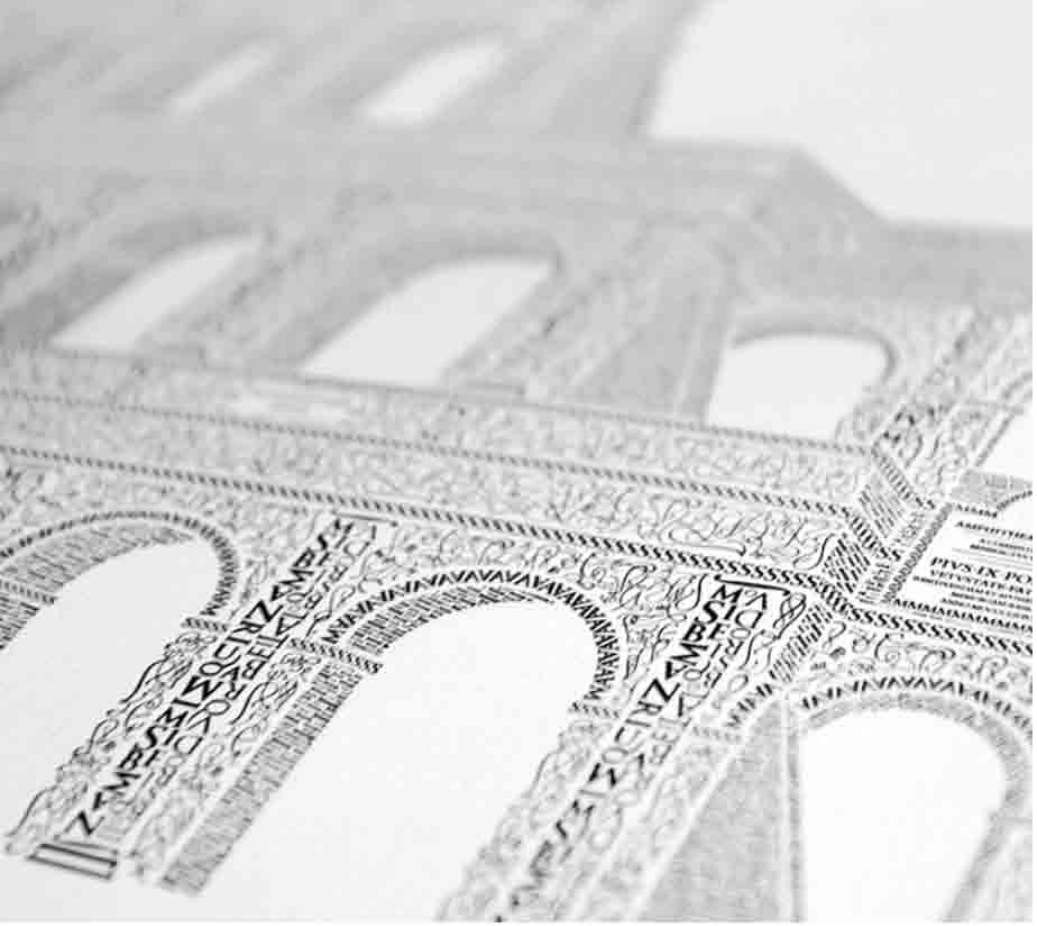

PERCORSO METABOLISMO OSSEO

ROMA
9__11
NOVEMBRE
2012

1° CORSO NAZIONALE DI AGGIORNAMENTO

Associazione Medici Endocrinologi

I PER[CORSI]AME

Iacopo Chiodini

UOC Endocrinologia e Diabetologia
Fondazione IRCCS Cà Granda, Milano
Dipartimento di Scienze Cliniche e di Comunità Università degli Studi di Milano

Clinical development of novel treatments for osteoporosis

	Target (function)	Drug class	Phase	Route
Antiresorptive drugs				
Denosumab*	RANK ligand (stem-cell factor for osteoclasts)	Antibody against RANKL	3 (completed)	SC
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Saracatinib	c-src kinase (enzyme involved in osteoclast activation)	c-src inhibitor	2	PO
Anabolic drugs				
MK-5442	CaSR (triggers PTH release if inhibited)	Calcilytic drug	2	PO
AMG 785	Sclerostin (inhibitor of the Wnt/β-catenin pathway)	Antibody against sclerostin	2	SC
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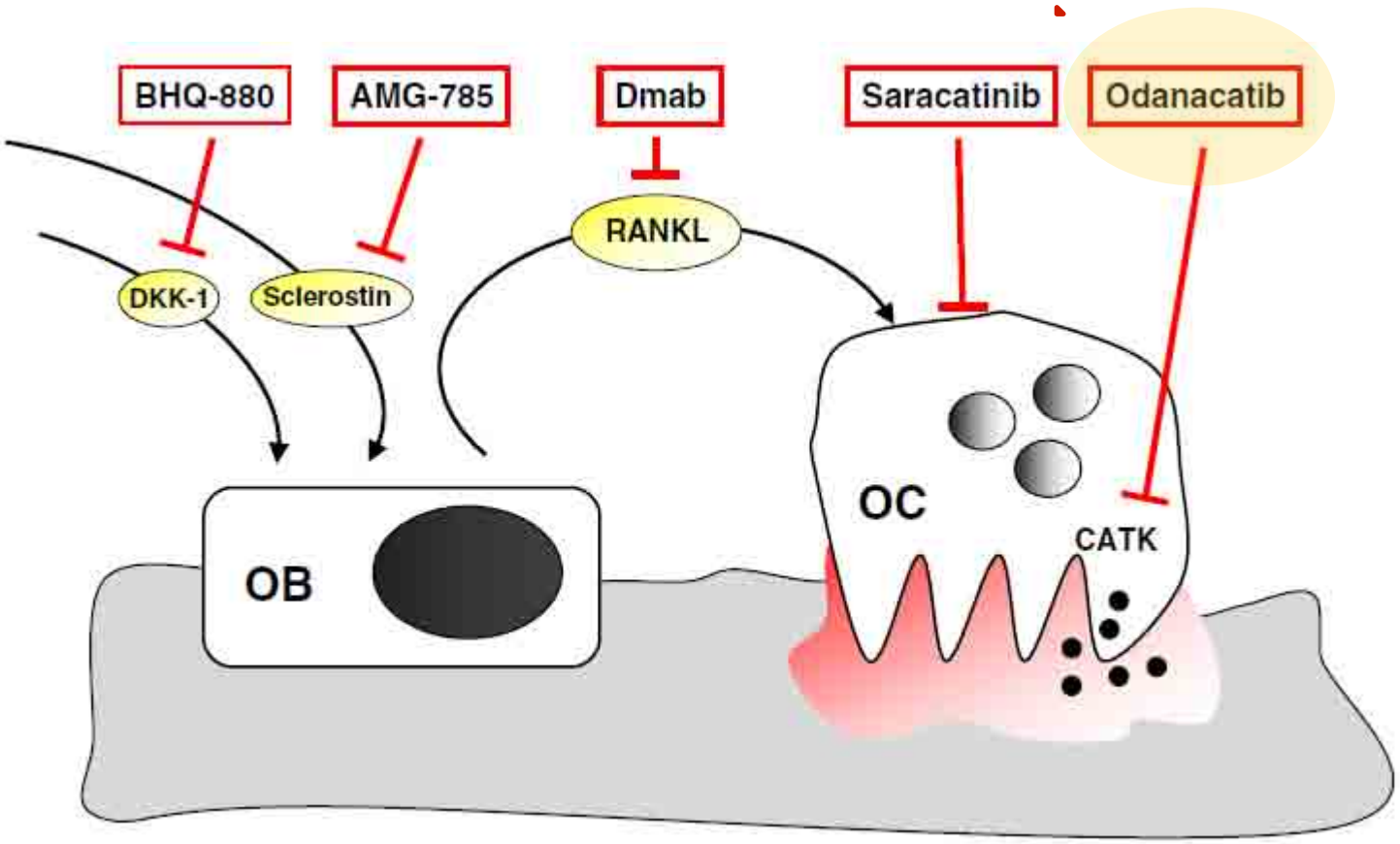
SC=subcutaneous. PO=per os. CaSR=calcium-sensing receptor. *Approved in Europe and USA in May/June, 2010.

Rachner TD et al, Lancet 2011

NOVEL BONE AGENTS UNDER EVALUATION FOR THE TREATMENT OF MALIGNANT OR BENIGN BONE DISEASE



Rachner TD et al, Pharmacology & Therapeutics 2012

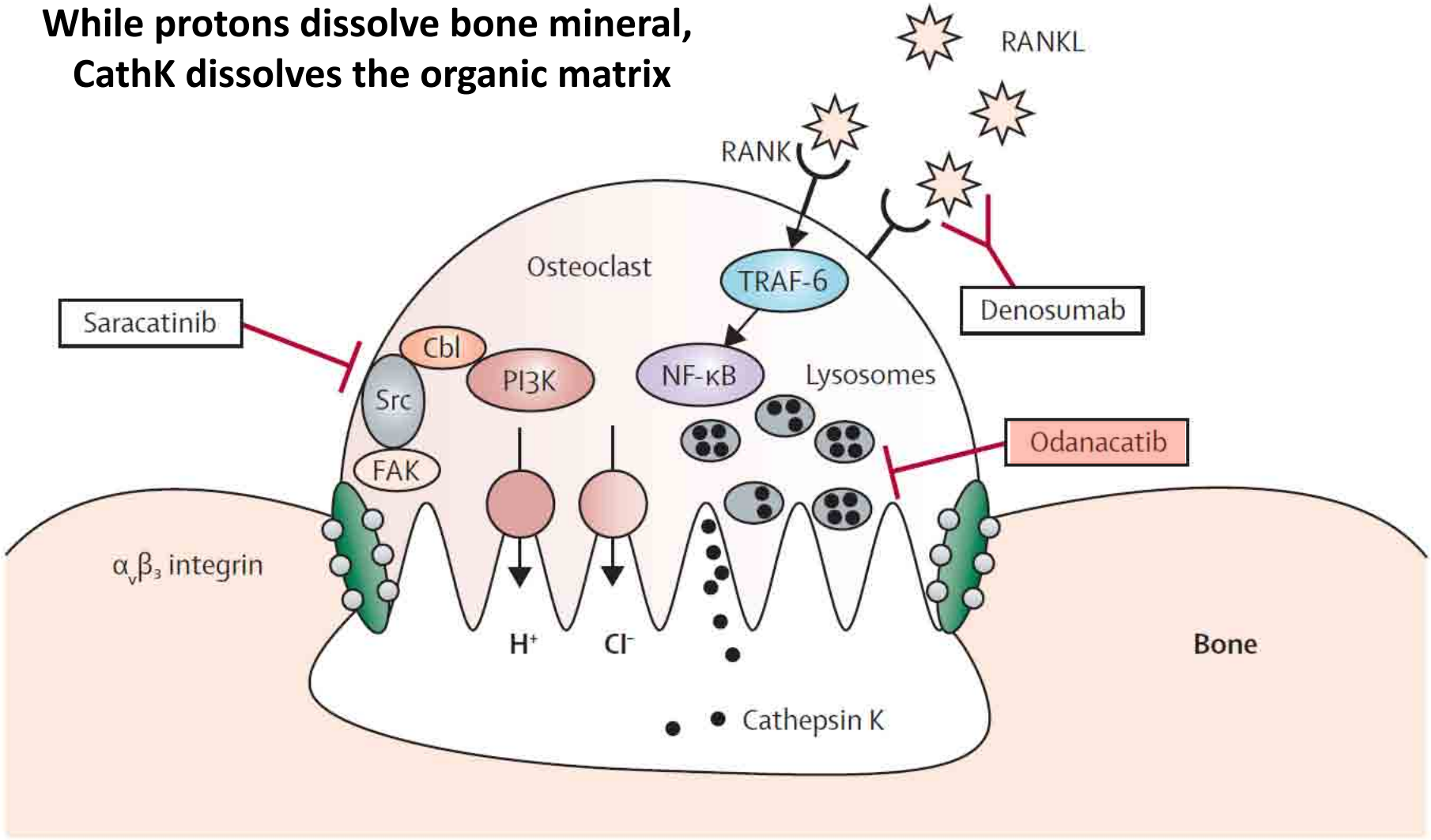
CATEPSIN K: PRECLINICAL EVIDENCES

- Cathepsin K-deficient mice develop osteopetrosis
  (Saftig et al., Proc Natl Acad Sci USA, 1998)

- In humans, a genetic mutation of Cathepsin K causes pycnodysostosis, characterized by short stature, short distal phalanges, prominent head and nose, a small jaw and osteosclerosis, predisposing to recurrent fractures, condition is sometimes referred to as the Toulouse–Lautrec syndrome.
(Gelb et al., Science 1996)

Osteoclast physiology and potential therapeutic targets

While protons dissolve bone mineral, CathK dissolves the organic matrix



Rachner TD et al, Lancet 2011

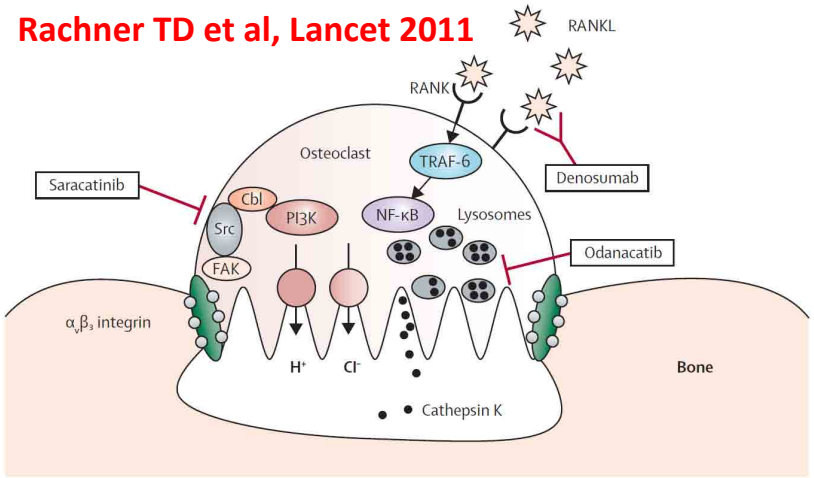
Fuller K et al, Bone 42 (2008) 200–211

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

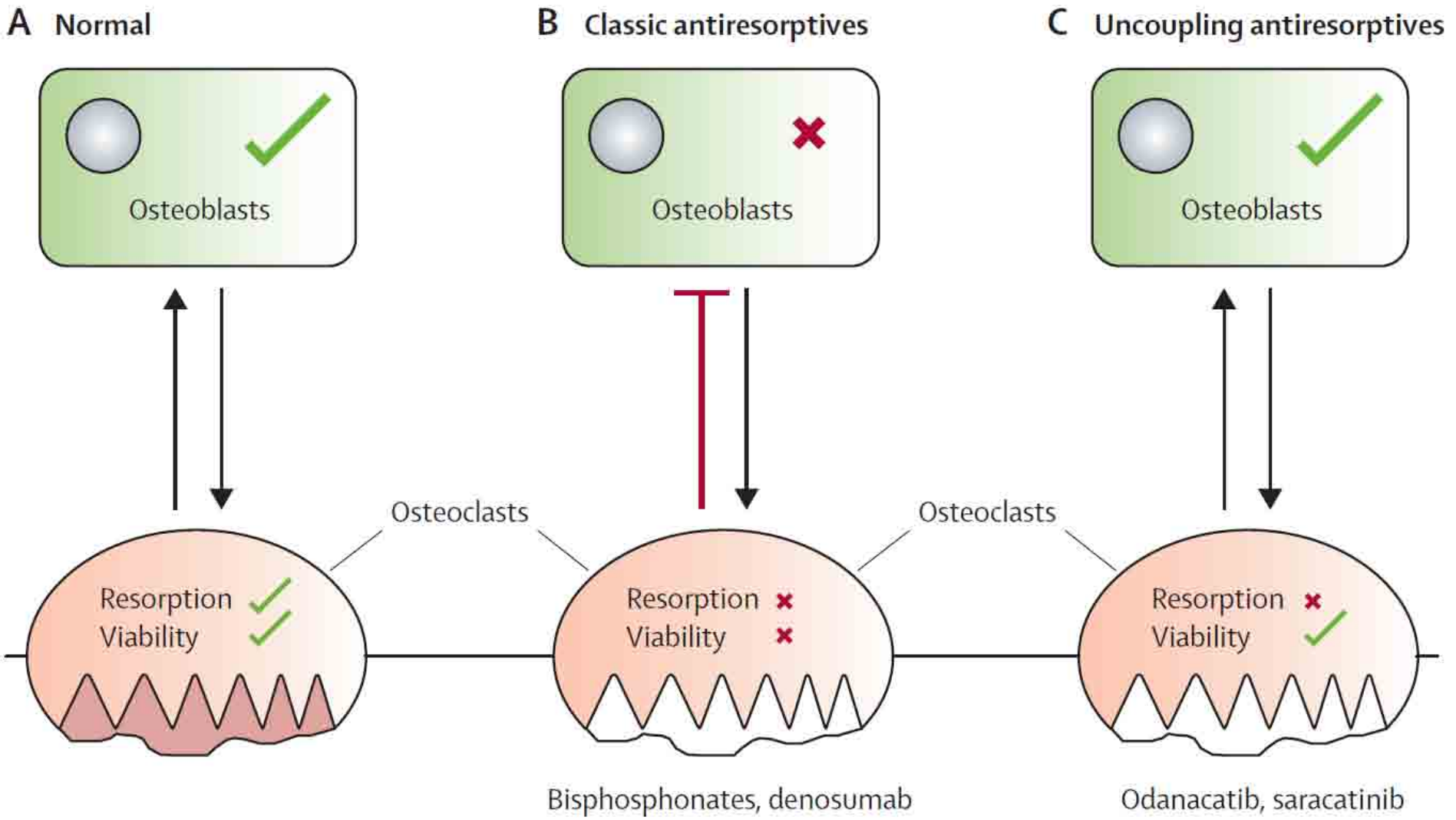
…Our observations support a model in which osteoclasts secrete protons, which release **growth factors** from the bone matrix. These are normally largely degraded, with collagen, in the resorptive hemivacuole and during transcytosis across the osteoclast, but in the presence of CathK inhibitor they are released intact.

It remains to be established whether this release is sufficient to cause therapeutically-significant stimulation of bone formation in vivo.

Rachner TD et al, Lancet 2011



Potential mechanisms of antiresorptive drugs



NOVEL BONE AGENTS UNDER EVALUATION FOR THE TREATMENT OF MALIGNANT OR BENIGN BONE DISEASE

Name	Target	Phase	OB/OC	PMO	CTIBL	Bone metastases
Denosumab	RANKL	Approved	OC	X	X	X[a]
Odanacatib	Cathepsin K	3	OC	X		
MK-5442	CaSR	2	OB	X		
AMG785	Sclerostin	2	OB	X		
BHQ-880	Dickkopf-1	2	OB	X		
ACE-011	Activin A	2	OB + OC	X		
Atrasentan	Endothelin-1	2/3	OB	X		
Nitroglycerin	?	OB+OC	X	X		

Abbreviations: CTIBL, cancer treatment induced bone loss; MBD, malignant bone disease; OB, osteoblast; OC, osteoclast; PMO, postmenopausal osteoporosis.

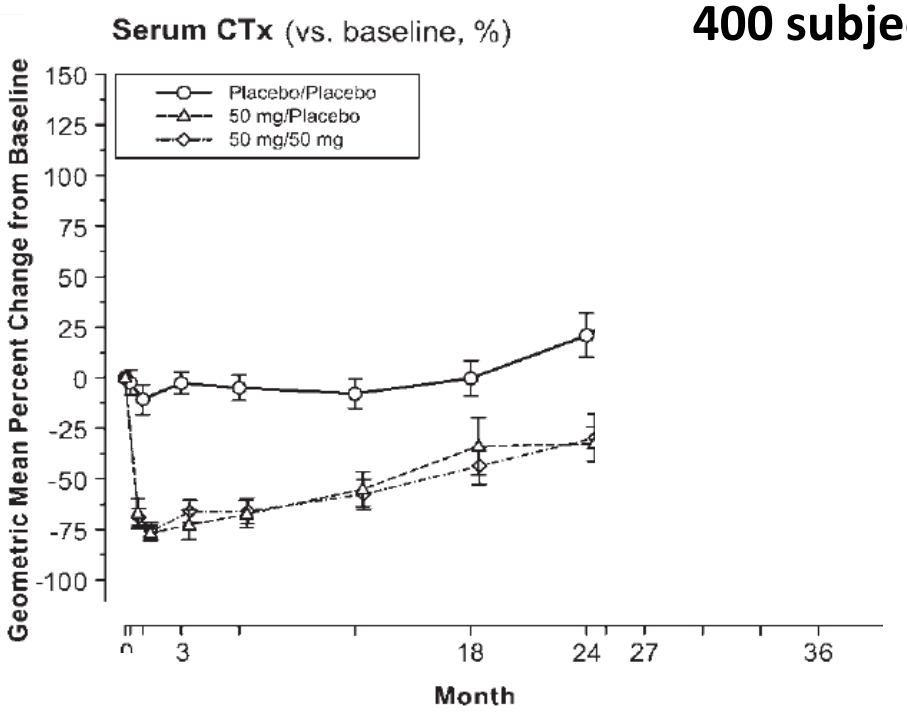
[a] Not for multiple myeloma.

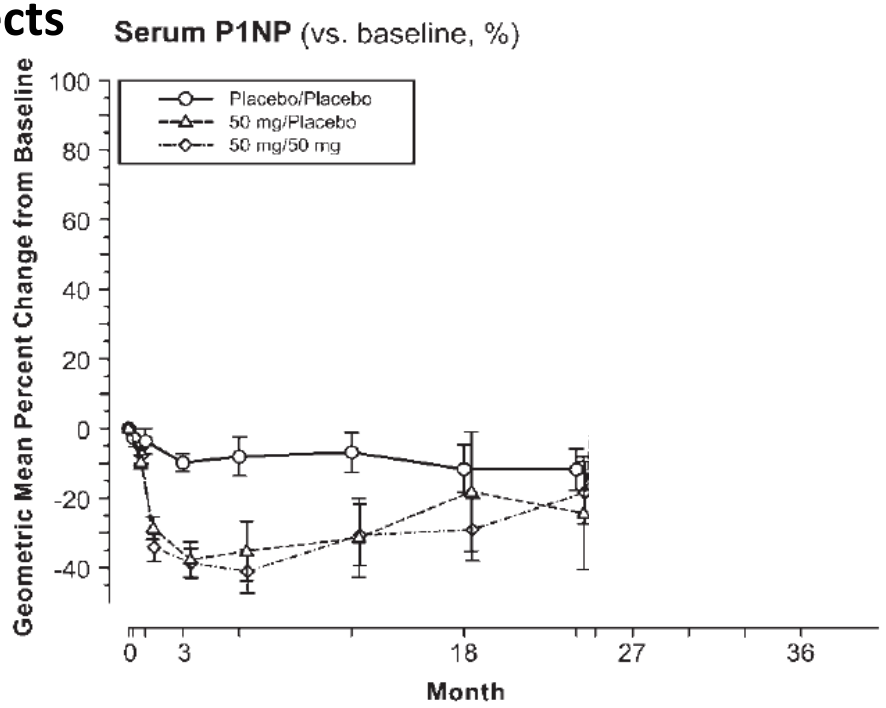
Rachner TD et al, Pharmacology & Therapeutics 2012

Bone HG et al JBMR 2010

Odanacatib in the Treatment of Postmenopausal Osteoporosis

400 subjects

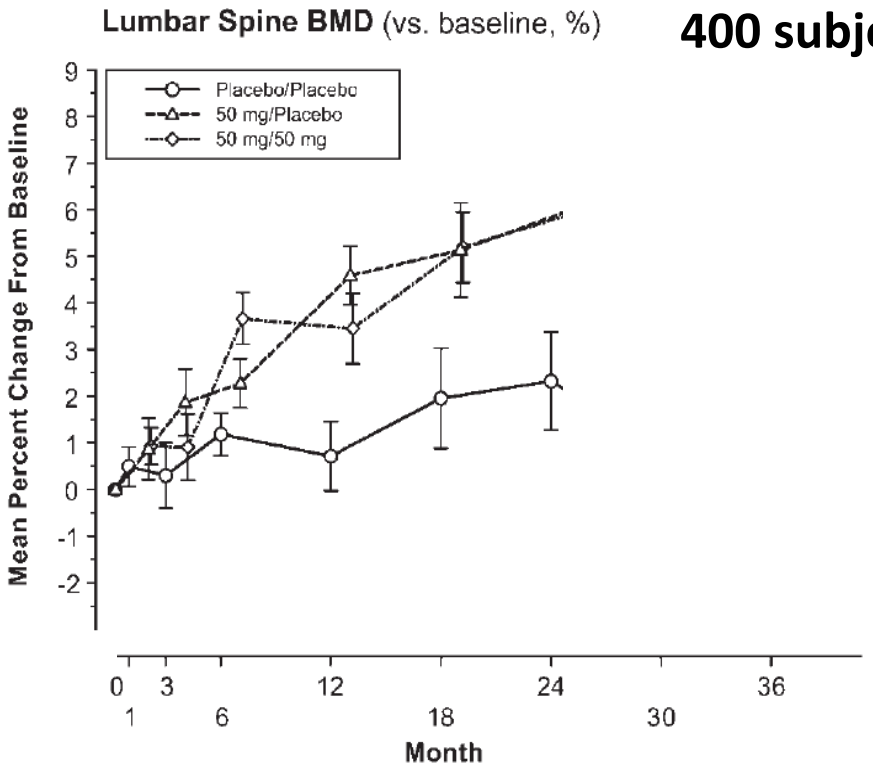




- **Once weekly oral administration**
- **Adverse reactions close to placebo, no scleroderma-like cutaneous lesions.**
- **Bone-resorption markers were dose-dependently peristently suppressed, modest and transient reduction of bone-formation markers**
- **ODN effects were reversible: bone resorption increased transiently following treatment discontinuation.**

Bone HG et al JBMR 2010

Odanacatib in the Treatment of Postmenopausal Osteoporosis



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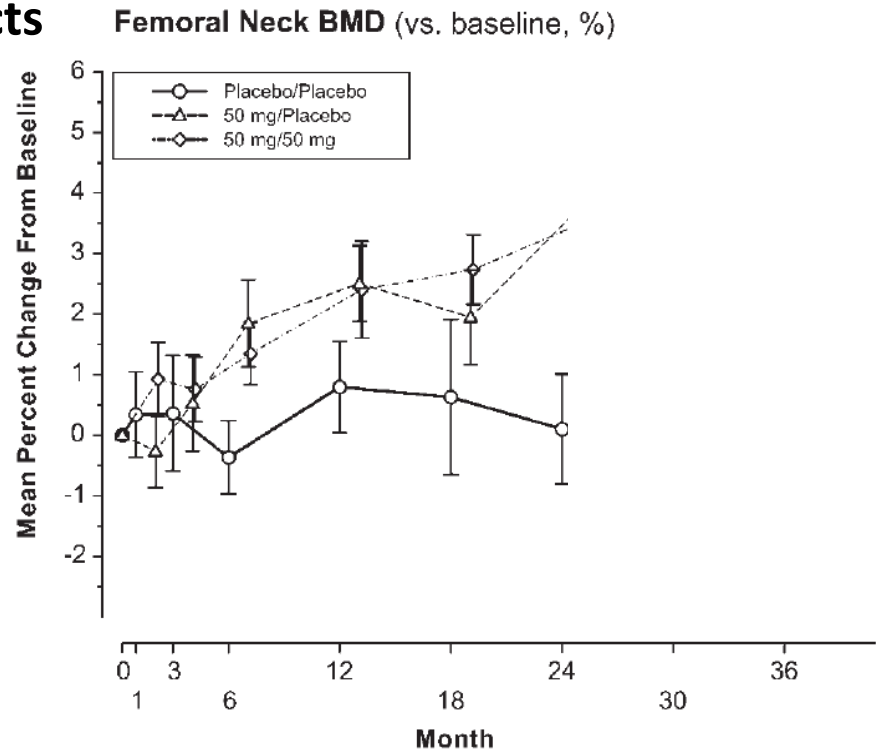
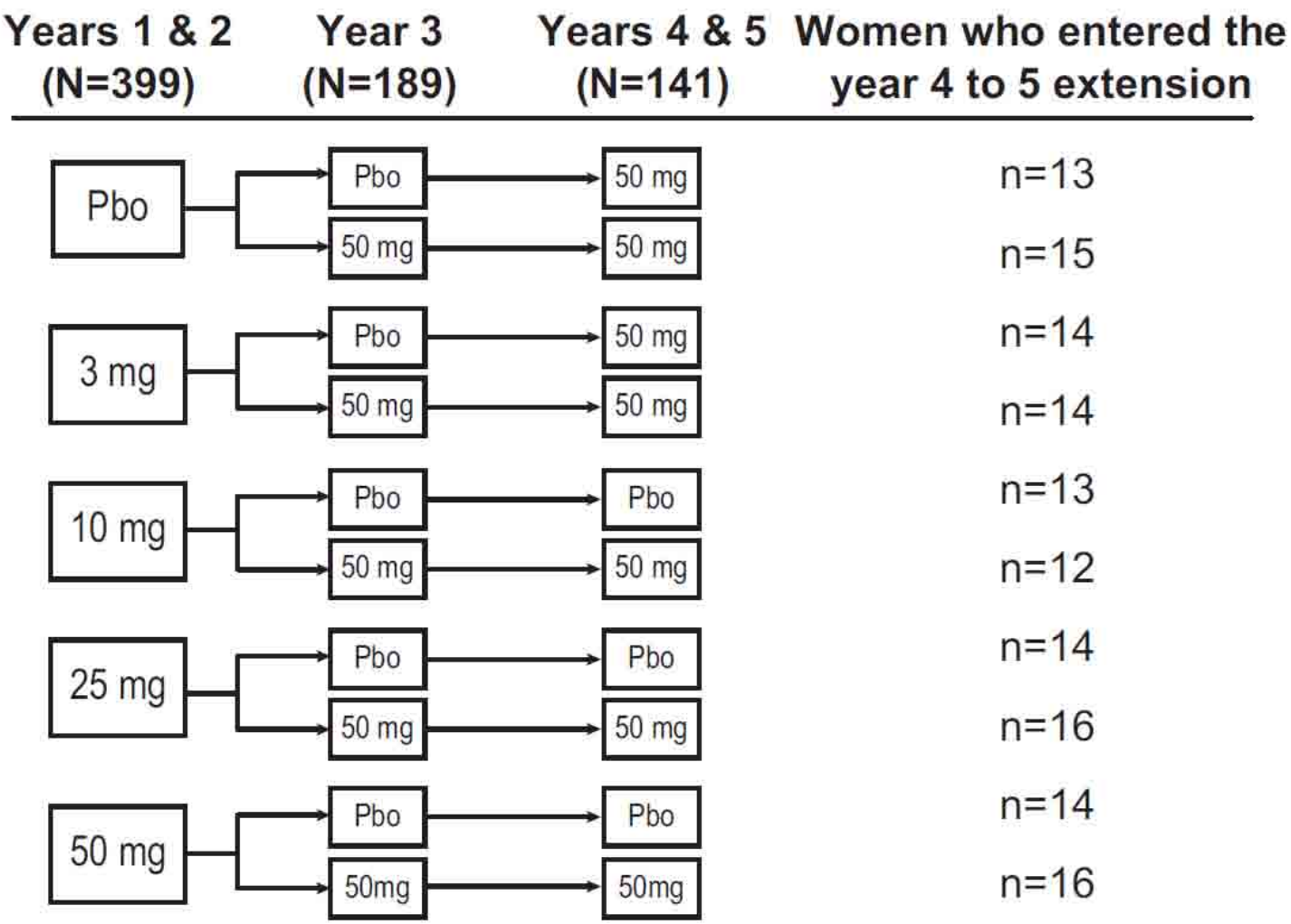


- **PM women (>5 years, aged 45-85 years), BMD T-scores between -2.0 and -3.5 (LF, FN, FT), no history of fragility fracture since menopause**
- **Increased LS BMD by 5.7% and total hip by 4.1% compared with placebo**
- **Histomorphometry (n=32): no suppression of bone formation rate**
- **Progressive increases in BMD**
- **ODN effects were reversible: BMD decreased following treatment discontinuation**

ODANACATIB IN THE TREATMENT OF POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY: FIVE YEARS OF CONTINUED THERAPY.



Langdahl B et al, J Bone Miner Res 2012

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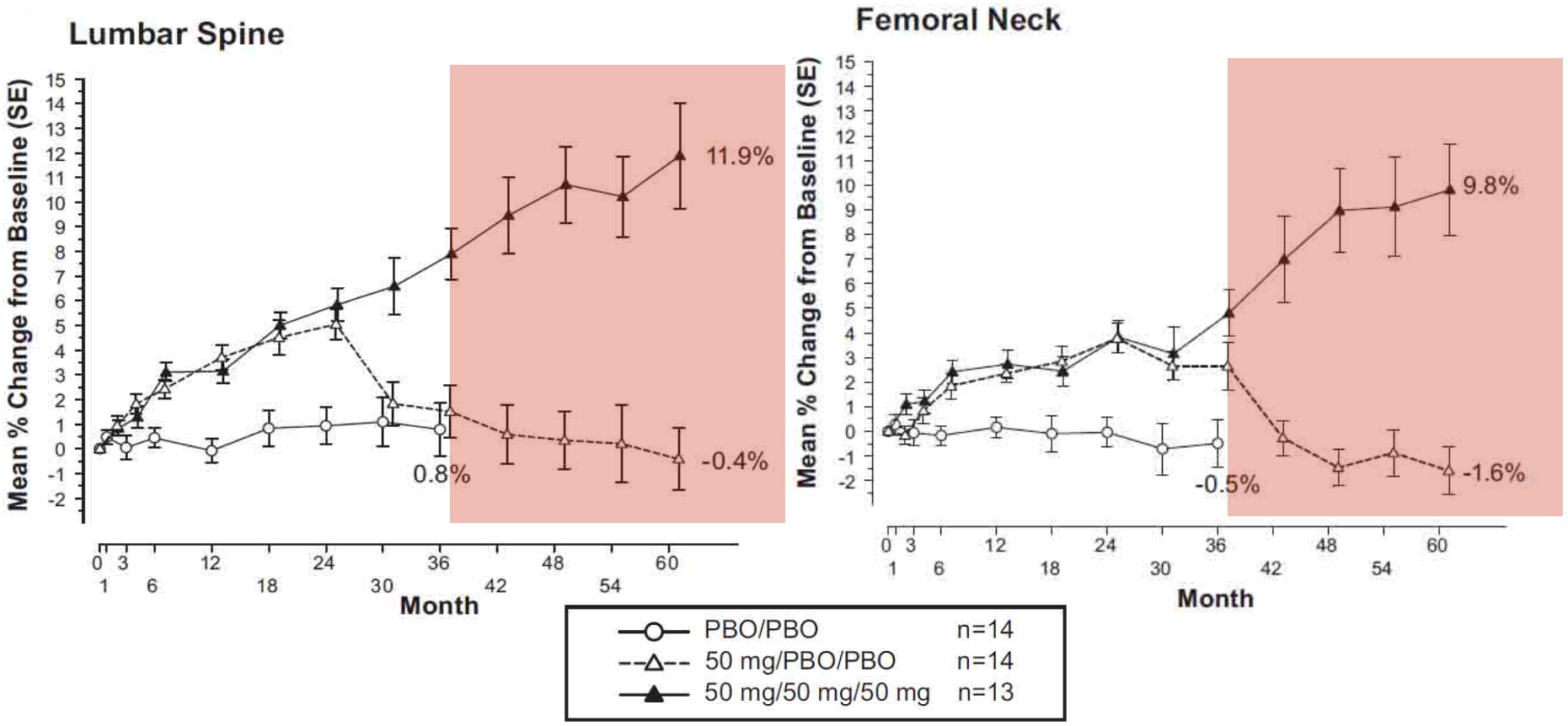


Langdahl B et al, J Bone Miner Res 2012

ODANACATIB IN THE TREATMENT OF POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY: FIVE YEARS OF CONTINUED THERAPY.

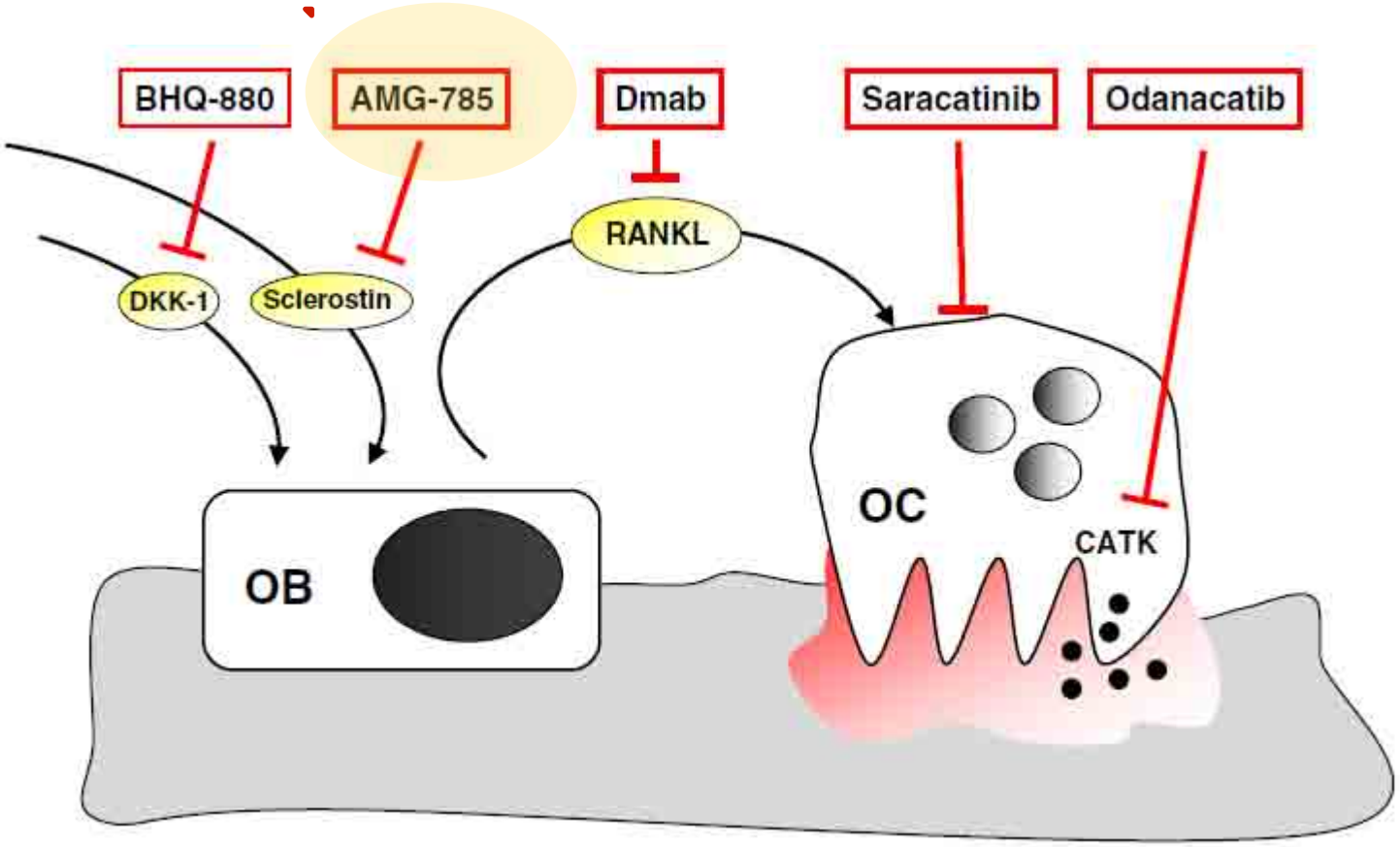
Biochemical marker	Years 1–2: 10, 25, or 50 mg Year 3: placebo Years 4–5: placebo		Years 1–2: 10, 25, or 50 mg Year 3: 50 mg Years 4–5: 50 mg	
	n	% change from baseline[a] (95% CI)	*n*	% change from baseline[a] (95% CI)
uNTX/Cr	25	3.6 (−18.2 to 31.3)	26	−55.6 (−69.8 to −34.7)
sCTX	25	−11.1 (−30.4 to 13.4)	27	−53.0 (−63.5 to −39.4)
uDPD/Cr	25	22.7 (−0.7 to 51.5)	27	9.9 (−10.4 to 34.8)
sBSAP	25	−10.1 (−15.5 to −4.4)	29	−15.0 (−22.5 to −6.9)
sP1NP	25	1.1 (−12.7 to 17.1)	29	7.2 (−8.6 to 25.8)
sTRAP5b	18	13.5 (3.7 to 24.1)	22	57.2 (41.0 to 75.2)
s1CTP	27	23.2 (8.4 to 40.1)	29	246.5 (194.8 to 307.3)

- higher levels of the cathepsin K substrate 1CTP confirm inhibition of the enzyme
- higher levels of TRAP5b suggest that the number of osteoclasts was not diminished but had increased
- lower levels of bone resorption markers
- similar levels of bone formation markers.

Women with ≥1	Treatment during years 4 and 5	
	ODN 50 mg (*n* = 100) *n* (%)	Placebo (*n* = 41) *n* (%)
AE	89 (89)	33 (81)
Serious AE	18 (18)	8 (20)
AE that led to discontinuation	3 (3)	0
Skin disorder	21 (21)	11 (27)
Urinary tract infection	14 (14)	2 (5)

Langdahl B et al, J Bone Miner Res 2012

NOVEL BONE AGENTS UNDER EVALUATION FOR THE TREATMENT OF MALIGNANT OR BENIGN BONE DISEASE



Rachner TD et al, Pharmacology & Therapeutics 2012

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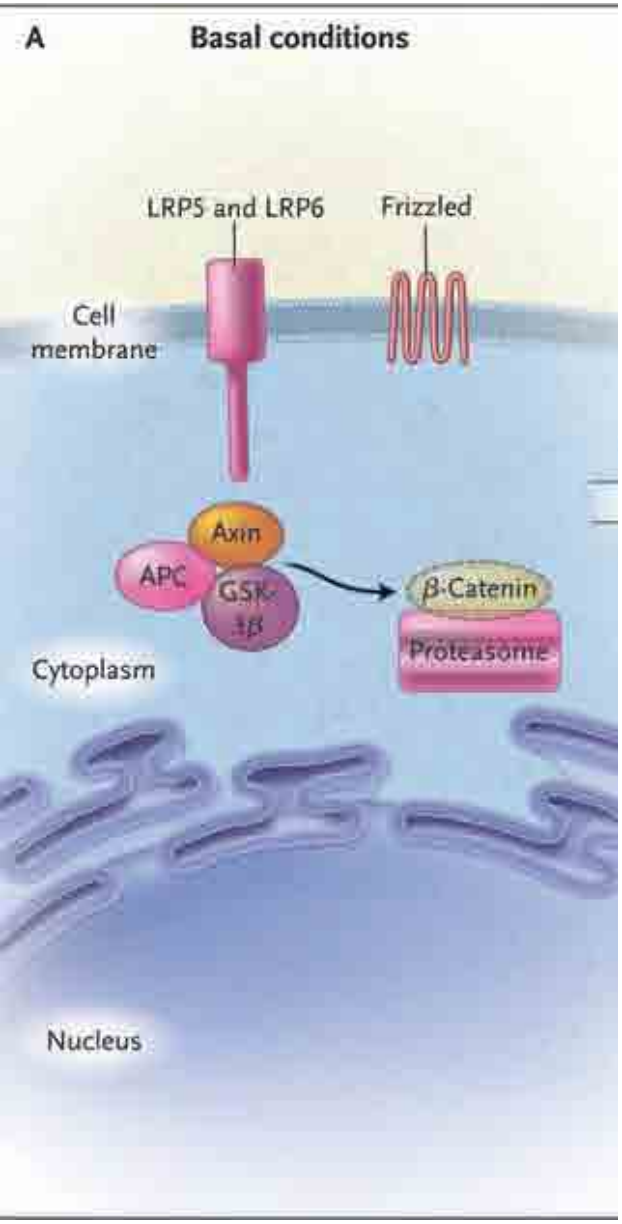
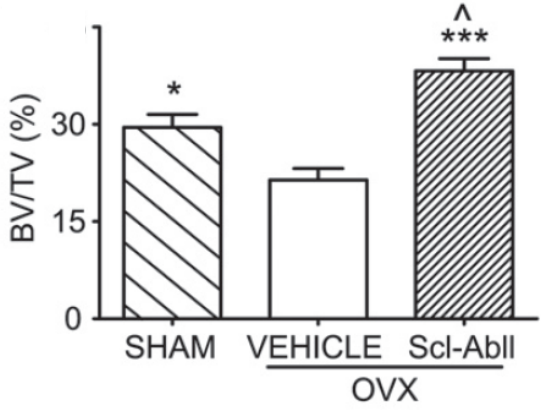
Rachner TD et al, Lancet 2011

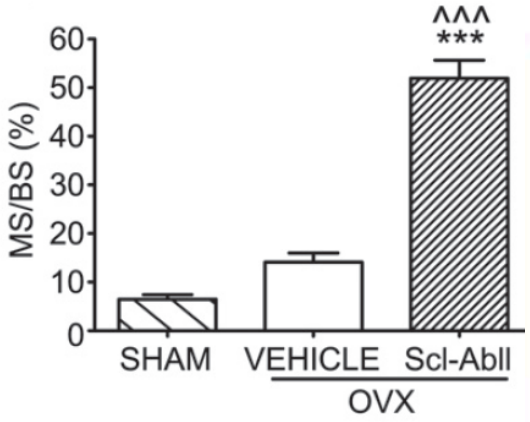
The Wnt-β Catenin signaling pathway in OB

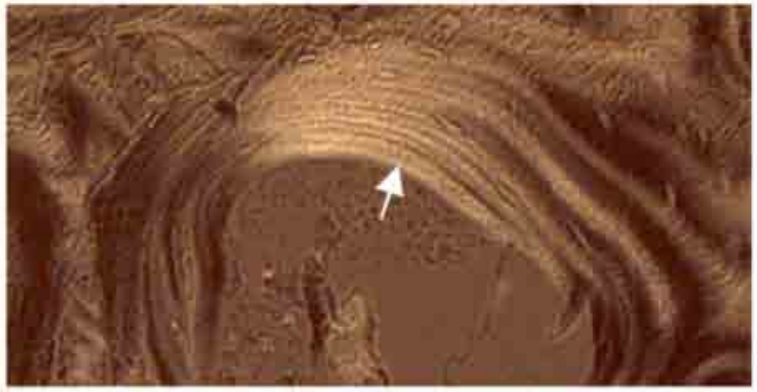


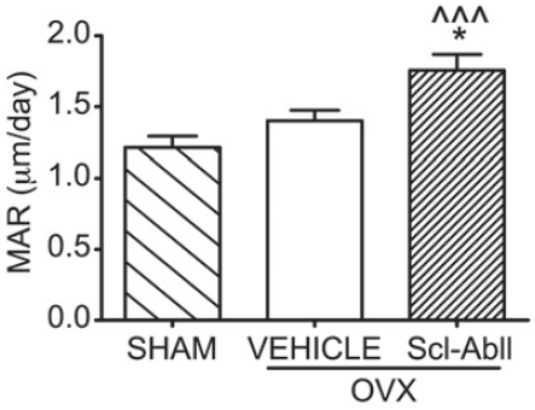
Canalis E et al. *NEJM* 2007

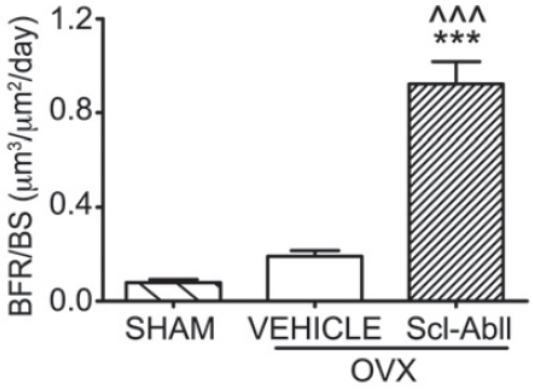
In a rat model Scl-AbII treatment increases trabecular bone volume and bone formation in lumbar vertebrae as assessed by histomorphometric analysis

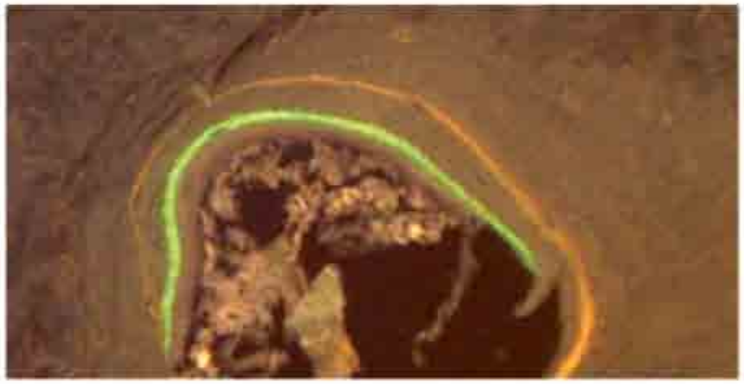








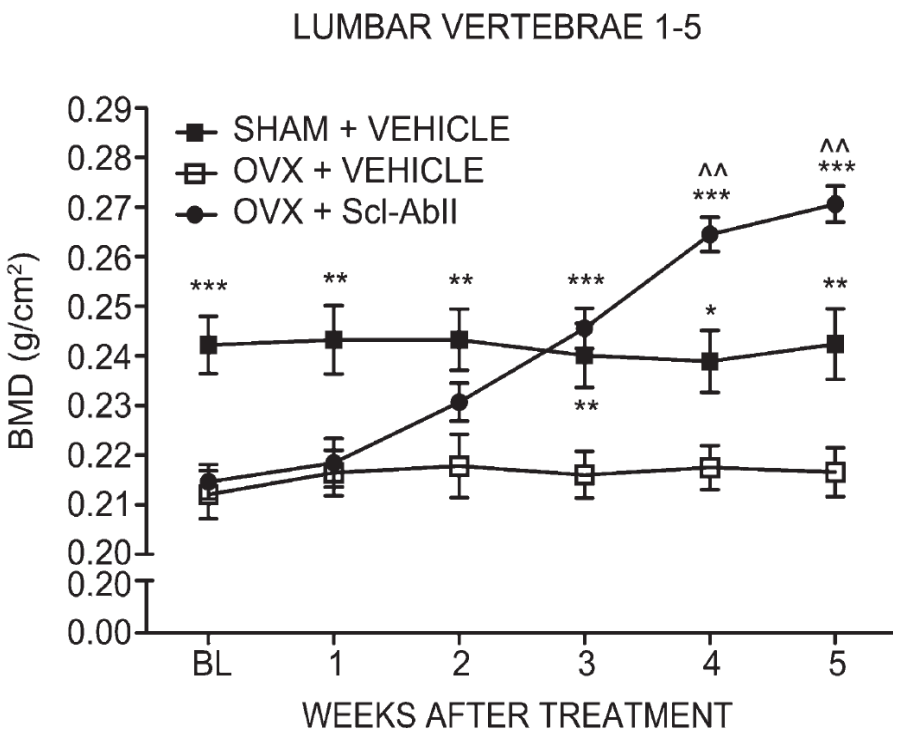


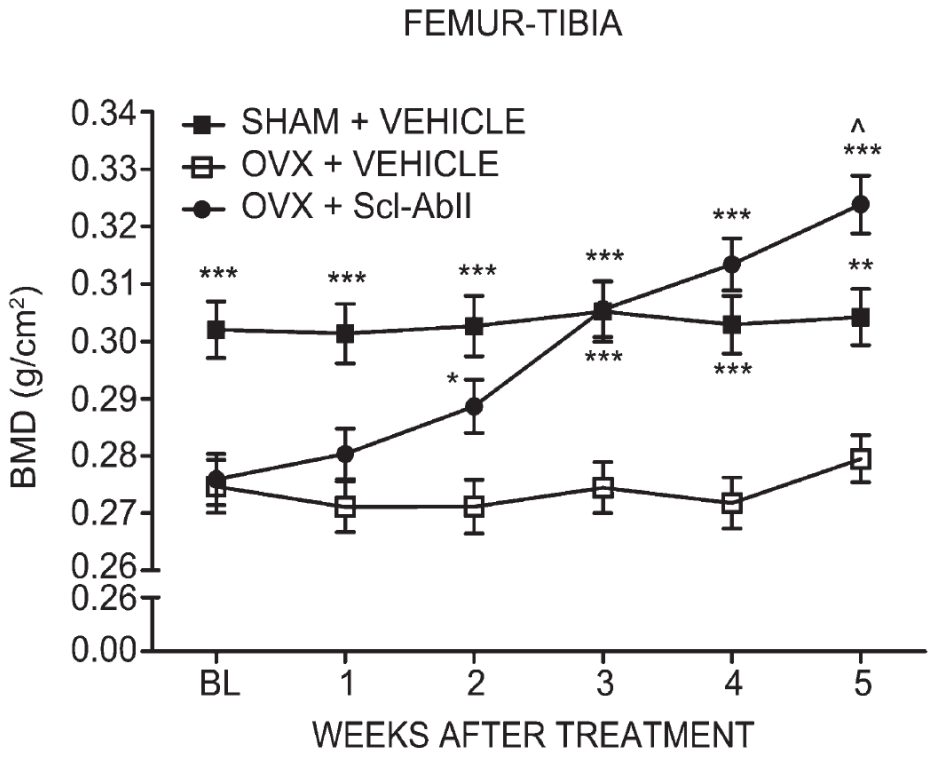


Li X et al, JBMR 2009

Li X et al, JBMR 2009

Sclerostin Antibody Treatment Increases Bone Formation, Mass, and Strength in a Rat Model of Postmenopausal Osteoporosis

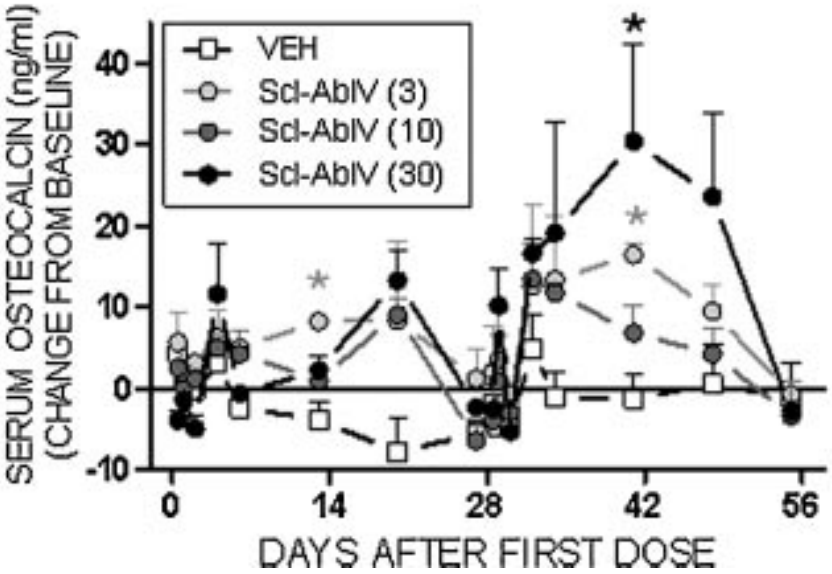


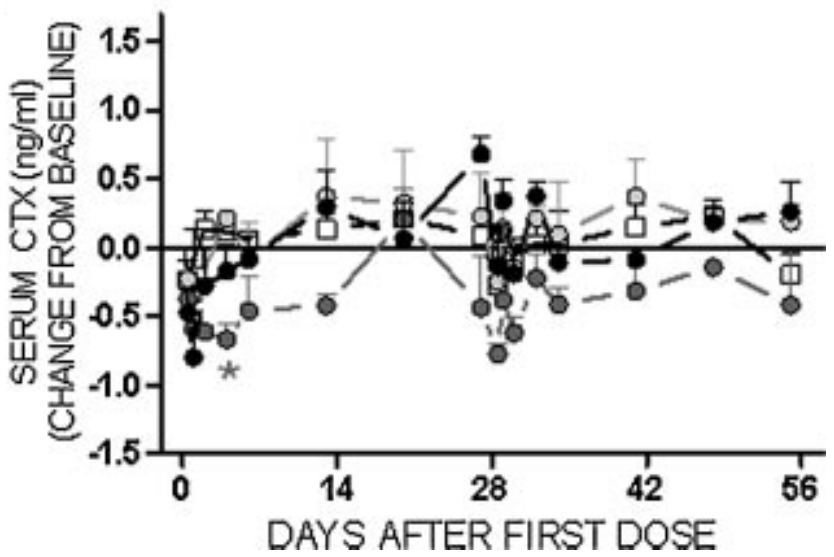


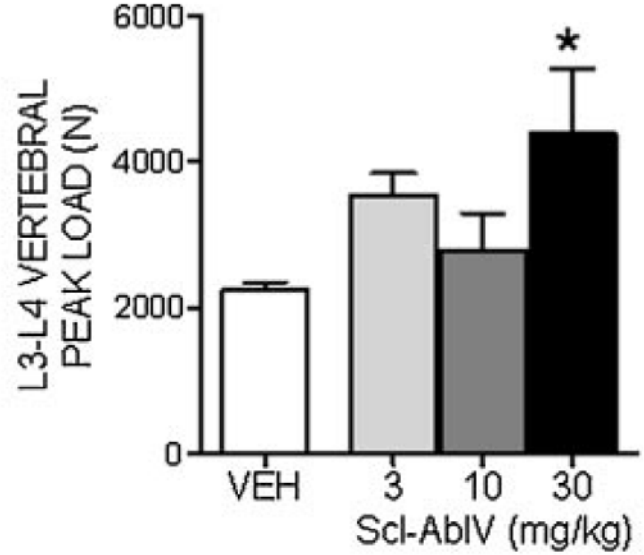
These preclinical results establish sclerostin's role as a pivotal negative regulator of bone formation in the aging skeleton and, furthermore, suggest that antibody-mediated inhibition of sclerostin represents a promising new therapeutic approach for the anabolic treatment of bone-related disorders, such as postmenopausal osteoporosis.

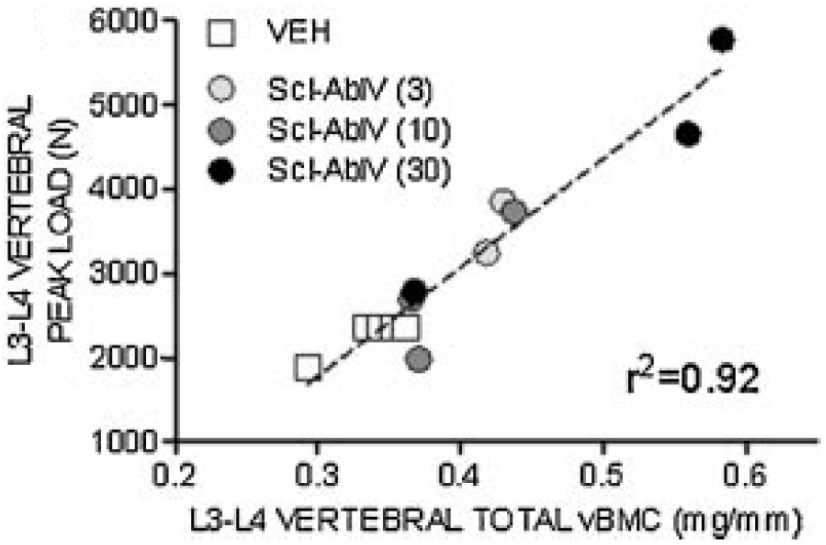
Ominsky MS et al, JBMR 2010

Two Doses of Sclerostin Antibody in Cynomolgus Monkeys Increases Bone Formation, Bone Mineral Density, and Bone Strength









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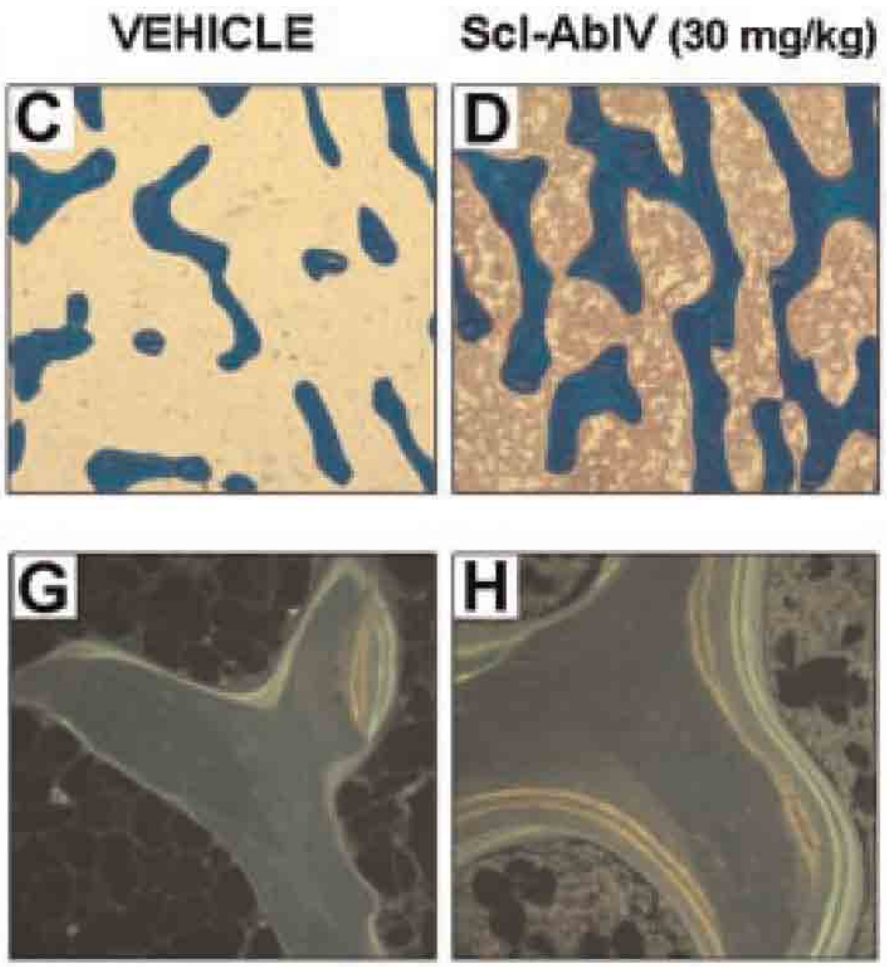
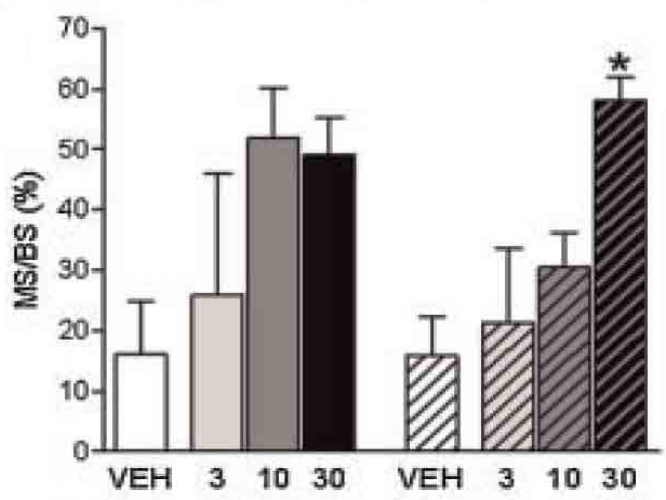
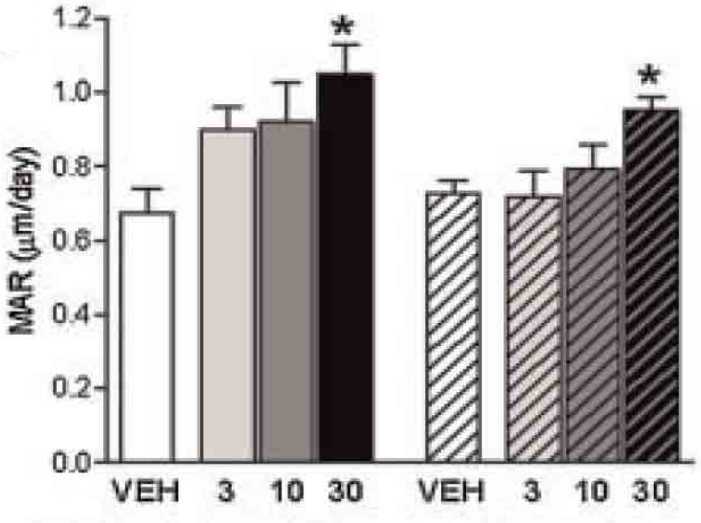
Proxymal Tibia



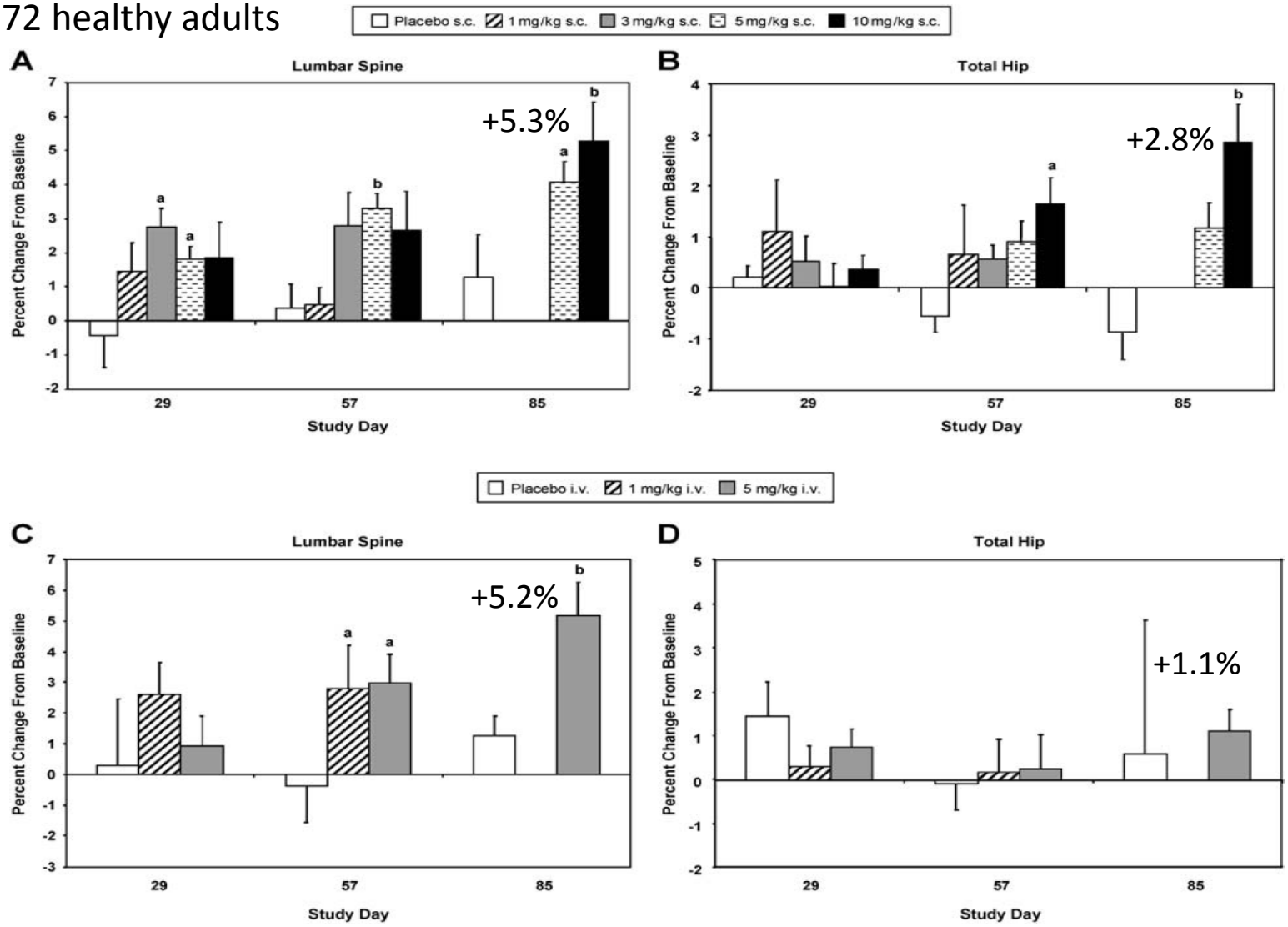




Padhi D et al, JBMR 2011

Single-Dose, Placebo-Controlled, Randomized Study of AMG 785, a Sclerostin Monoclonal Antibody

72 healthy adults



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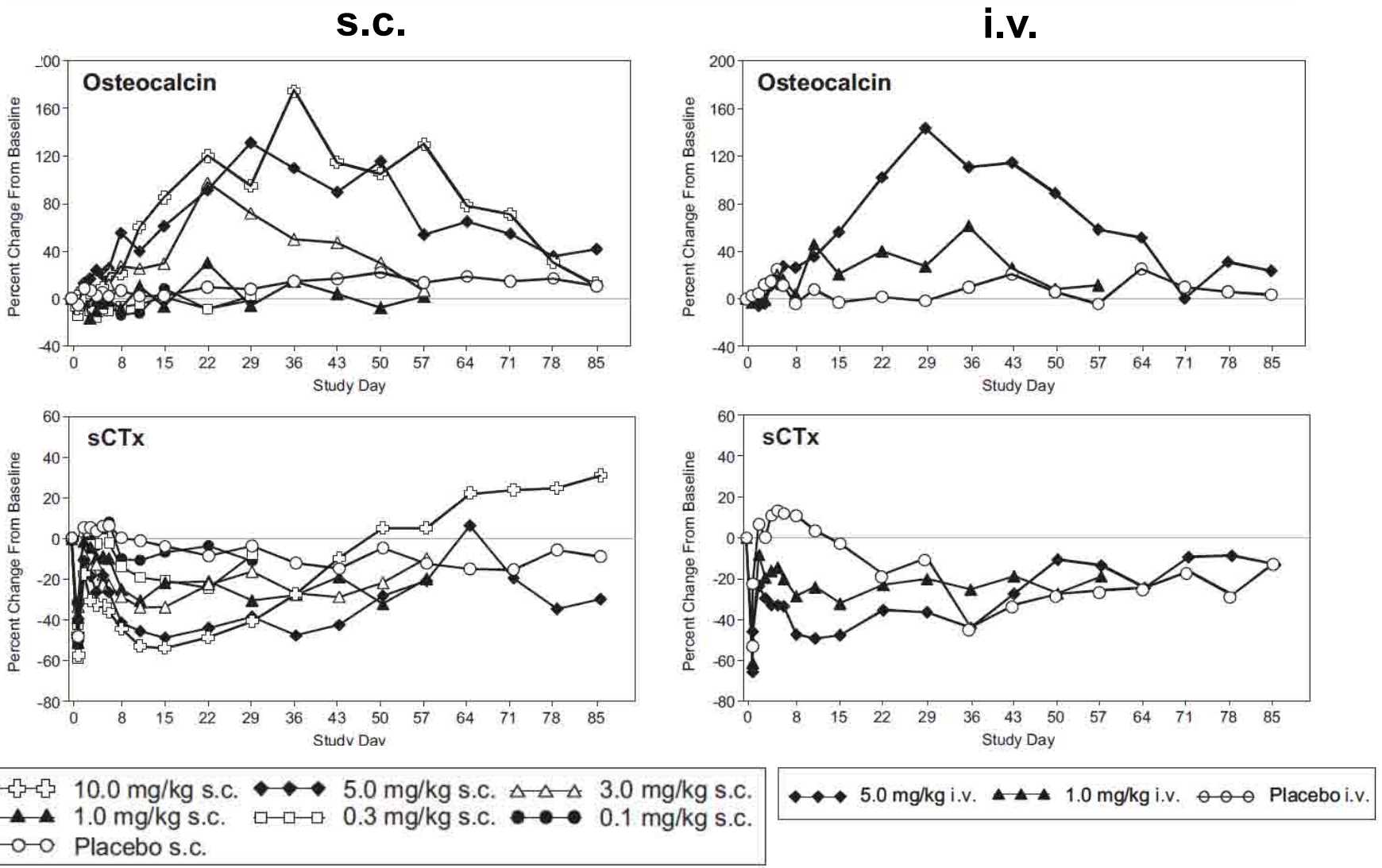

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- 72 soggetti sani trattati con AMG 785 o placebo (3:1) s.c. (0.1, 0.3, 1, 3, 5, or 10 mg/kg) o e.v. (1 o 5 mg/kg), follow-up: 85 giorni.
- Endpoints: sicurezza e tollerabilità (I), farmacocinetica, turnover markers, BMD (II).
- Ben tollerato; un caso di epatite aspecifica; no eventi fatali o sospensione dello studio.
- Farmacocinetica non lineare con la dose; aumento dose-dipendente di P1NP, BAP, e osteocalcina.
- Aumento del BMD significativo del 5.3% alla colonna e del 2.8% al femore rispetto a placebo.
- Sei soggetti nei gruppi trattati con I dosaggi maggiori hanno sviluppato ab anti-AMG 785, 2 dei quali neutralizzanti.
- Vi è in corso un trial di fase 2 contro alendronato e teriparatide

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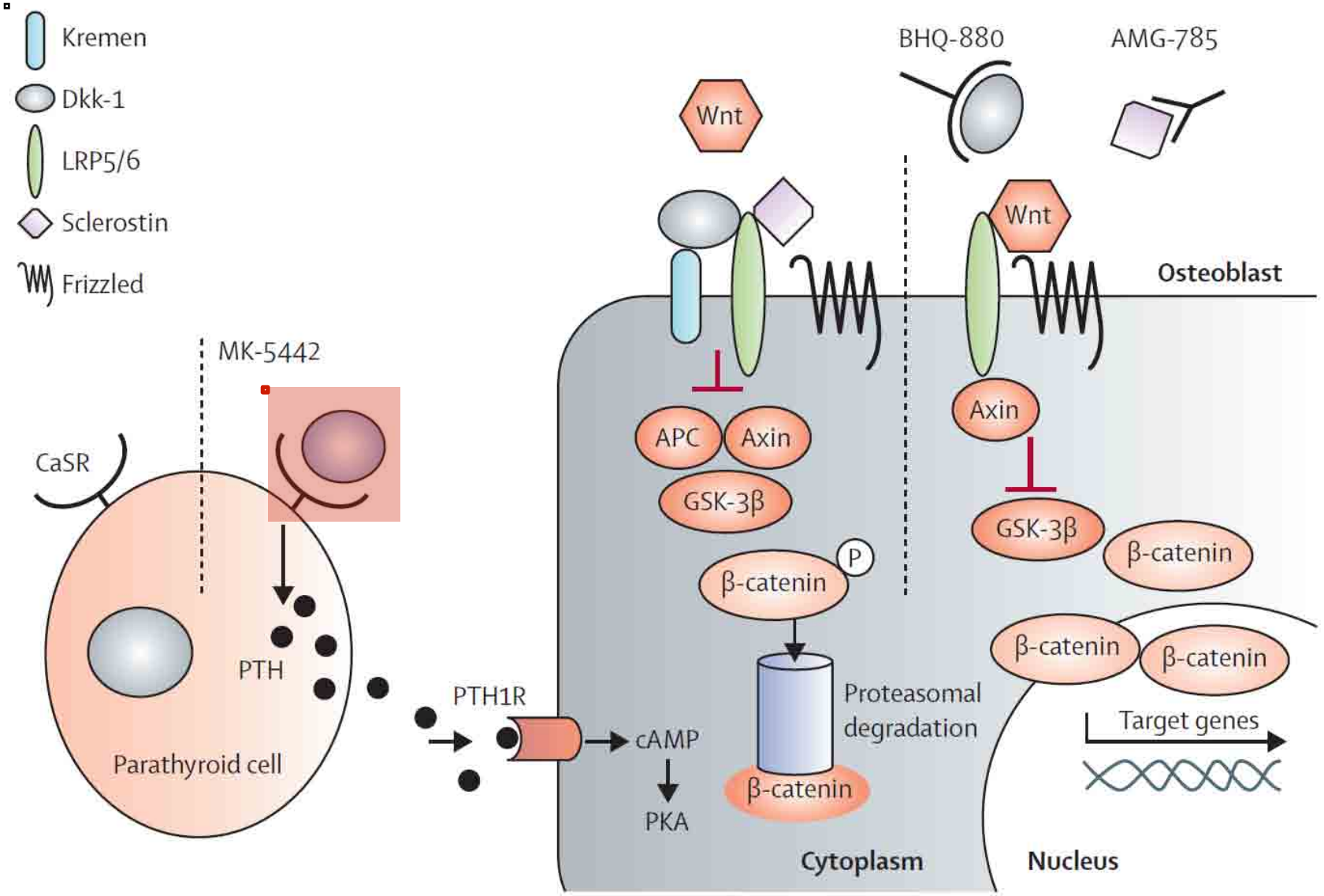
Rachner TD et al, Lancet 2011

Osteoblast physiology and potential therapeutic targets

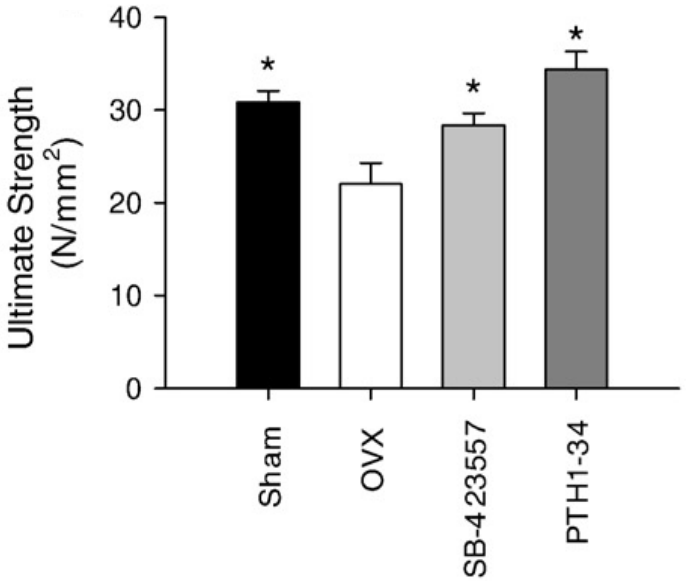


Rachner TD et al, Lancet 2011

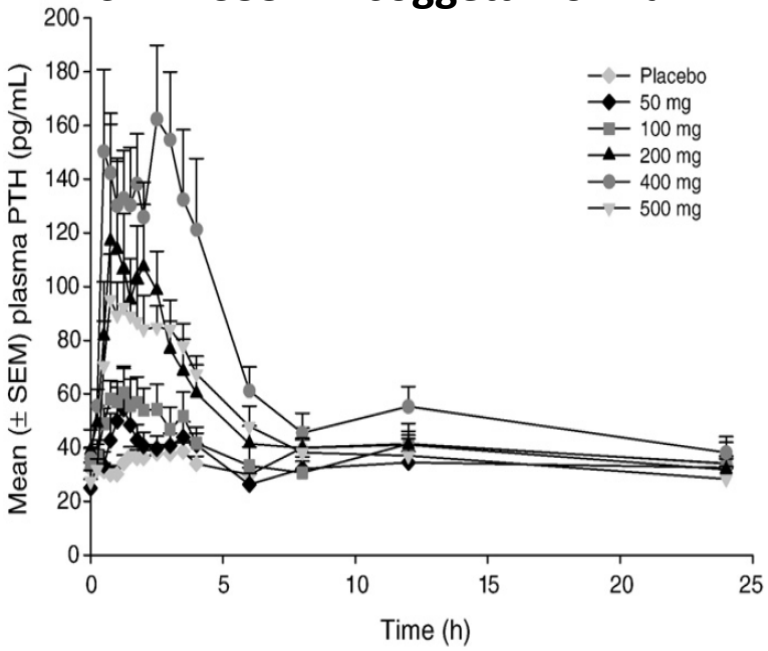
Kumar S et al, Bone 2010

An orally active calcium-sensing receptor antagonist that transiently increases plasma concentrations of PTH and stimulates bone formation

Resistenza al carico della V vertebra lombare dopo somministrazione di SB-423557 in ratti.



Concentrazioni plasmatiche di PTH dopo somministrazione orale di SB-423557 in soggetti normali.



La molecola calcio-litica più avanzata, MK-5442, è stata studiata in 2 studi di fase 2 in 900 donne post-menopausa. Non abbiamo ancora dati pubblicati.

TAKE HOME MESSAGES

Odanacatib è un inibitore della catepsina K, proteasi fondamentale nella degradazione del collagene.

Inibisce il riassorbimento scheletrico mantenendo vitale l'OC e senza influenzare la sintesi. Effetto reversibile.

Somministrato per via orale settimanale 50 mg in 400 donne postmenopausa con BMD tra -2.0 e -3.5 senza frattura, a 5 anni determina aumento del BMD del 12% alla colonna e del 10% al femore, senza effetti collaterali rilevanti.

AMG 785 è una molecola che inibisce sclerostina, proteina secreta dagli osteociti ed inibitore endogeno del sistema WNT-βcatenina, via implicata nella differenziazione ed attività osteoblastica.

Stimola l'apposizione con scarso effetto sul riassorbimento osseo

In uno studio contro placebo in 72 soggetti sani, 1 singola somminitrazione s.c. (10 mg/kg) o e.v. (5 mg/kg), ha determinato dopo 85 giorni un aumento del BMD significativo del 5.3% alla colonna e del 1.1-2.8% al femore, senza effetti collaterali rilevanti, ma con la formazione di ab neutralizzanti in 6 soggetti.

MK-5442 è una molecola calciolitica che mimando una condizione di ipocalcemia determina un rilascio intermittente di PTH.

Non abbiamo dati sulla massa ossea nell'uomo. Nell'animale è stato dimostrato aumentare la resistenza ossea su osso trabecolare

	Phase	n	Primary endpoint	Main results	Reference
Odanacatib					
Multiple oral doses in healthy adults and once-weekly doses in healthy adult women	1	62; 78	Safety and tolerability	No increase in adverse events; serum CTX decreased by 62% (50 or 100 mg per week); BSAP and osteocalcin remained unaffected	Stoch[62]
Treatment of postmenopausal osteoporosis	2	399	Percentage change from baseline BMD at lumbar spine after 24 months	Lumbar spine BMD +5·5% *vs* –0·2% with placebo	Bone[63]
Treatment of postmenopausal osteoporosis	3	16 716	Vertebral, hip, and clinical non-clinical fractures after 36 months	Expected to be completed in July 2012	NCT00529373
ONO-5334					
Postmenopausal women with low BMD	2	265	Percentage change from baseline BMD at lumbar spine after 12 months	Completed in October 2009, results pending	NCT 00532337
Saracatinib					
Multiple oral doses on bone turnover in healthy men	1	59	Effect on bone turnover of multiple daily oral dosing for up to 24 days	Serum CTX –88% (95% CI 84–91%) *vs* +17% with placebo ($p<0·001$); PINP +13 *vs* +17% with placebo (p=NS)	Hannon[64]
MK-5442 (calcilytic drug)					
Dose-ranging study in postmenopausal osteoporosis	2	384	Percentage change from baseline BMD at lumbar spine after 12 months	Expected to be completed in February, 2012	NCT00960934
Postmenopausal osteoporosis previously treated with alendronate	2	480	Percentage change from baseline BMD at lumbar spine *vs* alendronate after 12 months	Expected to be completed in August, 2012	NCT00996801
AMG 785 (antibody for sclerostin)					
Healthy men and postmenopausal women	1	74	Safety	No increase in adverse events; after 21 days 3 mg/kg increased PINP, osteocalcin, and BSAP by 60–100%	NCT01059435
Postmenopausal women with low BMD (*vs* alendronate and teriparatide)	2	419	Percentage change from baseline BMD at lumbar spine after 12 months	Expected to be completed in August, 2012	NCT00896532
BHQ 880 (antibody against dickkopf-1)					
Combination with zoledronic acid in relapsed or refractory myeloma patients	1–2	267	Time to skeletal-related event; changes in bone resorption and formation markers after 9 months	Expected to be completed in April, 2012	NCT00741377

NTX=N-terminal telopeptide of type 1 collagen. BMD=bone-mineral density. RR=relative risk. CTX=C-terminal telopeptide of type 1 collagen. BSAP=bone-specific alkaline phosphatase. PINP=serum procollagen propeptide of type 1 collagen.

Modified from, Rachner TD et al, Lancet 2011

THANK YOU !