PATHWAYS IN Osteoporosis

Denosumab efficacy and safety

IL/DNB/0036/14
November 2014

PATHWAYS IN
Osteoporosis

RANK Ligand pathway

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

- RANK Ligand (RANKL)

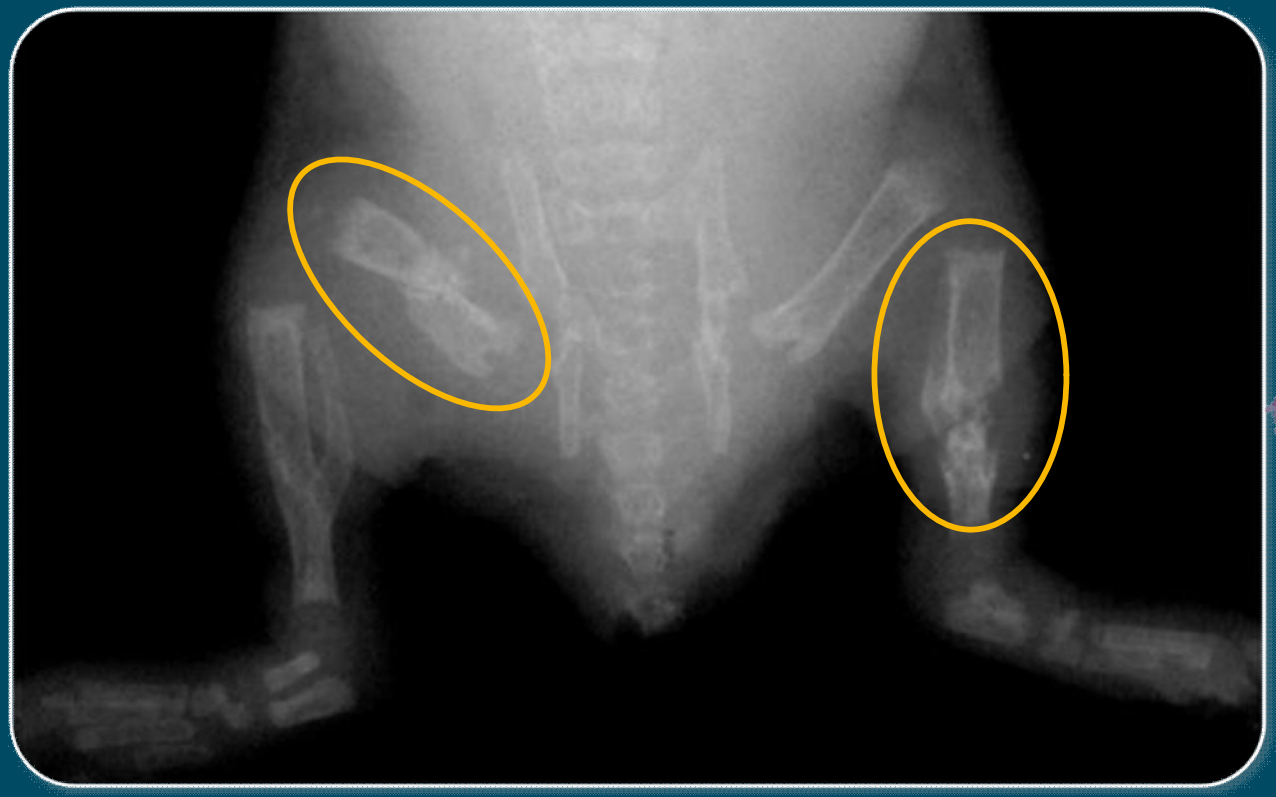
  - Signaling protein expressed by osteoblasts/bone lining cells[1]
  - Binds to RANK and promotes osteoclast formation, function and survival[2]
- RANK

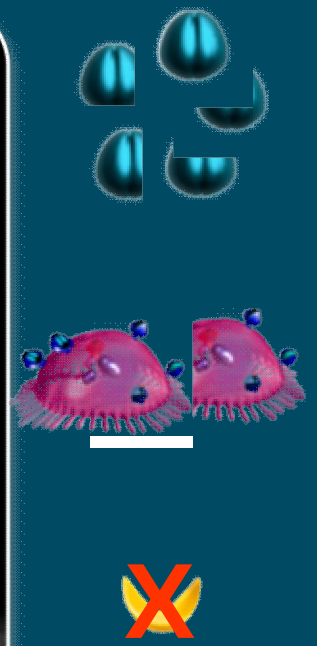
  - Expressed by osteoclasts and their precursors[1]
  - Activated by RANK Ligand binding[1]
- Osteoprotegerin (OPG)

  - Protein secreted by osteoblasts/bone lining cells[1]
  - Natural inhibitor of RANK Ligand[2]
  - Blocks RANK Ligand signaling to balance bone remodeling[2]

1. Boyle WJ, *et al*. *Nature* 2003;423:337–342.
2. Kostenuik PJ. *Curr Opin Pharmacol* 2005;5:618–625.

Unopposed RANK Ligand Activity Causes Long Bone Fragility Fractures

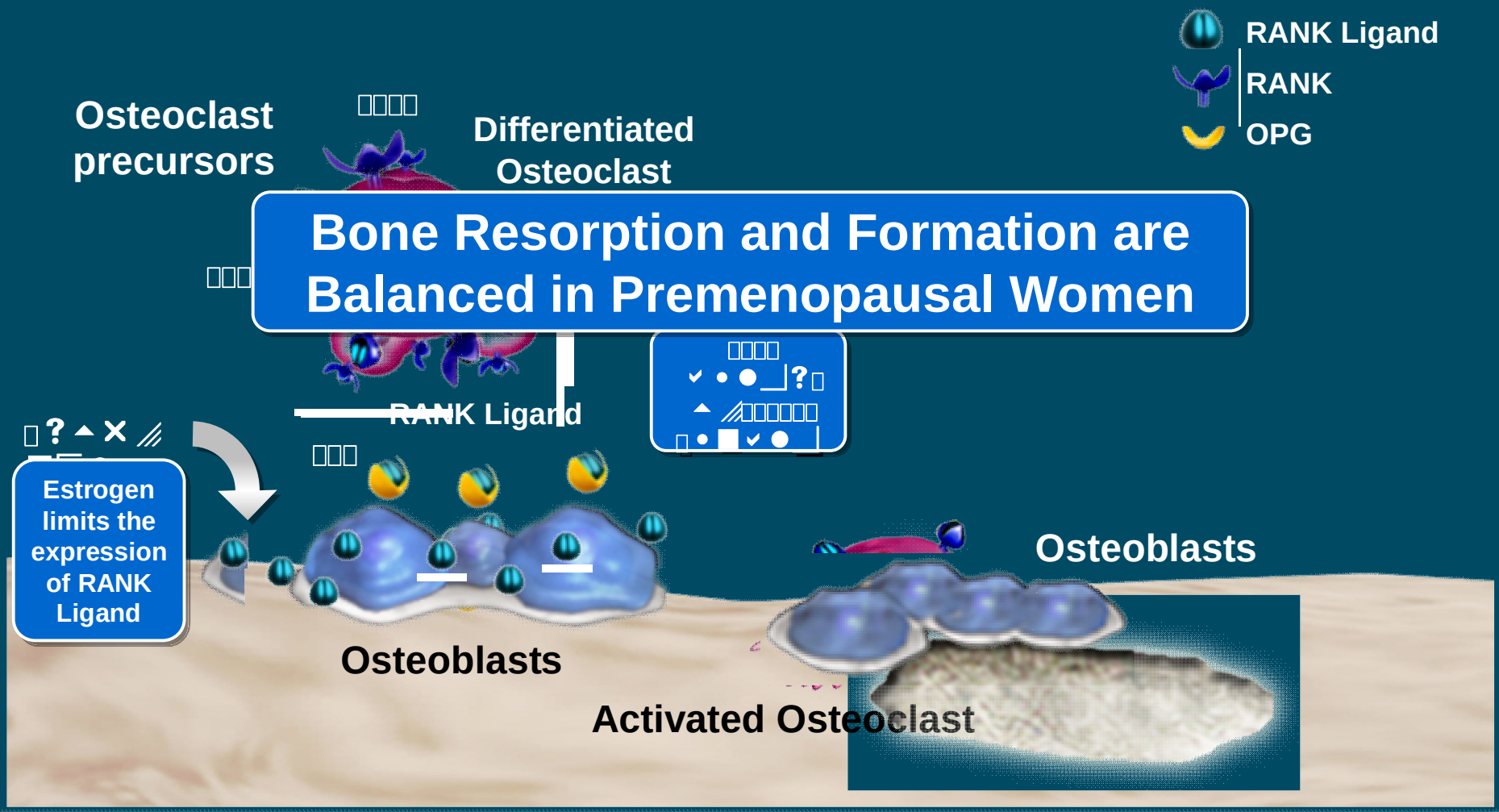




Radiograph of 1-month-old OPG knockout mouse with spontaneous fragility fractures

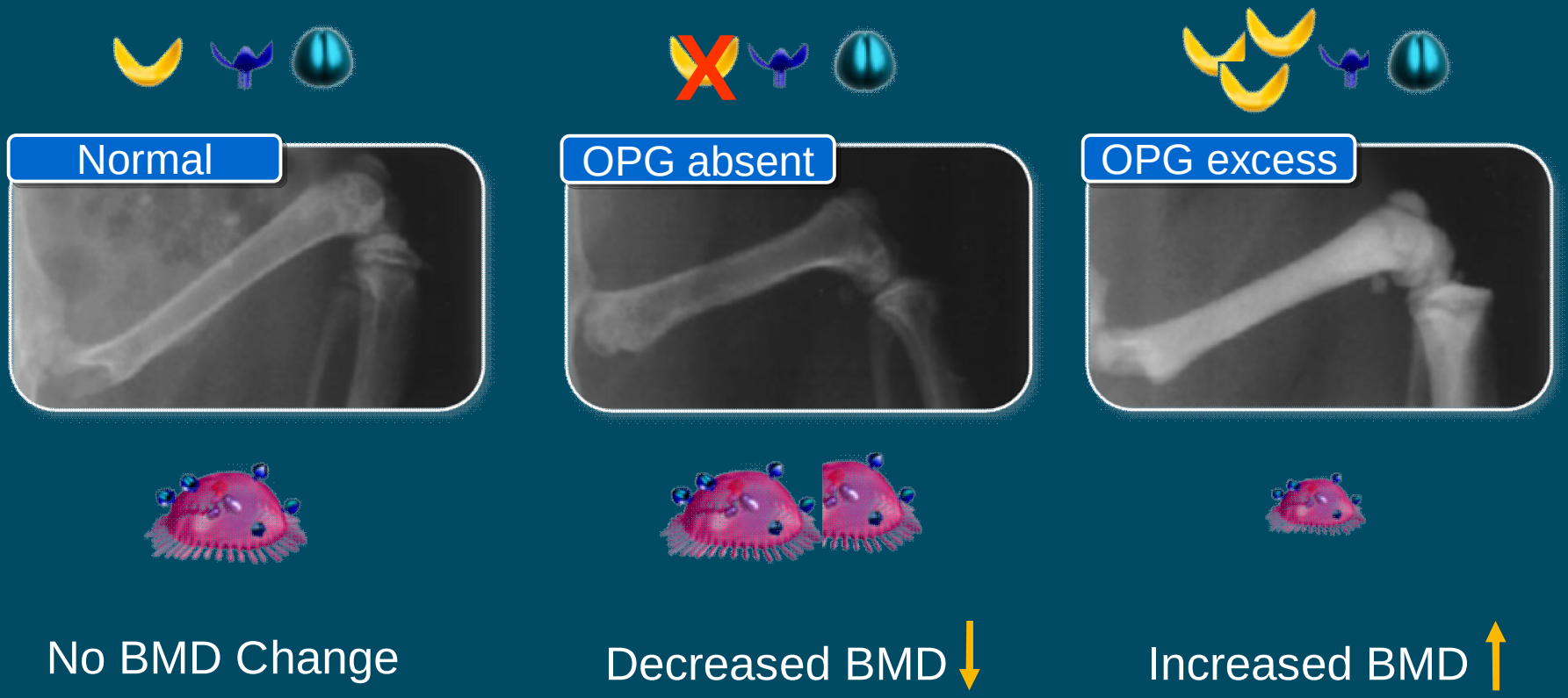
Bucay N, *et al. Genes Dev* 1998;12:1260–1268. Reprinted with permission.

OPG is the Natural Endogenous Inhibitor of RANK Ligand



Adapted from the following: Boyle WJ, *et al. Nature* 2003;423:337–342.
Kostenuik PJ, *et al. Curr Pharm Des* 2001;7:613–635.

Role of OPG in the Regulation of BMD



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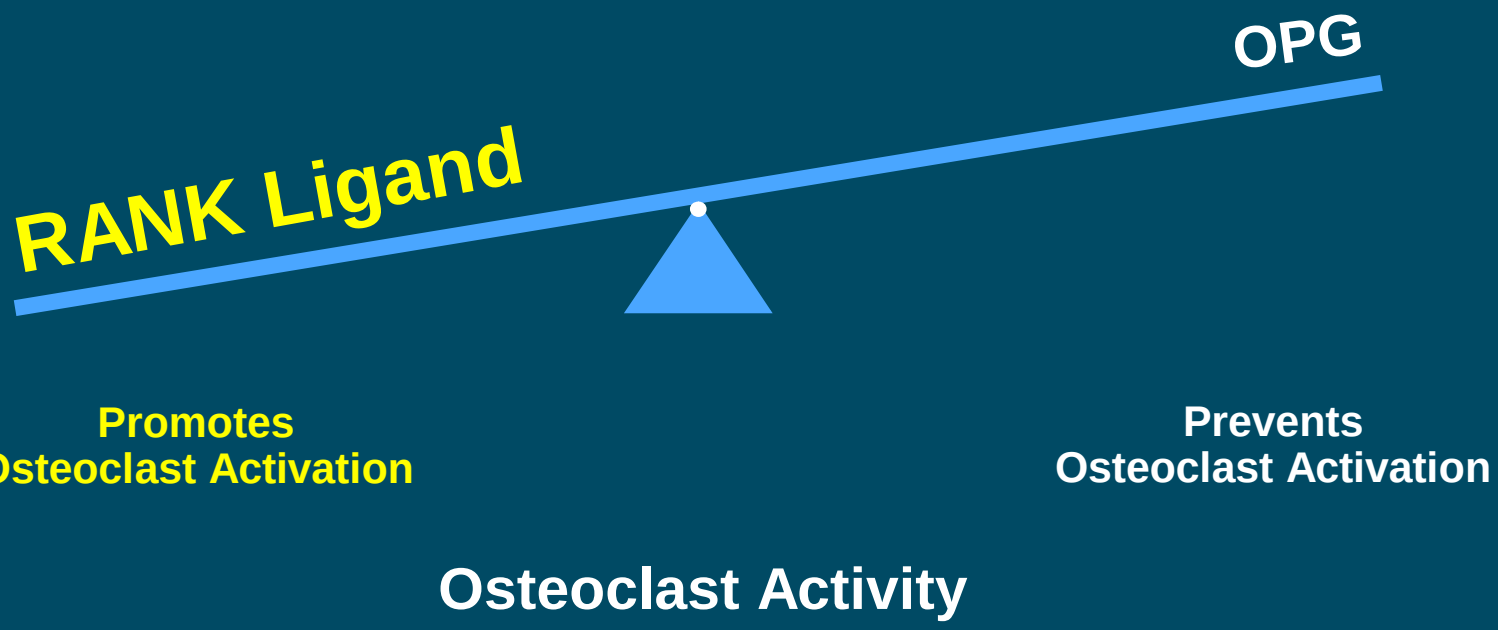
Bolon B, *et al. Arthritis Rheum* 2002;46:3121–3135.

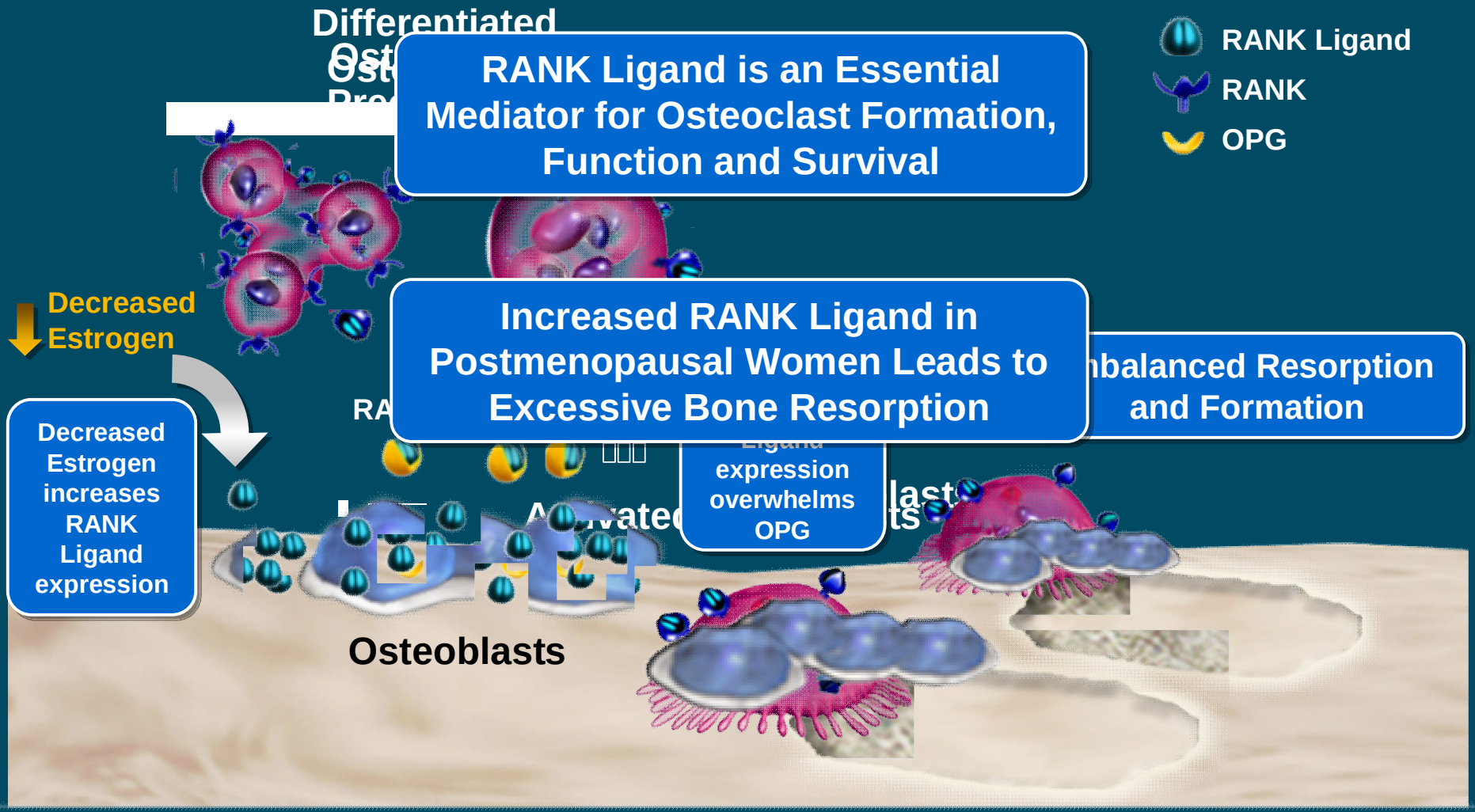
Increased RANK Ligand/OPG Ratio Promotes Bone Loss

- Alterations of the RANK Ligand/OPG ratio are critical in the pathogenesis of bone diseases that result from increased bone resorption



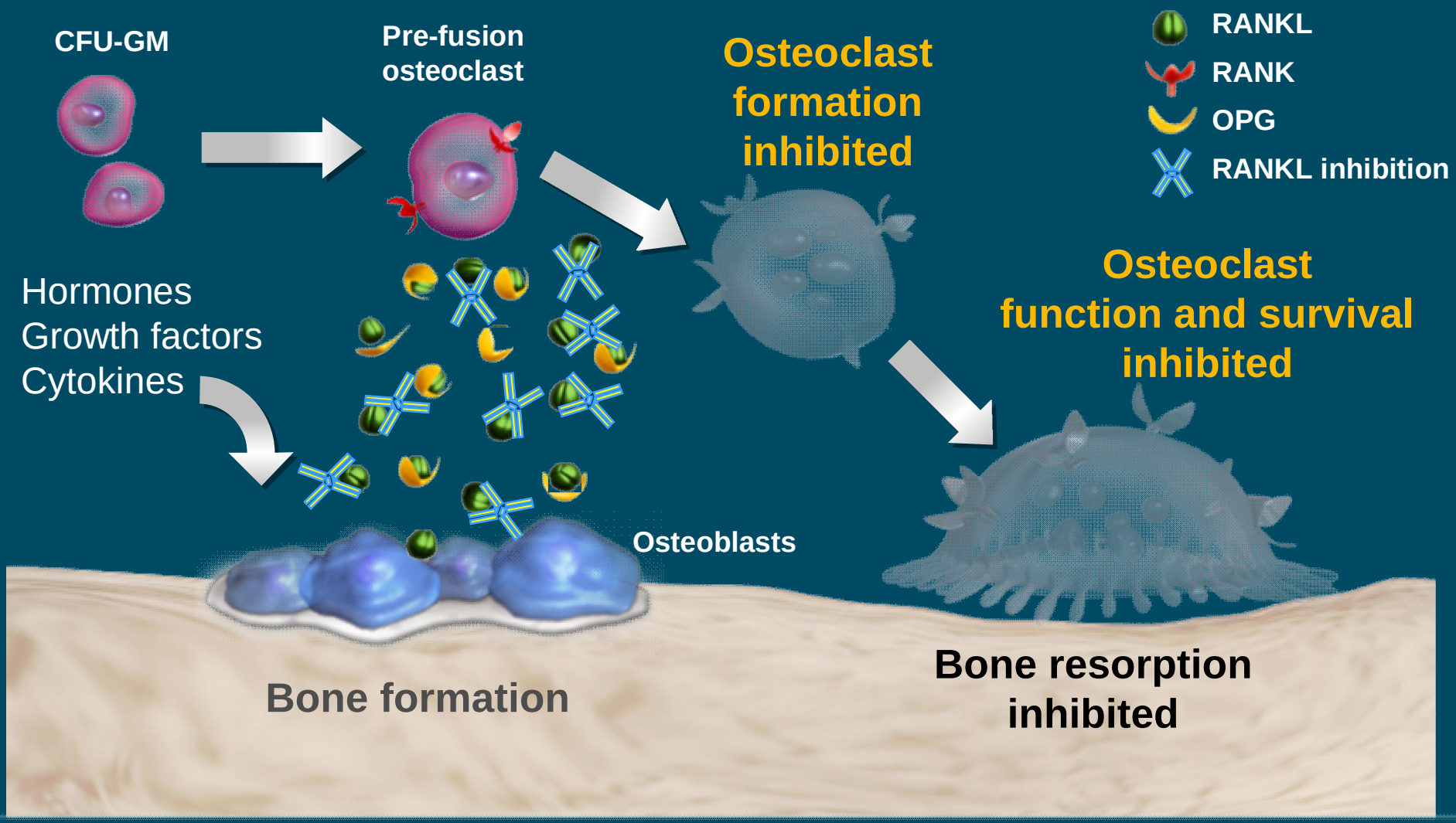
Adapted from: Hofbauer L, *et al. JAMA* 2004;292:490–495.

Reduction in Estrogen Increases RANK Ligand Expression, Causing Increased Bone Resorption



Adapted from the following: Boyle WJ, *et al. Nature* 2003;423:337–342.
Eghbali-Fatourechi G, *et al. J Clin Invest* 2003;111:1221–1230.

Inhibition of RANK Ligand

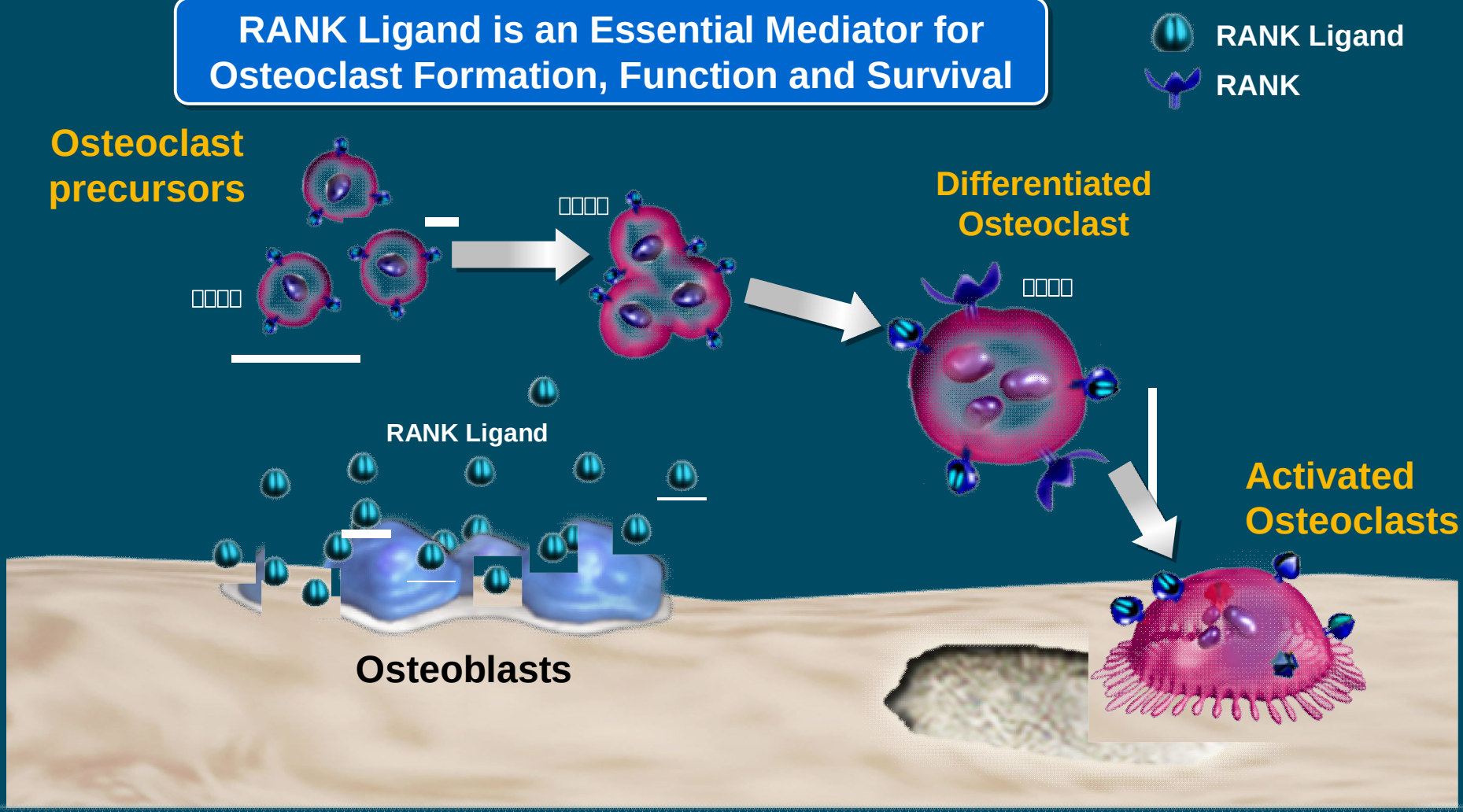


CFU-GM = colony-forming unit-granulocyte/macrophage

Adapted from: Boyle WJ, *et al. Nature* 2003;423:337–342.

The RANKL/RANK/OPG Pathway is Involved in Regulating Bone Remodeling

RANK Ligand is an Essential Mediator for Osteoclast Formation, Function and Survival



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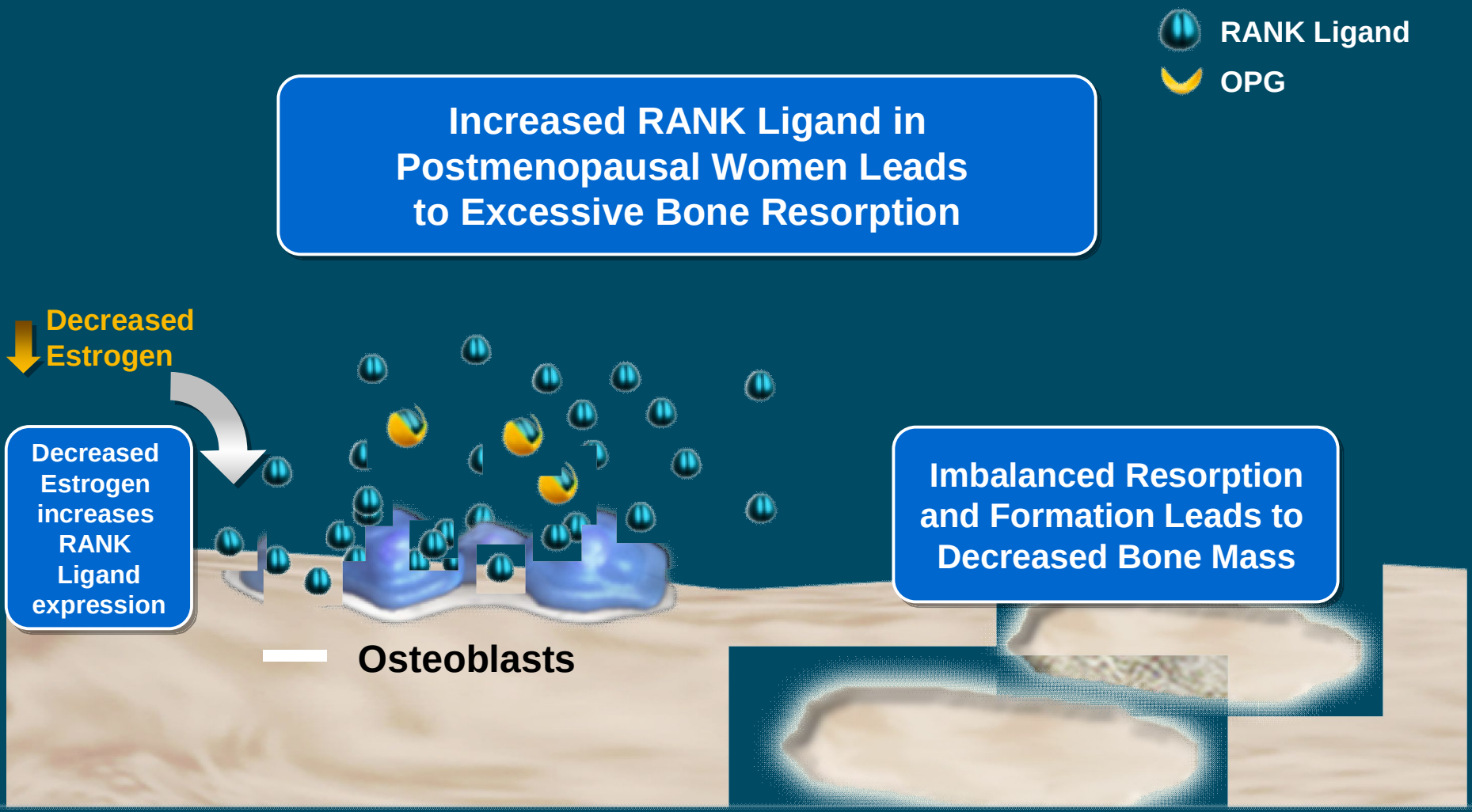
Reduction in Estrogen Increases RANK Ligand Expression, Causing Increased Bone Resorption



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PATHWAYS IN Osteoporosis

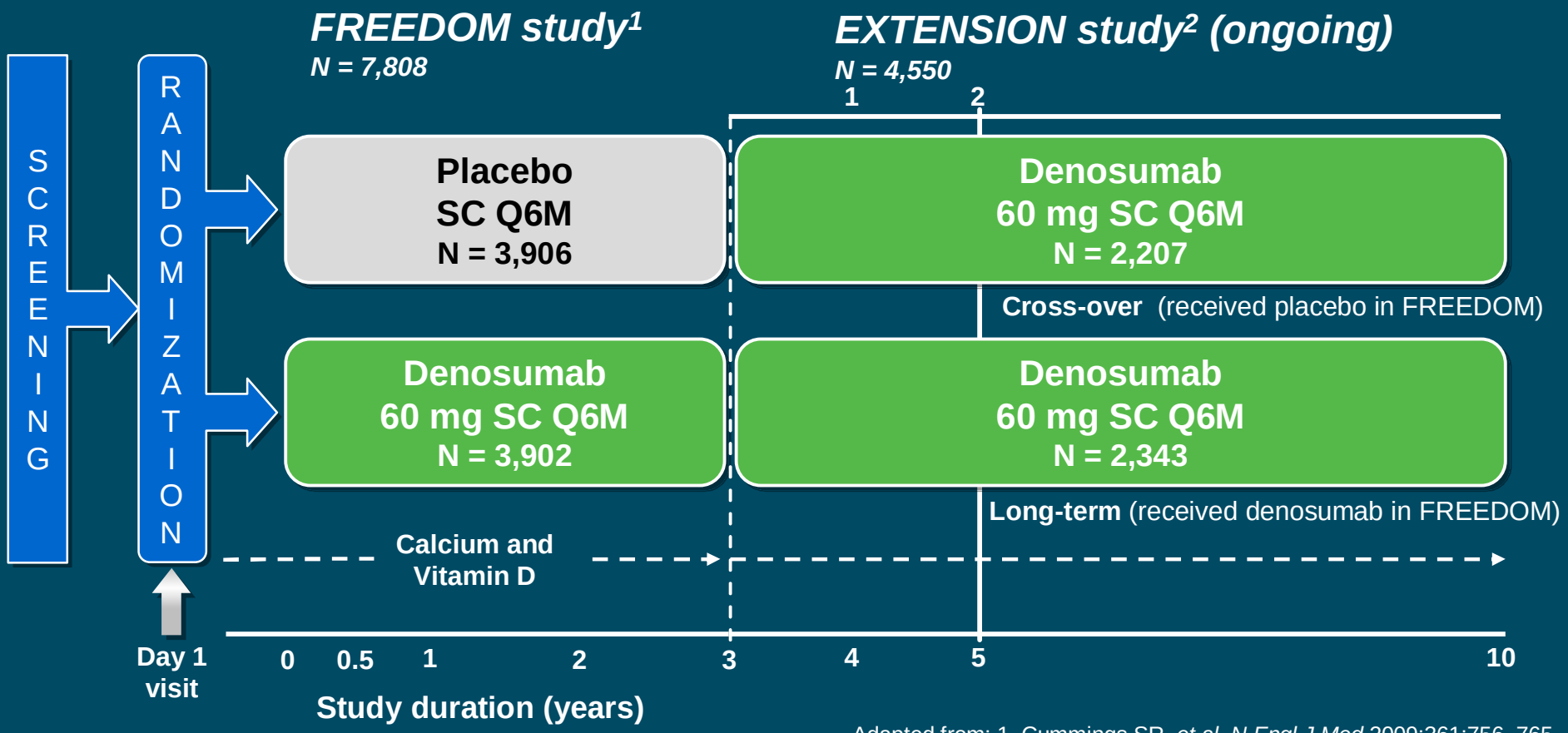
Denosumab Phase III data

FREEDOM

Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months

Phase III FREEDOM and FREEDOM EXTENSION Studies – Study Design

FREEDOM Trial: International multi-center, placebo-controlled study with open-label, single arm extension[1,2]



Adapted from: 1. Cummings SR, *et al. N Engl J Med* 2009;361:756–765.
2. Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

Baseline Demographics and Characteristics Similar Between Treatment Groups

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)

Data depicts patients included in the efficacy analysis, which excludes data from 60 patients at one study center (29 randomized to placebo, 31 randomized to denosumab) because participation of the study center was discontinued due to issues regarding study procedures and data reliability

*Excludes outlier values greater than 200 ng/mL

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

Baseline Demographics and Characteristics Similar Between Treatment Groups

FREEDOM Trial

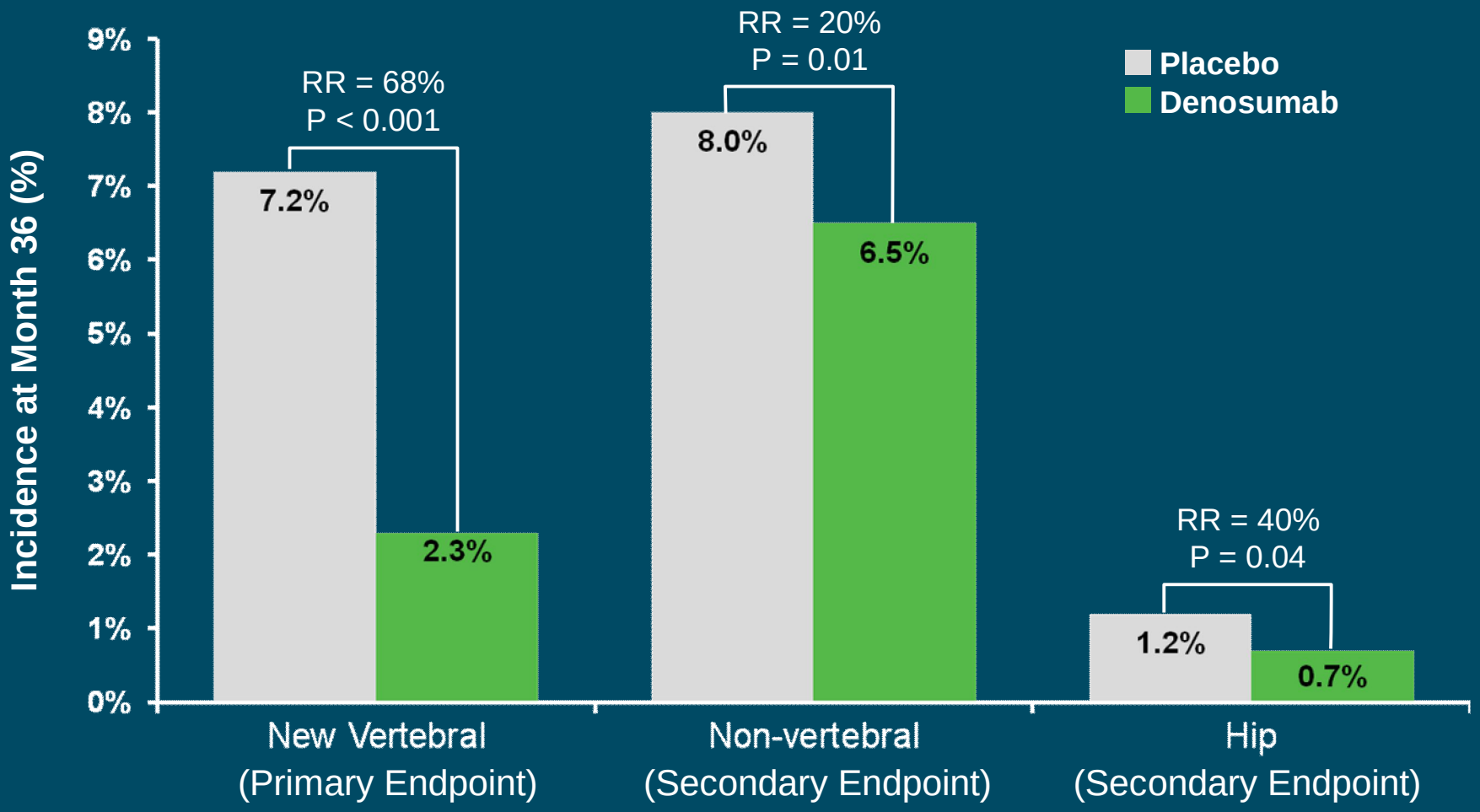
	Placebo (N = 3,906)	Denosumab 60 mg Q6M (N = 3,902)
Age group, N (%)		
60–64 years	208 (5.3)	206 (5.3)
≥65 years	3698 (95)	3696 (95)
≥75 years	1236 (32)	1235 (32)
Fracture risk by FRAX tool		
10-year osteoporotic fracture risk, %	18.7	18.5
10-year hip fracture risk, %	7.19	7.24

Data depicts patients included in the efficacy analysis, which excludes data from 60 patients at one study center (29 randomized to placebo, 31 randomized to denosumab) because participation of the study center was discontinued due to issues regarding study procedures and data reliability

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

Denosumab Reduced Risk of Vertebral, Non-vertebral and Hip Fractures at 36 Months

FREEDOM Trial

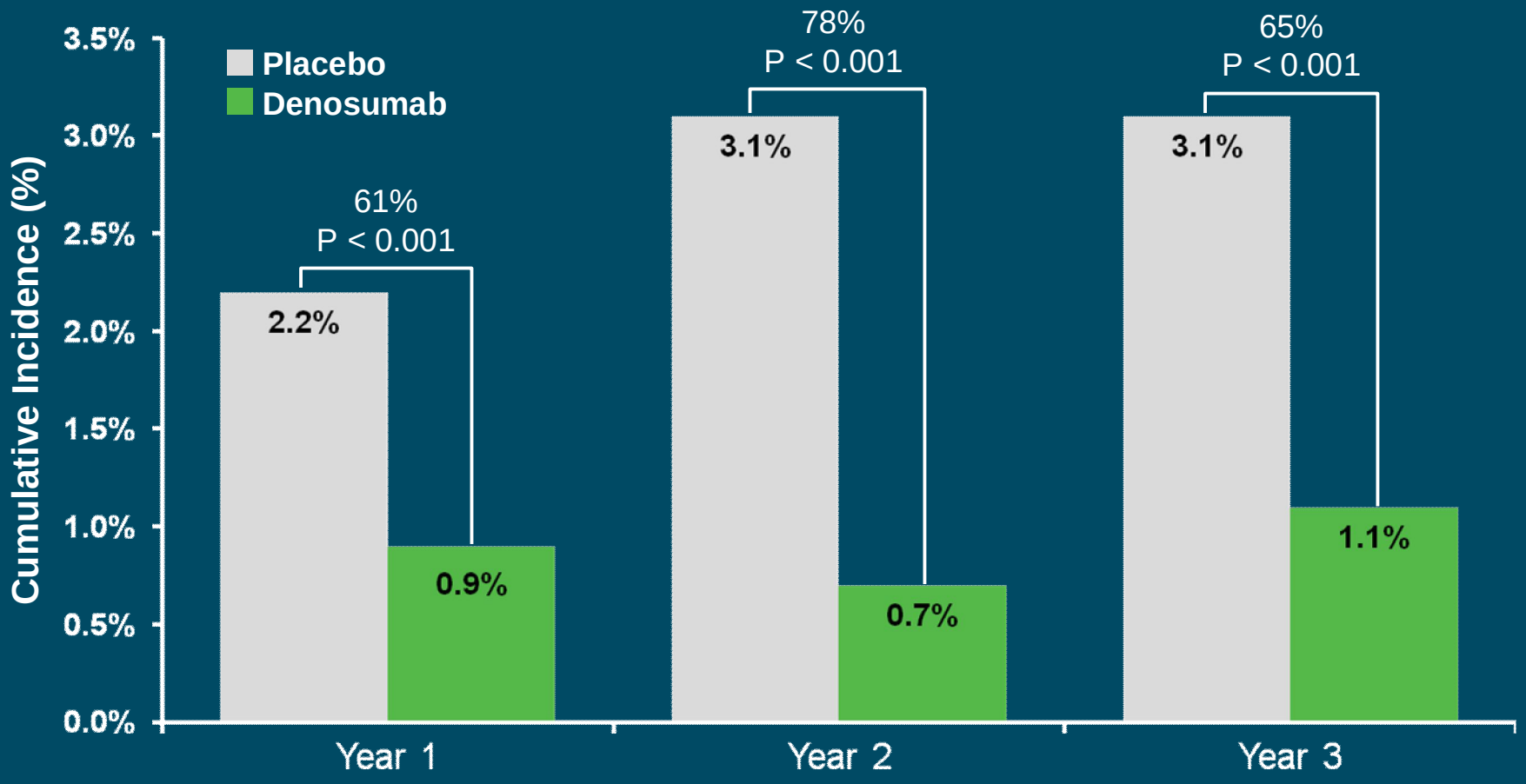


RR = risk reduction

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

Denosumab Reduced Risk of New Vertebral Fractures Each Year of Treatment

FREEDOM Trial

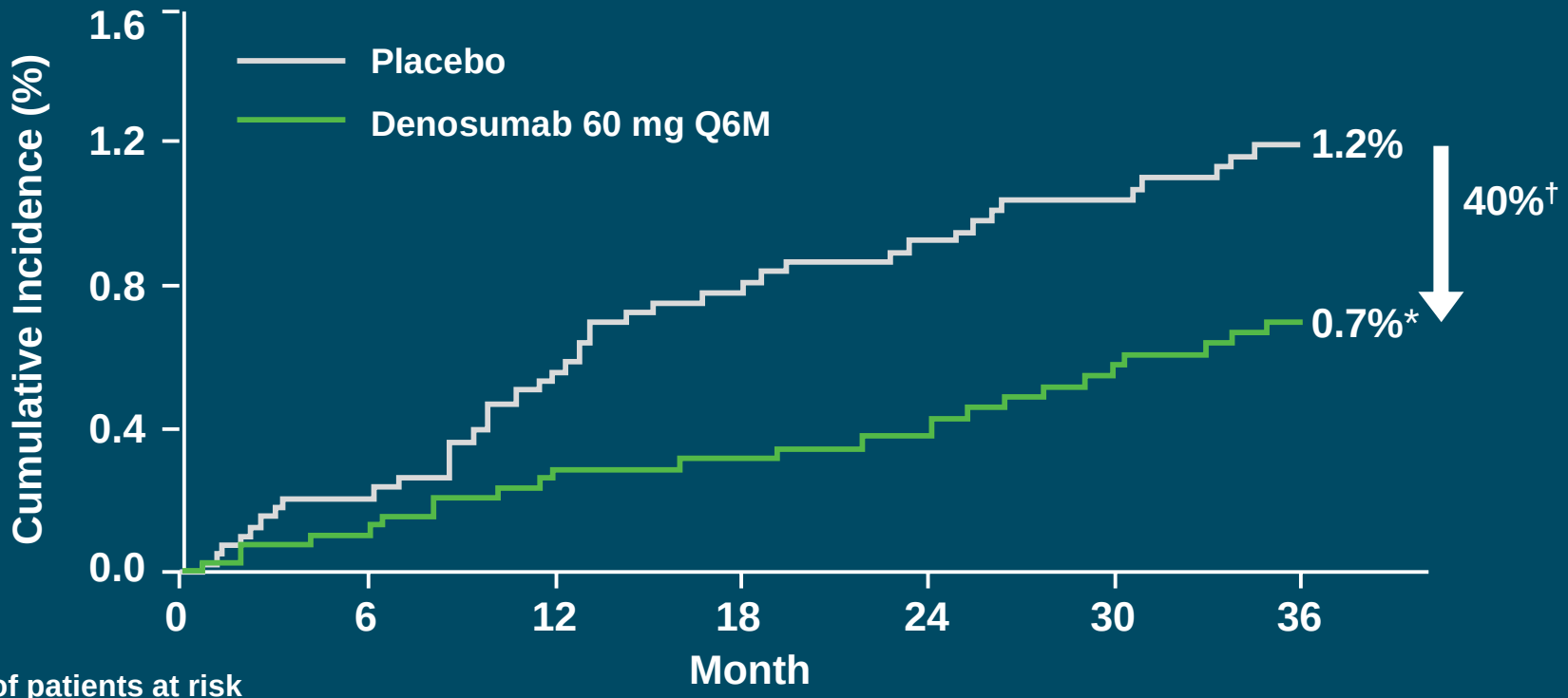


Intent-to-treat, last observation carried forward analysis
The percentage of new vertebral fractures was calculated using the number of patients with a baseline, and at least one post-baseline, spine x-ray evaluation

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

Denosumab Reduced Time to First Hip Fracture by 40% over 36 Months

FREEDOM Trial



Number of patients at risk							
Placebo, N	3,906	3,799	3,672	3,538	3,430	3,311	3,221
Denosumab, N	3,902	3,796	3,676	3,566	3,477	3,397	3,311

†Hip fractures were reduced by 40% (95% CI: 0.37, 0.97)
*P = 0.04

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

Adverse Event Profile of Denosumab Similar to Placebo over 36 Months

FREEDOM Trial

	Placebo (N = 3,876)	Denosumab 60 mg Q6M (N = 3,886)	P value
Adverse events, N (%)			
All adverse events	3,607 (93.1)	3,605 (92.8)	0.91
Serious adverse events	972 (25.1)	1,004 (25.8)	0.61
Deaths	90 (2.3)	70 (1.8)	0.08
Leading to study discontinuation	81 (2.1)	93 (2.4)	0.39
Leading to discontinuing the study drug	202 (5.2)	192 (4.9)	0.55

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

Adverse Events over 36 Months

FREEDOM Trial

	Placebo (N = 3,876)	Denosumab 60 mg Q6M (N = 3,886)
Adverse events, N (%)		
Infection	2,108 (54.4)	2,055 (52.9)
Malignancy	166 (4.3)	187 (4.8)
Injection-site reaction	26 (0.7)	33 (0.8)
Hypocalcemia	3 (0.1)	0 (0)
Delayed fracture healing	4 (0.1)	2 (0.05)
Femoral shaft fracture	3 (0.1)	0 (0)
Humerus non-union fracture	1 (0.03)	0 (0)
Osteonecrosis of the jaw	0 (0)	0 (0)
Adverse events occurring with ≥ 2% incidence and P ≤ 0.05, N (%)		
Eczema	65 (1.7)	118 (3.0)
Fall*	219 (5.7)	175 (4.5)
Flatulence	53 (1.4)	84 (2.2)

*Excludes falls occurring on the same day as a fracture

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

Serious Adverse Events over 36 Months

FREEDOM Trial

	Placebo (N = 3,876)	Denosumab 60 mg Q6M (N = 3,886)	P value
Serious adverse events, N (%)			
Malignancy	125 (3.2)	144 (3.7)	0.28
Infection	133 (3.4)	159 (4.1)	0.14
Cardiovascular events	178 (4.6)	186 (4.8)	0.74
Stroke	54 (1.4)	56 (1.4)	0.89
Coronary heart disease	39 (1.0)	47 (1.2)	0.41
Peripheral vascular disease	30 (0.8)	31 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Serious adverse events occurring with ≥ 0.1% incidence and P ≤ 0.01, N (%)			
Cellulitis (includes erysipelas)	1 (<0.1)	12 (0.3)	0.002
Concussion	11 (0.3)	1 (<0.1)	0.004

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

Summary

- In the FREEDOM study, denosumab 60 mg SC every 6 months for 3 years:
  - significantly reduced the risk of new vertebral, hip and non-vertebral fracture
  - and significantly increased lumbar spine and total hip BMD
- Denosumab was overall well tolerated

PATHWAYS IN Osteoporosis

Denosumab Long-term Data

FREEDOM EXTENSION

6-Year Data

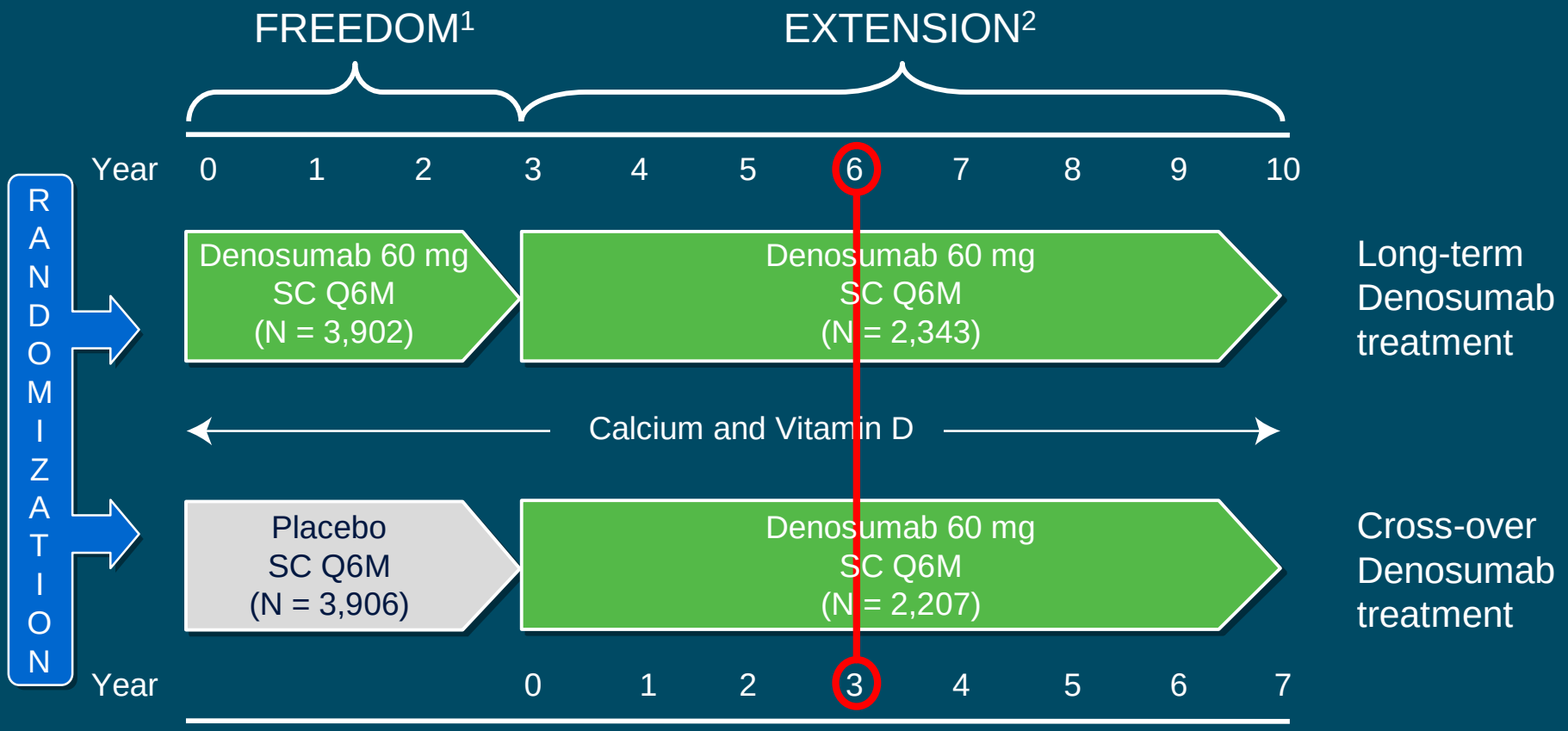
Design, Population and Outcome Measures

- Multicenter, international, open-label 3-year (of 7 years) extension study
- Study population
  - 4550 post-menopausal women (60−90 years old) who had completed the FREEDOM trial (completed the 3 year visit and did not miss > 1 dose of denosumab)
- Study outcomes
  - Primary outcome: Safety and tolerability
  - Secondary outcomes: changes in bone turnover markers and bone mineral density, and the incidence of vertebral and non-vertebral fractures

Bone H, *et al. J Clin Endocrinol Metab* 2013: epub.

Study Design

FREEDOM and FREEDOM EXTENSION Studies



SC Q6M = subcutaneous every 6 months

1. Cummings SR, *et al. N Engl J Med* 2009;361:756–765.
2. Bone H, *et al. J Clin Endocrinol Metab* 2013: epub.

Baseline Characteristics

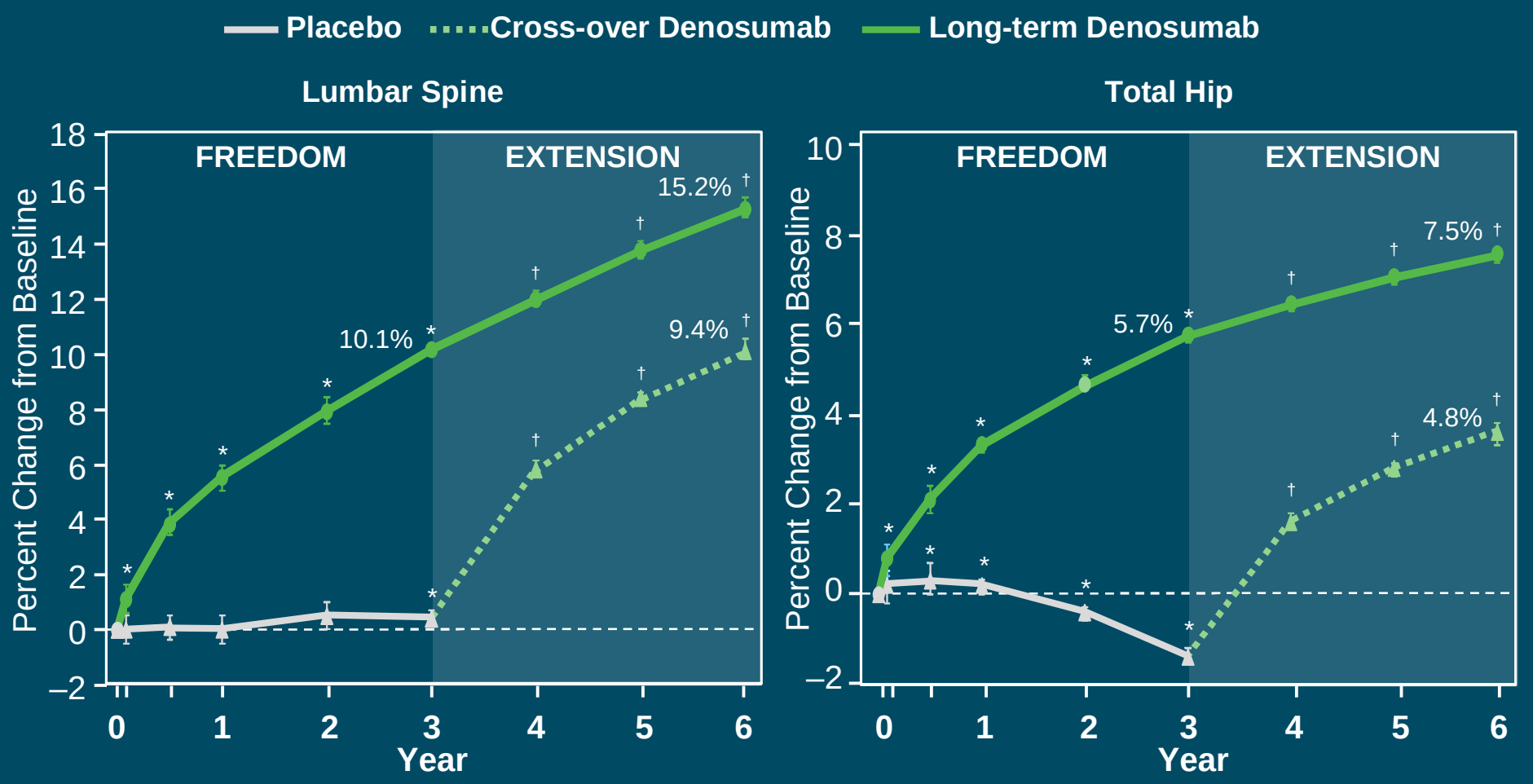
Phase III: FREEDOM and FREEDOM EXTENSION Studies

	Long-term denosumab treatment EXTENSION subjects (N = 2,343)		Cross-over denosumab treatment EXTENSION subjects (N = 2,207)	
	FREEDOM Baseline	**Extension Baseline**	**FREEDOM Baseline**	**Extension Baseline**
Age (years)	71.9 (5.0)	74.9 (5.0)	71.8 (5.1)	74.8 (5.1)
Age groups – n (%) ≥ 65 years ≥ 75 years	 2209 (94.3) 662 (28.3)	 2294 (97.9) 1258 (53.7)	 2067 (93.7) 624 (28.3)	 2149 (97.4) 1151 (52.2)
Year since menopause	23.7 (7.3)	26.7 (7.3)	23.7 (7.4)	26.7 (7.4)
Prevalent vertebral factures – n (%)	559 (23.9)	573 (24.5)	485 (22.0)	551 (25.0)
Prevalent non-vertebral factures at age ≥ 55 – n (%)	702 (30.0)	780 (33.3)	651 (29.5)	754 (34.2)
Lumbar spine BMD T-score	-2.83 (0.67)	-2.14 (0.80)	-2.84 (0.68)	-2.81 (0.75)
Total hip BMDT-score	-1.85 (0.79)	-1.50 (0.79)	-1.85 (0.79)	-1.93 (0.80)
CTX[a] (ng/mL) – median (Q1, Q3)	0.505 (0.357, 0.700)	0.182 (0.086, 0.555)	0.555 (0.420, 0.661)	0.568 (0.426, 0.728)
P1N[a] (µg/L) – median (Q1, Q3)	46.2 (31.5, 56.8)	17.3 (10.3, 26.0)	55.8 (42.5, 65.6)	48.8 (35.0, 67.6)

CTX = C-telopeptide; P1NP = N-terminal propeptide of type 1 collagen; N = Number of subjects enrolled in the extension
Data are means with standard deviations unless otherwise noted.
[a] Data are from subjects who were included in the BTM substudy

Bone H, *et al. J Clin Endocrinol Metab* 2013: epub.

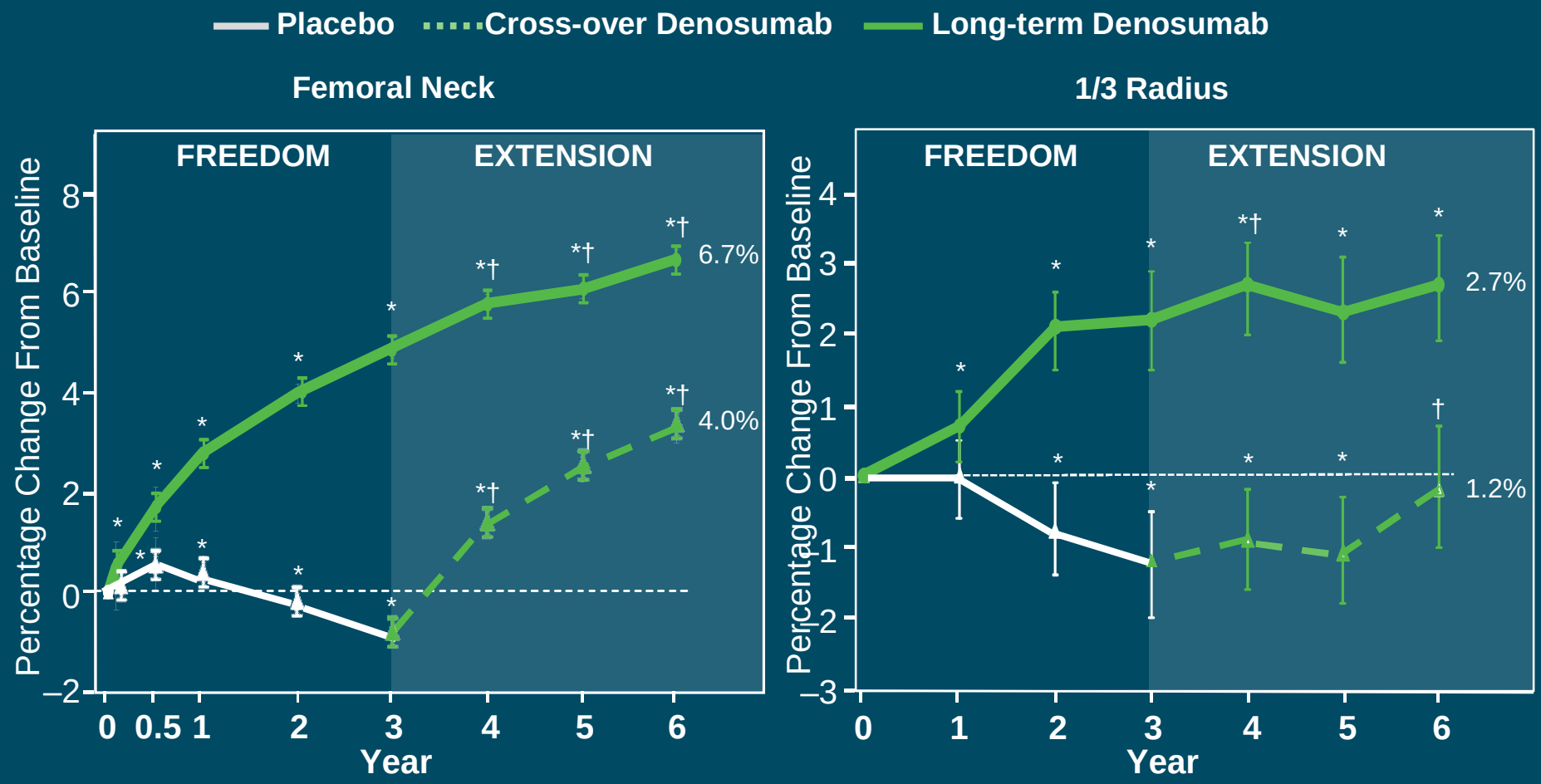
Continuation of Denosumab Treatment Increases Lumbar Spine and Total Hip BMD Year on Year



LS means and 95% confidence intervals. *P < 0.05 vs FREEDOM baseline;
†P < 0.05 vs FREEDDOM baseline and Extension baseline.
Numbers on the graphs represent the percent change in BMD while on denosumab treatment.

Bone H, *et al. J Clin Endocrinol Metab* 2013: epub.

Continuation of Denosumab Treatment for 6 years continued to increase BMD

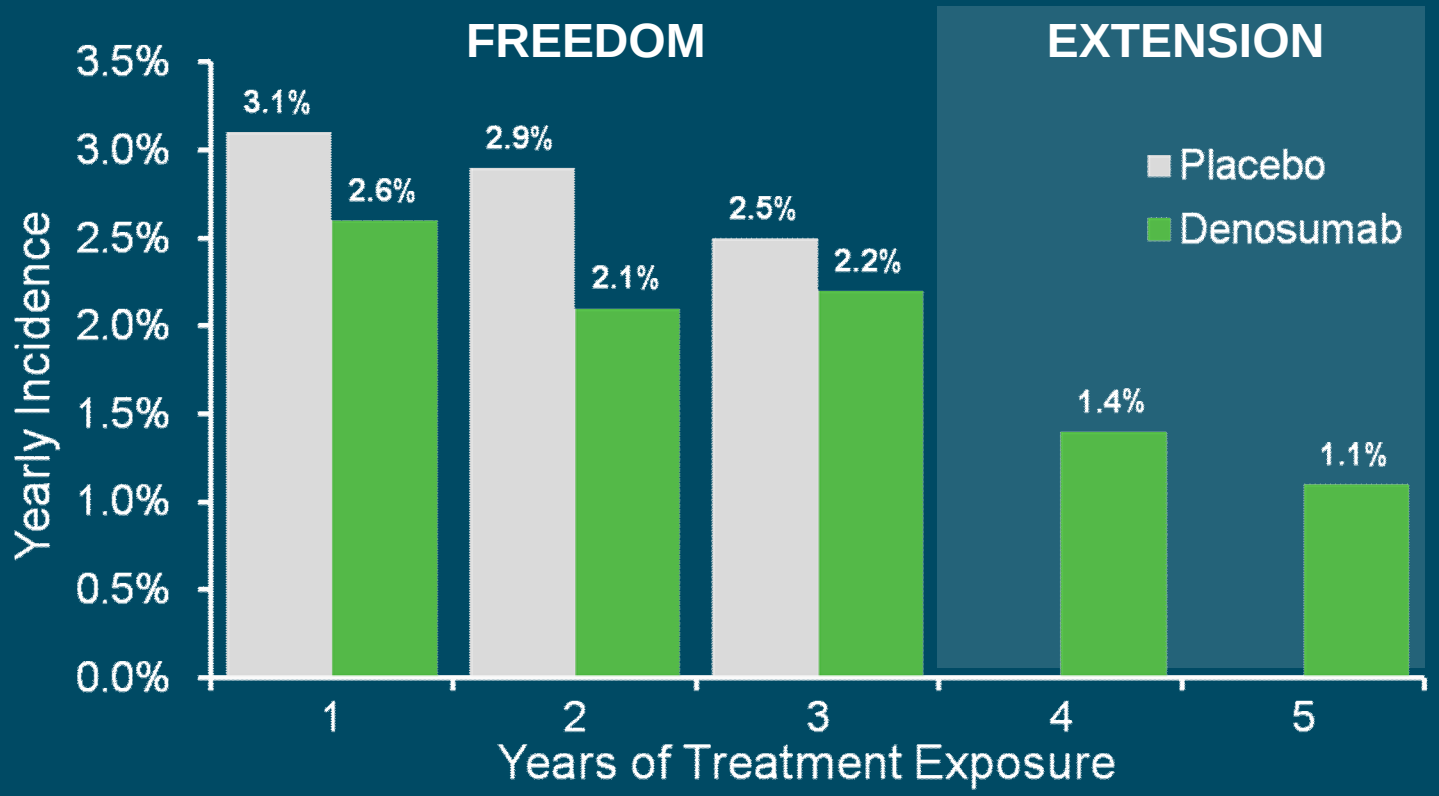


.
Data from the BMD sub study population are shown for the 1/3 radius, cross-over n = 36 and long-term n=65.
LS means and 95% confidence intervals. *P < 0.05 vs FREEDOM baseline; †P < 0.05 vs Extension baseline
Numbers on the graphs represent the percent change in BMD while on denosumab treatment.

Bone H, *et al. J Clin Endocrinol Metab* 2013: epub.

Continuation of Denosumab Maintains a Low Incidence of Non-vertebral Fractures

FREEDOM EXTENSION Study

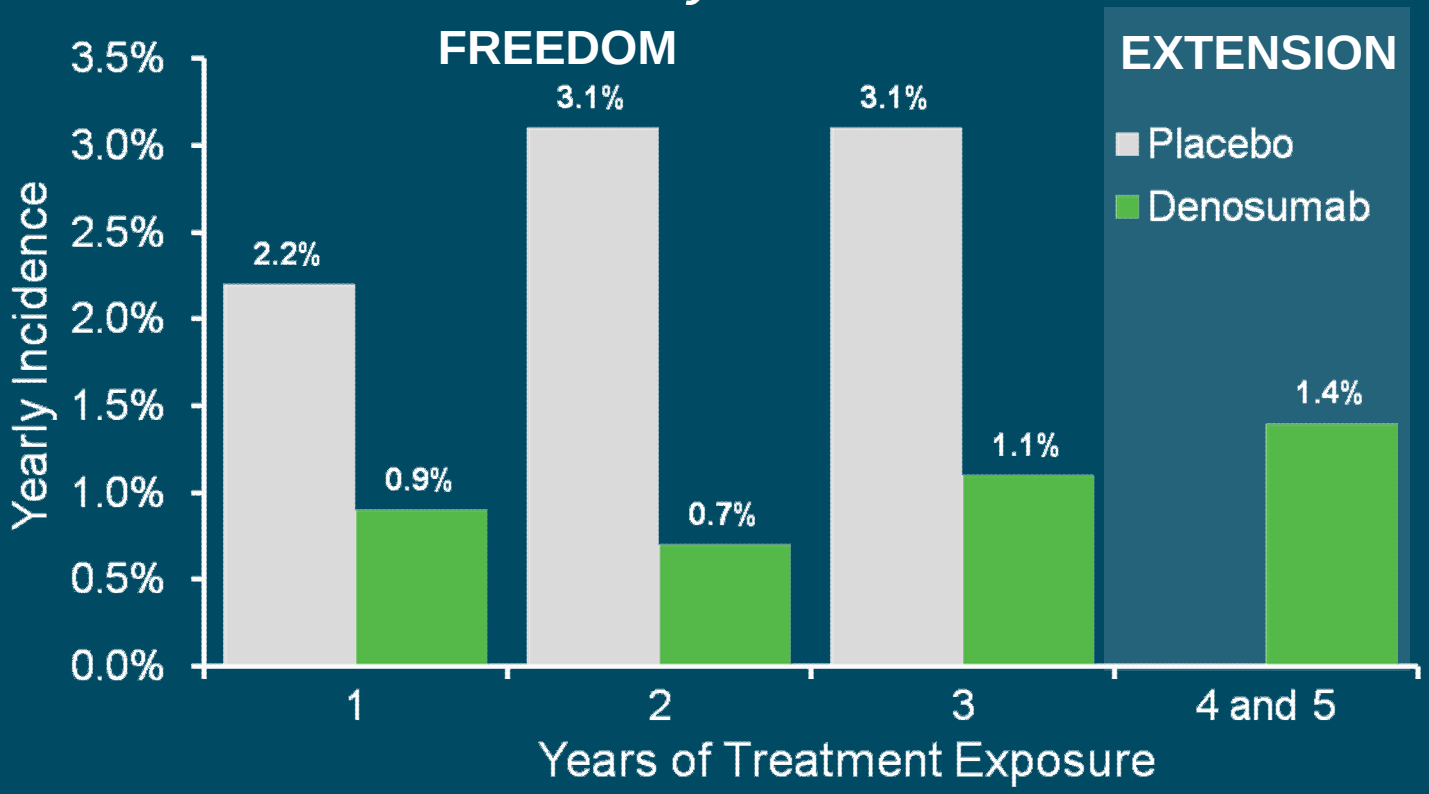


No. subjects with ≥ 1 fracture	**116**	**98**	**103**	**75**	**83**	**73**	**32**	**25**
No. subjects at beginning of each period	**3,906**	**3,902**	**3,688**	**3,682**	**3,454**	**3,487**	**2,343**	**2,242**

Adapted from: Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

Continuation of Denosumab Maintains a Low Incidence of New Vertebral Fractures

FREEDOM EXTENSION Study



No. subjects with ≥ 1 fracture	**82**	**32**	**107**	**24**	**98**	**35**	**59 (2-year total)**
No. subjects at beginning of each period	**3,691**	**3,702**	**3,400**	**3,453**	**3,186**	**3,247**	**2,100**

Adapted from: Papapoulos S, *et al. J Bone Miner Res* 2012;27:694–701.

Exposure-adjusted Subject Incidence of Adverse Events: Denosumab Treatment for 6 years Remained Well Tolerated

	Rate (exposure-adjusted subject incidence per 100 subject-years)			
	Placebo	Denosumab	Denosumab	
	FREEDOM Years 1 – 3 N = 3883 Rate (n)	**FREEDOM Years 1 – 3** N = 3879 Rate (n)	**EXTENSION Long-term Years 4 – 6** **N** = 2343 Rate (n)	**EXTENSION Cross-over Years 4 – 6** N = 2206 Rate (n)
All adverse events	156.1 (3614)	154.3 (3598)	106.2 (2067)	104.2 (1944)
Infections	30.7 (2113)	29.3 (2052)	23.4 (1070)	25.0 (1054)
Malignancies	1.6 (167)	1.8 (187)	1.9 (120)	1.8 (108)
Eczema	0.6 (67)	1.1 (119)	1.0 (65)	1.0 (57)
Hypocalcemia	<0.1 (3)	0	<0.1 (1)	<0.1 (6)
Pancreatitis	<0.1 (3)	<0.1 (7)	<0.1 (4*)	<0.1 (2)
Serious adverse events	10.4 (974)	10.6 (1002)	10.6 (597)	10.9 (573)
Infections	1.3 (134)	1.5 (160)	1.3 (82)	1.4 (81)
Cellulitis or erysipelas	<0.1 (1)	0.1 (12)	<0.1 (5)	<0.1 (1)
Fatal adverse events	0.8 (90)	0.6 (70)	0.7 (45)	0.7 (41)

ONJ: Six participants had events of ONJ confirmed by adjudication. Four cases in the long-term group and two cases in the cross-over group.
Atypical fracture: One case of atypical femoral fractures was positively adjudicated in the cross-over group.

N = number of subjects who received ≥ 1 dose of investigational product. Treatment groups are based on the original randomized treatments received in FREEDOM.
n = total number of subjects with an adverse event.
Adverse events coded using MedDRA v13.0.

Bone H, *et al. J Clin Endocrinol Metab* 2013: epub.

Summary

- Denosumab treatment for up to 6 years continued to show a favorable benefit/risk profile and was associated with:
  - sustained but not progressive decreases in bone turnover
  - continued increases in BMD
  - maintained low fracture rates
- Efficacy data from the cross-over group were consistent with observations from the original FREEDOM trial

Bone H, *et al. J Clin Endocrinol Metab* 2013: epub.

Prolia - indication

- **Therapeutic indications**
- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures
- Prolia PI MOH approved

Prolia – active ingredients and administration

Generic name of the drug and active ingredient

Prolia 60 mg solution for injection in a pre-filled syringe.

Each pre-filled syringe contains 60 mg of denosumab in 1 ml of solution (60 mg/ml).

Dosage and method of administration

The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

Patients must be adequately supplemented with calcium and vitamin D

Administration should be performed by an individual who has been adequately trained in injection techniques.

Prolia

MANUFACTURER

- Amgen Europe B.V.
- Breda
- The Netherlands

LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd.

25 Basel St., Petach Tikva 4900202

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Prolia – important information

- לדיווח תופעות לוואי il.safety@gsk.com **או** בטלפון 03-9297100
- שרות מידע רפואי il.medinfo@gsk.com
- **למידע מלא יש לעיין בעלון לרופא כפי שאושר ע"י משרד הבריאות**

Prolia - Contraindications

- **Contraindications**
- Hypocalcaemia
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of PI
- Pregnancy: Prolia may cause fetal harm when administered to a pregnant woman. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. Prolia is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

For full information please see MOH approved PI

Special warnings and precautions for use

- Calcium and Vitamin D supplementation
- Adequate intake of calcium and vitamin D is important in all patients.
- Precautions for use
- ***Hypocalcemia* -** It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.
- In the post-marketing setting, severe symptomatic hypocalcaemia has been reported , with most cases occurring in the first weeks of initiating therapy, but it can occur later.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Skin Infections*** - Patients receiving Prolia may develop skin infections (predominantly cellulitis) leading to hospitalization. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
- **Osteonecrosis of the jaw** has been reported rarely in clinical studies and in the post marketing setting in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis. Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (e.g. tooth extractions, dental implants, oral surgery), and co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck). It is important to evaluate patients for risk factors for ONJ before starting treatment. A dental examination with appropriate preventive dentistry is recommended prior to treatment with Prolia in patients with concomitant risk factors. All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment with Prolia. While on treatment, patients should avoid invasive dental procedures if possible.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Atypical Subtrochanteric and Diaphyseal Femoral Fractures -*** Atypical low-energy or low trauma *fractures of the* shaft have been reported in patients receiving Prolia. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-resorptive agents. During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Interruption of Prolia therapy should be considered, pending a risk/benefit assessment, on an individual basis.
- ***Suppression of Bone Turnover -*** In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Dry natural rubber*** - The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.
- ***Renal impairment*** - Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients, see above.
- Warnings for Excipients
- Patients with rare hereditary problems of fructose intolerance should not use Prolia. This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg i.e. essentially ‘sodium-free’.

For full information please see MOH approved PI