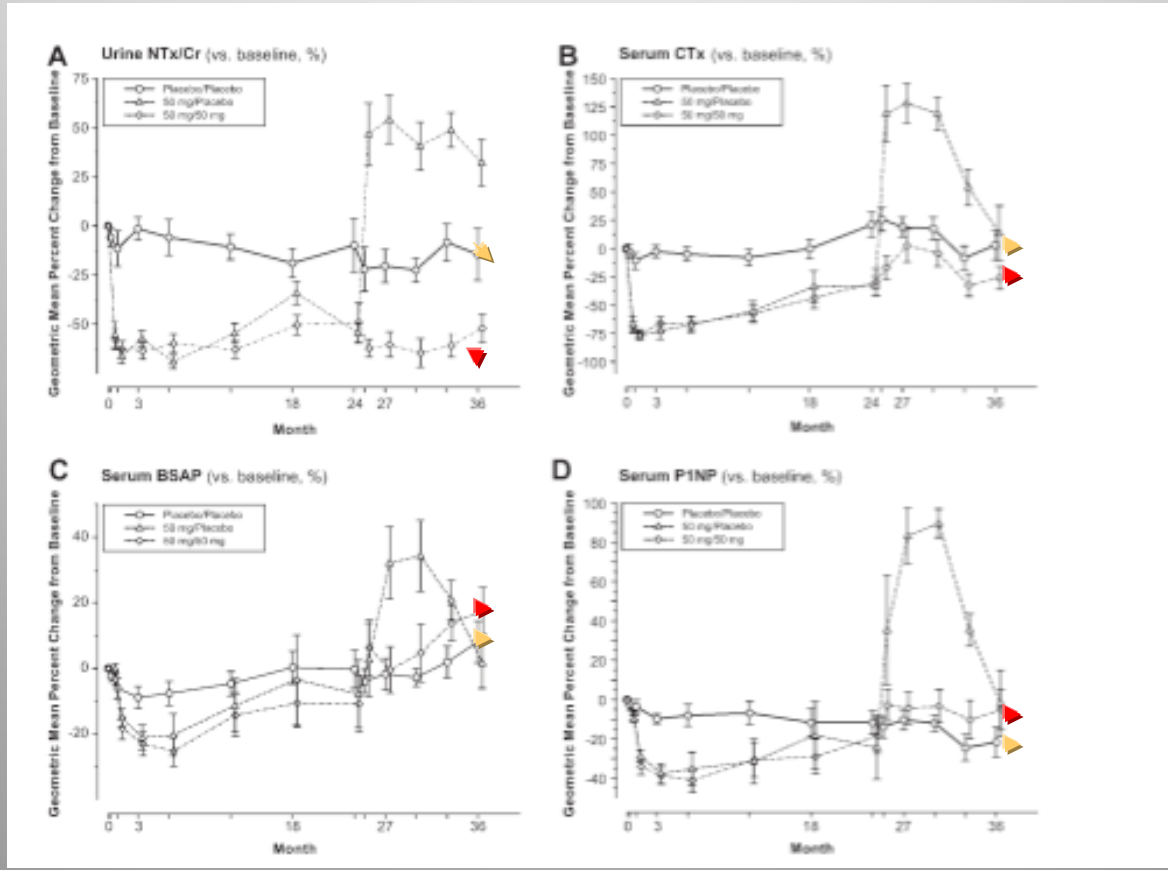

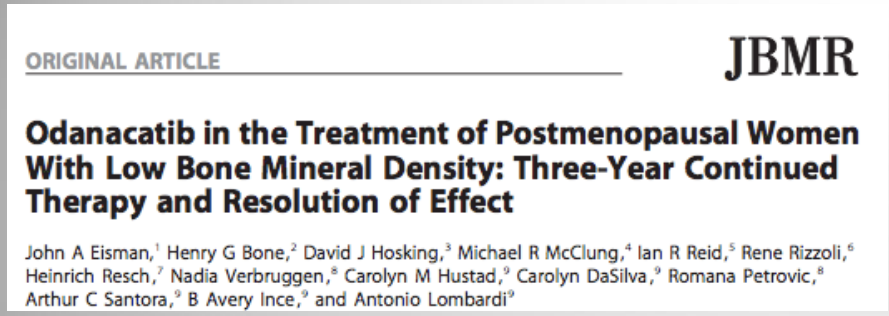

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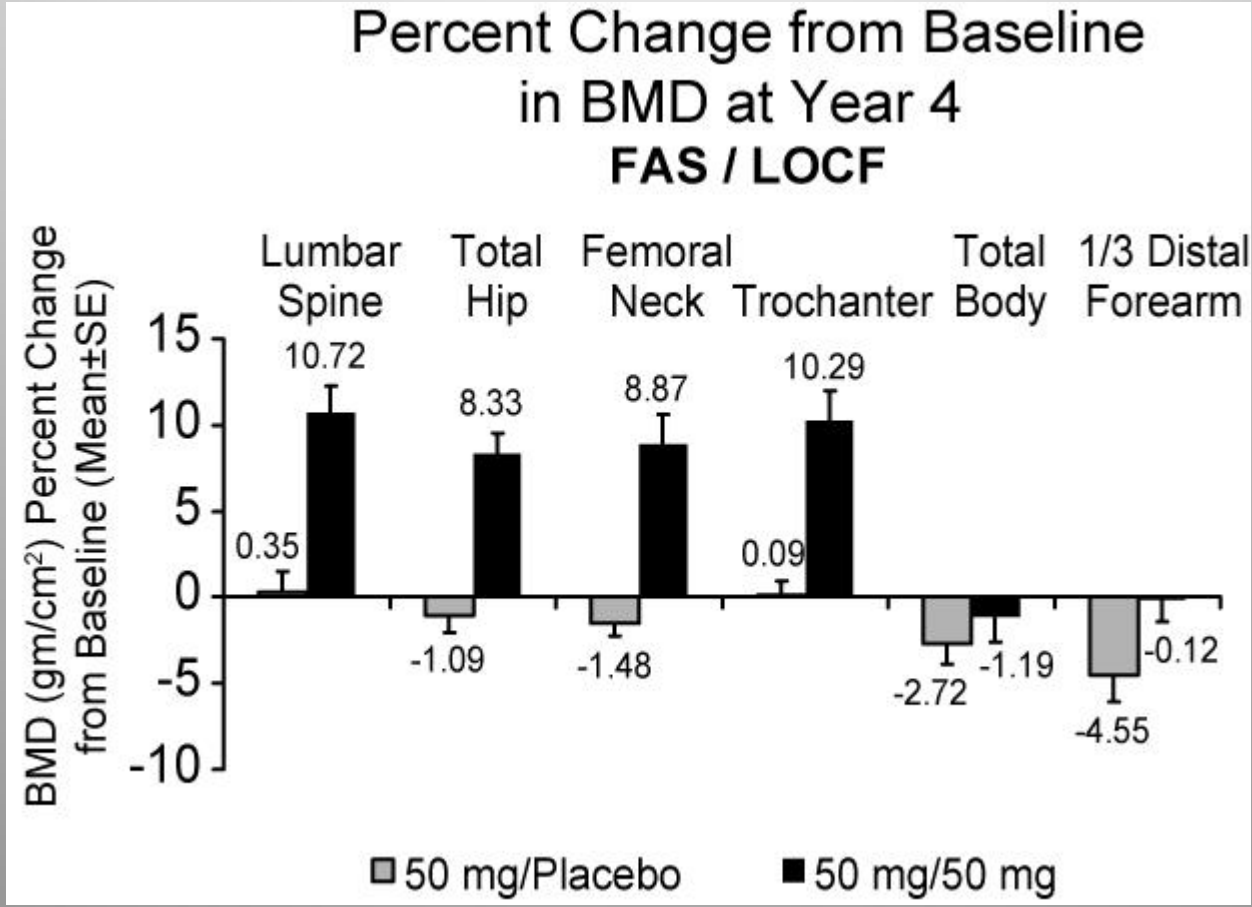
EFECTOS ADVERSOS

	Placebo	OD (50 mg)
EA clínicos	74 (80%)	76 (78 %)
EA serios	8 (9 %)	10 (10 %)
EA cutáneos	15 (16 %)	12 (12 %)
Abandono por EA	4 (4 %)	4 (4 %)
Infecciones urinarias	3 (3 %)	12 (12 %)

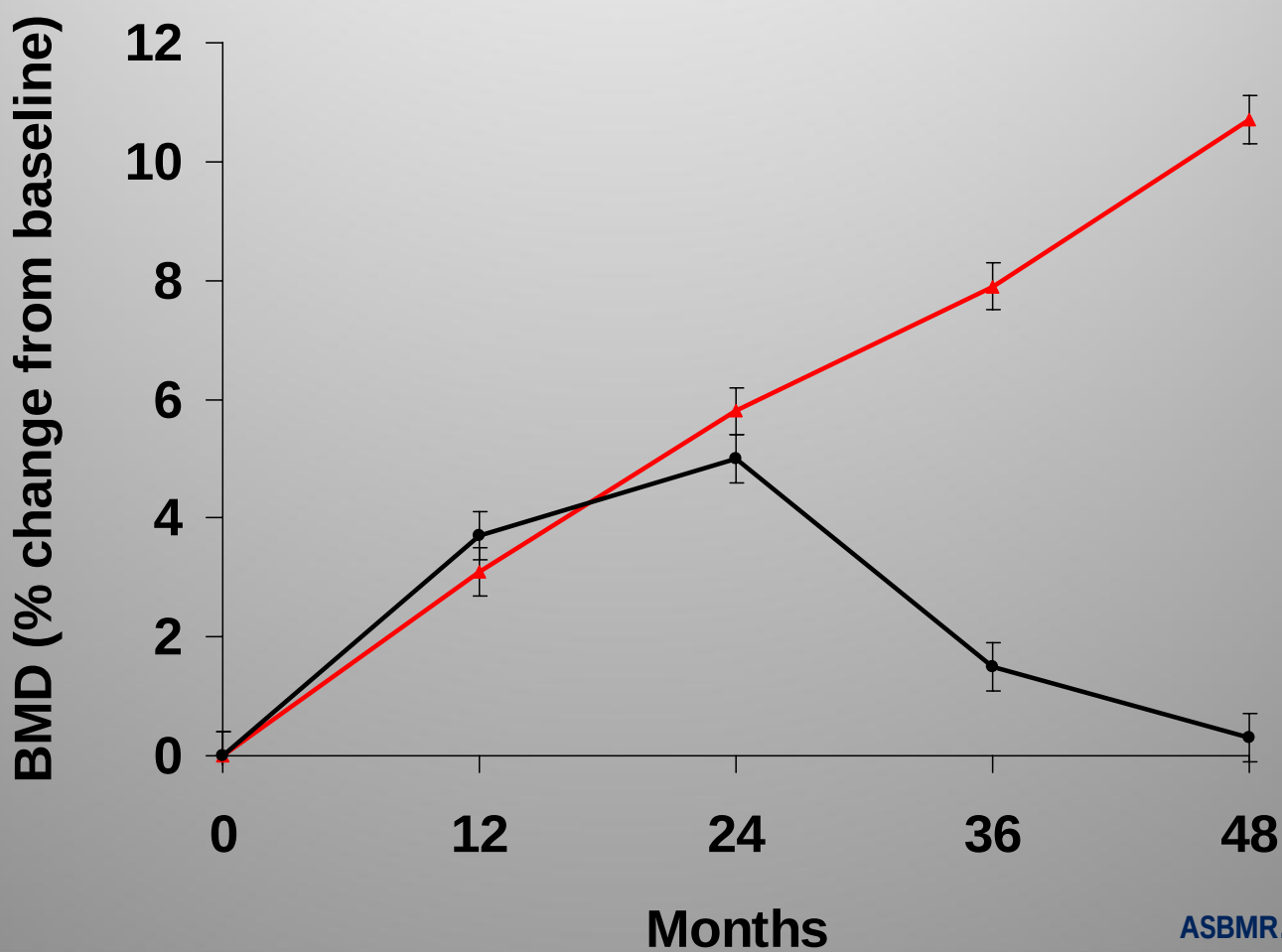
ESTUDIO EXTENSIÓN 4 AÑOS



N: 41 N:100

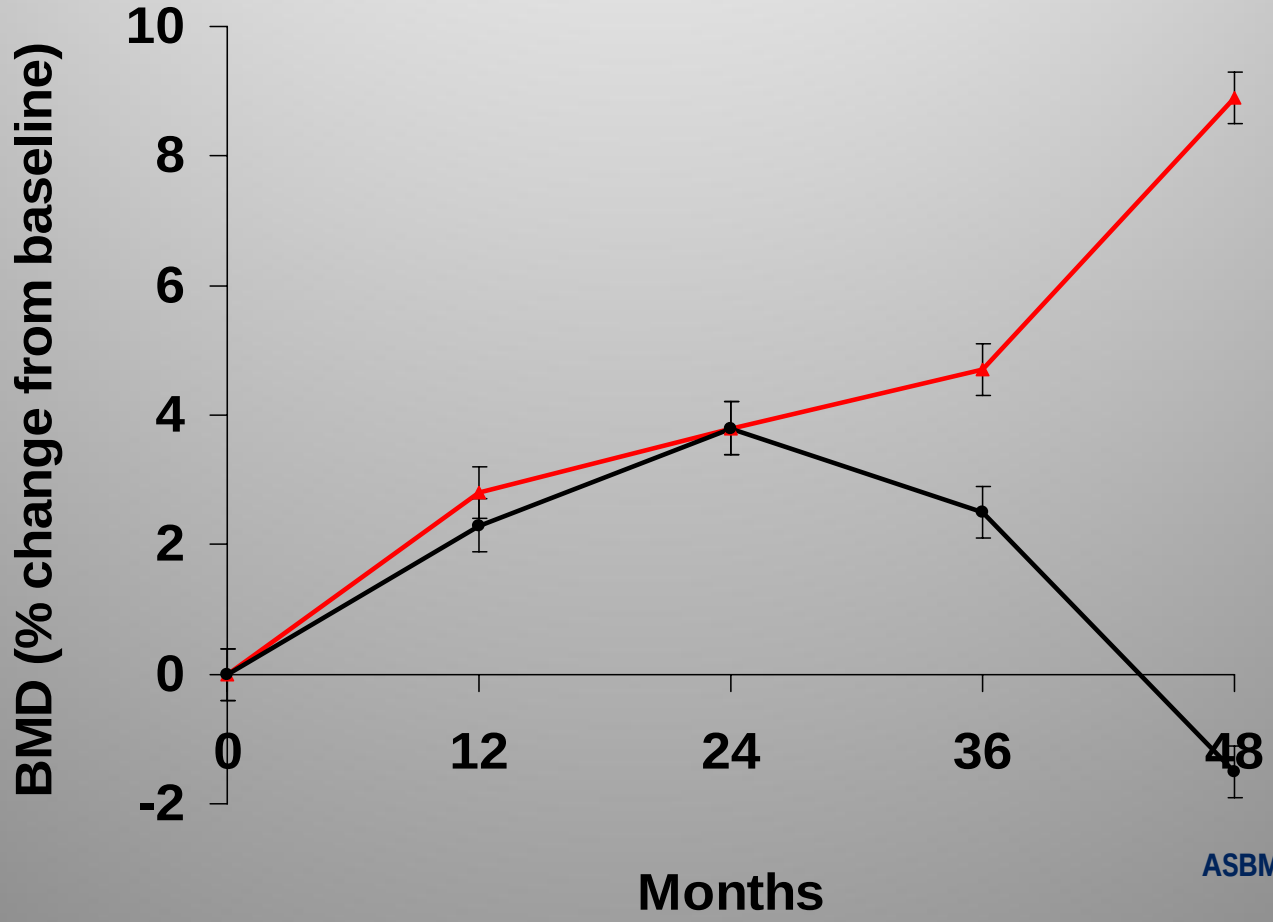
ASBMR. Toronto 2010

DMO: % CAMBIO COLUMNA LUMBAR



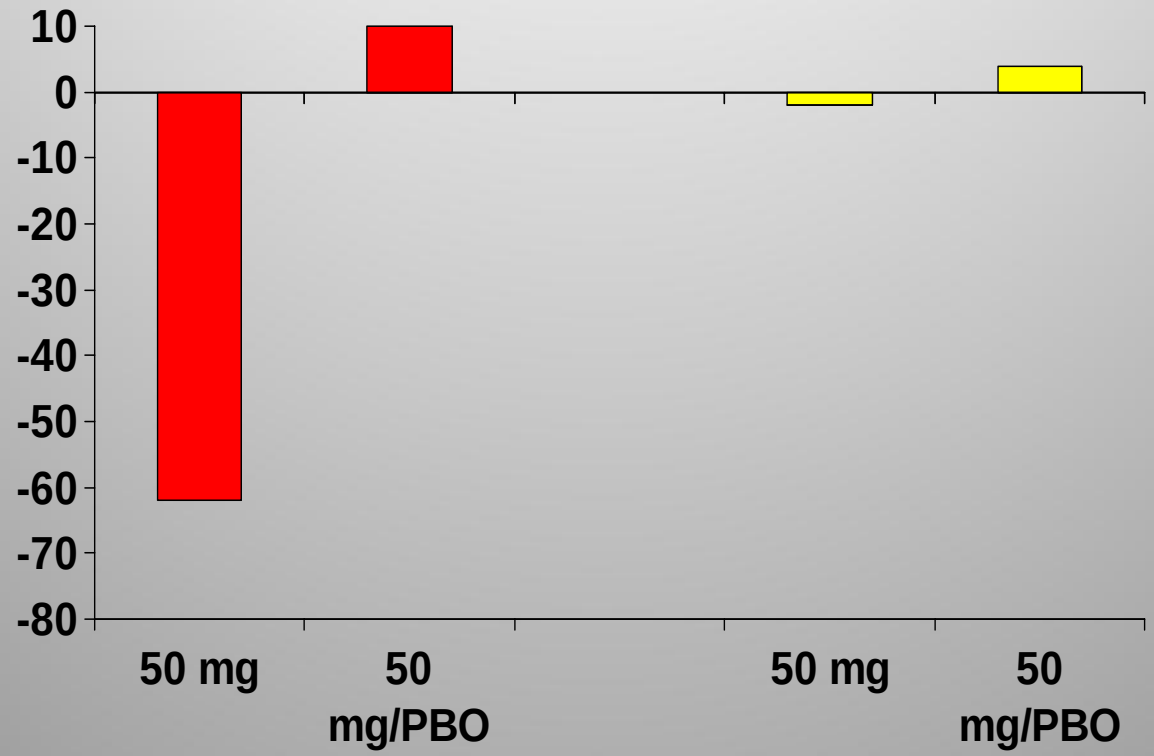
ASBMR. Toronto 2010

% CAMBIO EN TROCANTER



ASBMR. Toronto 2010

CAMBIOS MARCADORES REMODELADO ÓSEO

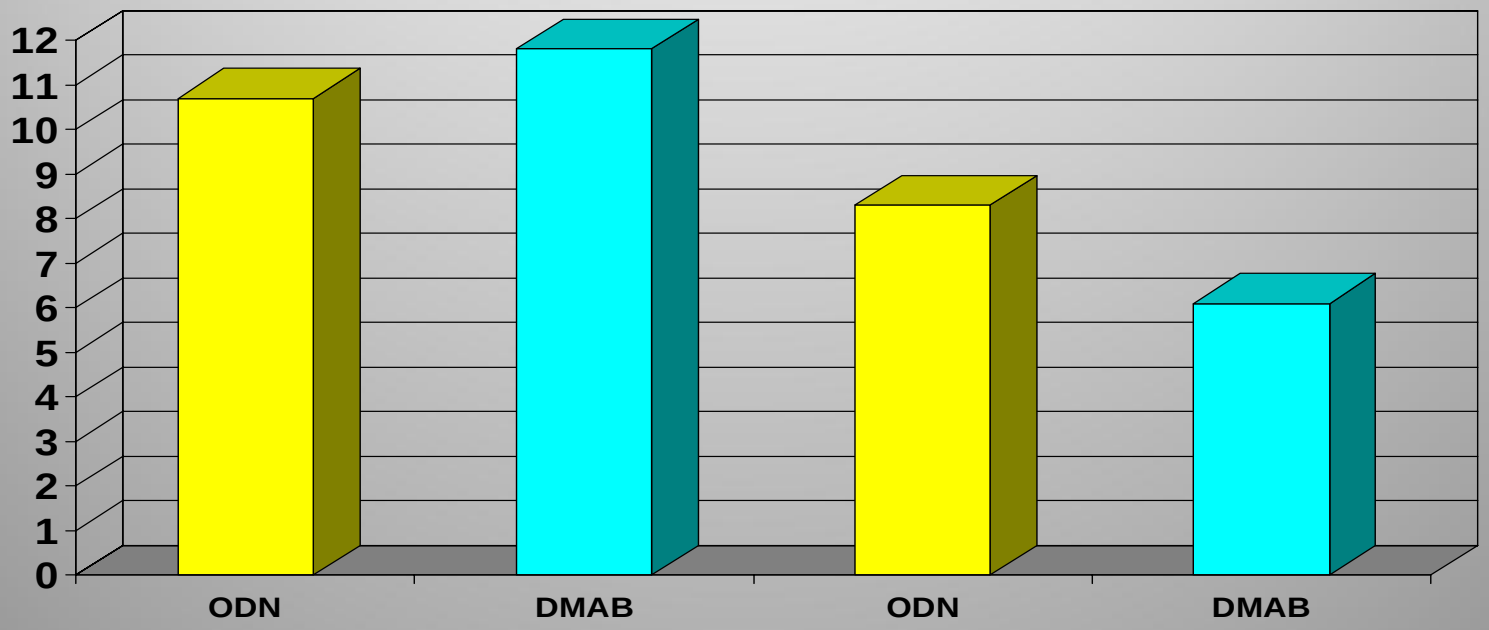


NTX

FA ósea

ASBMR. Toronto 2010

ODANACATIB-DENOSUMAB



COLUMNA

CADERA

RESUMEN

- **El tratamiento con odanacatib produce:**
- **Descenso rápido, reversible, de forma dosis-dependiente de los marcadores de resorción ósea**
- **Incrementa la densidad mineral ósea de forma dosis-dependiente**
- **Es seguro y bien tolerado**

ESTUDIO FASE III

ESTUDIO FASE III
(NCT 00529370)

- **Ensayo clínico aleatorizado, controlado con placebo, en fase III, para evaluar la reducción de fracturas en mujeres osteoporóticas postmenopáusicas**
- **16000 mujeres mayores de 65 años**
- **Fármaco : Odanacatib 50 mg semanal y 5600 UI semanales de vitamina D**

ESTUDIO FASE III
(NCT 00529370)

- **Criterios de inclusion:**
- **Mujer postmenopáusica > 65 años**
- **T-score en cadera total o cuello femoral < -2.5 y > -4**
- **Una fractura vertebral previa y T-score en cadera y cuello femoral < -1.5**

ESTUDIO FASE III
(NCT 00529370)

- **OBJETIVOS PRINCIPALES:**

- **Reduccion de fractura vertebral morfométrica, fractura de cadera y extravertebral**

OBJETIVOS SECUNDARIOS :

- **Reducción fractura vertebral clínica**
- **Reducción de pérdida de altura**
- **Incremento masa ósea**
- **Reducción marcadores de resorción**
- **Seguridad similar a placebo**


MUCHAS GRACIAS