

Novel Treatment Target for Osteoporosis

Annie Kung

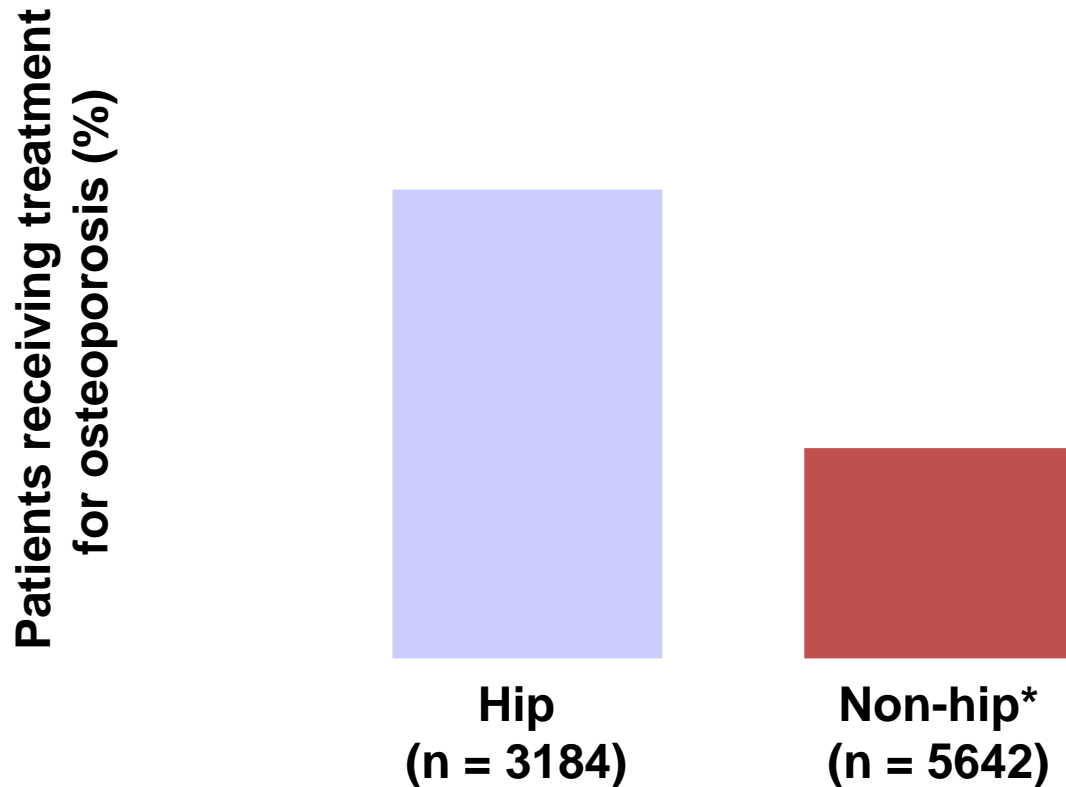
Specialist in Endocrinology, Diabetes &
Metabolism

Hon Clinical Professor, University of Hong Kong

Unmet Medical Needs in Osteoporosis

Most Women Do Not Receive Treatment During the Year Following an Osteoporosis-related Fracture

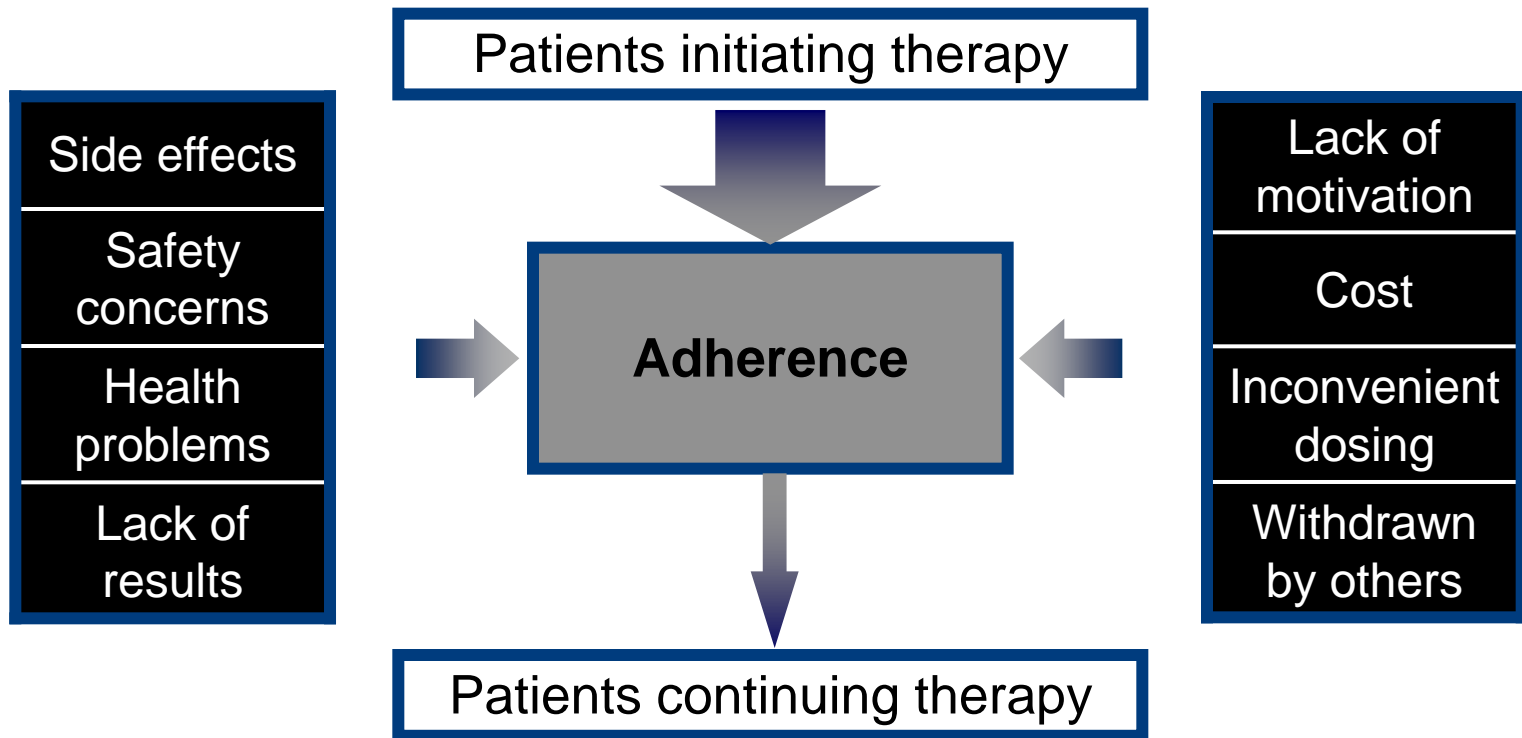
Interventions following low-trauma fracture
Oct-Dec 2006 (England, Wales and NI) n = 8826



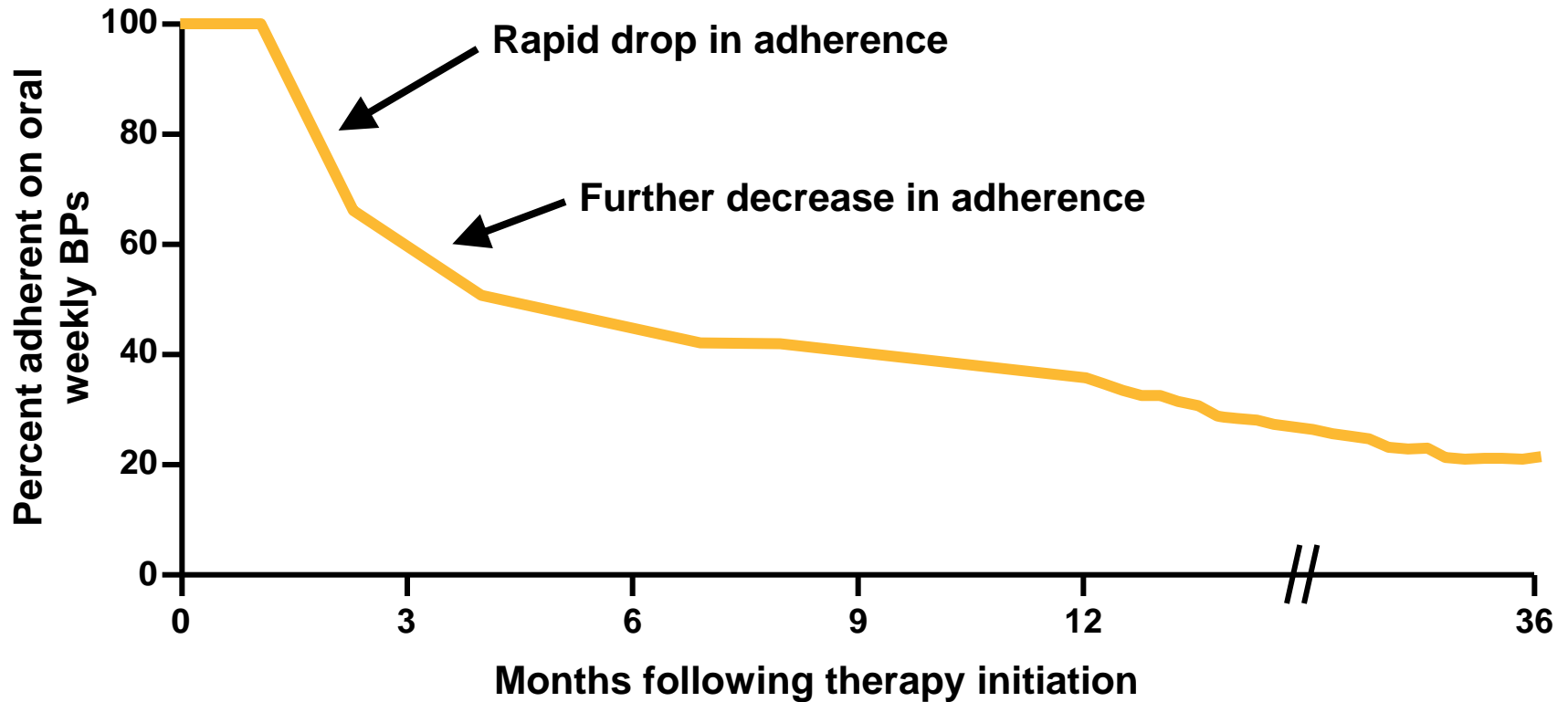
*Any fracture other than hip including vertebral fracture, radius and /or ulna fracture, humerus or pelvis fracture
National Clinical Audit of Falls and Bone Health (2007).

Osteoporosis Therapies and Patient Adherence

Less than 50% of patients persist with their osteoporosis therapy for more than 1 year

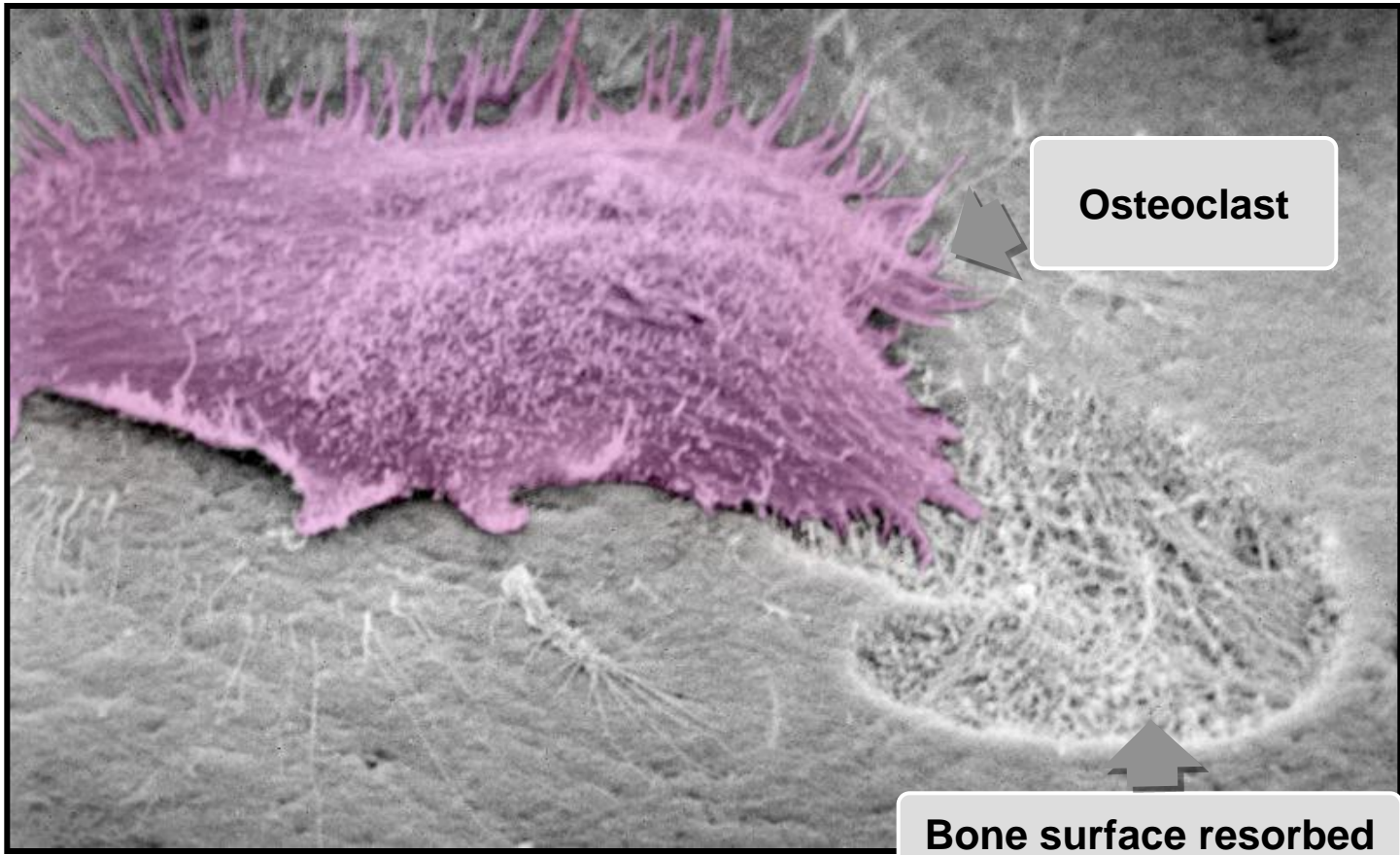


Many Patients Discontinue Oral Bisphosphonates Soon After Treatment Initiation



Bone Biology

Osteoclasts Are the Cells that Resorb Bone



Osteoclast

**Bone surface resorbed
by osteoclast**

Adapted from: http://www.brsoc.org.uk/gallery/arnett_osteoclast.jpg.
Electron micrograph photo reproduced with permission. © Tim Arnett, The Bone Research Society.

RANK Ligand Is an Essential Mediator of Osteoclast Formation, Function and Survival



RANK Ligand (RANKL)

- Signalling protein expressed by osteoblasts/bone lining cells
- Binds to RANK and promotes osteoclast formation, function and survival



RANK

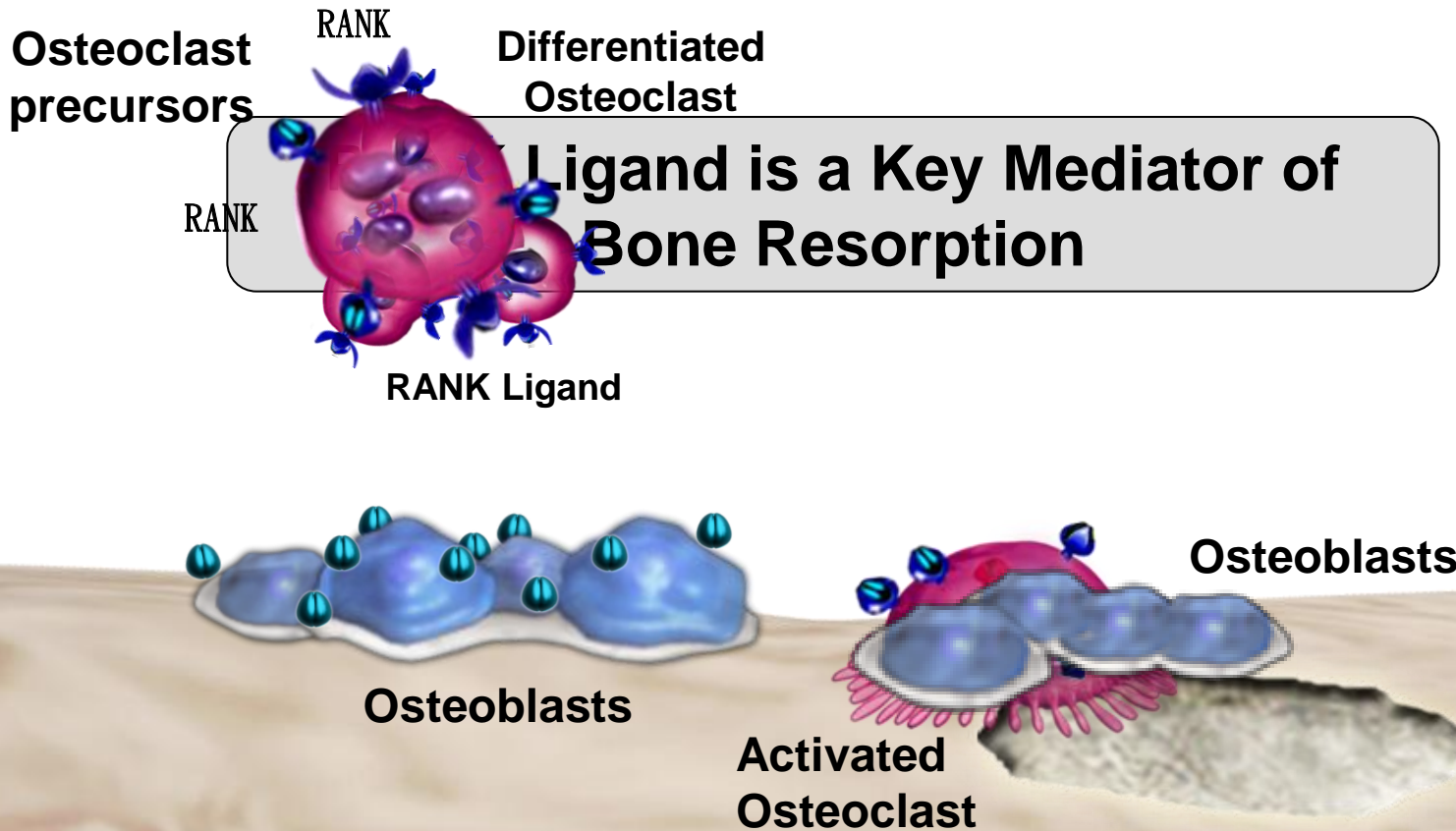
- Expressed by osteoclasts and their precursors
- Activated by RANK Ligand binding



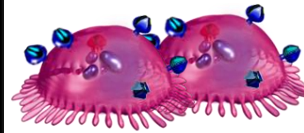
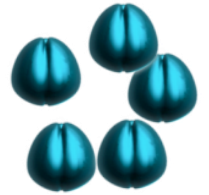
Osteoprotegerin (OPG)

- Protein secreted by osteoblasts/bone lining cells
- Natural inhibitor of RANK Ligand
- Blocks RANK Ligand signalling to balance bone remodelling

The RANKL/RANK/OPG Pathway Is Involved in Regulating Bone Remodelling

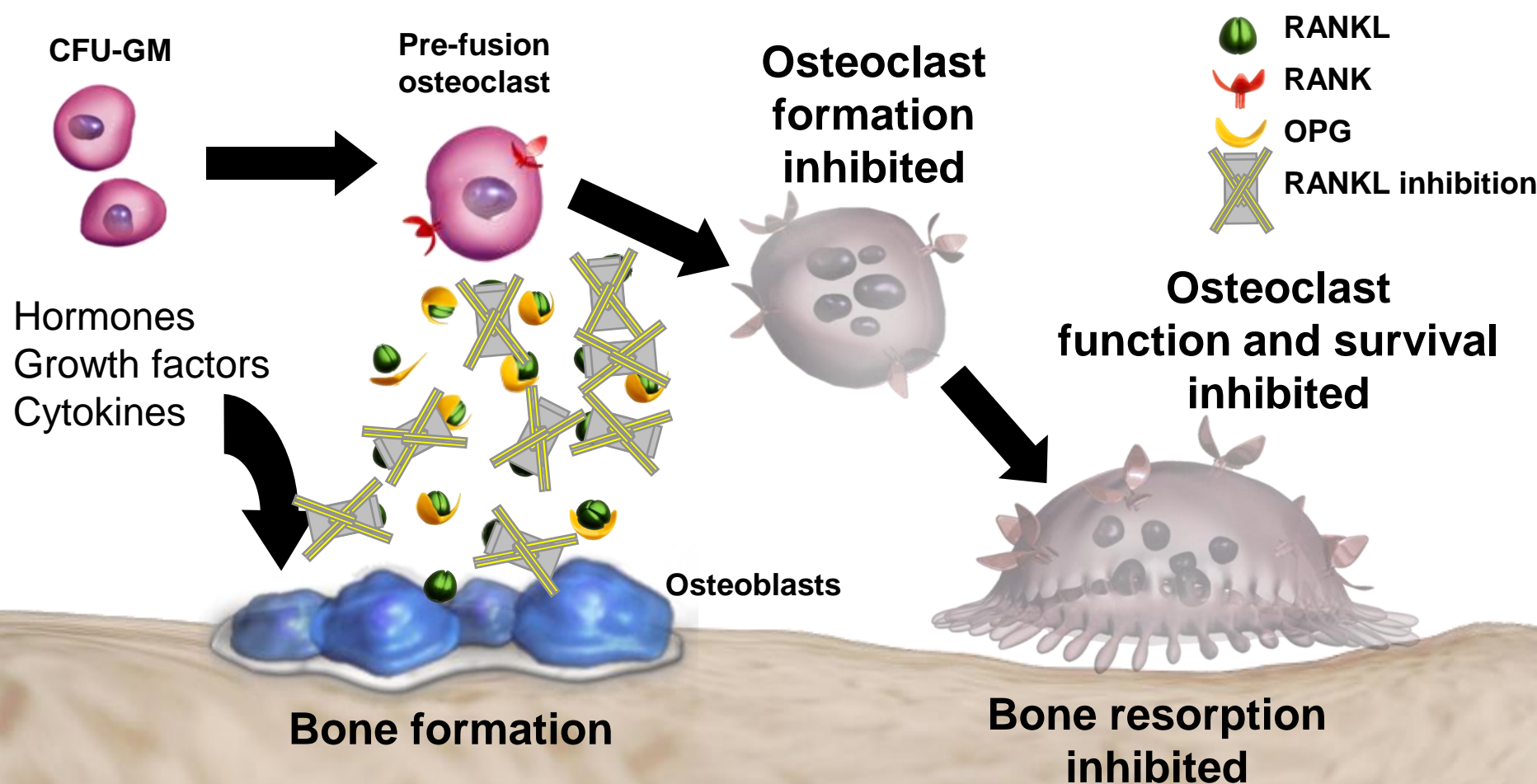


Unopposed RANK Ligand Activity Causes Long Bone Fragility Fractures



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

Inhibition of RANK Ligand – New Therapeutic Option



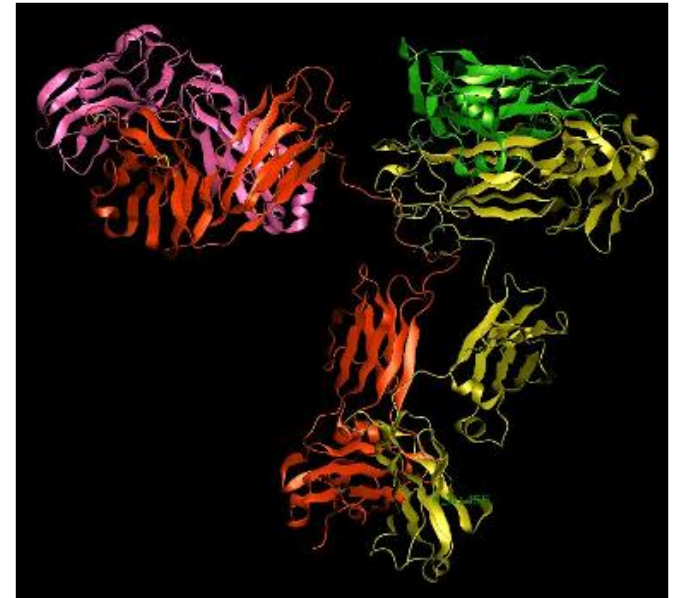
CFU-GM=colony forming unit granulocytemacrophage; M-CSF=macrophage colony stimulating factor.
Boyle WJ, et al. *Nature* 2003;423:337-342.

Denosumab pivotal studies

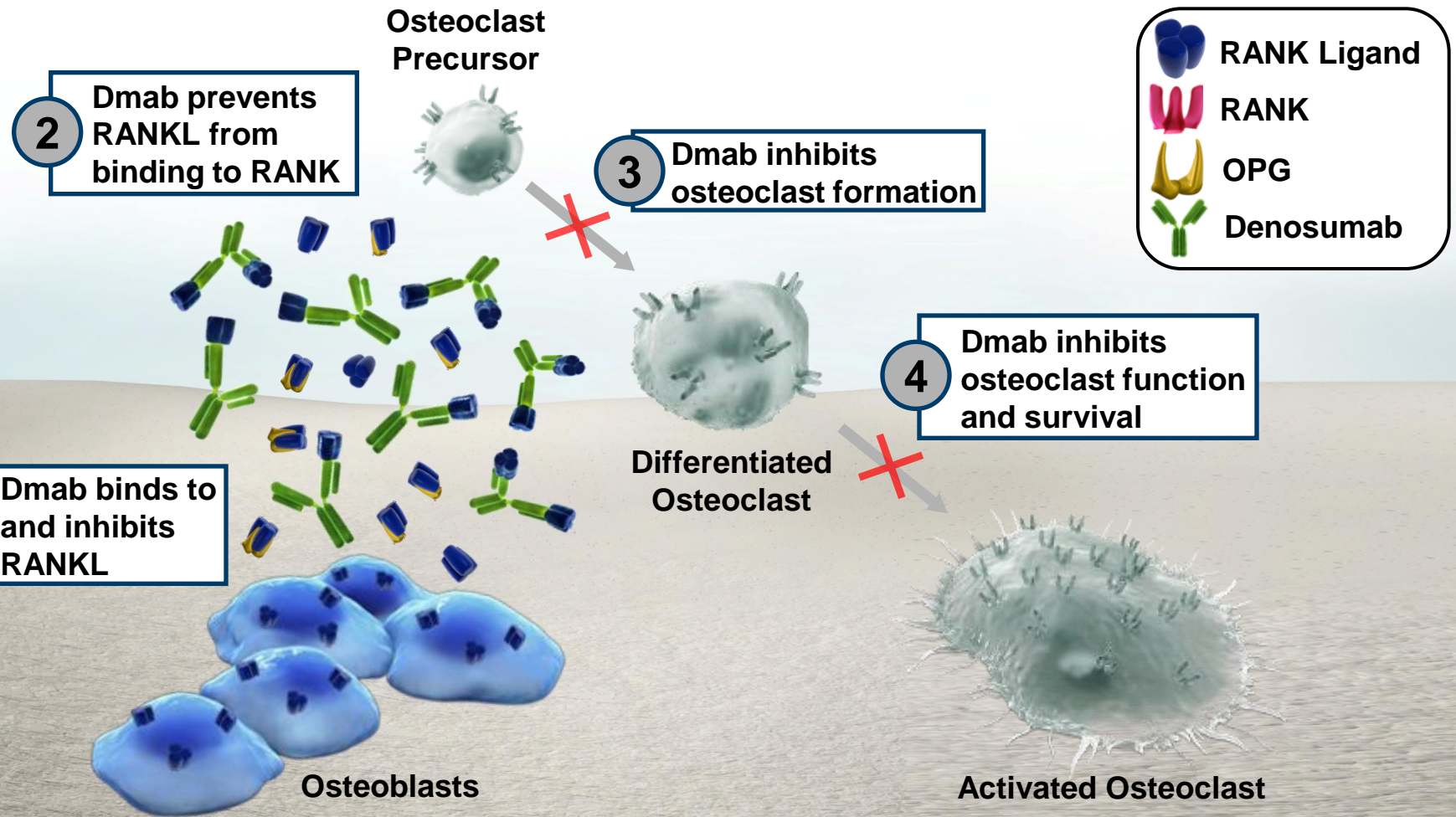
Pharmacologic Properties of Denosumab

- Fully human monoclonal antibody - IgG₂ isotype
- High affinity and specificity for human RANK Ligand
- Denosumab is a RANK ligand Antagonist
- Denosumab reduces the numbers and activity of osteoclast (antiresorptive)
- No neutralizing antibodies detected in clinical trials to date

Model of Denosumab

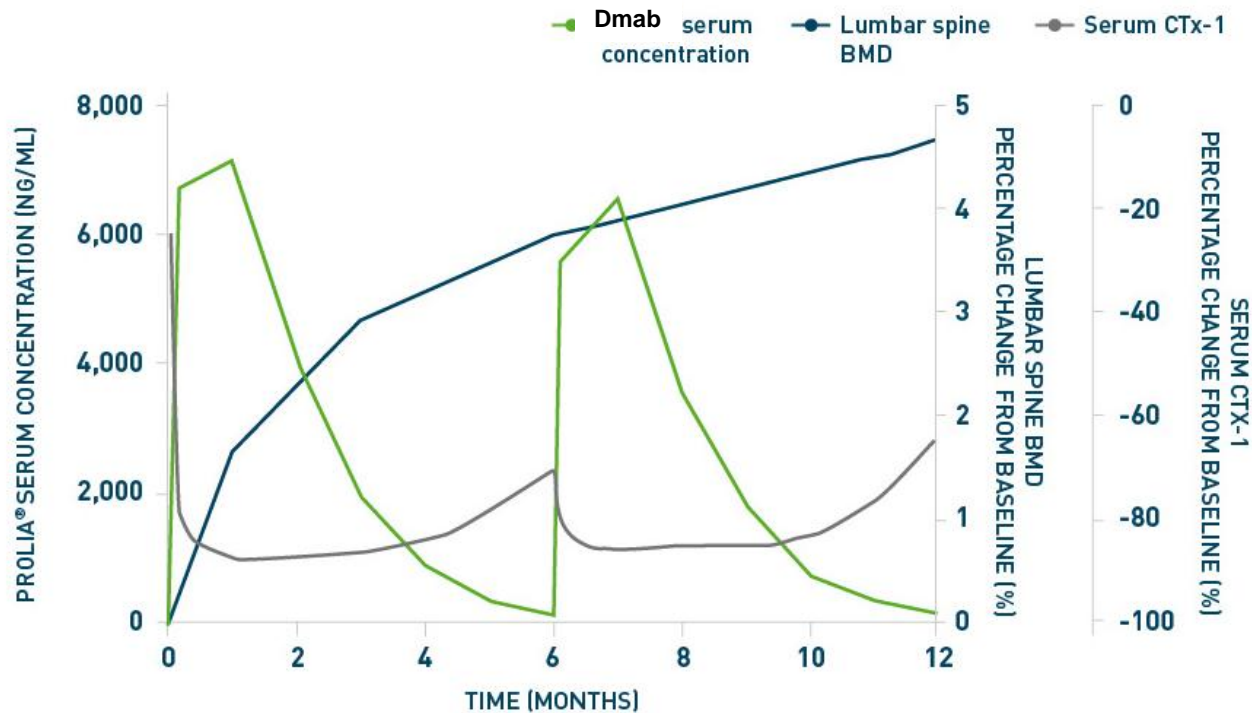


Denosumab (Dmab), a RANKL inhibitor, inhibits osteoclast formation, function and survival



Pharmacokinetic and Pharmacodynamic

- Serum CTx-1 levels fall rapidly, reflecting a fast reduction in bone turnover
- This effect is reversible as serum CTx-1 levels start to rise as denosumab is cleared from the circulation at the end of the 6 month dosing interval.¹

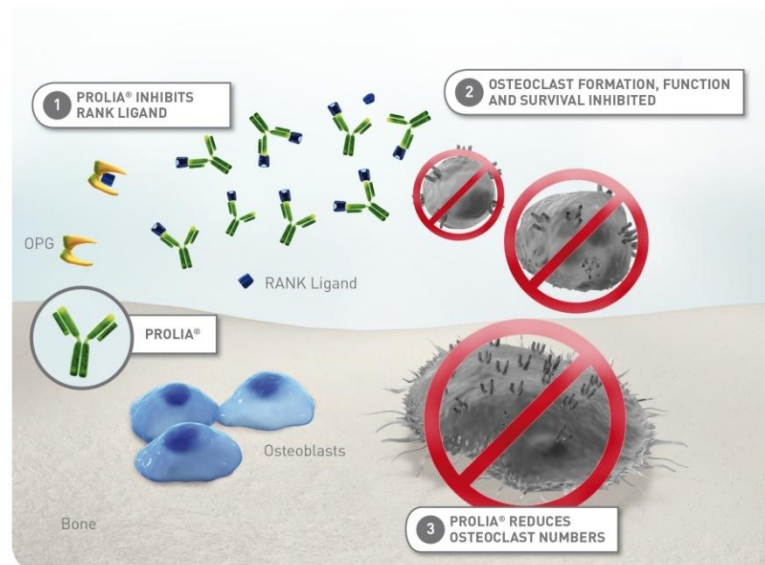


*CTx: C-telopeptide of collagen type 1. Serum CTx levels are a marker of bone resorption levels.

Denosumab has a different mode of action to bisphosphonates

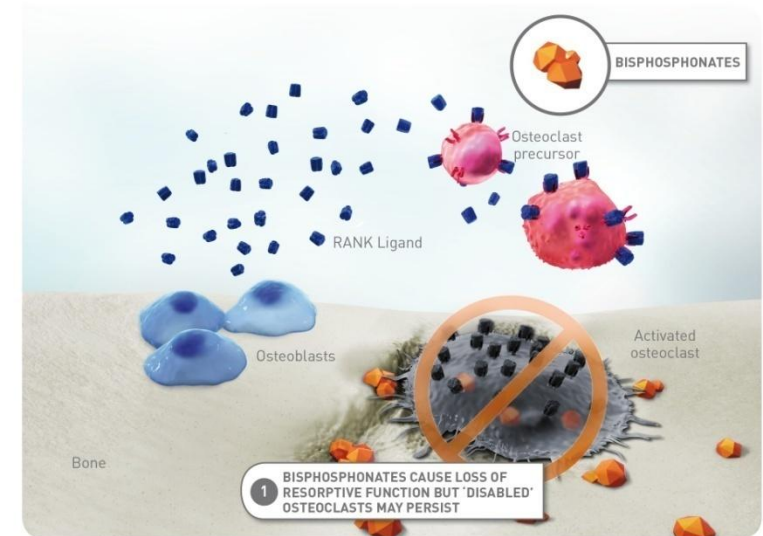
Denosumab inhibits osteoclast formation, function and survival^{1,2}

Denosumab mode of action



Bisphosphonates (BPs) bind to bone mineral at sites of bone resorption.^{3,4} BPs are cytotoxic and cause loss of resorptive function but inactive osteoclasts may persist^{3,4}

Bisphosphonate mode of action



1. Denosumab, Summary of Product Characteristics, 2010. 2. Boyle WJ *et al.* *Nature* 2003;423:337–342.
3. Drake MT *et al.* *Mayo Clin Proc* 2008;83:1032–1045. 4. Russell RGG *et al.* *Osteoporos Int* 2008;19:733–759.

	Bisphosphonate	Denosumab
Distribution	Bone mineral surface	Circulation in blood and extracellular fluid
Pharmacological effect	Mainly seen in trabecular sites	In both trabecular and cortical sites
Onset of action	IV: fast onset; oral: slow onset	Faster onset of action than oral alendronate
Duration of action and reversibility of effect after discontinuation	Depends on type of BP and length of treatment. Slow offset of action	Fully reversible and relatively rapid offset of action
Excretion	Excreted via the kidney, contraindicated to severe renal impairment	Cleared by reticuloendothelial system independent of renal clear

Content:

Phase 3

DECIDE

*Head-to-Head Denosumab Versus Alendronate
(DECIDE)*

STAND

Alendronate-to-Denosumab Transition (STAND)

FREEDOM 3-Year

*Fracture Reduction Efficacy With Denosumab
(FREEDOM)*

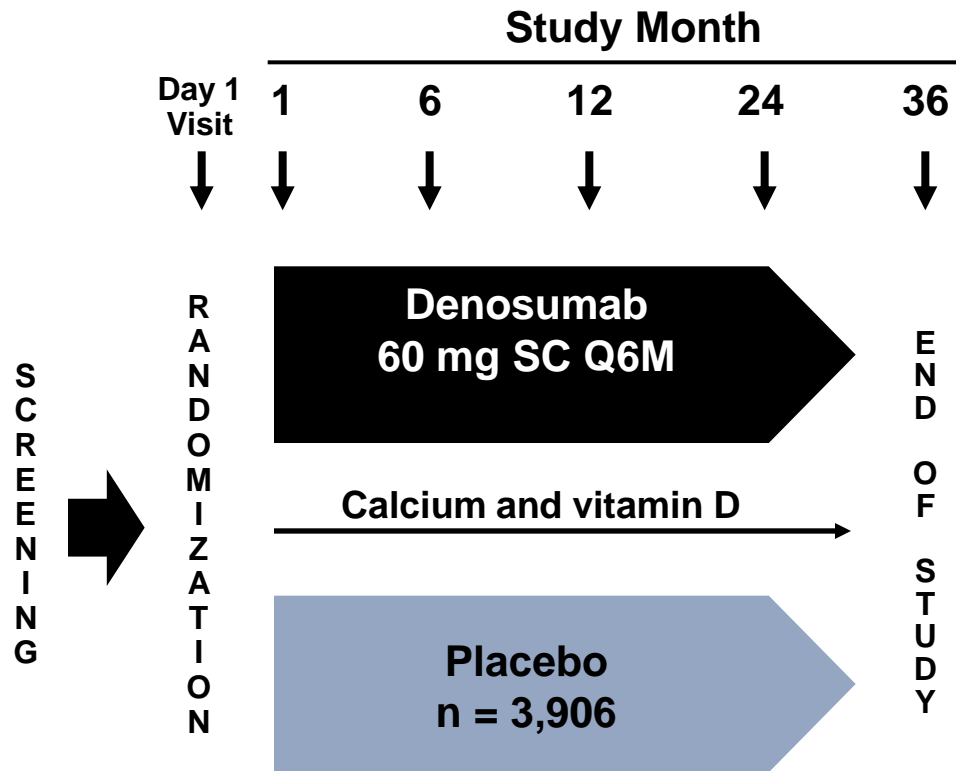
The Effects of Denosumab on Vertebral, Nonvertebral, and Hip Fracture in Women With Osteoporosis:

The FREEDOM Trial

*Fracture REduction Evaluation of
Denosumab in Osteoporosis Every
6 Months*

Study Design

Phase 3: The FREEDOM Trial



Study population

- 7,808 postmenopausal women
- T-score < -2.5 at the lumbar spine or total hip and not < -4.0 at either site
- Exclusion any severe or > 2 moderate vertebral fractures

Primary endpoint

- New vertebral fracture over 36 months

Secondary endpoints

- Time to nonvertebral fracture
- Time to hip fracture

- International, placebo-controlled study

Selected Baseline Characteristics and Patient Disposition

Phase 3: The 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)

FREEDOM: The effect of Denosumab on fracture risks at 36 Months (7,762 subjects, Dmab Q6M x 3 years)

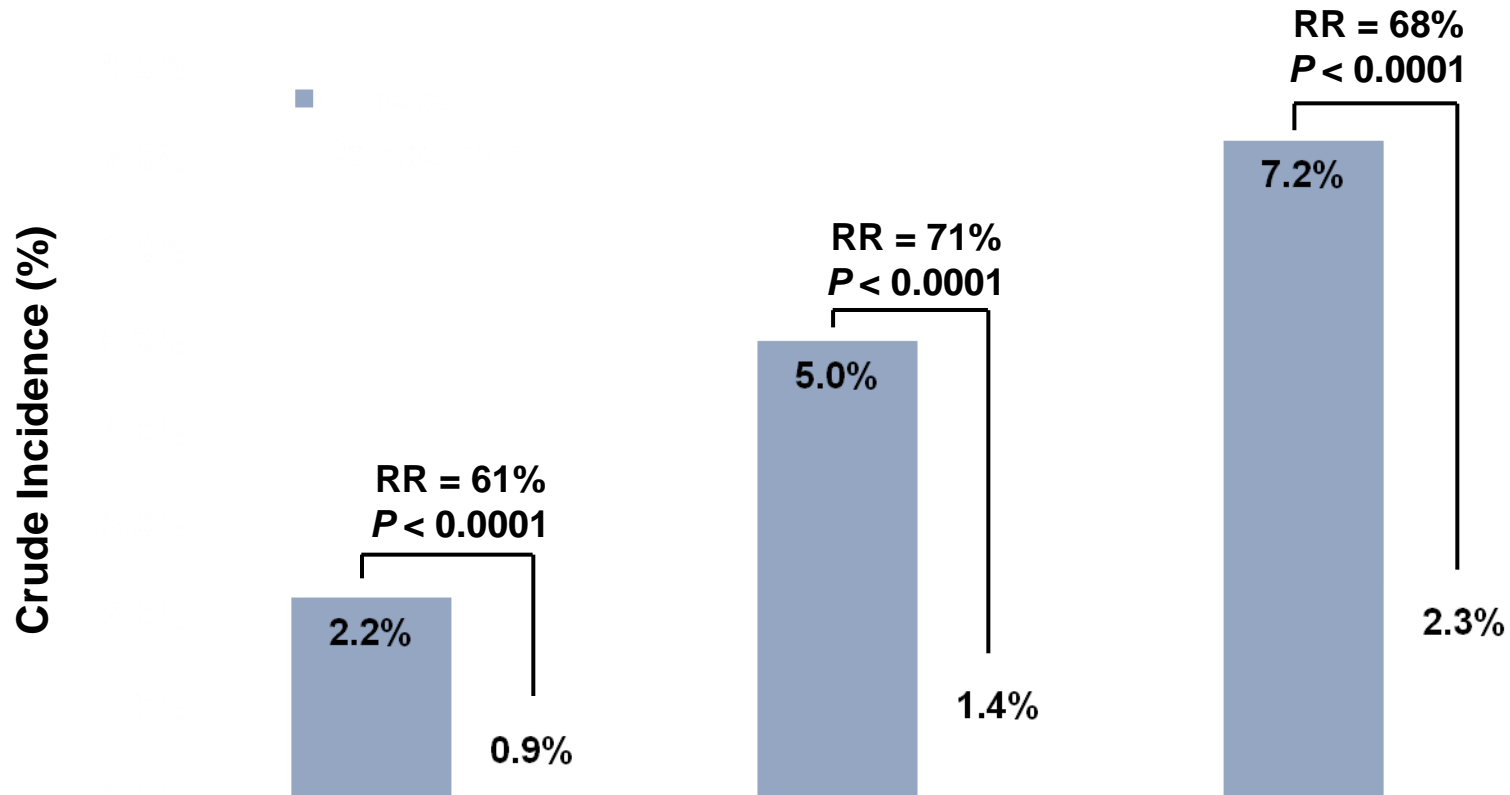


Primary Endpoint

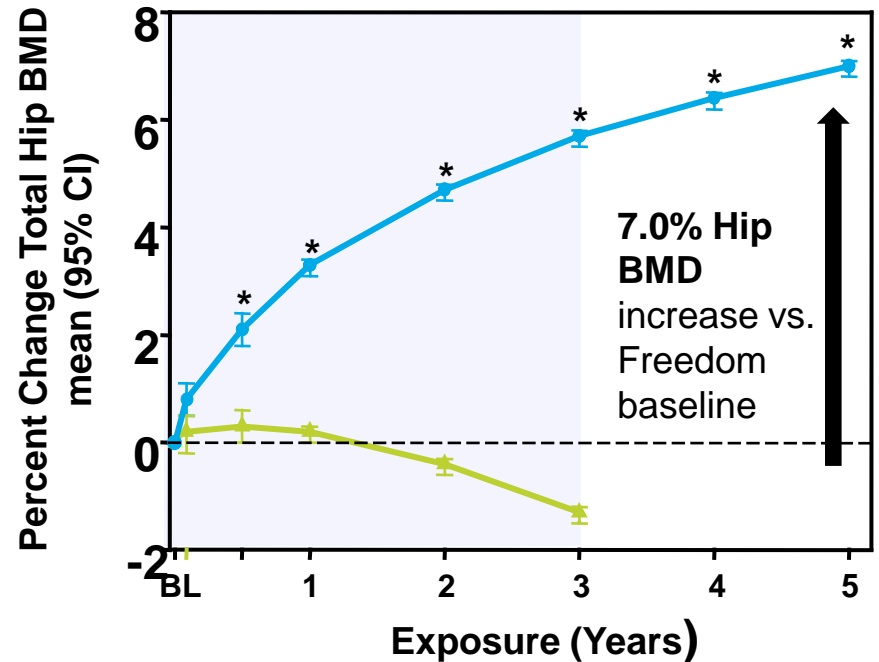
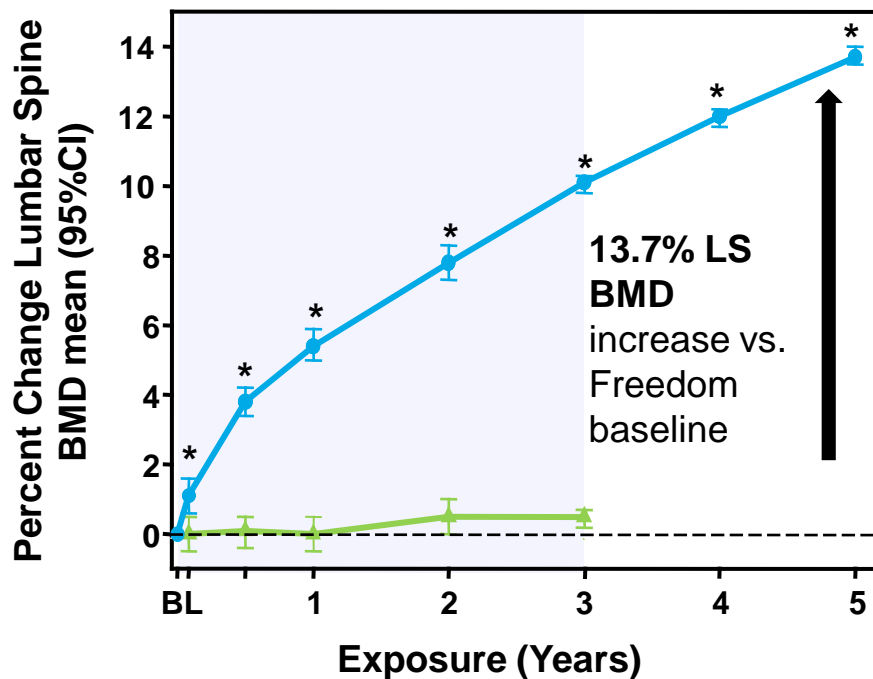
RR = risk reduction

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

FREEDOM: The Effect of Denosumab on New Vertebral Fractures At Month 12, 24, and 36



FREEDOM Extension Study: BMD continued to significantly increase in Year 4 and 5



*p < 0.002 from placebo and baseline

BMD continued to significantly increase in years 4 and 5 with long-term denosumab treatment

● Denosumab long-term (N=2208)
▲ Placebo (N=2088)

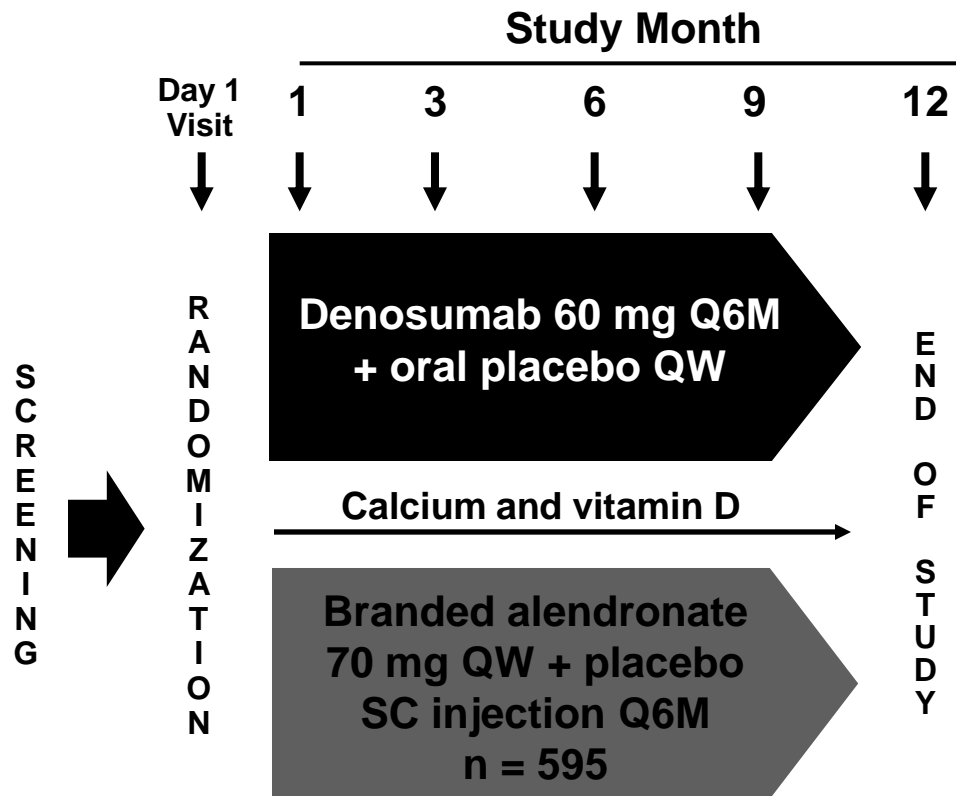
Phase 3 Data on the Effects of Denosumab or Alendronate (ALN) on Bone Mineral Density:

The Phase 3 DECIDE Initiation Study

*Determining Efficacy: Comparison of Initiating Denosumab
vs Alendronate (DECIDE)*

Study Design

The Phase 3 DECIDE 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

- **Multicenter, double-blind, double-dummy, active-controlled study**

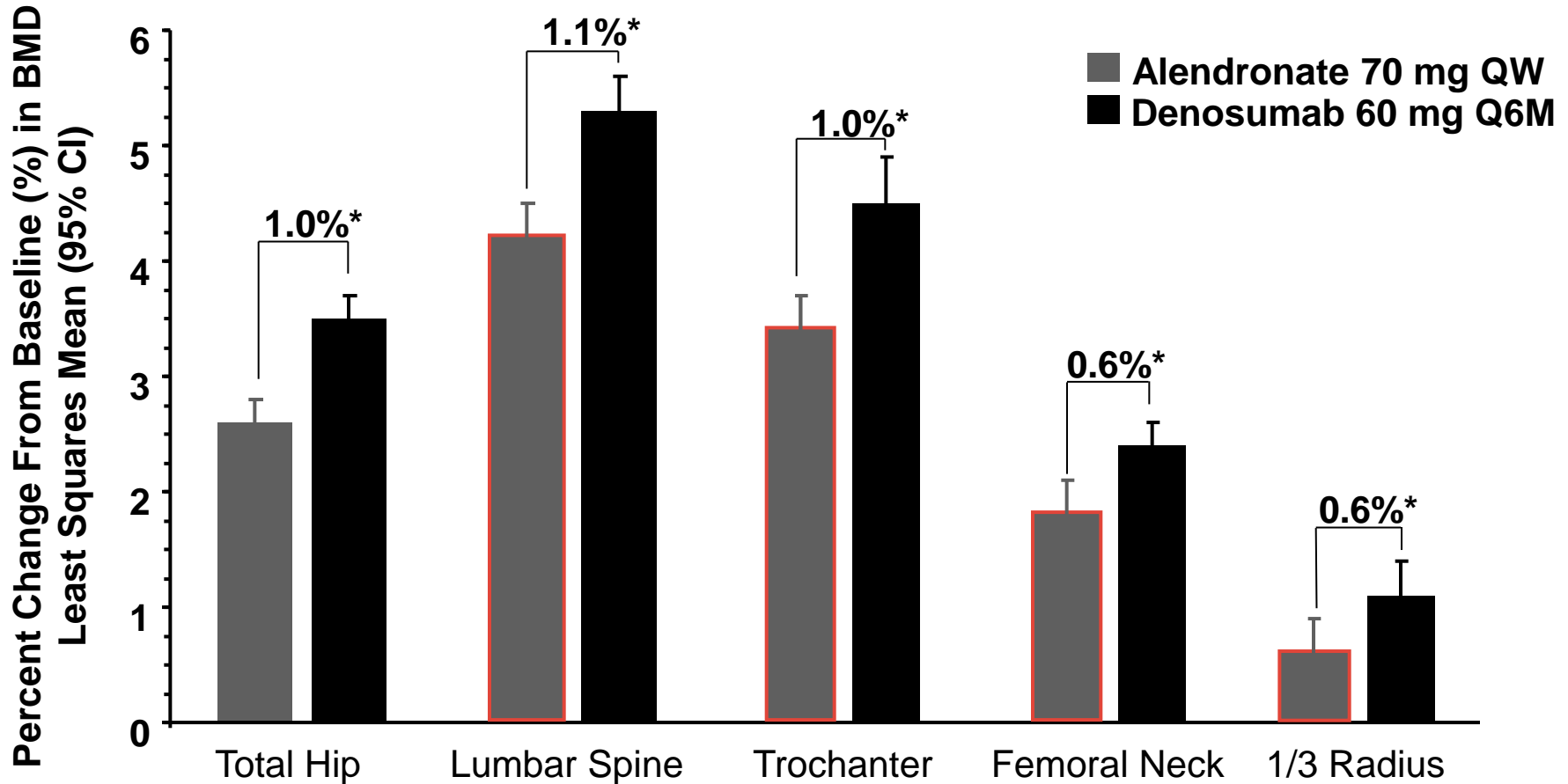
BMD data results are not meant to imply fracture efficacy and should not be extrapolated to predict differences in fracture efficacy. Head-to-head fracture studies have not been conducted.

Q6M = once every 6 months; QW = once weekly; SC = subcutaneous; BMD = bone mineral density

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

BMD at Month 12 for All Measured Skeletal Sites

The Phase 3 DECIDE Study



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.

* $P \leq 0.0001$.

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

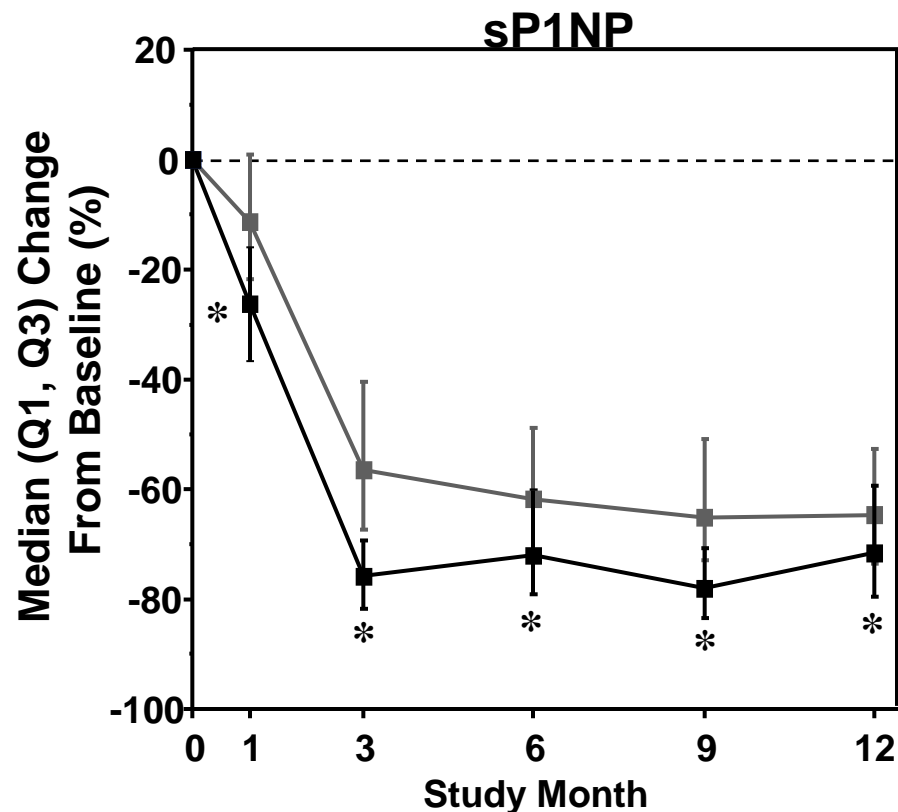
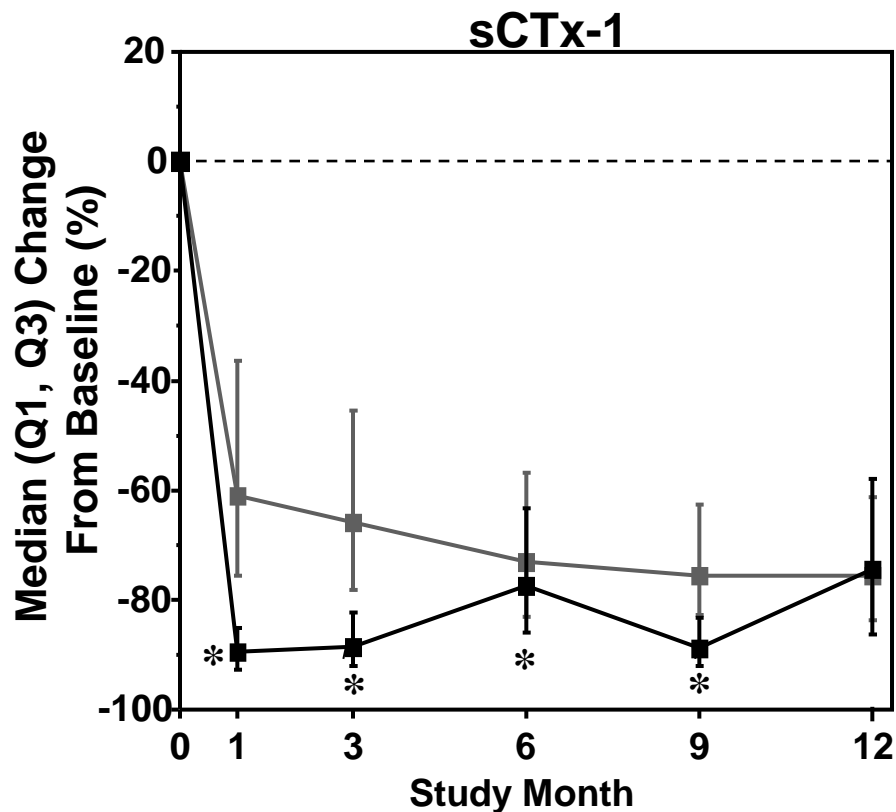
Brown JP, et al. Presented at: 35th Annual European Symposium on Calcified Tissues; May 24-28, 2008; Barcelona, Spain. Late breaking abstract LB2.

Effect of Treatment on Bone Turnover Markers

The Phase 3 DECIDE Study

■ Alendronate 70 mg QW

■ Denosumab 60 mg Q6M



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.

* $P \leq 0.0001$.

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

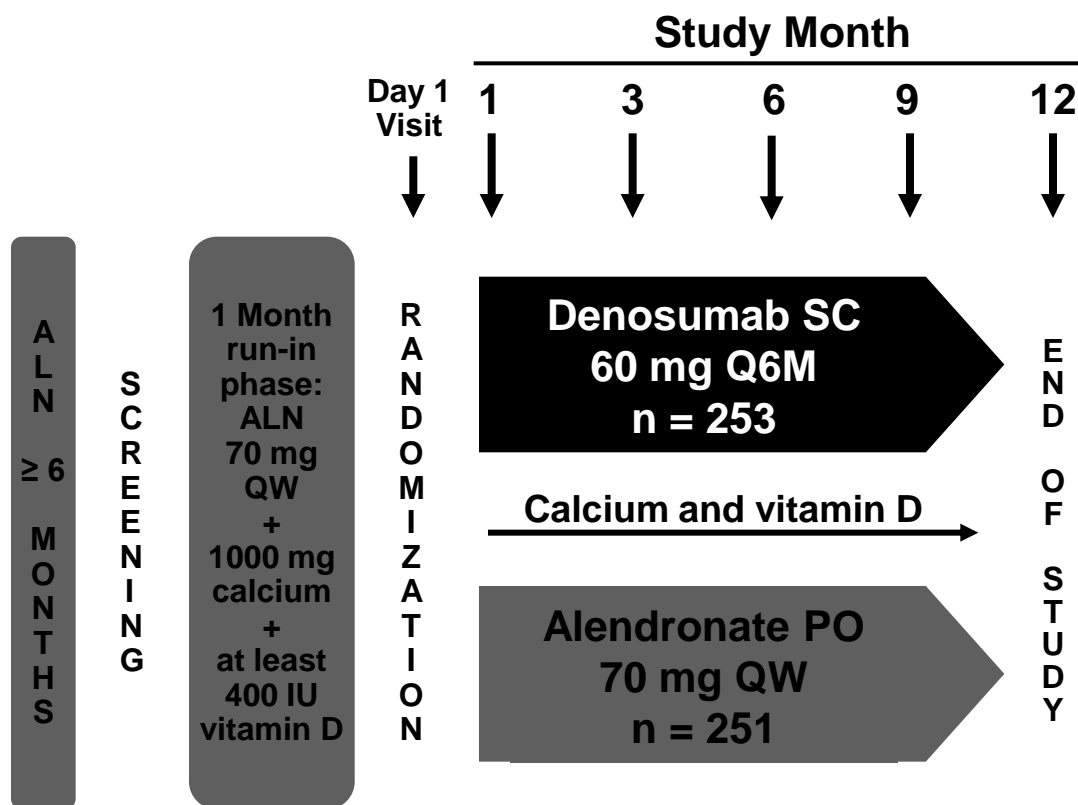
Phase 3 Data on the Effects of Denosumab or Alendronate on Bone Mineral Density, Bone Turnover Markers, and Safety in Postmenopausal Women With Low Bone Mineral Density Previously Treated With Alendronate:

Phase 3 Transition STAND Study

Study of Transitioning from AleNdronate to Denosumab (STAND)

Study Design

The Phase 3 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

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.

ALN = alendronate; QW = once weekly; SC = subcutaneously; Q6M = once every 6 months; PO = orally; BMD = bone mineral density;

CTX-I = type 1 C-telopeptide

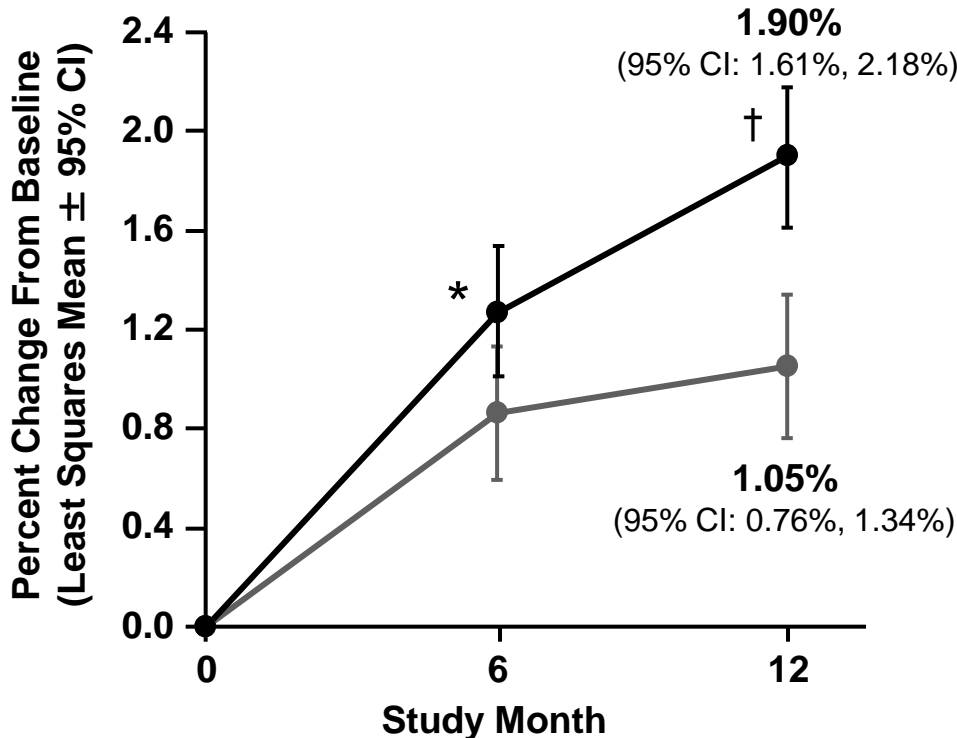
Kendler DL, et al. *J Bone Miner Res.* 2010;25:72-81.

Effects of Treatment on BMD Over 12 Months

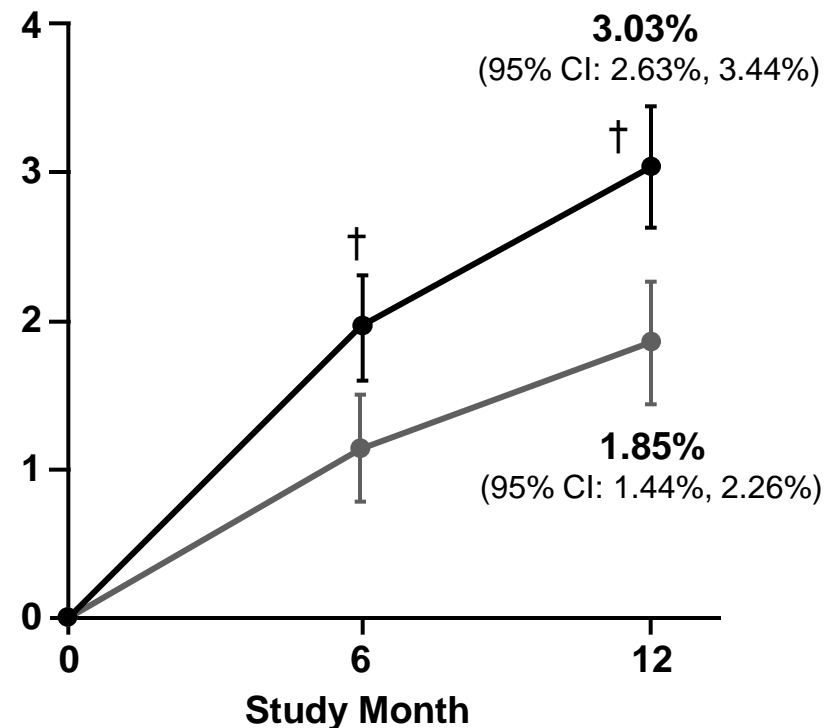
The Phase 3 STAND Study

—●— Alendronate 70 mg QW (n = 241) —●— Denosumab 60 mg Q6M (n = 246)

Total Hip (primary endpoint)



Lumbar Spine (secondary endpoint)



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.

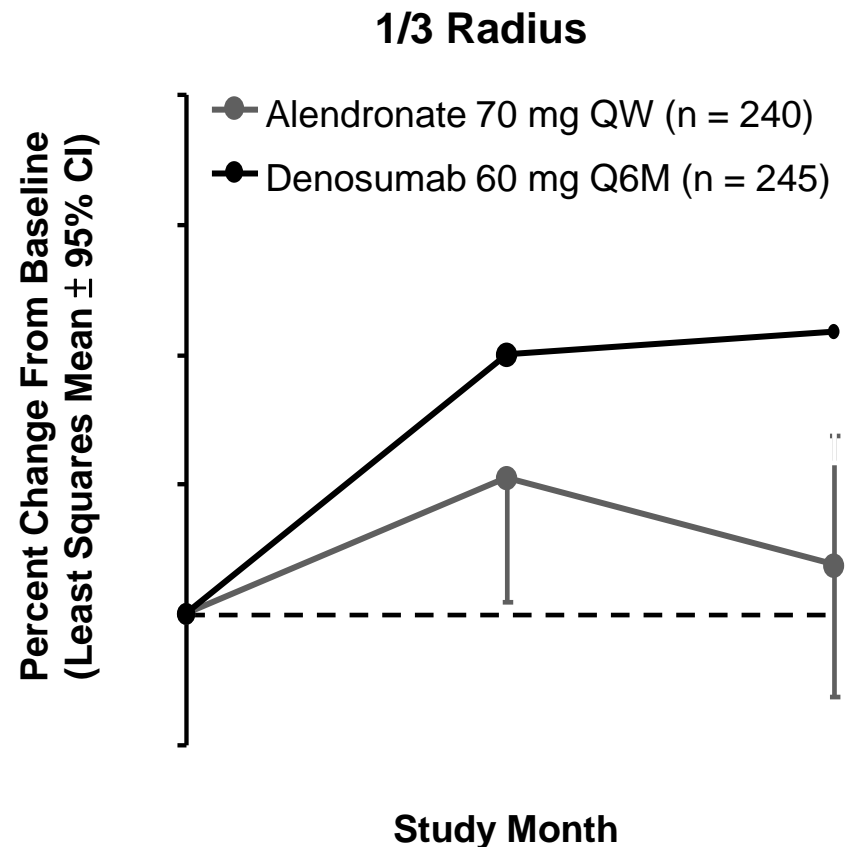
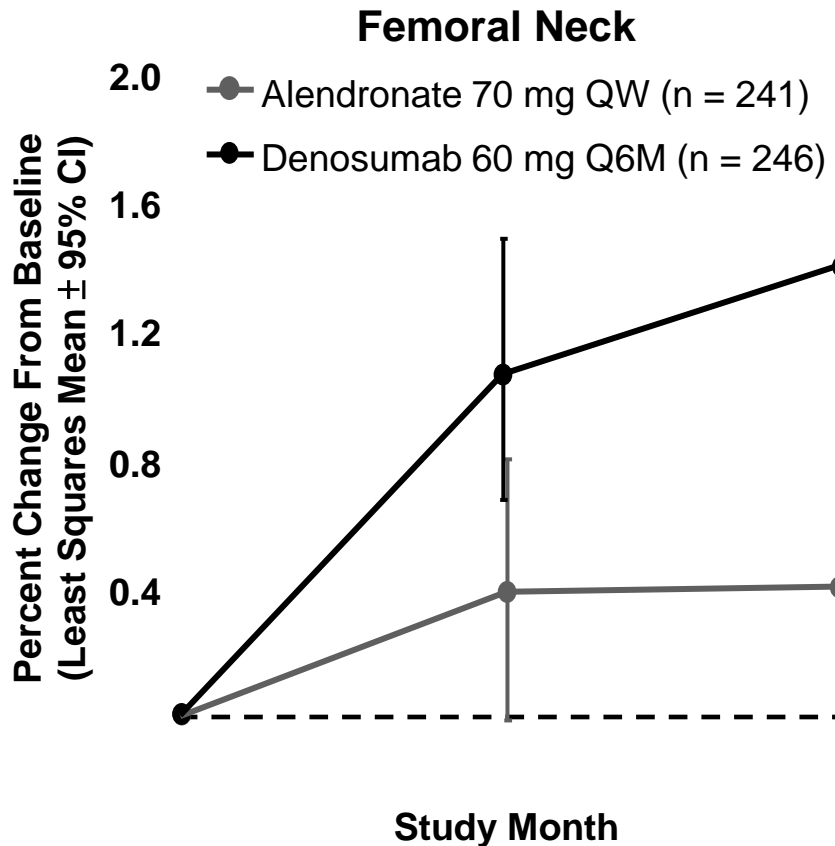
n = number of patients who have a baseline and ≥ 1 postbaseline evaluation.

* $P < 0.05$; † $P < 0.01$; CI = confidence interval

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

Kendler D, et al. *J Bone Miner Res.* 2008;23(suppl 1):S473. Abstract M395 and poster.

Improved BMD at month 12 at the femoral neck and 1/3 Radius



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.

n = number of patients who have a baseline and ≥ 1 postbaseline evaluation.

* $P < 0.01$.

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

Kendler D, et al. *J Bone Miner Res.* 2008;23(suppl 1):S473. Abstract M395 and poster.

Safety Profile & Others

Summary of adverse effects

Rate per 100-Patient-Years

	FREEDOM		EXTENSION
	Placebo N = 3883 Rate (Event)	Denosumab N = 3879 Rate (Event)	Denosumab Long-Term Treatment Subjects N = 2343 Rate (Event)
All	237	235	180
Infections	40.2	39.8	33.3
Eczema	0.7	1.3	1.1
Hypocalcemia	< 0.1 (3)	0	< 0.1 (1)
Serious	16.4	17.3	15.3
Infections	1.4	1.8	1.4
Cellulitis or Erysipelas	< 0.1 (1)	0.1 (13)	< 0.1 (3)
Malignancies	1.8	2.0	2.1
Osteonecrosis of the jaw	0	0	0
Atypical fracture	0	0	0

2 subjects had AE adjudicated to ONJ in the group that received placebo followed by denosumab.

More about safety profile

- No dose adjustment required in patients with renal impairment¹
- No difference in injection site reactions as compared to placebo²
- No neutralising antibodies were observed in clinical trials¹
- Low potential for drug–drug interactions¹
- Not incorporated into the bone matrix³

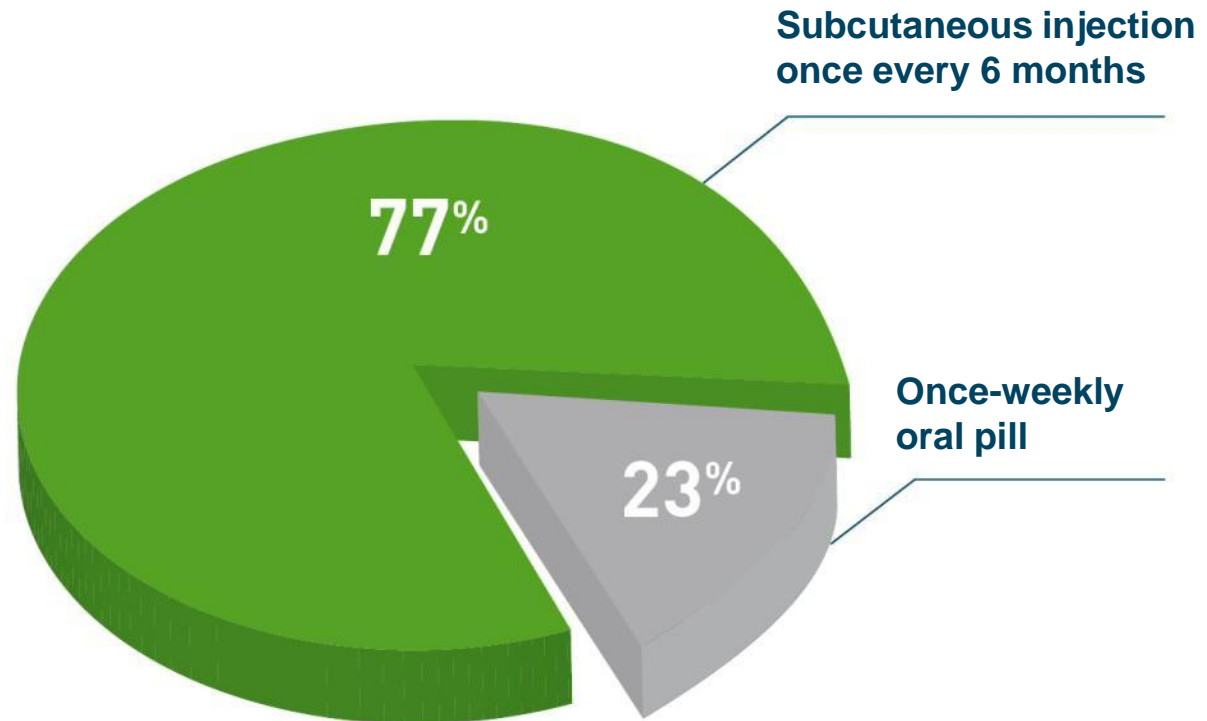
§ A s with other anti-resorptive agents:

- Hypocalcaemia is contraindicated ¹
- Adequate intake of calcium and Vit D is important¹

1. Prolia®, Product Information 2011. 2. Cummings SR *et al.* *N Engl J Med* 2009;361:756–765.
3. Kostenuik P *et al.* *Bone Miner Res* 2009;24:182–195.

Preference of 6-monthly subcutaneous injection over a weekly oral pill

Percentage of patients reporting greater preference of regimen (n=1322)¹



Among patients reporting a preference: n = 1,322. 65% of the Prolia® group and 64% of the alendronate group stated they preferred the 6-monthly injection, giving an average of 64% patients who preferred the 6-monthly injection. 19% of patients in both groups preferred the once-weekly tablet, meaning that overall 83% of patients expressed a preference. Therefore, of patients who expressed a preference, 77% (64/83) preferred the 6-monthly injection.

1. Kendler DL. *Osteoporos Int* 2010;21:837–846.

Expert Opinion on Denosumab

REVIEW ARTICLE

Pharmacoeconomics 2011; 29 (11): 951-961
1170-7690/11/0011-0951/\$49.95/0

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Denosumab for the Prevention of Osteoporotic Fractures in Post-Menopausal Women

A NICE Single Technology Appraisal

Graham Scotland,¹ Norman Waugh,² Pamela Royle,² Paul McNamee,¹ Rob Henderson³ and Rosemary Hollick⁴

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Contents

Abstract	951
1. The Decision Problem	953
2. The Independent Evidence Review Group (ERG) Review	954

■ A NICE Single Technology Appraisal:

- an **effective treatment** for the prevention of osteoporotic fractures in post-menopausal women
- administered in primary care, denosumab provides a **cost-effective treatment option** for certain groups of post-menopausal women **at increased risk of fracture**

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR
THE DIAGNOSIS AND TREATMENT OF
POSTMENOPAUSAL OSTEOPOROSIS**

*Nelson B. Watts, MD, FACP, MACE; John P. Bilezikian, MD, MACE;
Pauline M. Camacho, MD, FACE; Susan L. Greenspan, MD, FACP, FACE;
Steven T. Harris, MD, FACE; Stephen F. Hodgson, MD, FACP, MACE;
Michael Kleerekoper, MD, MACE; Marjorie M. Luckey, MD, FACE;
Michael R. McClung, MD, FACP, FACE;
Rachel Pessah Pollack, MD; Steven M. Petak, MD, JD, FACE, FCLM*

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NATIONAL
OSTEOPOROSIS
GUIDELINE GROUP

Guideline for
the diagnosis and
management of
osteoporosis
in postmenopausal women
and men from the age of
50 years in the UK

	Class	Efficacy against fracture		
		Vertebral ^{1,2}	Hip ^{1,2}	Non-vertebral
Denosumab	RANK L Inhibitor	Y	Y	Y ^{1,2}
Alendronate	Bisphosphonate	Y	Y	Y ^{1,2}
Ibandronic PO	Bisphosphonate	Y	No effect	No effect ^{1/} subset ²
Risedronate	Bisphosphonate	Y	Y	Y ^{1,2}
Ibandronic IV	Bisphosphonate	Y	No data ³	No data ³
Zoledronic	Bisphosphonate	Y	Y	Y ^{1,2}
Strontium	Others	Y	Subset ²	Y
Teriparatide	PTH	Y	No effect	Y ^{1,2}

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Rachel Pessah Pollack, MD; Steven M. Petak, MD, JD, FACE, FCLM*

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AACE Postmenopausal O:

3.7. What Drugs Can Be Used to Treat Osteoporosis?

Use drugs with proven antifracture efficacy:

- **R22.** Use alendronate, risedronate, zoledronic acid, and denosumab as the first line of therapy (**Grade A; BEL 1**).
- **R23.** Use ibandronate as a second-line agent (**Grade A; BEL 1**).
- **R24.** Use raloxifene as a second- or third-line agent (**Grade A; BEL 1**).
- **R25.** Use calcitonin as the last line of therapy (**Grade C; BEL 2**).
- **R26.** Use teriparatide for patients with very high fracture risk or patients in whom bisphosphonate therapy has failed (**Grade A; BEL 1**).
- **R27.** Advise against the use of combination therapy (**Grade B; BEL 2**).

Conclusions

- Despite widely available treatments many patients are still left unprotected
- Adherence to existing conventional therapy is suboptimal
- The discovery of the RANK/RANKL/OPG pathway is a major breakthrough in bone biology
- RANK Ligand inhibition represents a therapeutic option for inhibiting the formation, function and survival of osteoclasts, and improving bone health for patients with osteoporosis
- Denosumab has a physiological mode of action by targeting the RANK Ligand pathway
- Denosumab significantly reduces risk of vertebral, hip and non-vertebral fractures in women with postmenopausal osteoporosis
- No dose adjustment for renal impaired cases when using denosumab
- Denosumab is a 6-monthly subcutaneous injection