제18차 대한산부인과내분비학회

새로운 골다공증 치료제
Denosumab

인제대학교 해운대백병원
산부인과 전 균 호

Contents

I. Denosumab

II. Key clinical trials summary

- *[FREEDOM] : Denosumab Vs. Placebo*
- *[DECIDE] [STAND] : Denosumab Vs. Alendronate*
- *Denosumab Vs. Zoledronic acid*

III. Adverse events, tolerability of denosumab

IV. Place of Denosumab in the Mx. of osteoporosis, / Recommendations

Estrogen & Bone remodelling

- Estrogen – multifactorial impact on bone

Anti-resorptive action

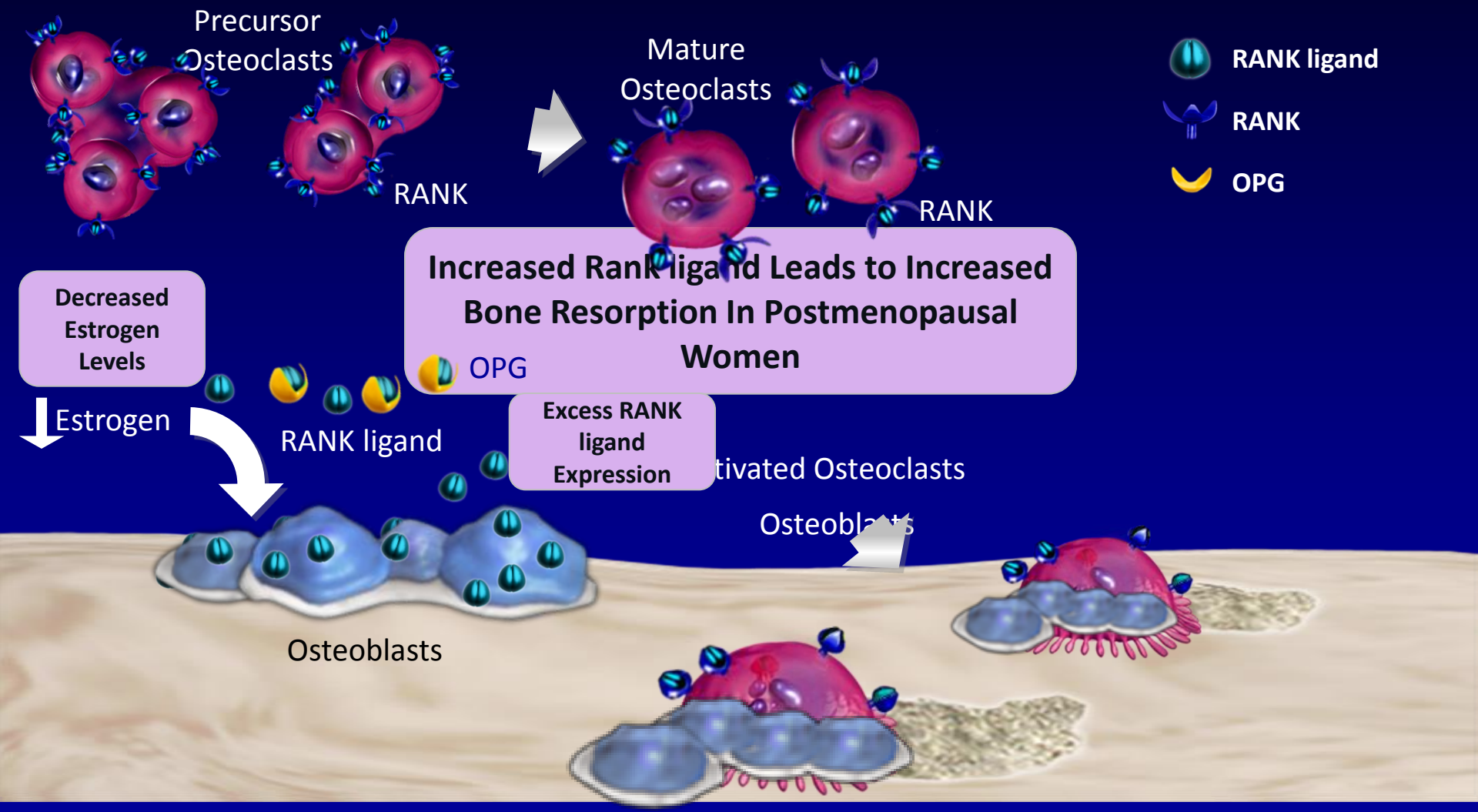
- **RANKL production ↓**
- Osteoprotegrin gene expression ↑
- Proresorptive cytokines synthesis↓

Bone formation

- Synthesis of the main growth factor: TGF-β, BMP6, IGF-1 ↑
- 1,25 (OH)D3, GH, progesterone expression receptors ↑

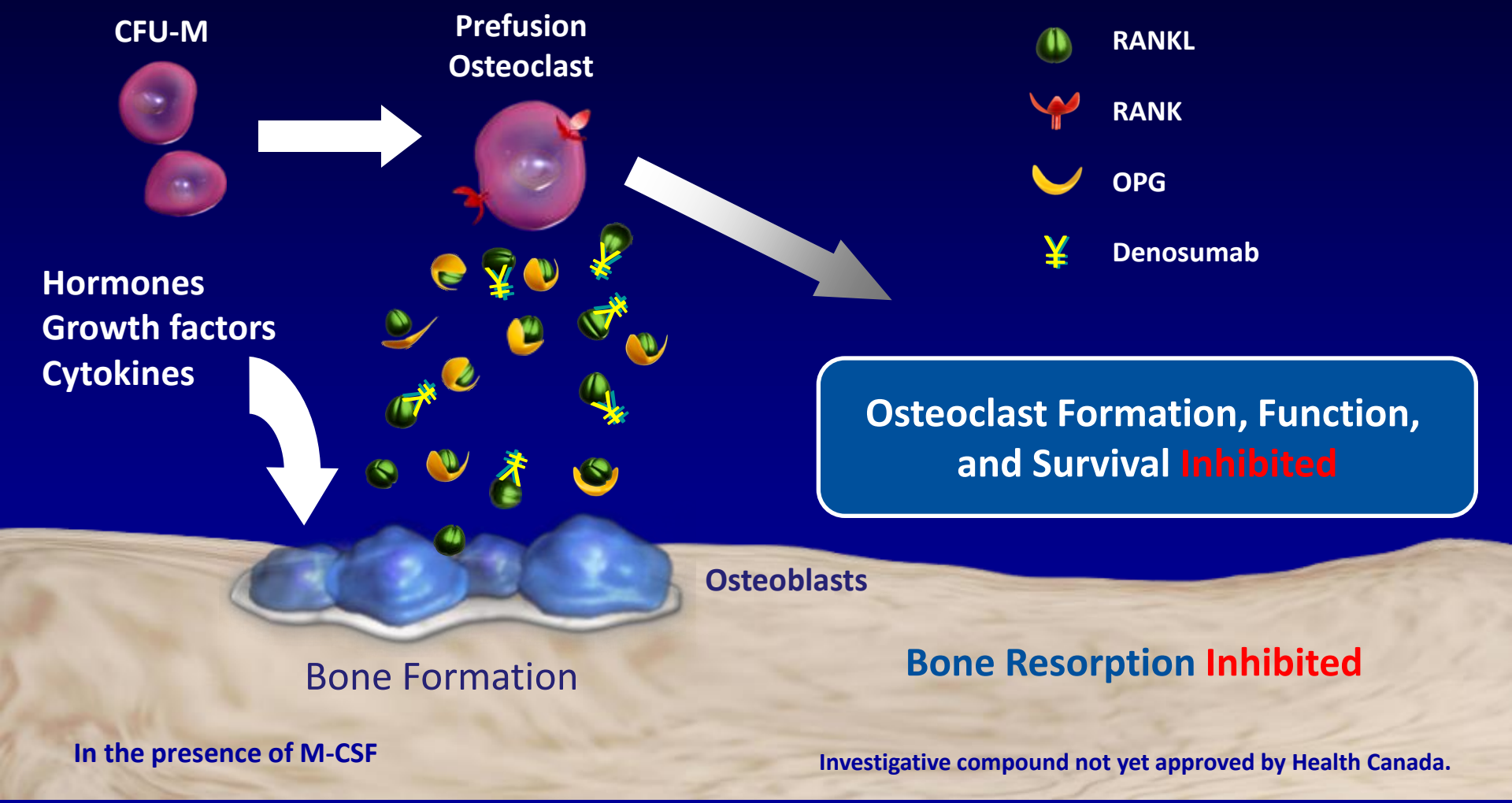
Meczekalski B et al. Gyne Endo 2010;26(9):652–657

Reduction in estrogen increases RANK Ligand expression, causing increased bone resorption



Adapted from: Boyle WJ, *et al. Nature*. 2003;423:337-342. Hofbauer LC, Schoppet M. *JAMA*. 2004;292:490-495.

Denosumab binds RANKL and inhibits osteoclast formation, function, and survival

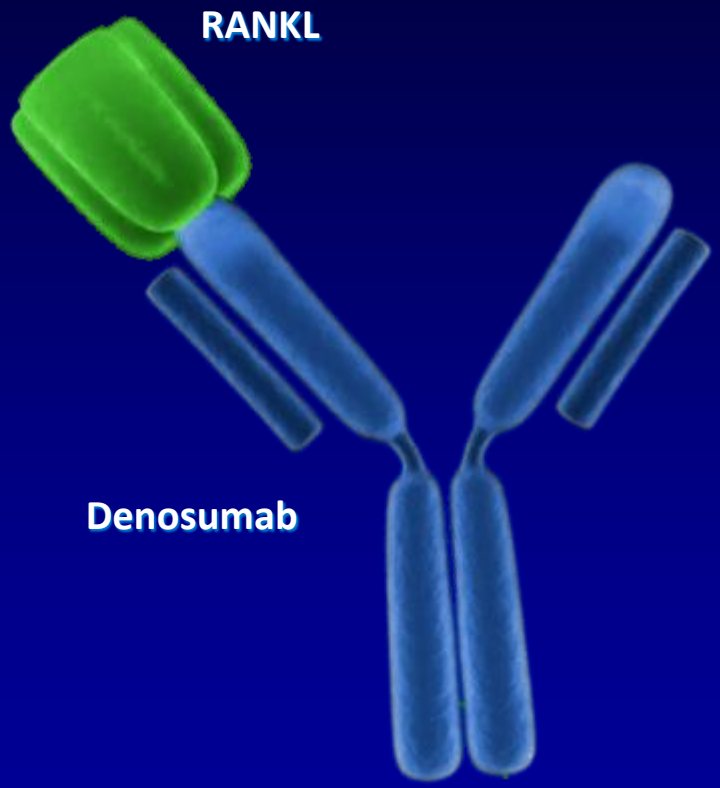


Adapted from Boyle WJ, et al. *Nature*. 2003;423:337-342

Denosumab - Targeting the Essential Mediator of Postmenopausal Bone Loss

- **Denosumab**
  - Fully human IgG2 monoclonal antibody
  - High-affinity and highly specific targeting RANKL
  - Inhibition of osteoclast formation, function, and survival

- **Properties of a monoclonal antibody to inhibit RANKL**
  - Is not incorporated into bone
  - Fast action, reversible effect
  - No dose adjustment required for patients with renal impairment



Bekker et al J Bone Miner Res. 2004; 19:1059. Kostenuik PJ, *et al. J Bone Miner Res*. 2009;24:182, Prolia Product Monograph , Amgen Canada 2010

Anti-fracture efficacy of the most frequently used treatments for postmenopausal osteoporosis

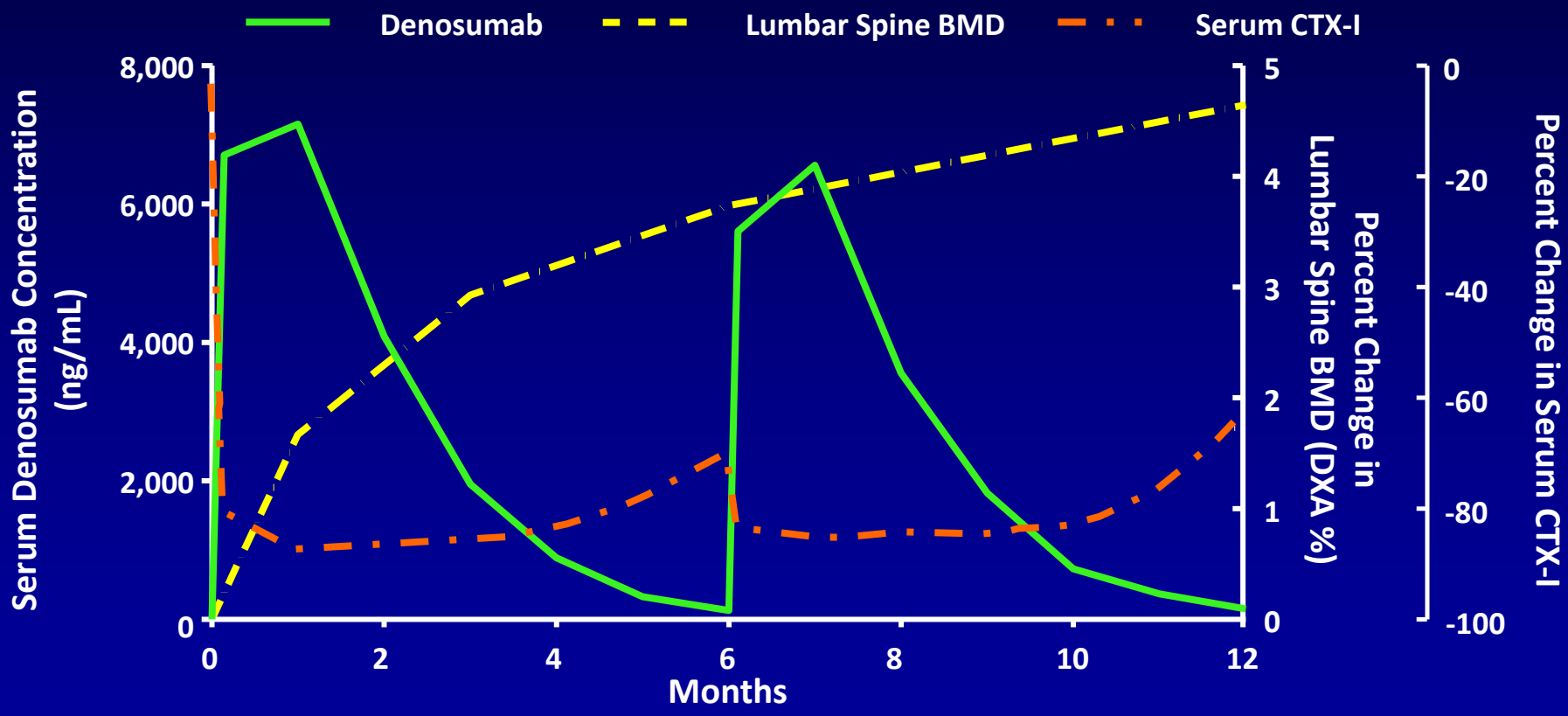
	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	Osteoporosis	Established osteoporosis[a]	Osteoporosis	Established osteoporosis[a]
Alendronate	+	+	NA	+ (including hip)
Risedronate	+	+	NA	+ (including hip)
Ibandronate	NA	+	NA	+[b]
Zoledronic acid	+	+	NA	+[c]
Raloxifene	+	+	NA	NA
Teiparatide and PTH	NA	+	NA	+[d]
Strontium ranelate	+	+[c]	+ (including hip[b])	+ (including hip[b])
Denosumab	+	+	+ (including hip)	+[c]

NA. no evidence available +: effective
a. Women with a prior vertebral fracture
b. In subsets of patients only (post hoc analysis)
c. Mixed group of patients with or without prevalent vertebral fractures
d. Shown for teriparatide only

Adapted from Kanis et al. Osteoporos Int. 2013 Jan;24(1):23-57

Pharmacokinetic and Pharmacodynamic Properties of Denosumab

- The pharmacokinetic and pharmacodynamic properties of denosumab support the 60 mg SC Q6M dosing regimen

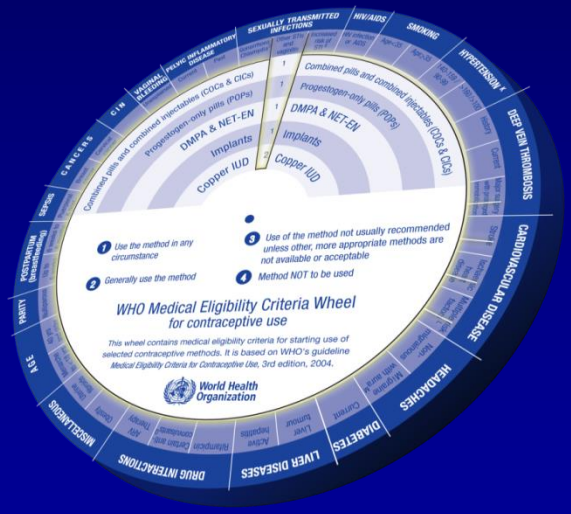


Q6M = once every 6 months; BMD = bone mineral density; CTX-I = type I C-telopeptide; DXA = dual-energy x-ray absorptiometry

McClung MR, et al. *N Engl J Med*. 2006;23:821-831. Peterson MC, et al. *J Bone Miner Res*. 2005;20(suppl 1):S293. Abstract SU446 and poster.

II. Key clinical trials summary

[FREEDOM / DECIDE / STAND studies]



Study design

FREEDOM

Inclusion Criteria
- Postmenopausal women with osteoporosis (- 4.0 ≤ BMD T-score < -2.5)
- 60 - 90 years old

N = 7868

Exclusion Criteria
- Any severe or > 2 moderate prevalent vertebral fx

RANDOMIZATION

→ Denosumab 60mg sc q6m

→ Placebo

36 months

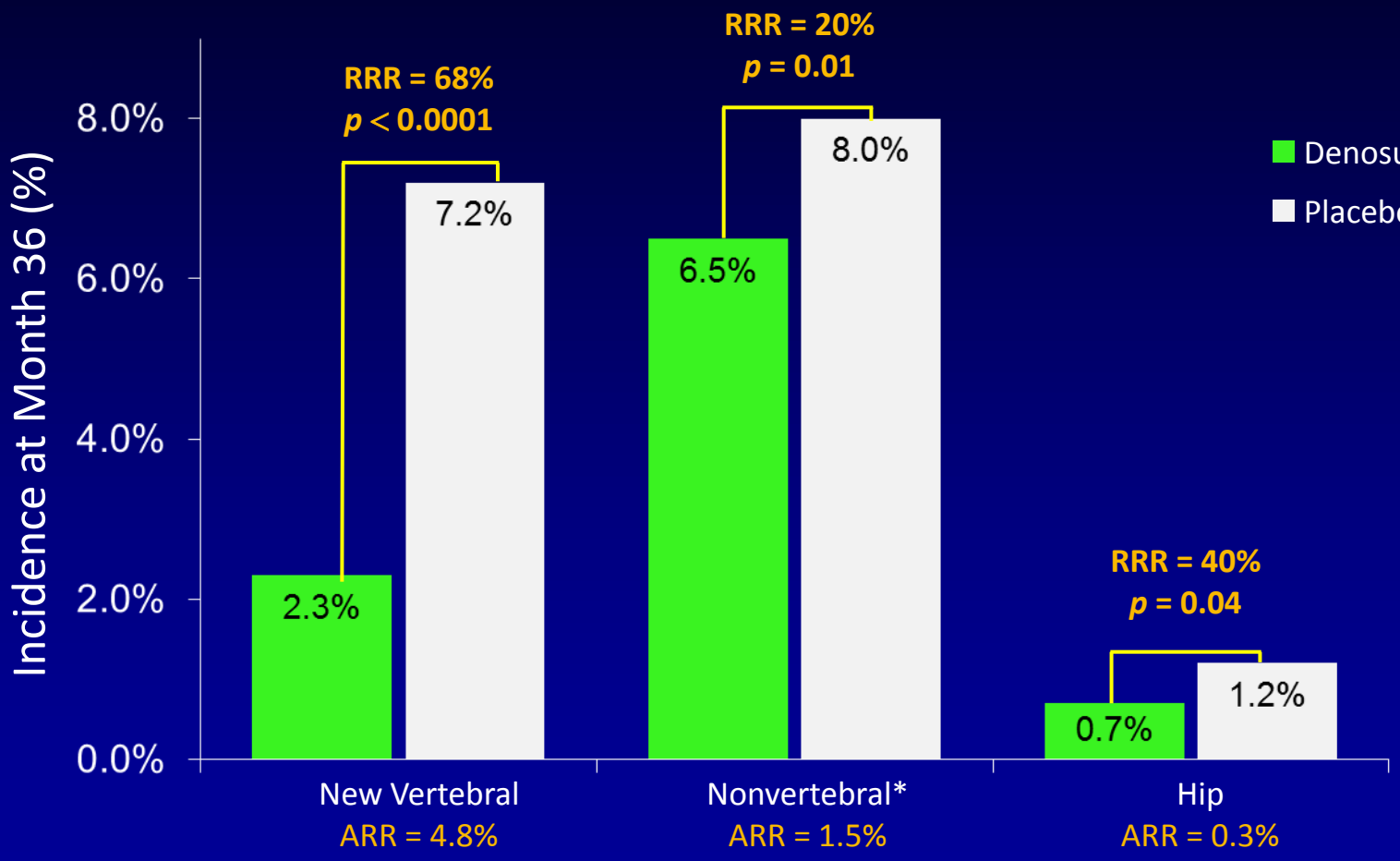
Primary Endpoints:
- **Incidence of new vertebral fractures**
- **Safety and tolerability profile of denosumab**

Secondary Endpoints:
- » Time to first non-vertebral fracture
- » Time to first hip fracture

Cummings SR, *et al. New Engl J Med.* 2009; 361: 756-65.

Effect of Denosumab on Fracture Risk at 36 Months

FREEDOM



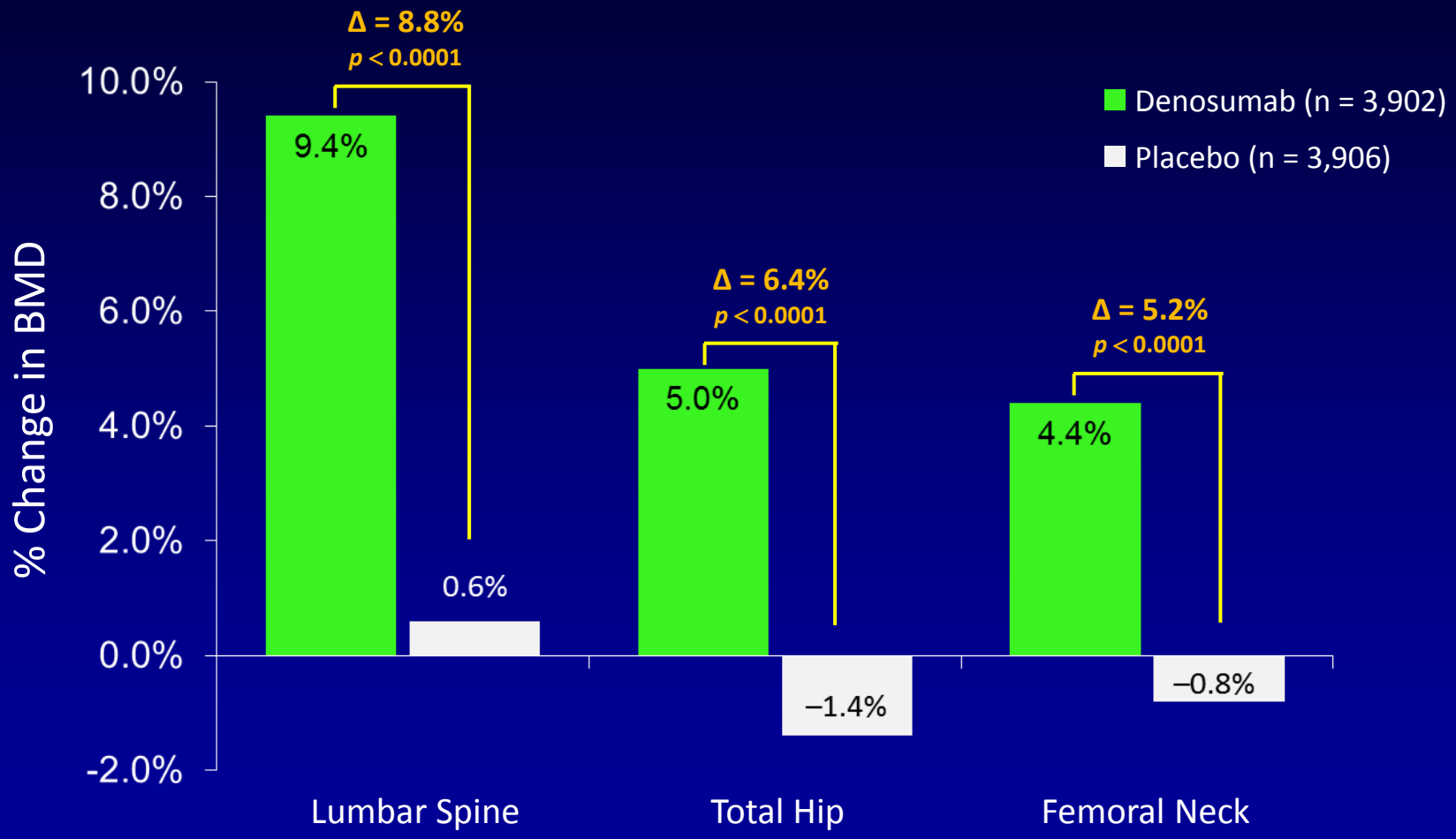
*Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.

RRR = relative risk reduction; ARR = absolute risk reduction

Cummings SR, et al. *N Engl J Med*. 2009;361:756-765. Prolia® (denosumab) prescribing information, Amgen.

Change in BMD at 36 Months With Denosumab

FREEDOM

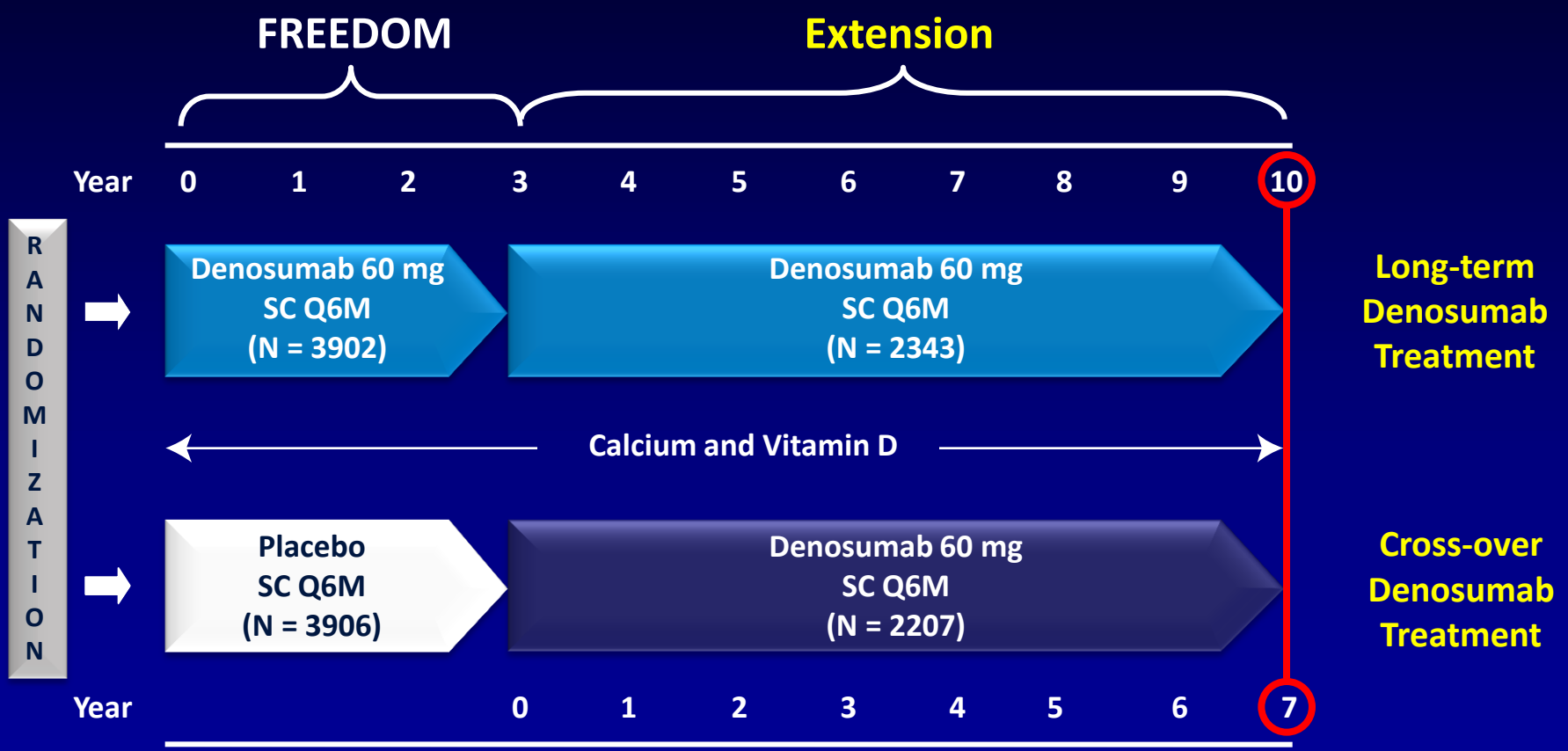


BMD = bone mineral density

Prolia® (denosumab) prescribing information, Amgen.
Data on file, Amgen. 2008.

FREEDOM Extension Study Design

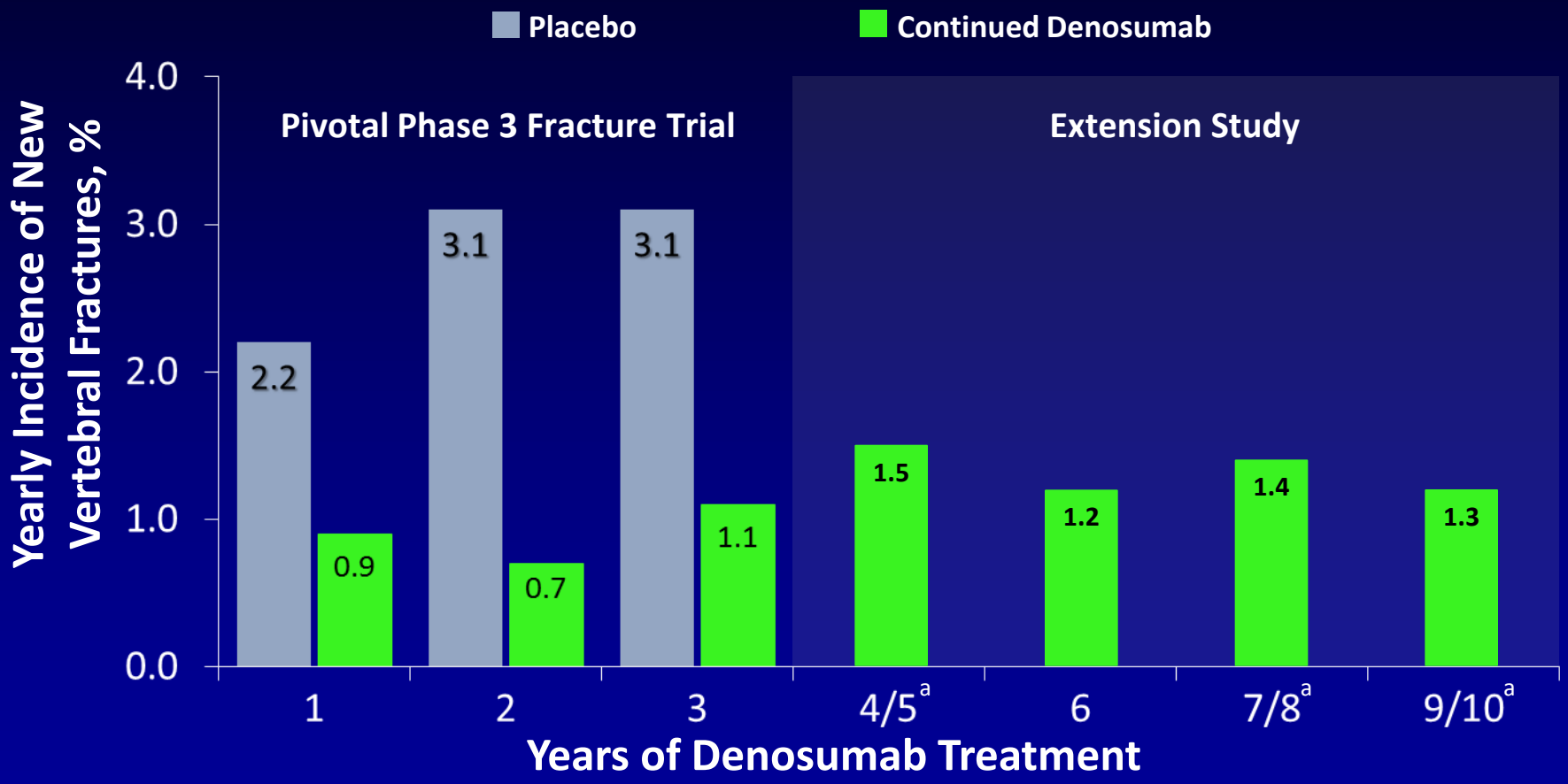
International, multicenter, open-label, single-arm study



Key Inclusion Criteria for the Extension:

- Completed the FREEDOM study (completed the 3-year visit, did not discontinue investigational product, and did not miss > 1 dose)
- Not receiving any other osteoporosis medications

Yearly Incidence of New Vertebral Fractures Through 10 Years

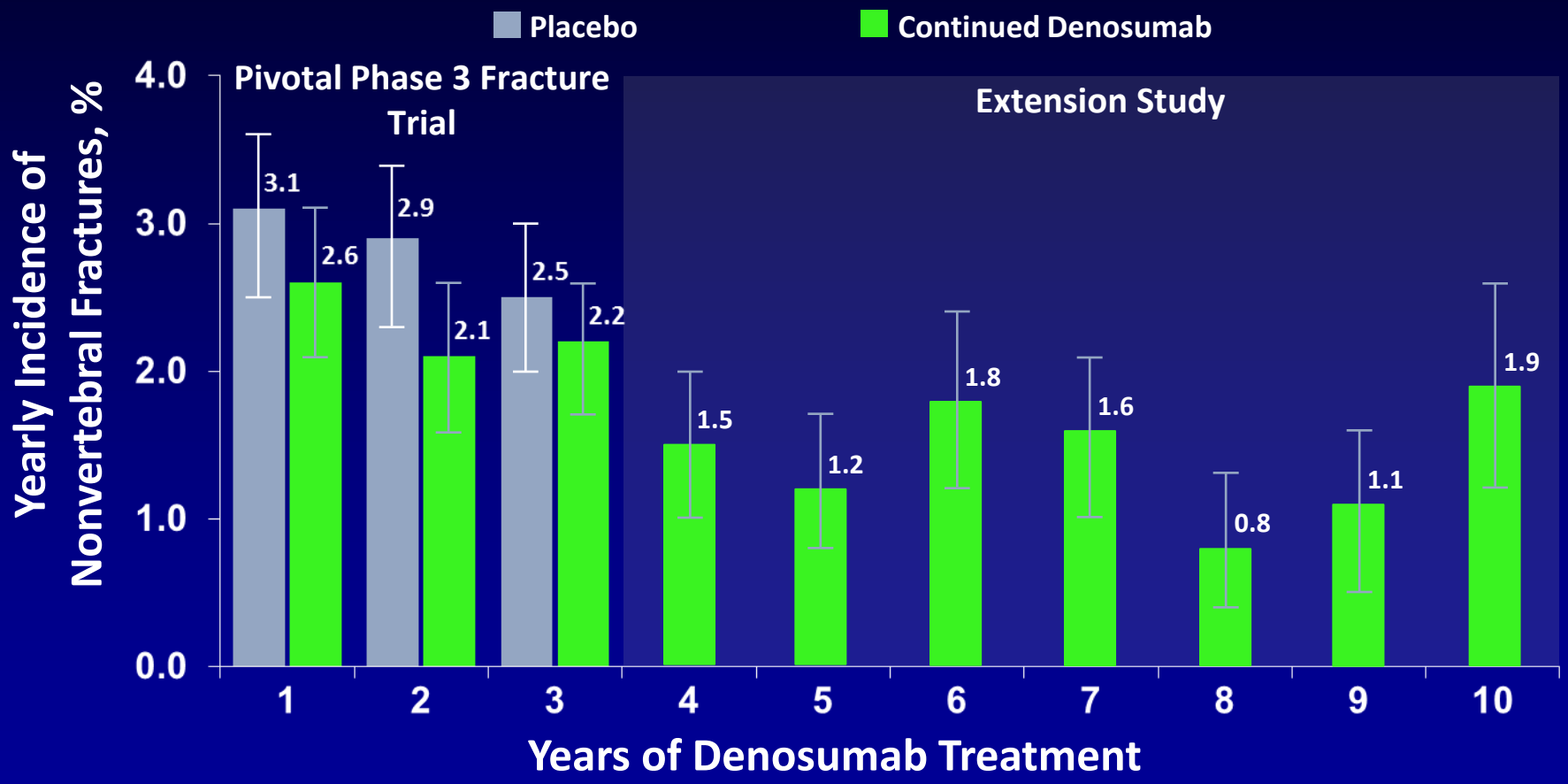


The primary endpoint of the open-label extension study was safety and tolerability of denosumab for up to 10 yrs. Fractures were collected as AEs in this study.

[a]Annualized incidence: (2-year incidence) / 2.

Adapted from: Bone HG, et al. Presented at: American Society of Bone and Mineral Research; October 12, 2015; Seattle, WA. Oral presentation LB-1157.

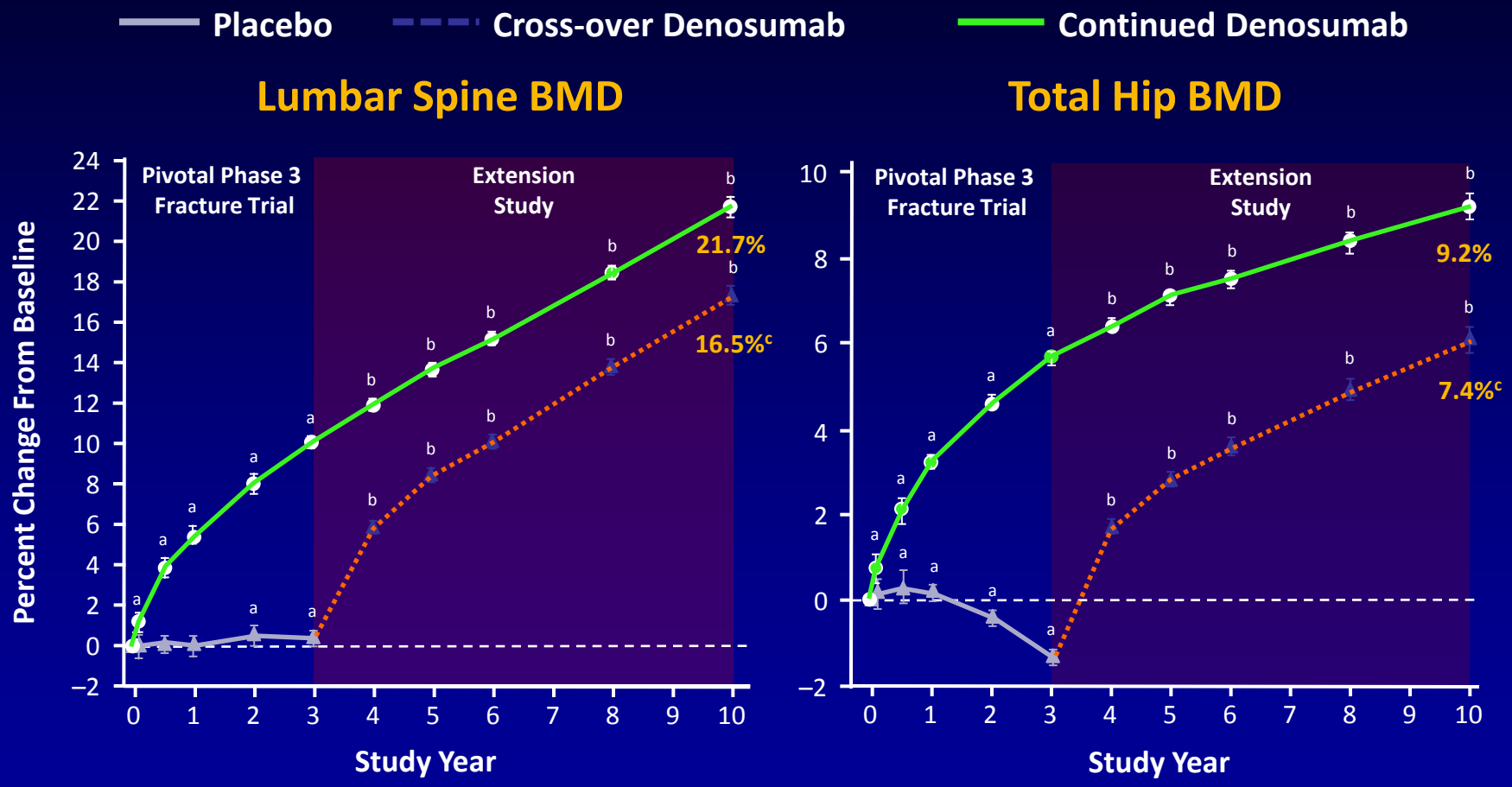
Yearly Incidence of Nonvertebral Fractures Through 10 Years



The primary endpoint of the open-label extension study was safety and tolerability of denosumab for up to 10 yrs. Fractures were collected as AEs in this study.

Adapted from: Bone HG, et al. Presented at: American Society of Bone and Mineral Research; October 12, 2015; Seattle, WA. Oral presentation LB-1157.

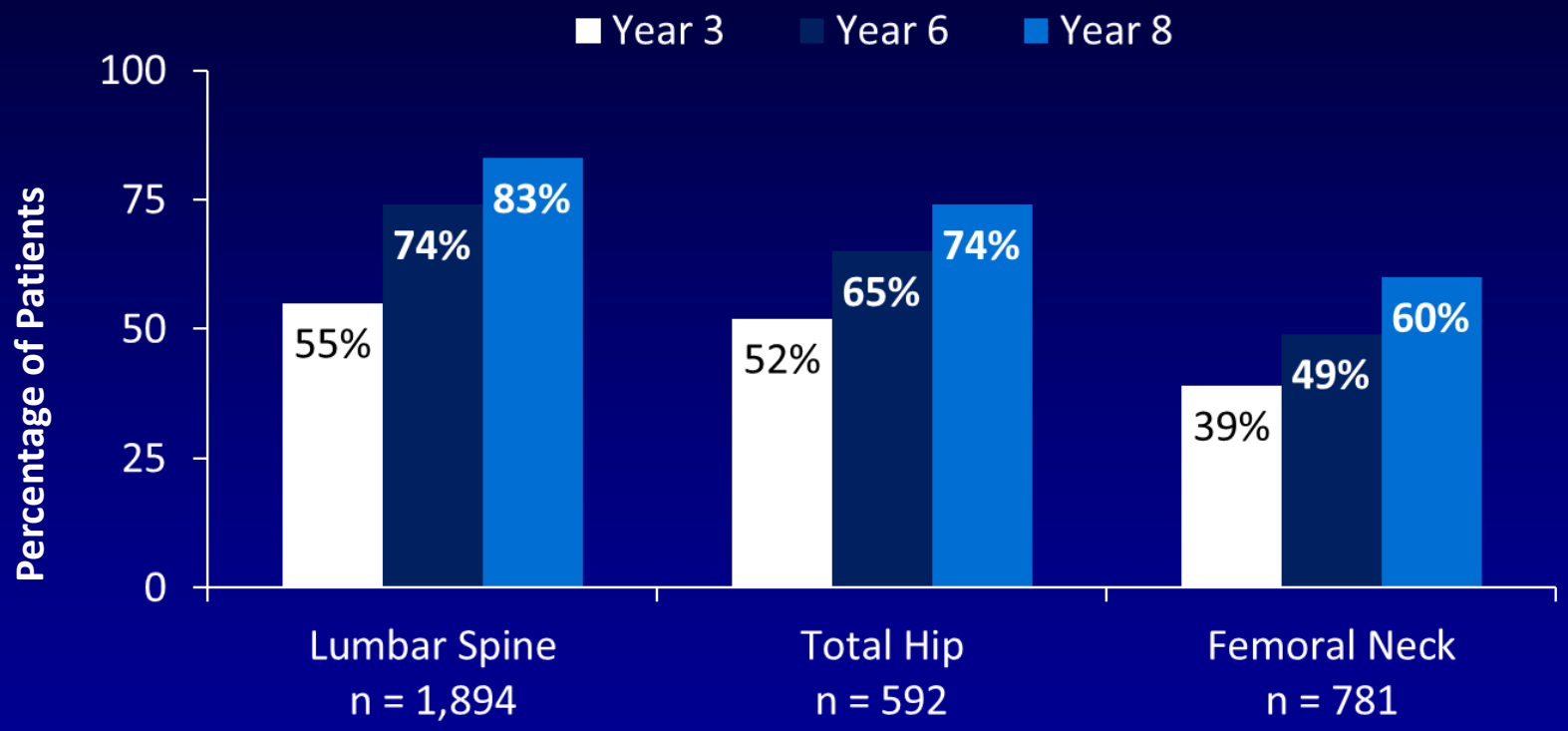
Change in Lumbar Spine and Total Hip BMD Through 10 Years With Denosumab Treatment



Data represents LS means and 95% CI.
[a]$p < 0.05$ vs Pivotal Phase 3 study baseline; [b]$p < 0.05$ vs Pivotal Phase 3 study baseline and extension baseline; [c]Percentage change while on denosumab treatment.
BMD = bone mineral density; LS = least-squares; CI = confidence interval

Adapted from: Bone HG, et al. Presented at: American Society of Bone and Mineral Research; October 12, 2015; Seattle, WA. Oral presentation LB-1157.

Patients with a T-Score ≤ –2.5 at Baseline Attaining a T-score > –2.5 Over Time



n = number of subjects enrolled in the extension study who had a T-score ≤ –2.5 at the lumbar spine, total hip, or femoral neck at baseline in the pivotal phase 3 trial.

Adapted from: Ferrari S, et al. Presented at: American Society of Bone and Mineral Research, September 12-15, 2014, Houston, TX. Poster FR0391/SA0391.

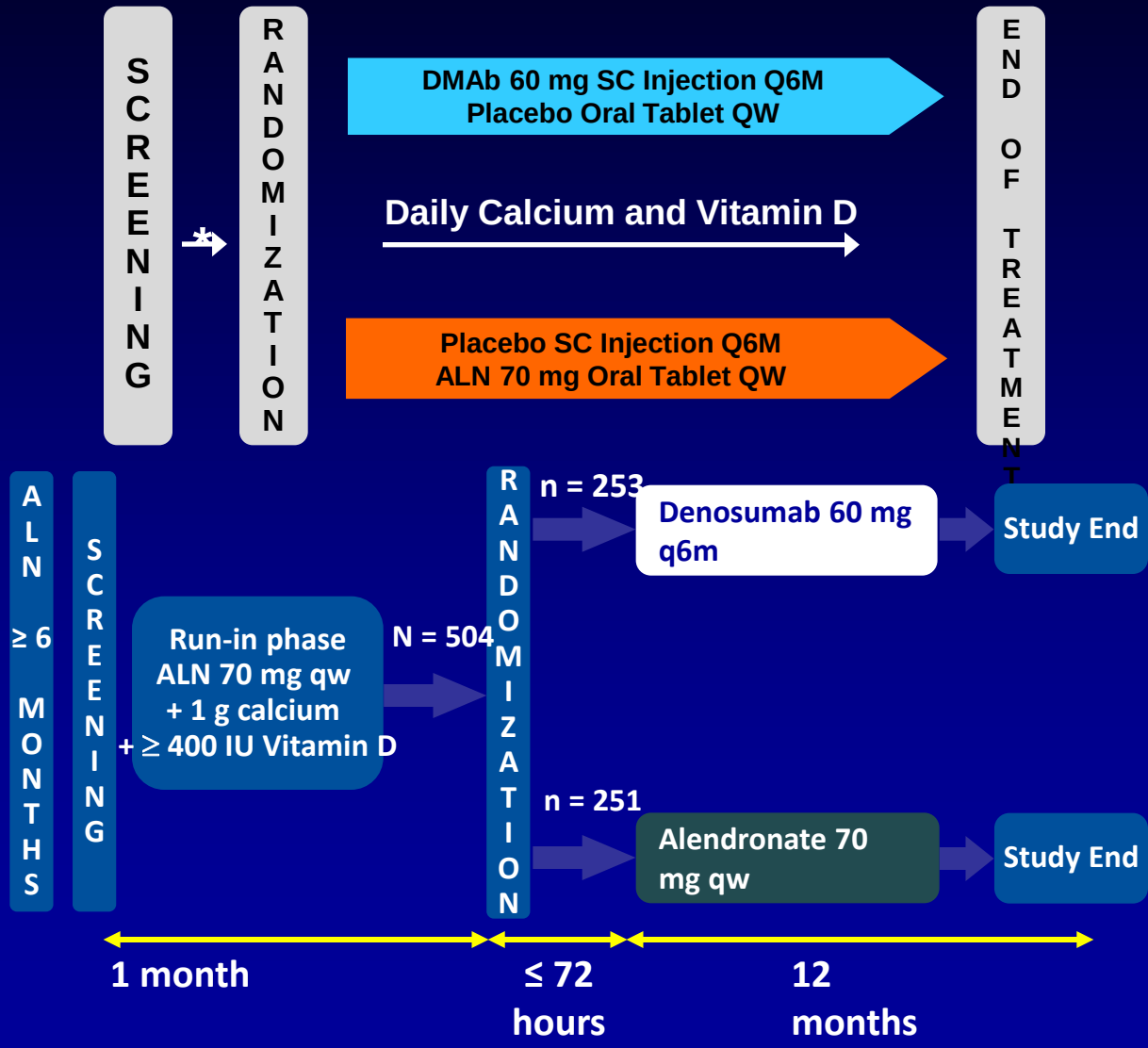
DECIDE and STAND Studies - Comparative DMAb vs ALN Studies

DECIDE (N = 1189)

- Postmenopausal women naïve to osteoporosis treatment
- T-score ≤ –2.0 at the lumbar spine or total hip

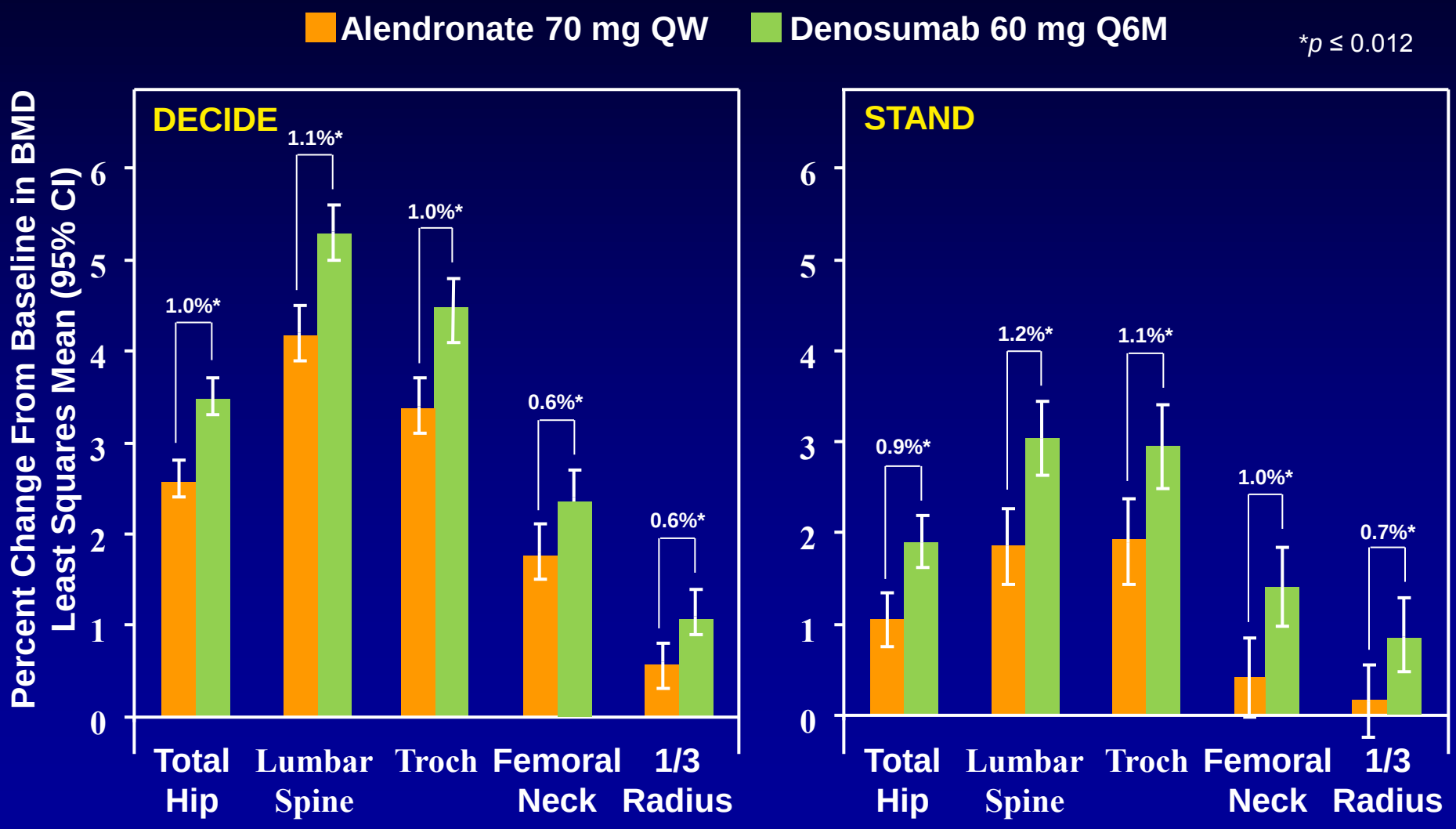
STAND (N = 504)

- Postmenopausal women who had received ALN treatment equivalent to 70 mg QW for ≥ 6 months immediately prior to screening
- T-score ≤ –2.0 and ≥ –4.0 at the lumbar spine or total hip



Brown JP, et al. *J Bone Miner Res.* 2009;24:153-161; Kendler DL, et al. *J Bone Miner Res*. 2010;25:72-8

DECIDE and STAND: comparison in BMD changes for all measured skeletal sites at month 12



Brown JP, et al. *J Bone Miner Res.* 2009;24:153-161; Kendler DL, et al. *J Bone Miner Res*. 2010;25:72-8

Denosumab vs. Zoledronic acid

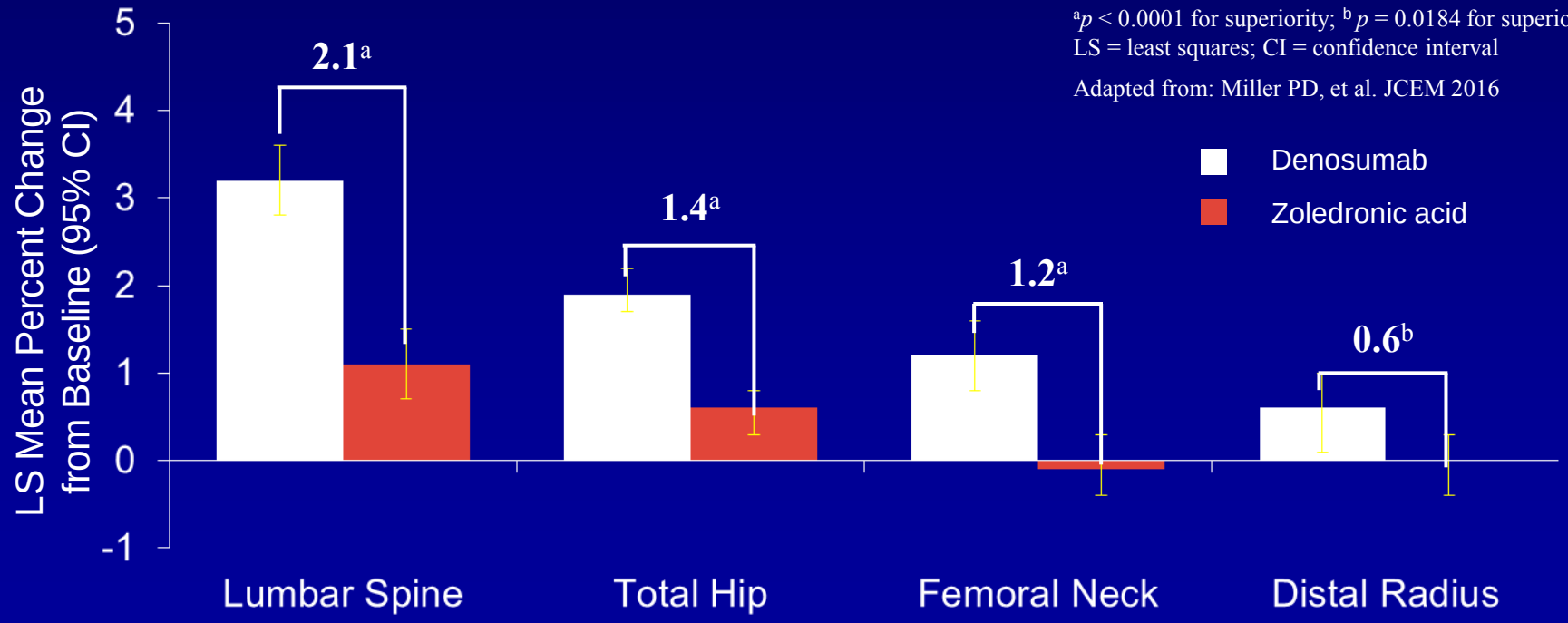
JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ORIGINAL ARTICLE

Denosumab or Zoledronic Acid in Postmenopausal Women With Osteoporosis Previously Treated With Oral Bisphosphonates

PD Miller,[1] N Pannacciulli,[2] JP Brown,[3] E Czerwinski,[4] BS Nedergaard,[5], MA Bolognese,[6] J Malouf,[7] HG Bone,[8] JY Reginster,[9] A Singer,[10] C Wang,[2] RB Wagman,[2] SR Cummings[11]

- **Denosumab demonstrated significantly greater BMD gains at month 12 compared to zoledronic acid at all skeletal sites measured**



[a]$p < 0.0001$ for superiority; [b]$p = 0.0184$ for superiority
LS = least squares; CI = confidence interval

Adapted from: Miller PD, et al. JCEM 2016

Denosumab vs. Zoledronic acid

Journal of Bone and Mineral Research
JBMR
ASBMR
The American Society for Bone and Mineral Research
Explore this journal >

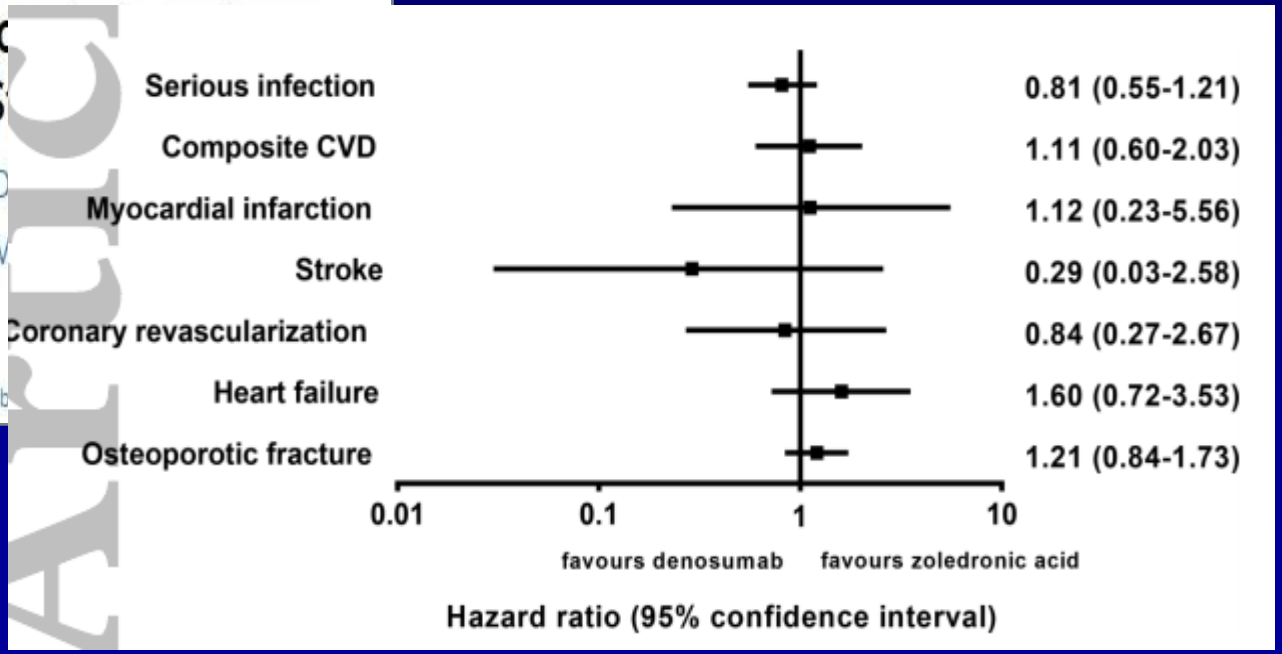
Original Article

Comparative Safety and Effectiveness of Denosumab Versus Zoledronic With Osteoporosis: A Cohort S

Nam-Kyong Choi PhD ✉, Daniel H. Solomon MD
Theodore N. Tsacogianis MPH, Joan E. Landon M
Seoyoung C. Kim MD, ScD, MSCE

Accepted manuscript online: 13 October 2016 Full pub

- 2467 patients in each group
- Risk of serious infection and cardiovascular disease (CVD) and osteoporotic fracture.



lll. Adverse events, tolerability of denosumab

Adverse Events Over 36 Months *(continued)*

FREEDOM

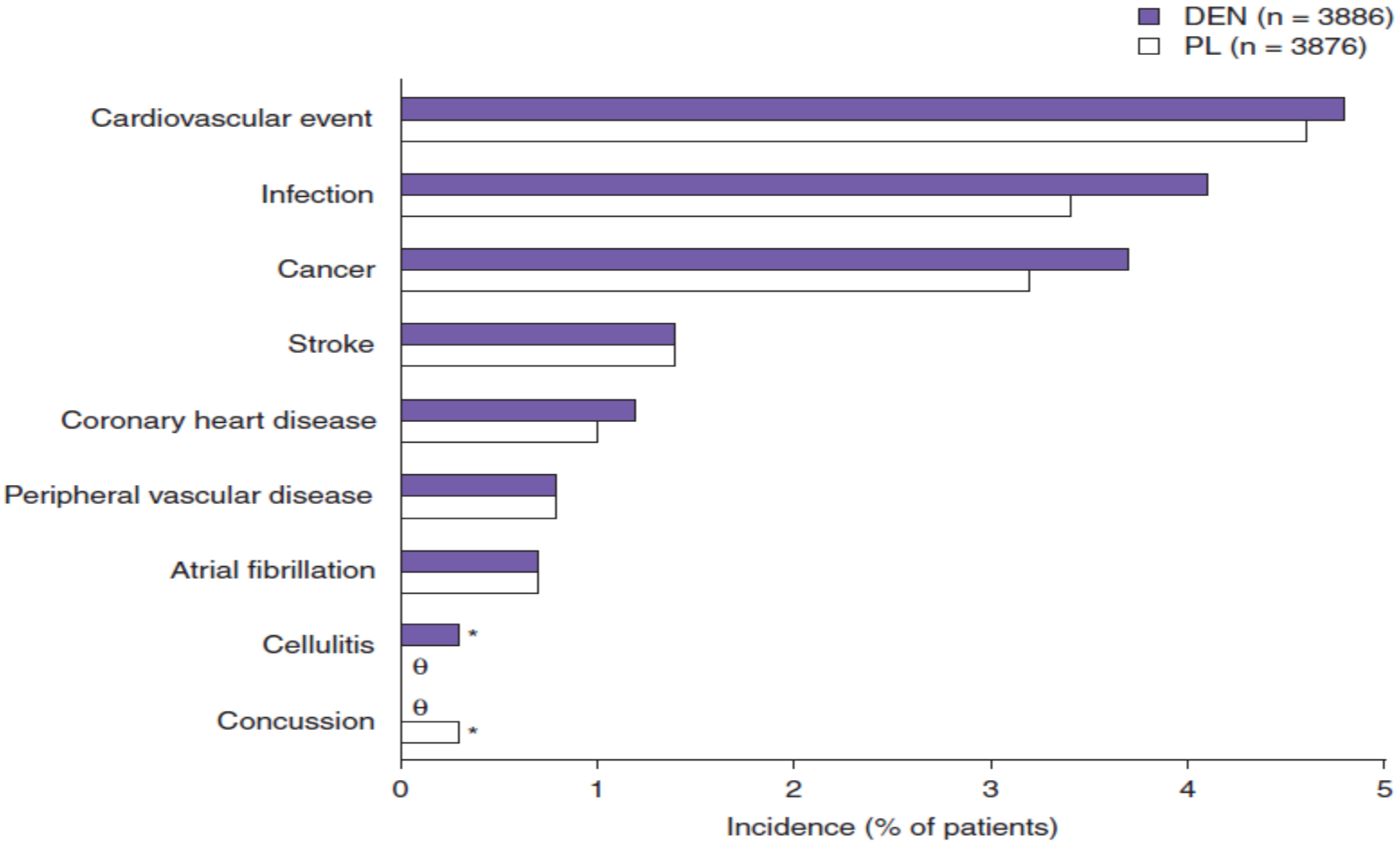
Adverse events, n (%)	Placebo (n = 3,876)	Denosumab 60 mg Q6M (n = 3,886)
Adverse events		
Infection	2,108 (54.4)	2,055 (52.9)
Malignancy	166 (4.3)	187 (4.8)
Injection site reaction	26 (0.7)	33 (0.8)
Hypocalcemia	3 (0.1)	0 (0)
Delayed fracture healing	4 (0.1)	2 (0.05)
Femoral shaft fracture	3 (0.1)	0 (0)
Humerus nonunion fracture	1 (0.03)	0 (0)
Osteonecrosis of the jaw	0 (0)	0 (0)
Adverse events occurring with ≥ 2% incidence and $P \leq 0.05$		
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

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

Severe Adverse Events Over 36 Months

FREEDOM



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

Adverse events

DAPS Study

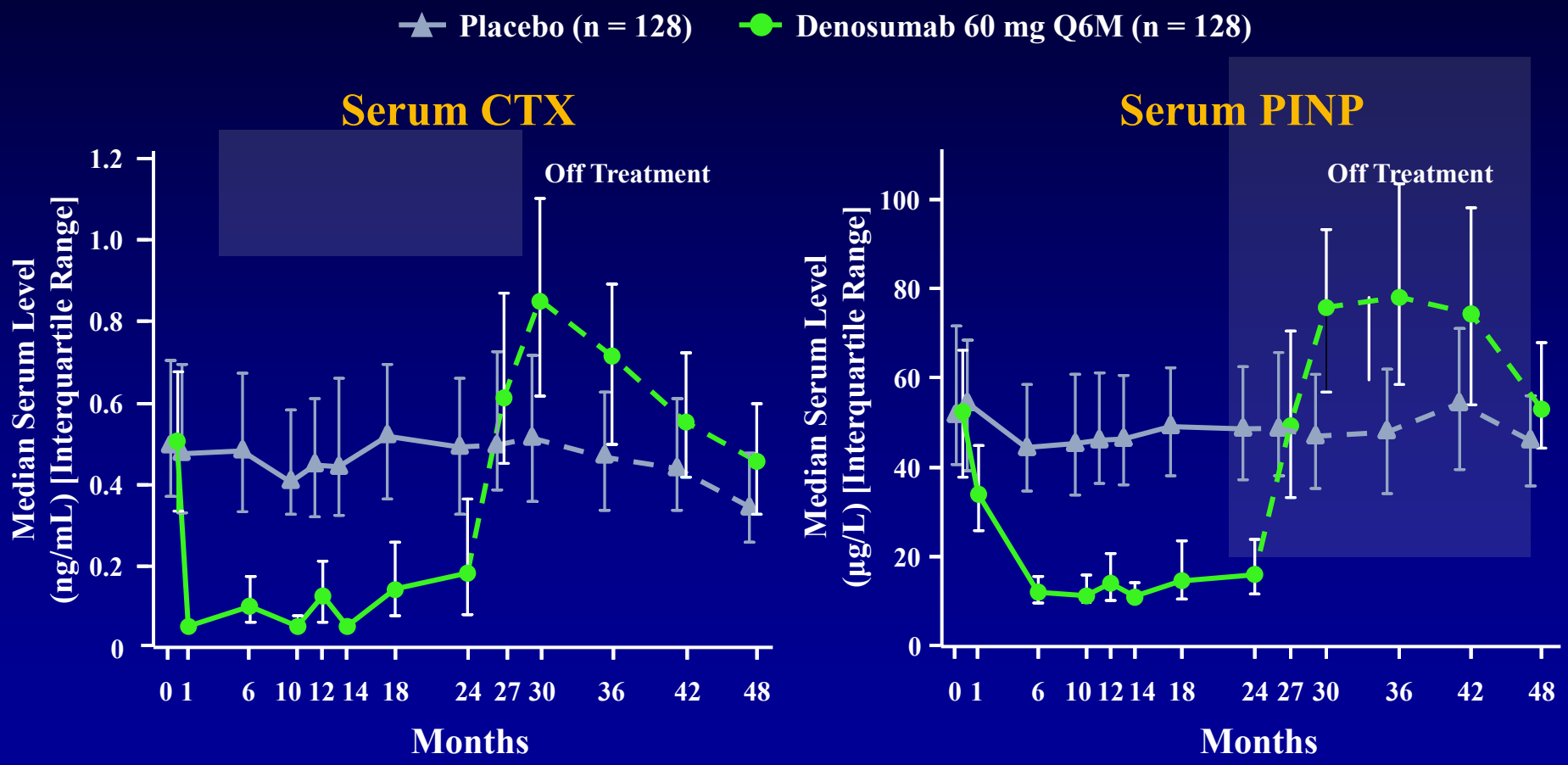
	ALN/DMAB Sequence		DMAB/ALN Sequence		Overall Study	
	1st Year: ALN N = 118	2nd Year: DMAB N = 106	1st Year: DMAB N = 125	2nd Year: ALN N = 110	ALN N = 228	DMAB N = 230
Any Adverse Event, n (%)	76 (64.4)	58 (54.7)	93 (74.4)	68 (61.8)	144 (63.2)	151 (65.7)
Serious Adverse Event, n (%)	5 (4.2)	4 (3.8)	4 (3.2)	4 (3.6)	9 (3.9)	8 (3.5)
Adverse Events of Fracture, n (%)	1 (0.8)	3 (2.8)	1 (0.8)	1 (0.9)	2 (0.9)	4 (1.7)
Adverse Events of Osteoporotic Fracture, n (%)	0 (0)	2 (1.9)	1 (0.8)	1 (0.9)	1 (0.4)	3 (1.3)
Adverse Events ≥ 5% Frequency in Either Treatment Group, n (%)						
Arthralgia	8 (6.8)	3 (2.8)	11 (8.8)	7 (6.4)	15 (6.6)	14 (6.1)
Pain in Extremity	5 (4.2)	5 (4.7)	9 (7.2)	4 (3.6)	9 (3.9)	14 (6.1)
Back Pain	10 (8.5)	4 (3.8)	5 (4.0)	3 (2.7)	13 (5.7)	9 (3.9)
Osteoarthritis	5 (4.2)	6 (5.7)	2 (1.6)	3 (2.7)	8 (3.5)	8 (3.5)
Headache	7 (5.9)	3 (2.8)	4 (3.2)	3 (2.7)	10 (4.4)	7 (3.0)
Cough	6 (5.1)	1 (0.9)	5 (4.0)	5 (4.5)	11 (4.8)	6 (2.6)

Includes only treatment-emergent adverse events occurring on or before the end of the specific treatment period
N = number of patients who received at least 1 dose of study drug during the specific treatment period
n = number of patients reporting at least one adverse event during the specific treatment period
McClung MR, et al. Presented at: The International Society for Clinical Densitometry; April 6-9, 2011; Miami, FL. Poster 116.

Ⅳ. Place of Denosumab in the Management of osteoporosis, / Recommendations

Effect of Denosumab Discontinuation on Bone Turnover Markers

Phase 3 Prevention Trial – Extension Study



Adapted from: Bone HG, et al. *J Clin Endocrinol Metab*. 2011;96:972-980.

Vertebral Fractures after denosumab discontinuation

Osteoporos Int (2016) 27:1917–1921
DOI 10.1007/s00198-015-3458-6

SHORT COMMUNICATION

Rebound-associated vertebral fractures after discontinuation of denosumab—from clinic and biomechanics

Severe rebound-associated vertebral fractures after denosumab discontinuation: nine clinical cases report

Olivier Lamy, Elena Gonzalez-Rodriguez, Delphine Stoll, Didier Hans, Bérengère Aubry-Rozier

Bone Unit, Lausanne University Hospital, Lausanne, Switzerland

JCEM THE JOURNAL OF ENDOCRINOLOGY

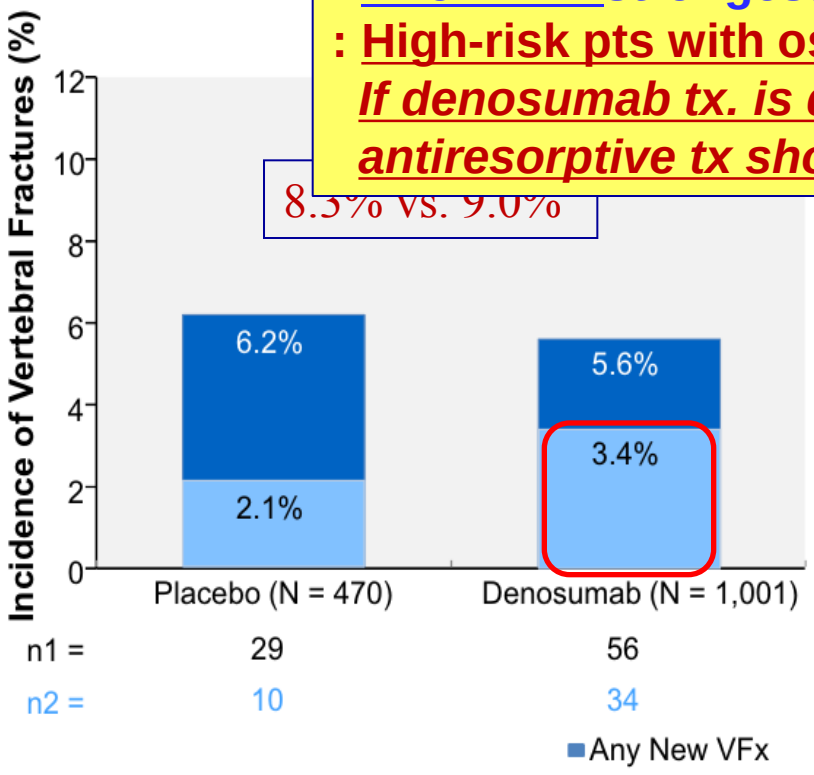
- Denosumab discontinuation is associated with a severe bone turnover rebound (BTR) and a rapid loss of BMD.
- All VFs – spontaneous, high number of VFs (mean=5.5), rapidly after last denosumab injection (9~16mon.), vertebroplasty was asso. with a high number of New VFs.
- The severe BTR is involved in microdamage accumulation in trabecular bone and thus promotes VFs.
- The management and/or treatment regimens after denosumab discontinuation ?

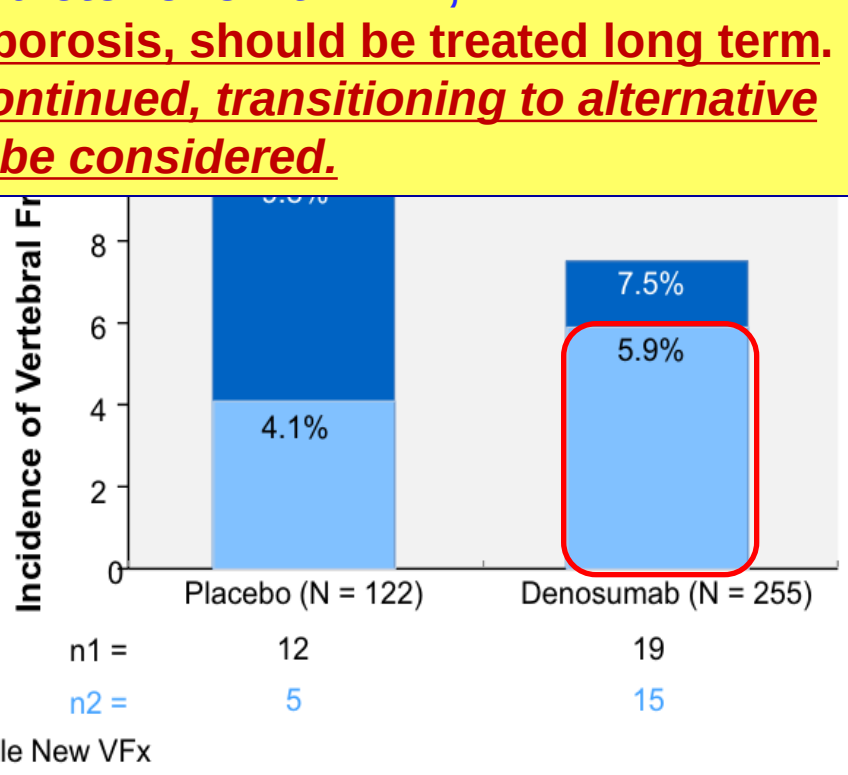
Discontinuation of Denosumab & Vertebral Fracture Incidence

: Analysis from FREEDOM and Its Extension *(Brwon JP et al. ASBMR; Sept,2016)*

ANY VS MULTIPLE NEW OFF-TREATMENT VERTEBRAL FRACTURES

: the incidence of multiple new VFx ↑?
: Prior VFx- strongest predictor of off-tx. VFx,
: High-risk pts with osteoporosis, should be treated long term.
If denosumab tx. is discontinued, transitioning to alternative antiresorptive tx should be considered.





Any New VFx Multiple New VFx

Recommendations on denosumab

Guidelines	Recommendations
AACE[1]	Denosumab as one of the first line recommendations along with alendronate, risedronate, zoledronic acid
Osteoporosis Canada[2]	Denosumab is recommended as one of the first line therapies for preventing hip, nonvertebral and vertebral fractures for menopausal women (other recommended first line therapies include alendronate, risedronate, zoledronic)
OSHK[3]	Denosumab is recommended as one of the first-line drugs for treatment of postmenopausal osteoporosis

1. Watts NB et al. Endocr Pract. 2010; 16 (3) 1-37.
2. Papaioannou A et al. CMAJ 2010: 182(17): 1864-1873
3. Hong Kong Med J Vol 19 No 2 Supplement 2

Experts' opinion on denosumab (OSHK)

- **Recommended as one of the first-line drugs for treatment of postmenopausal osteoporosis.**

- **Especially indicated in patients with :**

- **polypharmacy**
- **poor compliance to oral drugs,**
- **contraindications to oral bisphosphonate therapy**
- **no effect with BPs treatment**
- **prolonged bisphosphonate treatment**
- **renal impairment up to stage 4 chronic kidney disease**

Hong Kong Med J 2013;19(2):1-40

Summary (I)

- Denosumab, a reversible RANKL inhibitor, is a new antiresorptive agent with a novel mechanism.
- Clinical efficacy (3~10yrs)
  - reduced the risk of vertebral, nonvertevral and hip fractures vs. placebo (FREEDOM study)
  - sustained increase of BMD vs. alendronate tx. (DECIDE, STAND study)
- Overall favourable tolerability,
  - Denosumab tx.~ cellulitis (SAE), eczema, flatulence ↑
- Advantage in the frequency (q 6Mon) and route of administration (SC) ⇒ adherence ↑

Summary (II)

- **After discontinuation of denosumab**

  ⇒ **transient increase in bone turnover markers above baseline ⇒ Fracture risk ↑? : recent case reports.**

  ⇒ **consider transitioning to an alternative antiresorptive tx. like bisphosponate**

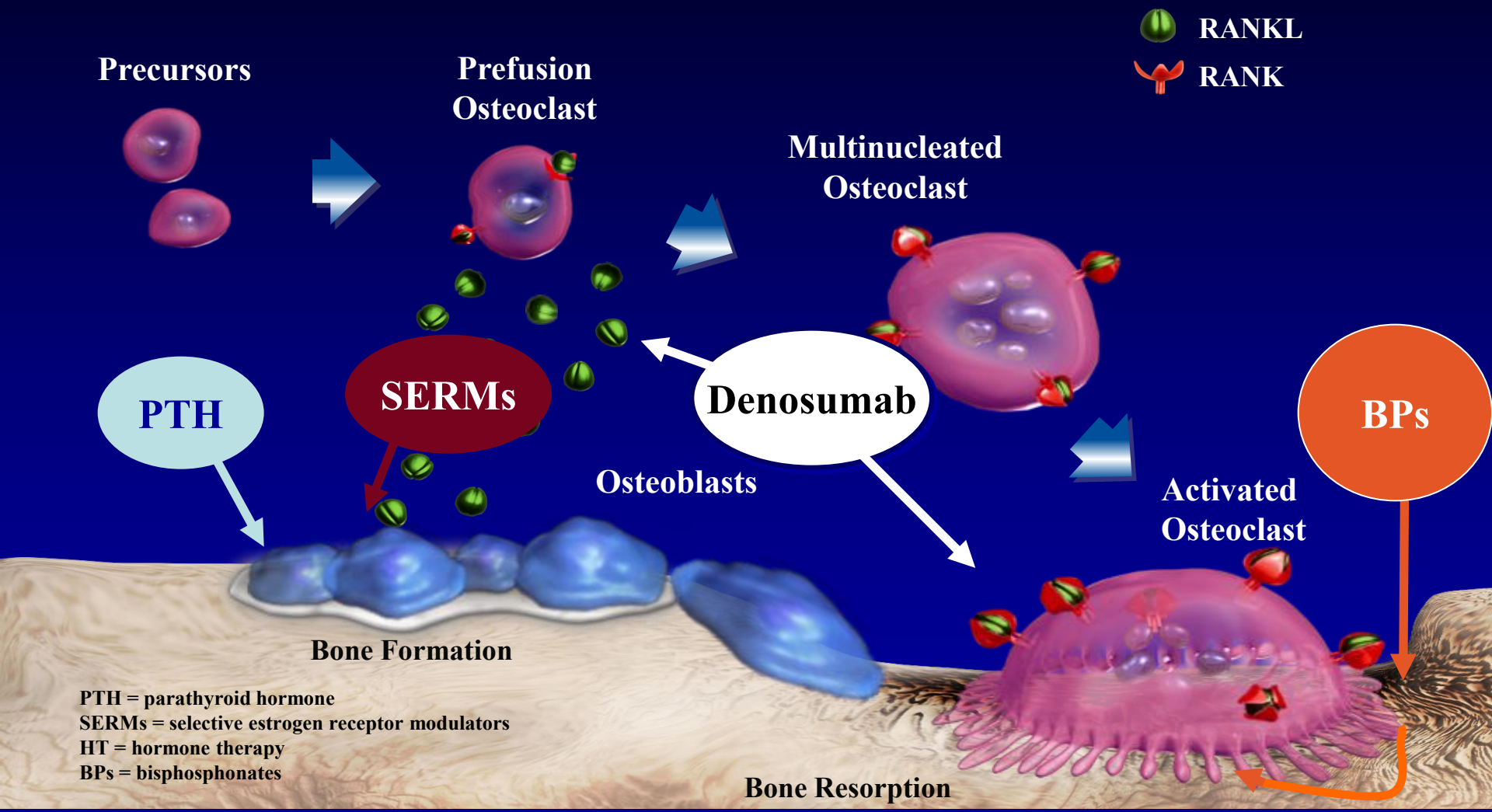
- **How long to treat with Denosumab?**

  - High-risk patients with osteoporosis

  : a chronic condition and should be treated long term.

Thank you for Your Attention !!

Site of action of pharmacologic therapies (direct or indirect)



PTH = parathyroid hormone
SERMs = selective estrogen receptor modulators
HT = hormone therapy
BPs = bisphosphonates

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