새로운 골다공증 치료 약제

RANKL monoclonal Ab
프롤리아

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Key milestones in the lifecourse of osteoporosis therapy

HRT

Calcitonin

Oral BPN

Raloxifene

Teriparatide QD

IV BPN

Denosumab

Bazedoxifene

Teriparatide QW

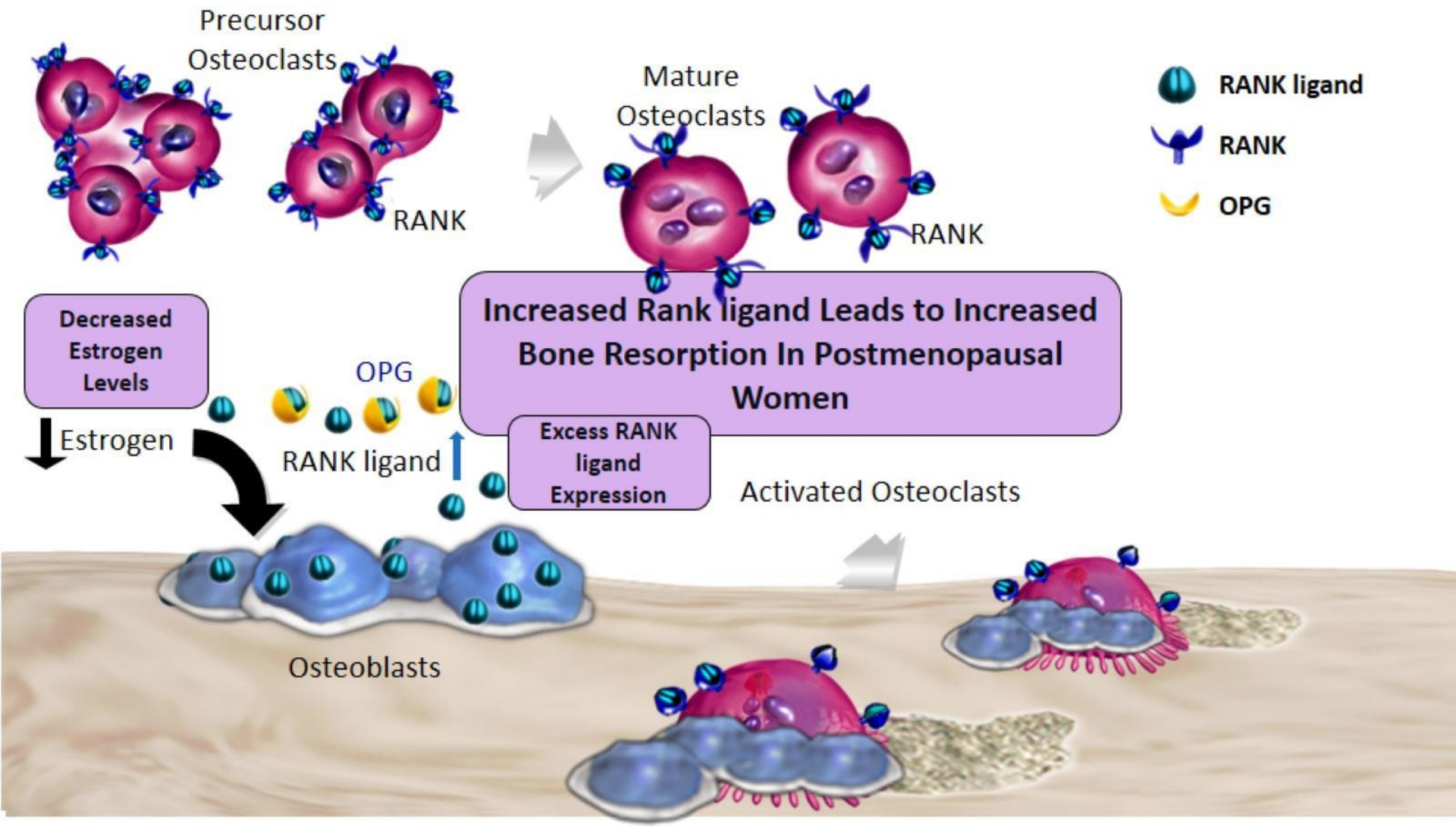
1960~ | 1991 | 1995 | 1999 | 2002 | 2004 | 2006/7 | 2010 | 2012 | ? | ??

Strontium ranelate

Anti-sclerostin

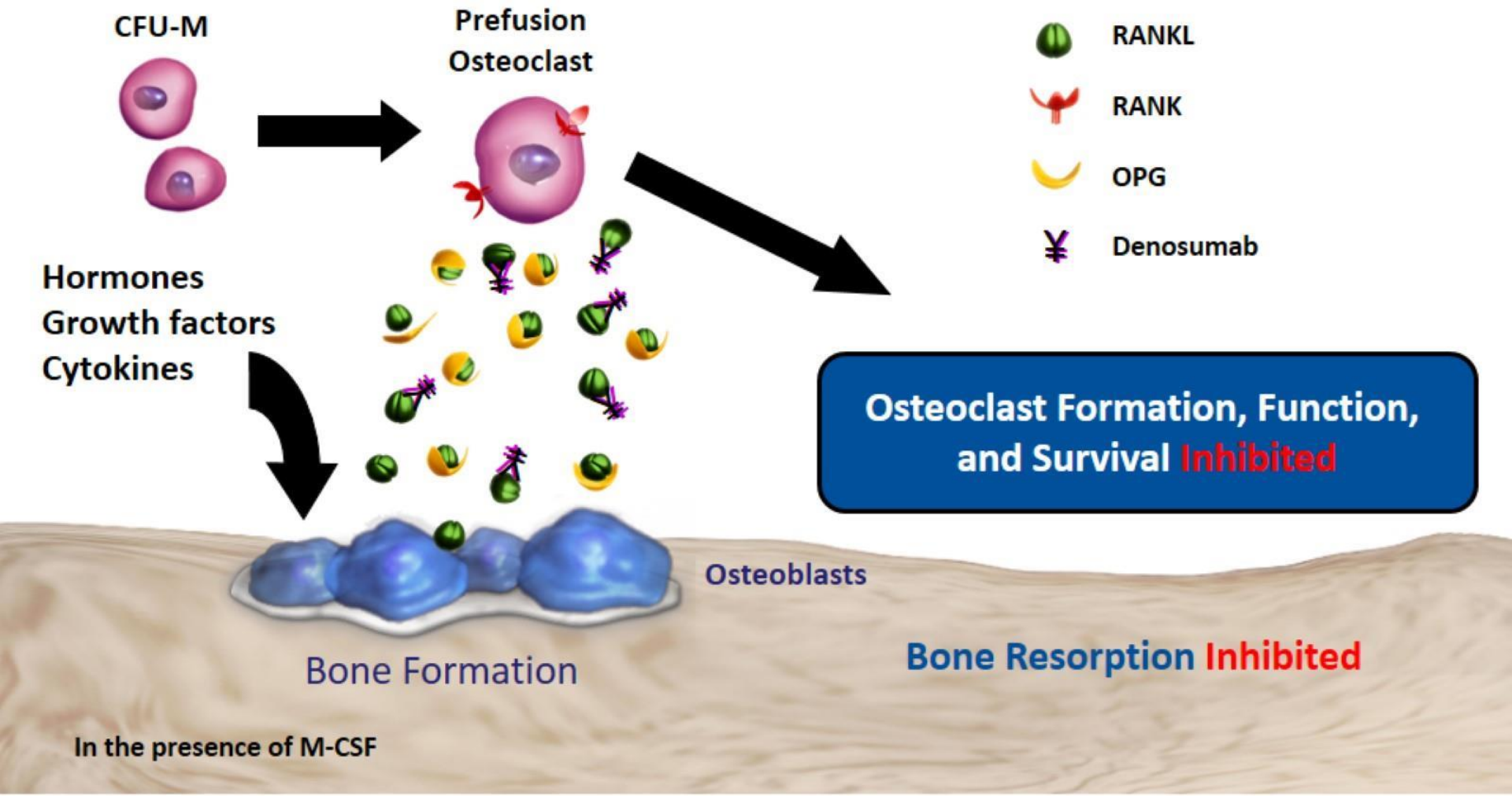
Cathepsin K inhibitors

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.

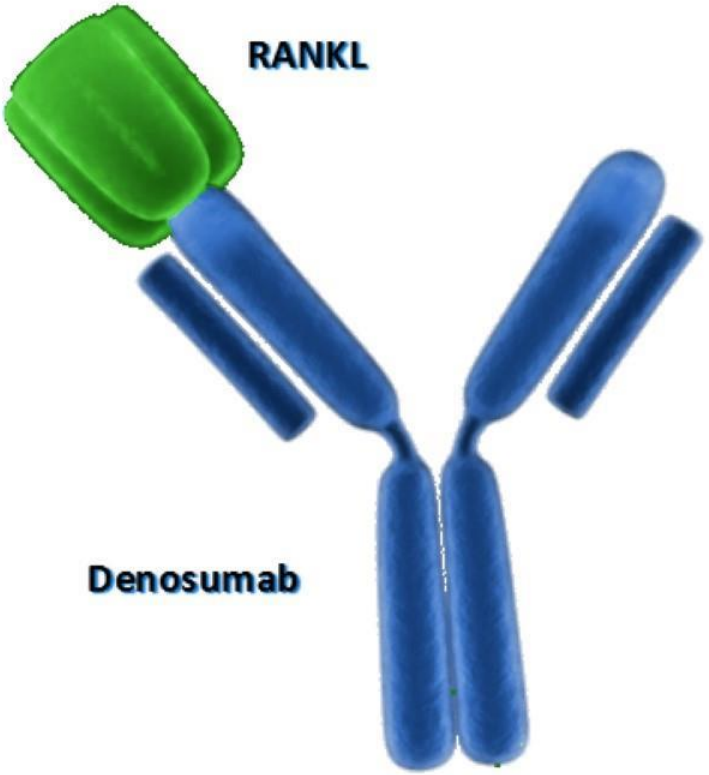
Denosumab binds RANKL and inhibits osteoclast formation, function, and survival



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

Targeting the Essential Mediator of Postmenopausal Bone Loss

- **Denosumab**
  - Fully human IgG2 monoclonal antibody
  - High-affinity and highly specific targeting RANKL
  - No detectable binding to TNF-α, TNF-β, TRAIL, or CD40 ligand
  - 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

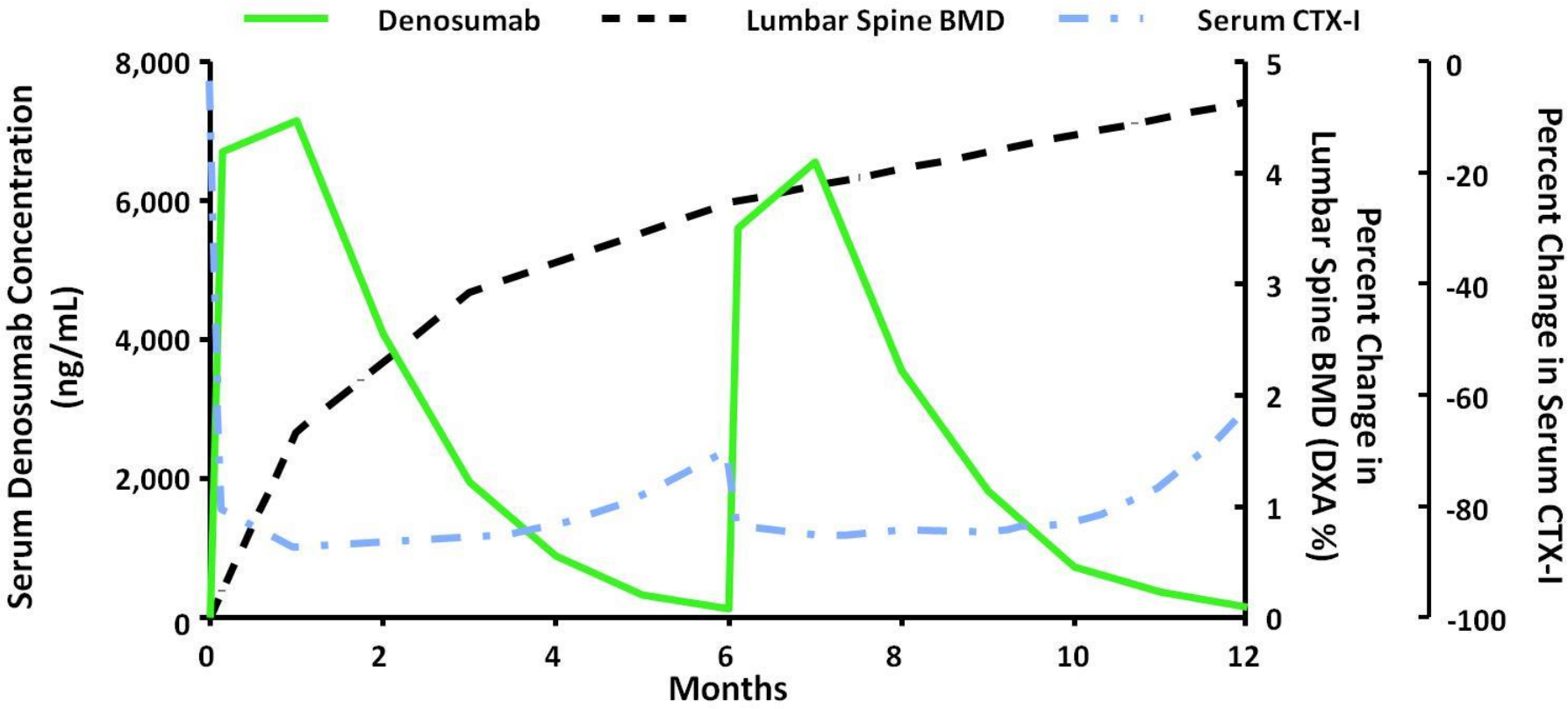
Properties of ideal osteoporosis treatment

- **Anti-fracture efficacy** at various skeletal sites, begins within months of starting therapy
- persists with **Long –term therapy**
- **High safety margin**, both skeletal and extra skeletal
- Mode of administration and treatment interval translate into **patient's adherence**

- But, …. wane when treatment is stopped….even with BPs

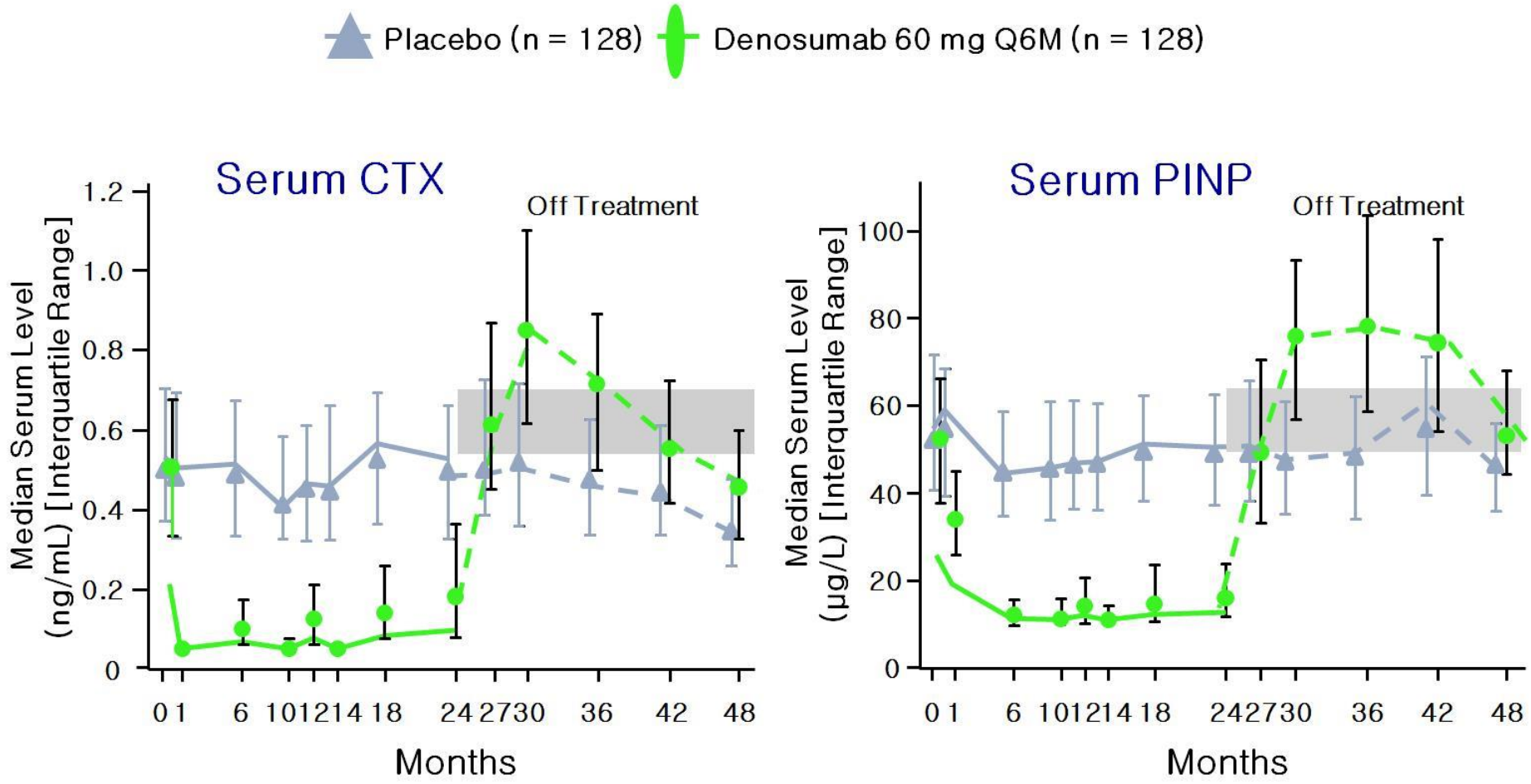
Pharmacokinetic and Pharmacodynamic Properties

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



Effect of Denosumab Discontinuation on Bone Turnover Markers

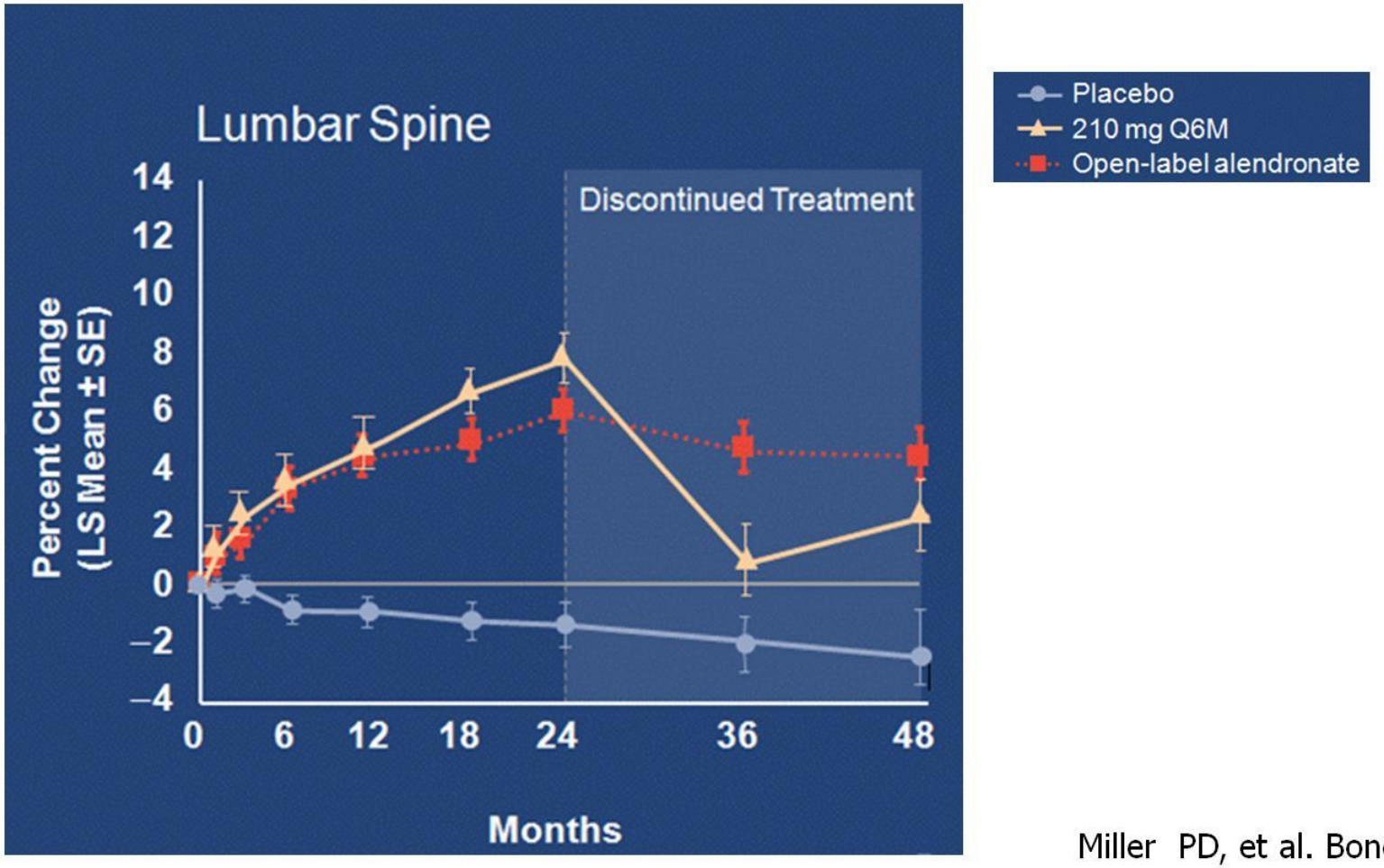
Phase 3 Prevention Trial – Extension Study



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

Effect of Denosumab Discontinuation and retreatment on BMD (Phase 2)

Changes in Lumbar Spine BMD After Discontinuation of Denosumab
Postmenopausal Women With Low BMD



Miller PD, et al. Bone 2008

Clinical Research Summary

STUDY/CITATION	STUDY DESIGN	STUDY POPULATION	ENDPOINTS & KEY RESULTS
PROLIA EFFICACY AND SAFETY VS. PLACEBO IN POSTMENOPAUSAL OSTEOPOROSIS			
FREEDOM Cummings SR, *et al. N Engl J Med* 2009;361:756–65.	• Multi-centre, randomised, double-blind, placebo-controlled trial • 7,808 postmenopausal women were randomised to receive Prolia 60mg SC Q6M or placebo for 3 years	• **Inclusion** – Women aged 60–90 years – BMD T-score of < –2.5 to ≥ –4.0 at lumbar spine or total hip • **Exclusion** – Any severe or > 2 moderate vertebral fractures	• **Primary efficacy endpoint:** – New vertebral fractures at 3 years: ↓ 68% RRR (p<0.001) • **Secondary efficacy endpoints:** – Hip fractures at 3 years: ↓ 40% RRR (p=0.04) – Non-vertebral fractures at 3 years: ↓ 20% RRR (p=0.01)
FREEDOM High risk group Post-hoc analysis Boonen S, *et al. J Clin Endocrinol Metab* 2011; 96:1727–36.	• Post-hoc fracture incidence analyses of FREEDOM in women with known risk factors for fracture.	**Vertebral fracture analysis** • Women enrolled in FREEDOM with multiple **and/or** moderate or severe prevalent vertebral fractures **and/or** a femoral neck BMD T-score of ≤ –2.5 **Hip fracture analysis** • Women enrolled in FREEDOM age ≥ 75 years and/or with a femoral neck BMD T-score of ≤ –2.5	• **Fracture risk in high-risk patients:** – Prolia significantly ↓ new vertebral fractures in women with multiple and/or severe prevalent vertebral fractures (16.6% placebo vs. 7.5% denosumab; p< 0.001) – Prolia significantly ↓ hip fractures in subjects ≥ 75 year (2.3% placebo vs. 0.9% denosumab; p<0.01) or with a baseline femoral neck BMD T-score ≤ 2.5 (2.8% placebo vs. 1.4% Prolia; p=0.02)
FREEDOM Extension(10yr) Papapoulos S, *et al. Osteoporos Int* 2015;26:2773-83. + Supplementary appendix	• Multi-centre, international, open-label, follow-up of FREEDOM • 4,550 patients (2,343 long-term, 2,207 cross-over) enrolled in the FREEDOM extension study – 66% remain in study at the end of year 8 • All patients received open-label Prolia Q6M	• **Inclusion** – Must have completed the pivotal phase 3 fracture trial (received denosumab or placebo) – Did not discontinue or miss ≥ 1 dose of investigational product – Not receiving any other osteoporosis medications • **Length of Prolia treatment (end year 8)** – Long-term group = 8 years Prolia – Cross-over group = 5 years Prolia	• **Primary safety endpoint:** – Prolia was well tolerated by patients treated for up to 8 years – No increased frequency of any adverse event compared with the 3 year FREEDOM study • **Secondary efficacy endpoints:** – Sustained low incidence of new vertebral, non-vertebral and hip fractures – Continuous and cumulative 8-year gains in BMD: ↑18.4% (lumbar spine) and 8.3% (total hip) (all p<0.05) – Sustained ↓in BTMs (sCTX and P1NP)

FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months.

FREEDOM trial

Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

Steven R. Cummings, M.D., Javier San Martin, M.D., Michael R. McClung, M.D., Ethel S. Siris, M.D., Richard Eastell, M.D., Ian R. Reid, M.D., Pierre Delmas, M.D., Ph.D., Holly B. Zoog, Ph.D., Matt Austin, M.S., Andrea Wang, M.A., Stepan Kutilek, M.D., Silvano Adami, M.D., Ph.D., Jose Zanchetta, M.D., Cesar Libanati, M.D., Suresh Siddhanti, Ph.D., and Claus Christiansen, M.D., for the FREEDOM Trial*

- 7868 women (age 60-90)
- BMD T score -2.5 ~ -4.0
- 60mg denosumab or placebo SC q6M for 3yr
- 1st end point : new vertebral Fx
- 2nd end point : time to nonvertebral and hip Fx

NEJM 2009

Baseline characteristics

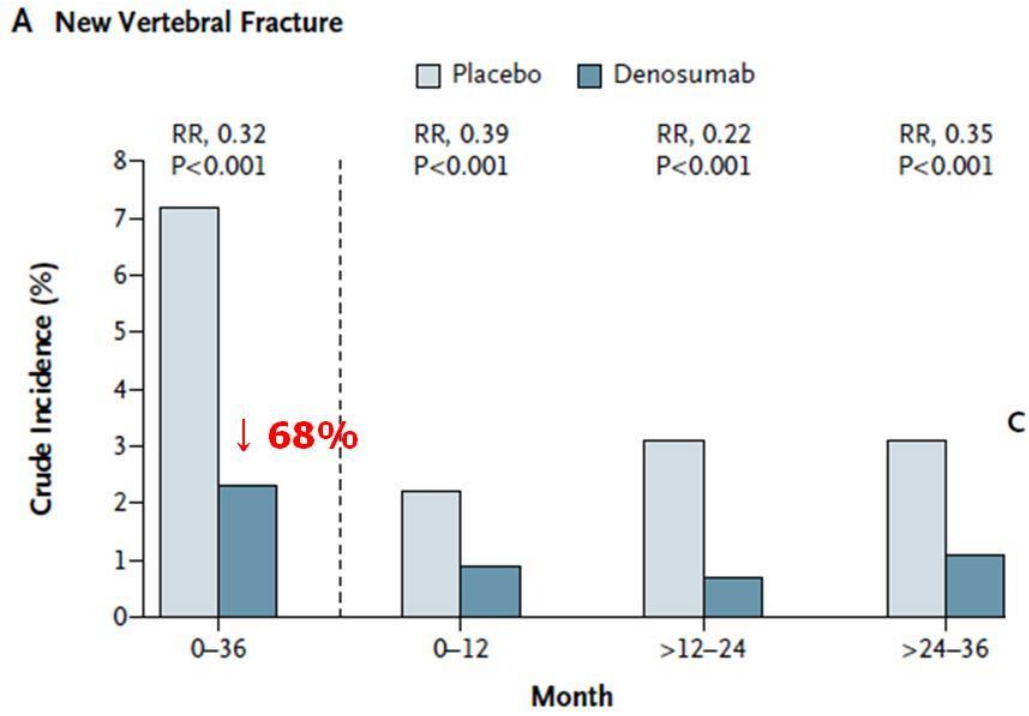
	Placebo	Denosumab
Randomized*	3,906	3,902
Age, years	72.3 (5.2)	72.3 (5.2)
Lumbar spine T-score	-2.8 (0.7)	-2.8 (0.7)
Total hip T-score	-1.9 (0.8)	-1.9 (0.8)
Femoral neck T-score	-2.2 (0.7)	-2.2 (0.7)
Prevalent vertebral fracture	23.4%	23.8%

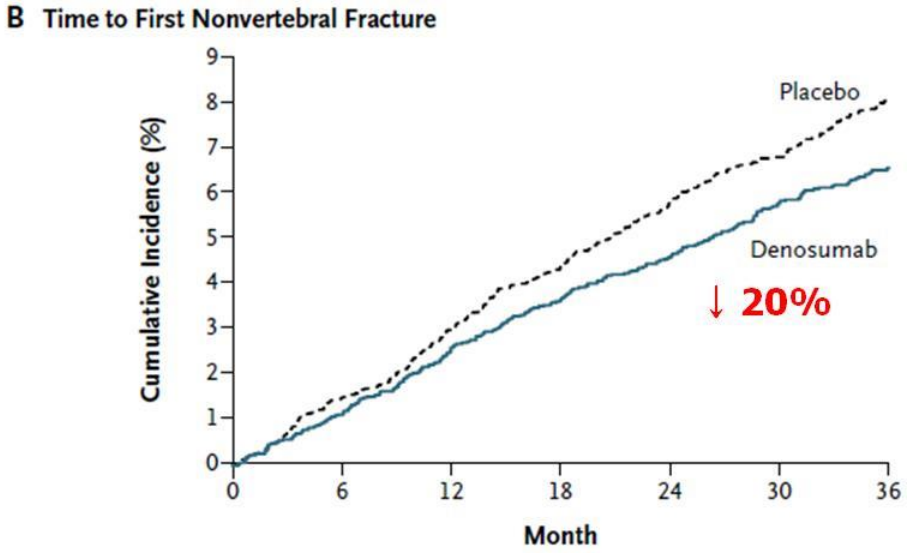
FIT : Prevalent vertebral fracture 70%

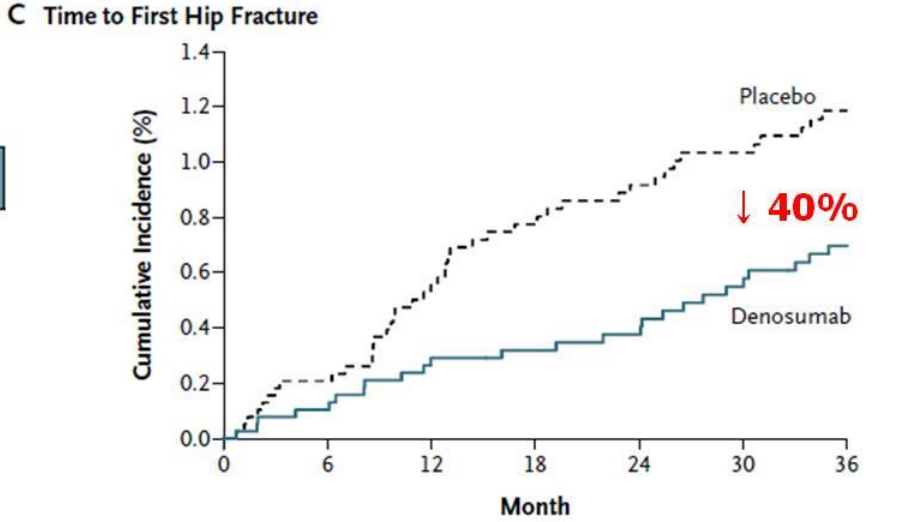
***Subjects included in the efficacy analysis; values are mean (SD) or percent.**

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

Incidence of Fractures

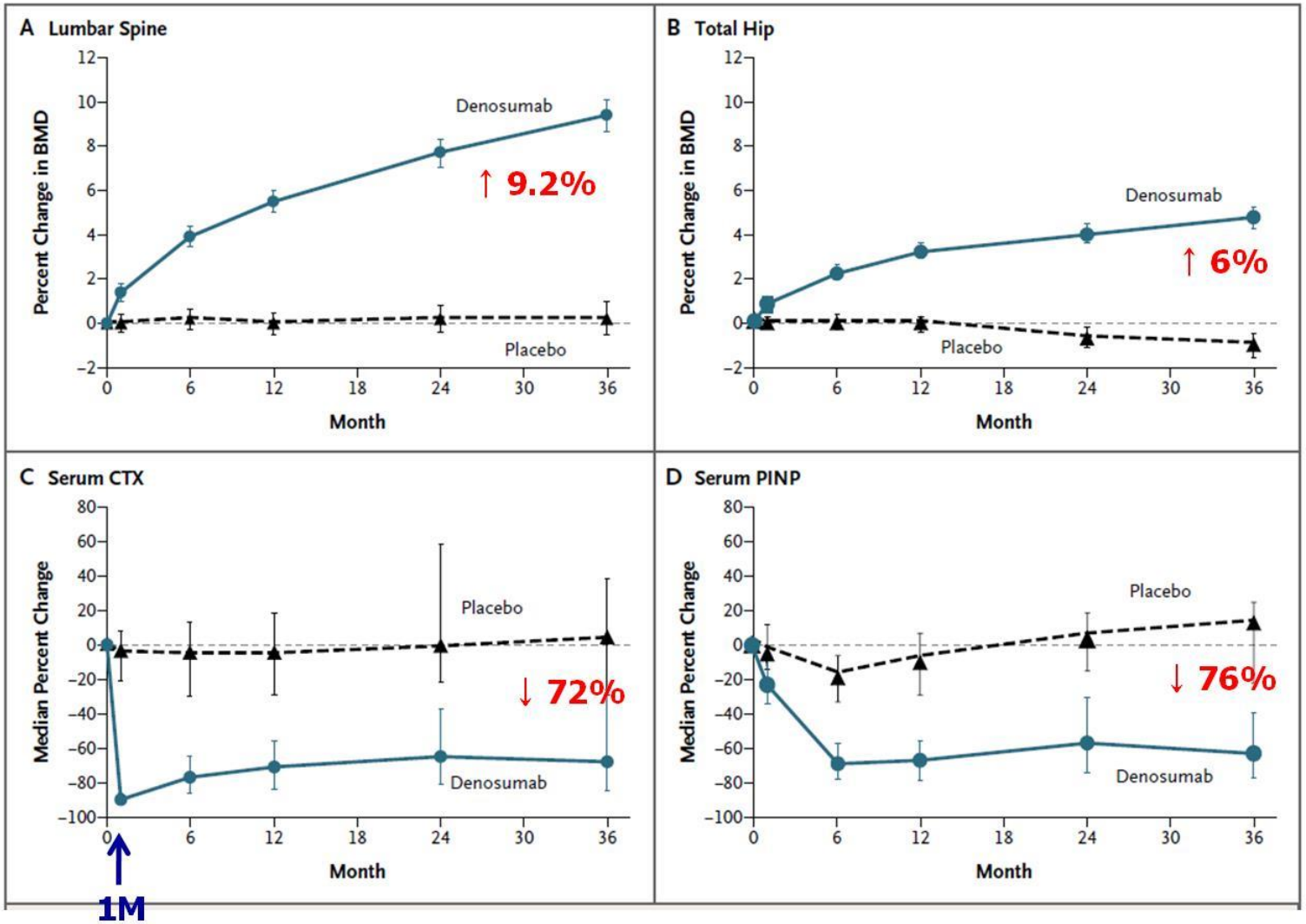






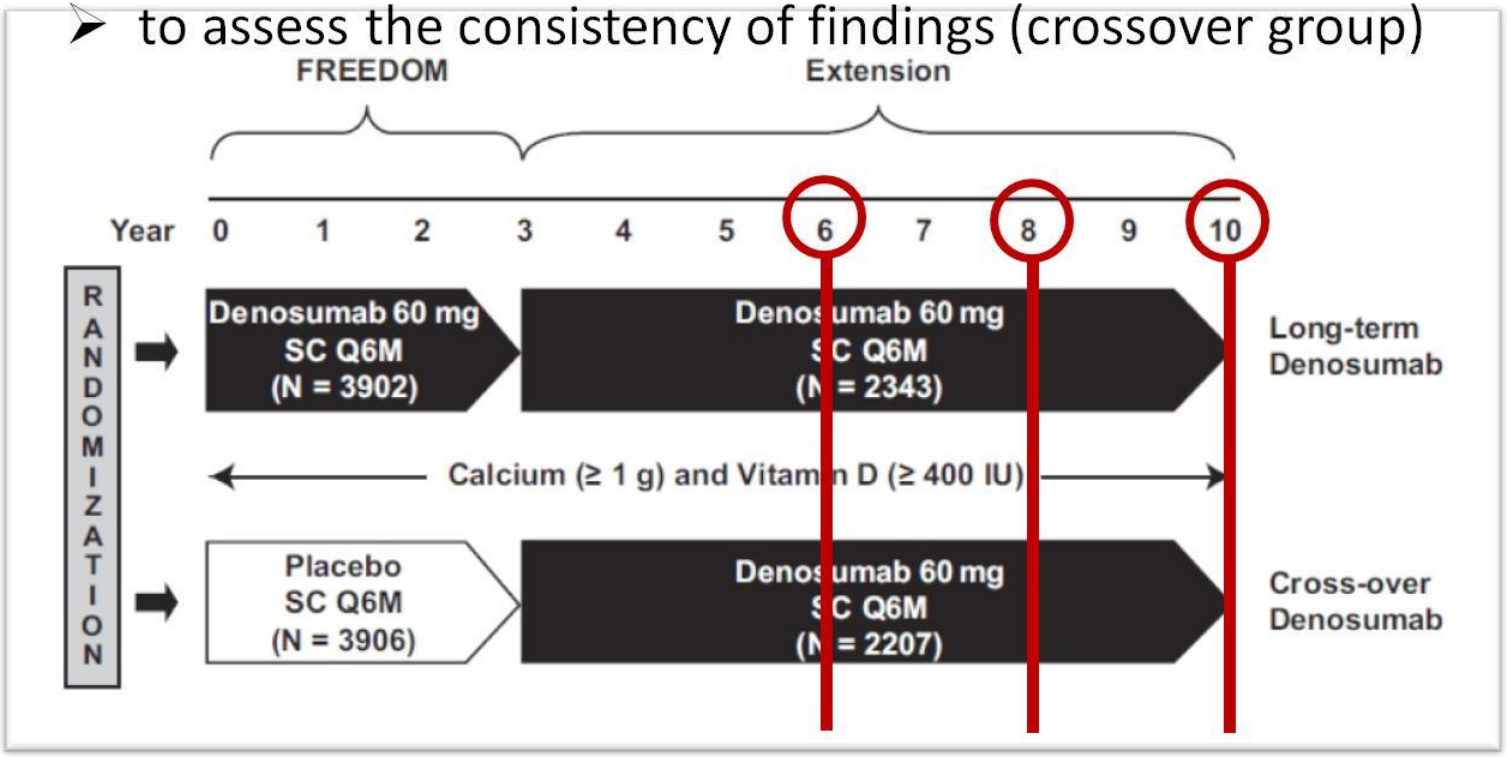
Percent Changes in BMD and BTM.

Rapid onset !

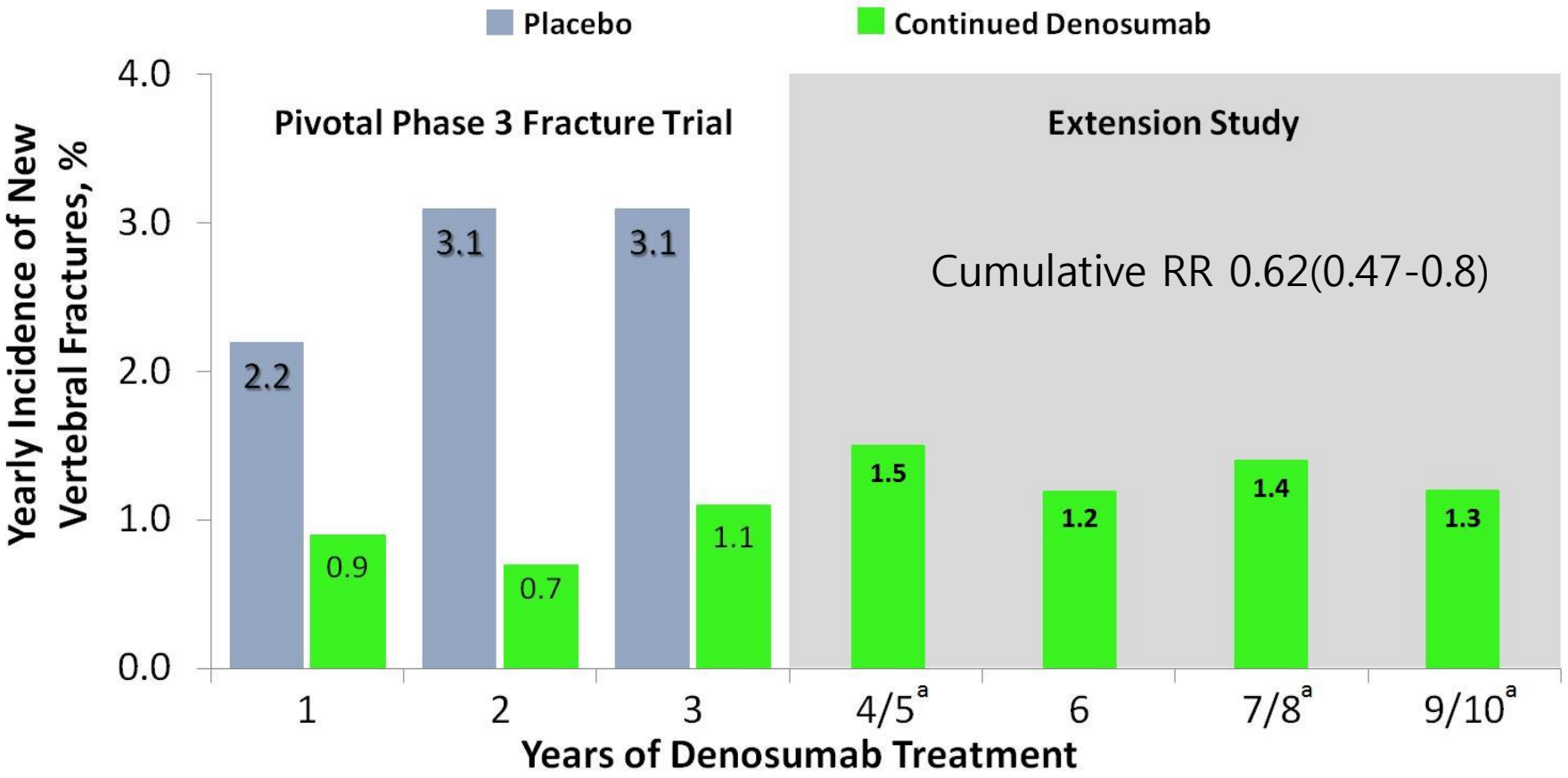


FREEDOM study - Extension

- Extension trial, 7 years, n=4550
- The purposes of the study extension
  - ➢ to evaluate the long-term safety and Efficacy (long term group)
  - ➢ to assess the consistency of findings (crossover group)



New Vertebral Fractures Through 10 Years

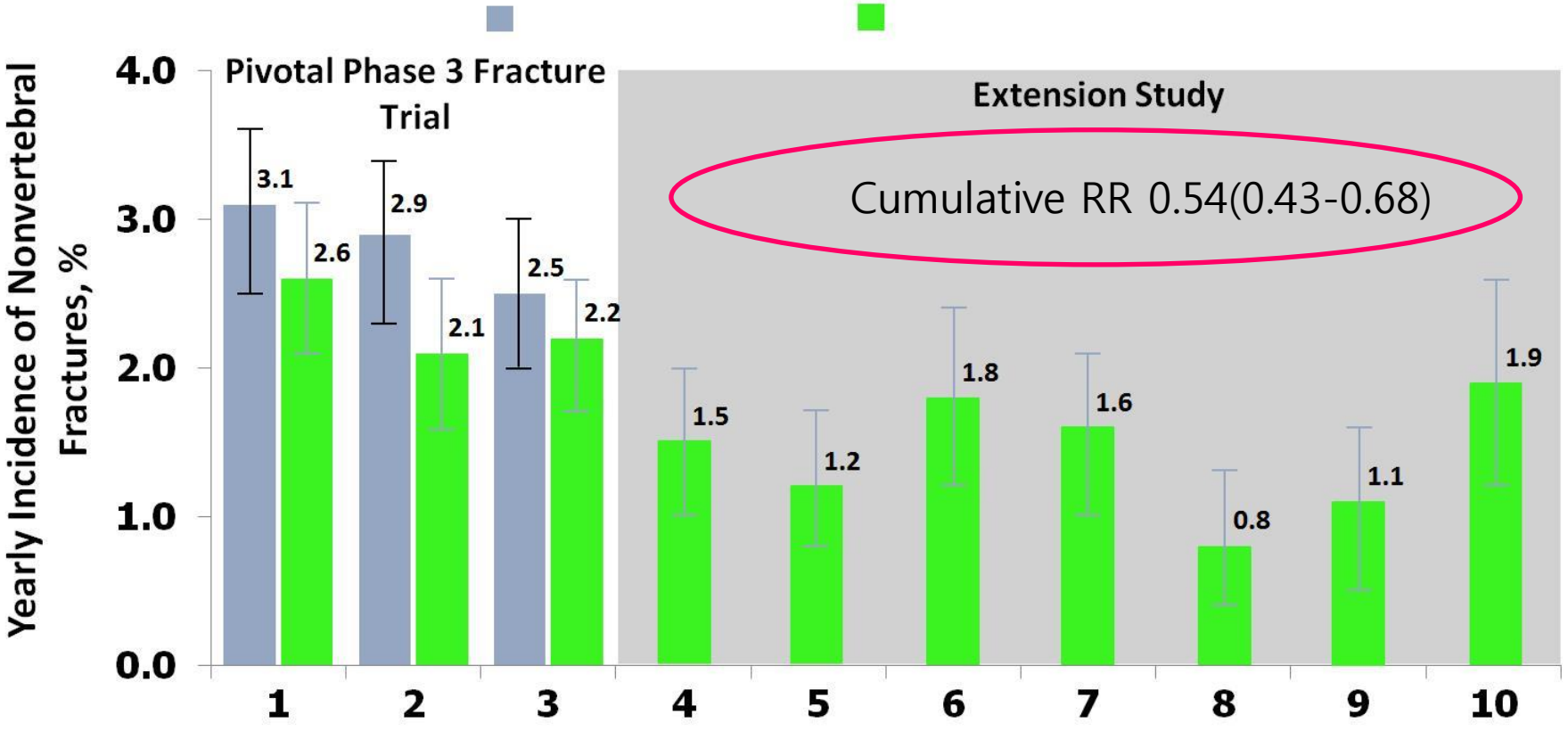


The primary endpoint of the open-label extension study was safety and tolerability of denosumab for up to 10 yrs. Fractures were collected as AEs in this study.

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

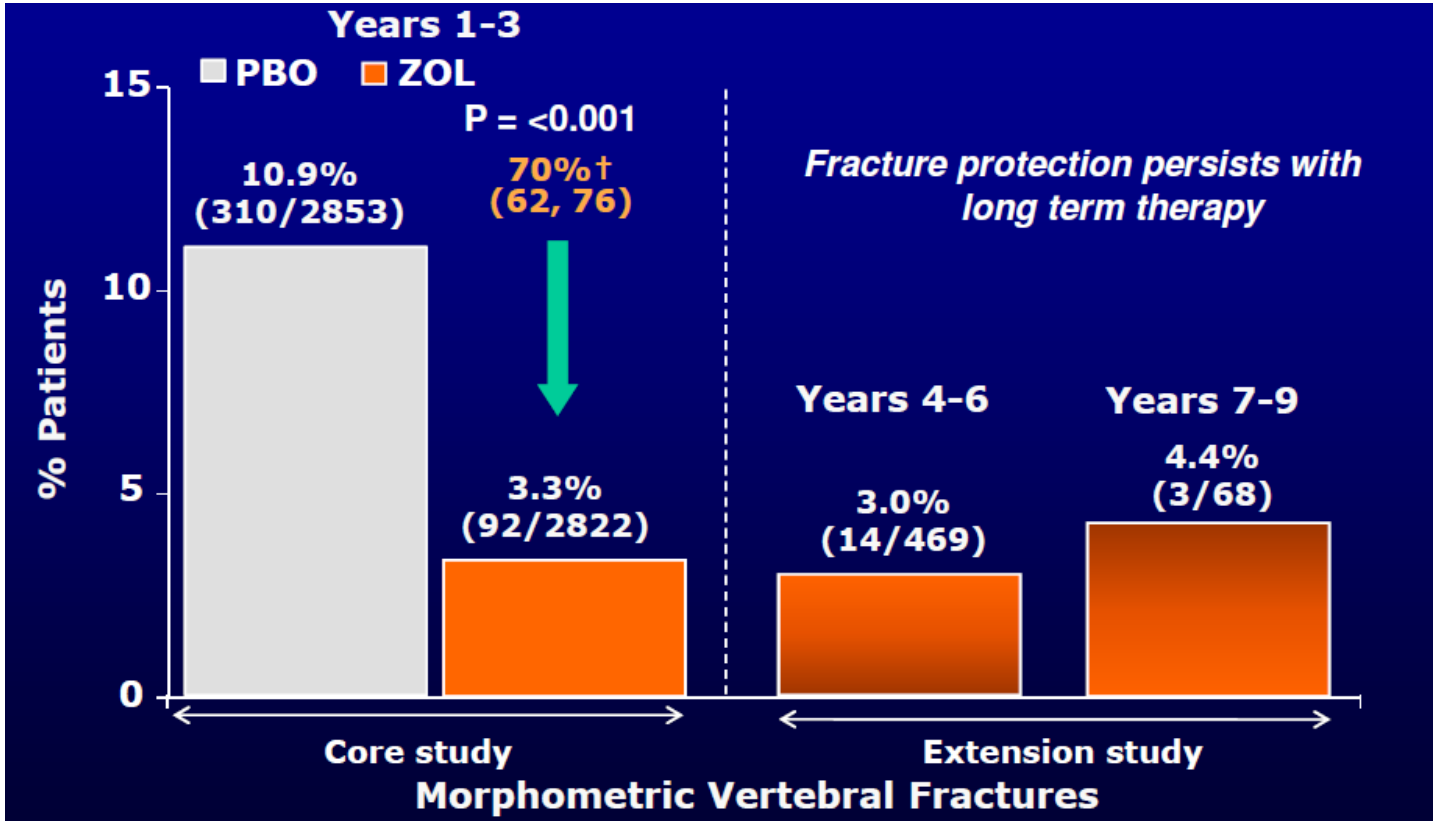
Adapted from: Bone HG, et al. Presented at: American Society of Bone and Mineral Research; October 12, 2015; Seattle, WA. Oral presentation LB-1157.

Nonvertebral Fractures Through 10 Years



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

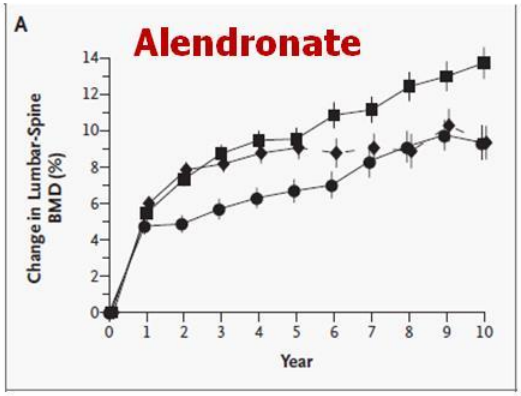
VFx with Zoledronic Acid

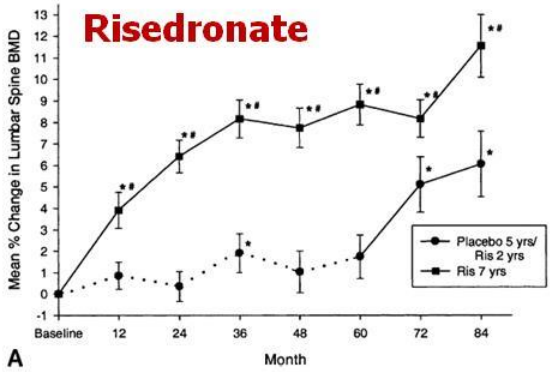


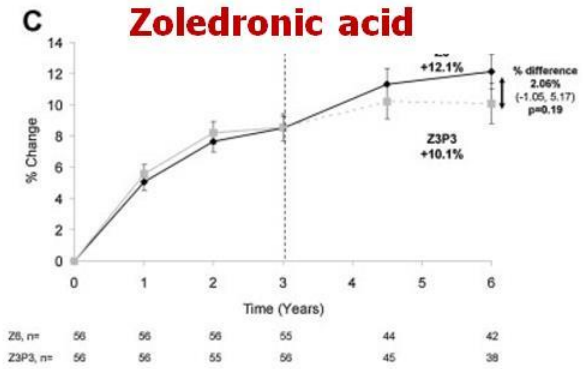
Black DM et al JBMR 2015

Limitation of BPN
Long term effect in BMD

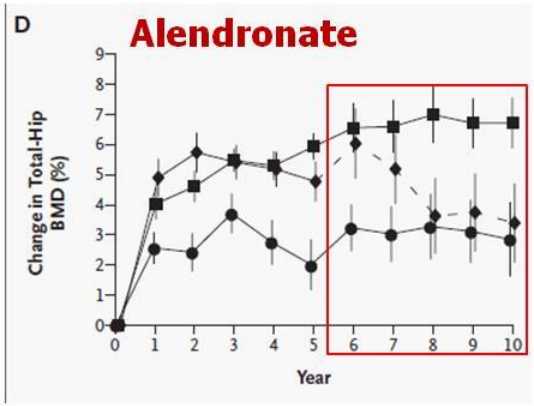
Continuous increase at lumbar spine BMD

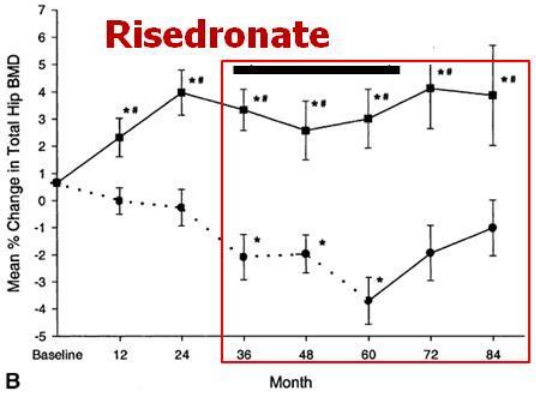


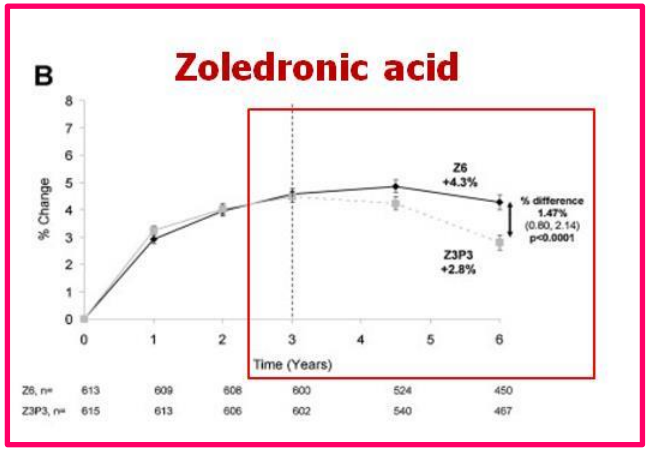




Plateau at total hip BMD

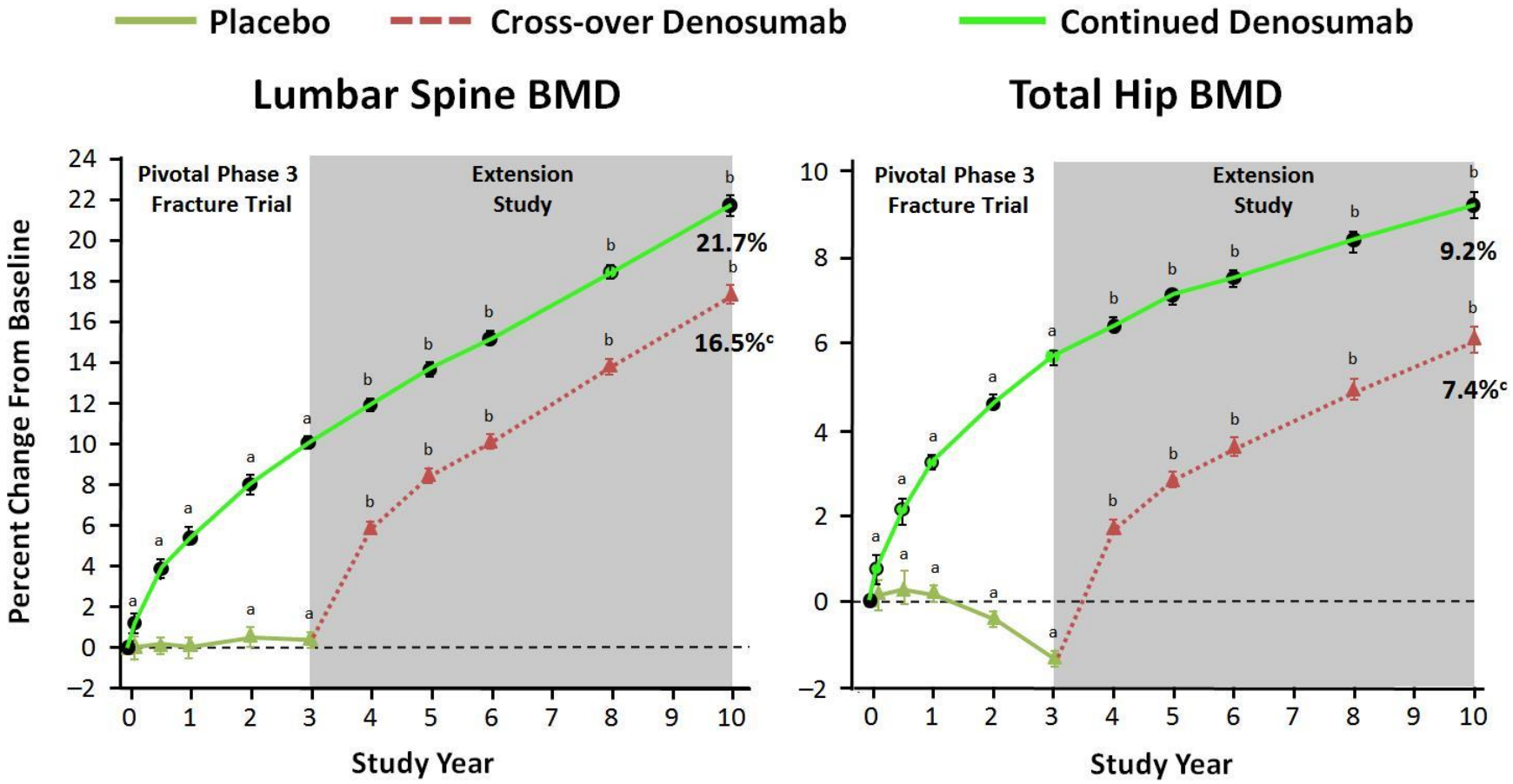






Bone HG et al. N Engl J Med 2004; 350:1189-1199
Mellstrom DD et al. Calcif Tissue Int 2004; 75:462–468
Black DM et al. JBMR 2012; 27:243–254

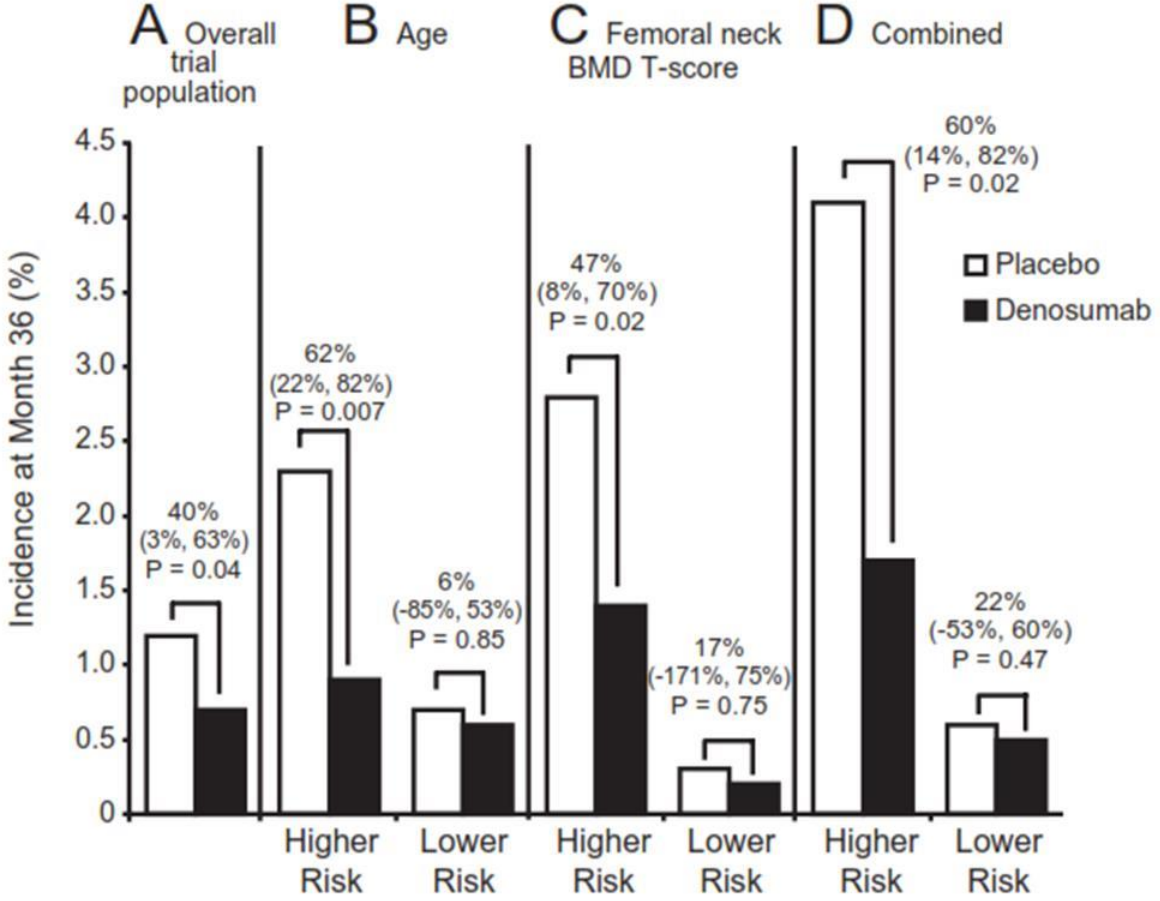
Change in Lumbar Spine and Total Hip BMD Through 10 Years



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

FREEDOM trial – post hoc analysis

- RRR in hip Fx with denosumab for 36 months



- B: Age ≥75 yrs
- C: FN BMD ≤-2.5
- D: age and BMD

Boonen S, J Clin Endocrinol Metab, 2011

Efficacy of Osteoporosis Therapy in Very Elderly

Drug	Fracture type	1-year results		3-year results	
		RRR	p-value	RRR	p-value
ALN (FIT) #	Vertebral	-	-	38%	<0.05
RIS (HIP) **	Hip	-	-	(20%)	ns
RIS (VERT & HIP) **	Hip	-	-	-	-
	Non-vertebral	-	-	(?)	ns
	Vertebral	81%	<0.001	44%	0.003
ZOL (HORIZON) #	Hip	(26%)	ns	(17%)	ns
	Non-vertebral	(15%)	ns	27%	0.002
	Vertebral	61%	0.009	66%	<0.001
DMAB (FREEDOM) #	Hip	-	-	62%	0.007
	Vertebral	-	-	64%	<0.001
TPT (FPT) #	Non-vertebral	(25%)	ns	-	-
	Vertebral	65%	<0.05	-	-

** ≥80 yrs, # ≥75 yrs

Boonen S et al. J Clin Endocrinol Metab 2011

Clinical Research Summary

STUDY/CITATION	STUDY DESIGN	STUDY POPULATION	ENDPOINTS & KEY RESULTS
PROLIA EFFICACY AND SAFETY VS. BISPHOSPHONATES IN POSTMENOPAUSAL OSTEOPOROSIS			
DECIDE Brown JP, *et al. J Bone Miner Res* 2009;24: 153–61. ALN vs Dmab	• 1 year, international, randomised, double-blind, double-dummy, active-controlled, non-inferiority study comparing the efficacy of Prolia vs. alendronate • 1,189 treatment-naïve† postmenopausal women received either Prolia 60mg SC Q6M or oral alendronate 70mg QWK for 12 months	• **Inclusion** – Post-menopausal women – BMD T-score of ≤ -2.0 at lumbar spine or total hip	• **Primary non-inferiority endpoint at 12 months:** – Prolia significantly ↑ BMD vs alendronate at 12 months: 3.5% vs 2.6% ($p < 0.0001$) • **Pre-specified superiority testing at 12 months:** – Significantly greater ↑ BMD in subjects treated with Prolia vs alendronate at all measured skeletal sites (all $p \leq 0.001$)
STAND Kendler DL, *et al. J Bone Miner Res* 2010; 25:72–81. ALN → Dmab	• 1 year, international, randomised, double-blind, double-dummy, active-controlled, non-inferiority study comparing the efficacy of transitioning from alendronate to Prolia vs. continued therapy with alendronate • 504 subjects were randomised to either Prolia 60mg SC Q6M, or oral alendronate 70mg QWK for 12 months	• **Inclusion** – Postmenopausal women previously treated with ALN 70 mg QW or equivalent for ≥6 months – BMD T-score of ≤ –2.0 to ≥ –4.0 at lumbar spine or total hip	• **Primary non-inferiority endpoint at 12 months:** – Total hip BMD ↑ by 1.9% at 12 months in subjects transitioned to Prolia vs a 1.05% ($p< 0.01$) in subjects continuing on alendronate therapy • **Pre-specified superiority testing at 12 months:** – Significantly greater ↑ BMD in subjects treated with Prolia vs alendronate at all measured skeletal sites (all $p \leq 0.05$)
TTR Roux C, *et al. Bone* 2014;58:48–54. ALN → RSN **TTI** ALN → IBN	• 1 year, international, randomised, open-label, parallel-group study comparing the efficacy of transitioning from alendronate to Prolia vs. risedronate in patients sub-optimally treated with alendronate • 870 subjects were randomised to either Prolia 60mg SC Q6M or oral risedronate 150mg QM for 12 months	• **Inclusion** – Postmenopausal women aged ≥ 55 years – ALN therapy (daily or weekly) ≥ 1 month and have stopped treatment or with insufficient adherence (OS-MMAS < 6)	• **Primary efficacy endpoint at 12 months:** – Prolia significantly ↑ BMD compared with risedronate at the total hip 2.0% vs 0.5% ($p<0.0001$) • **Secondary efficacy endpoints at 12 months:** – Prolia significantly ↑ BMD at femoral neck (1.4% vs 0%) and lumbar spine (3.4% vs 1.1%). $p<0.0001$ at all sites – 85.8% of risedronate-treated subjects received ≥ 24 tablets through 12 months, and 96.7% of Prolia-treated subjects received the 2 scheduled injections

DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus Alendronate
STAND, Study of Transitioning from Alendronate to Denosumab; TTR, Transition to Risedronate ; TTI, Transition to Ibandronate

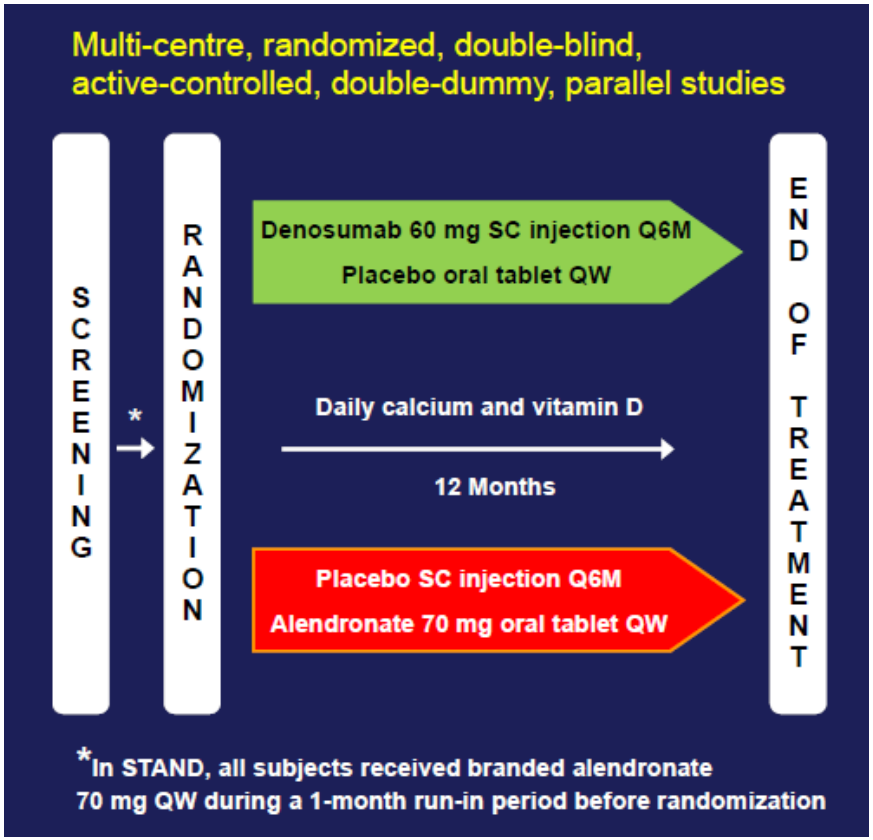
Head-to-head comparison studies

- DECIDE

- PMW who naïve to osteoporosis treatment (n = 1189)

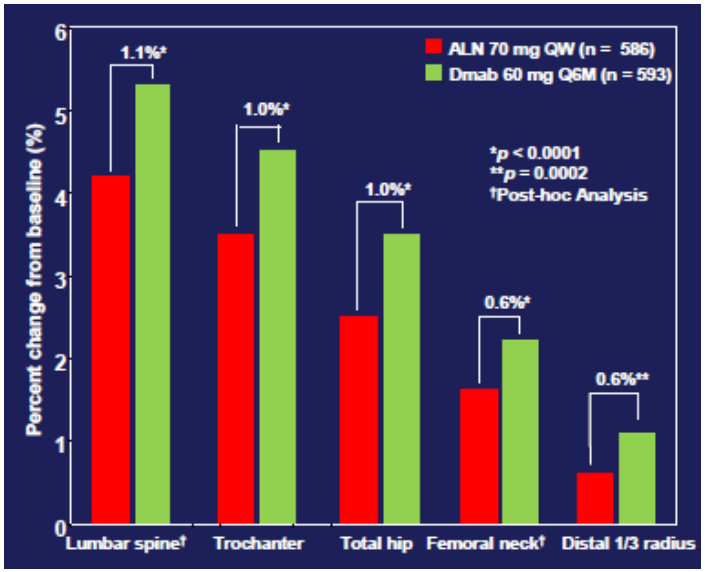
- T-score ≤–2.0 at the lumbar spine or total hip

Brown JP et al. J Bone Miner Res 2009

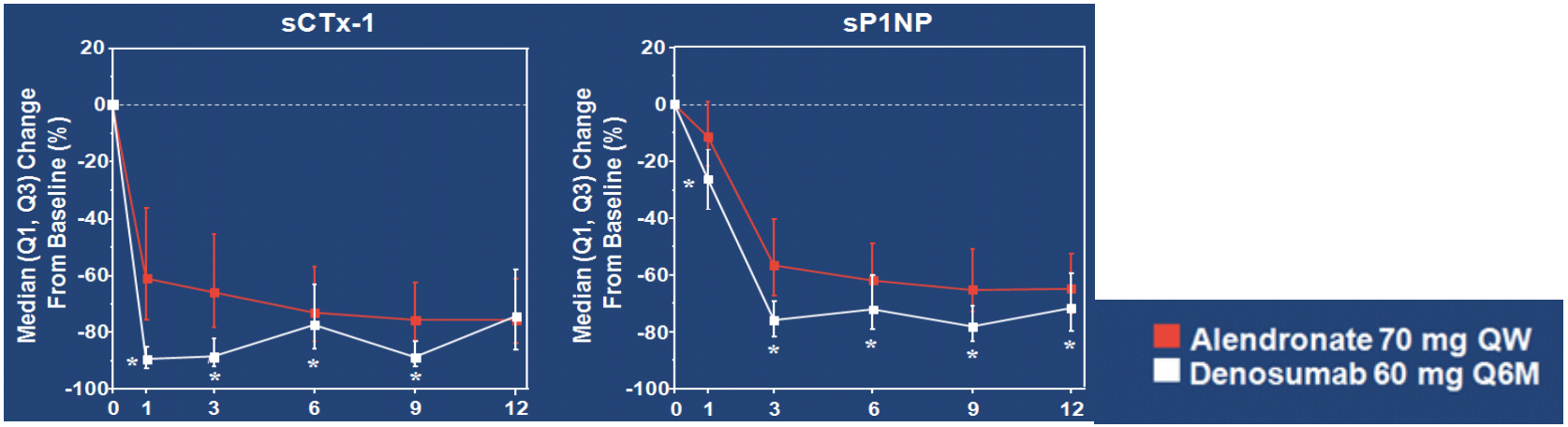


DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus Alendronate

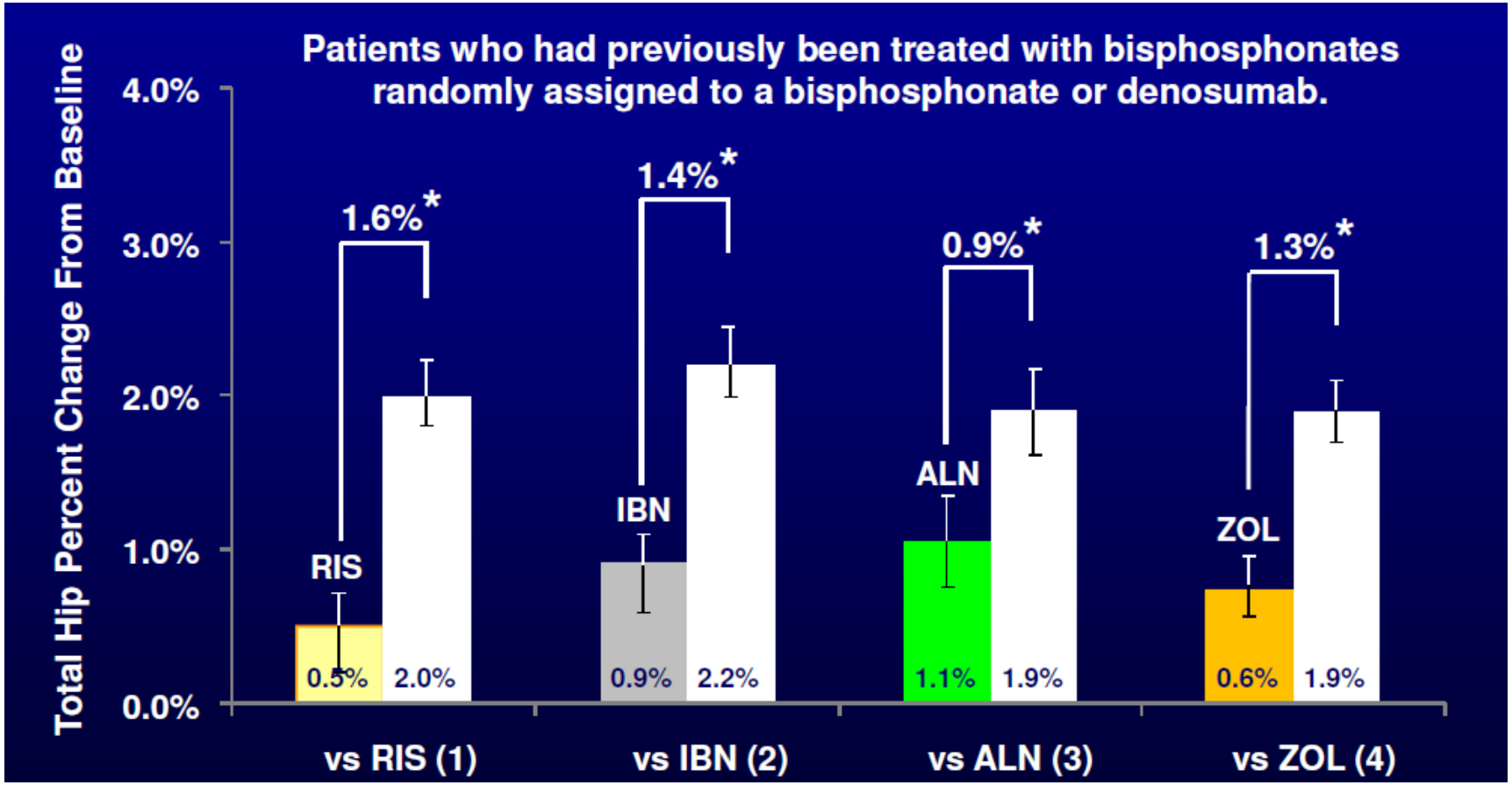
DECIDE Study : BMD and BTM



Greater BMD Increases With Dmab vs ALN in Subjects Naïve from BPs

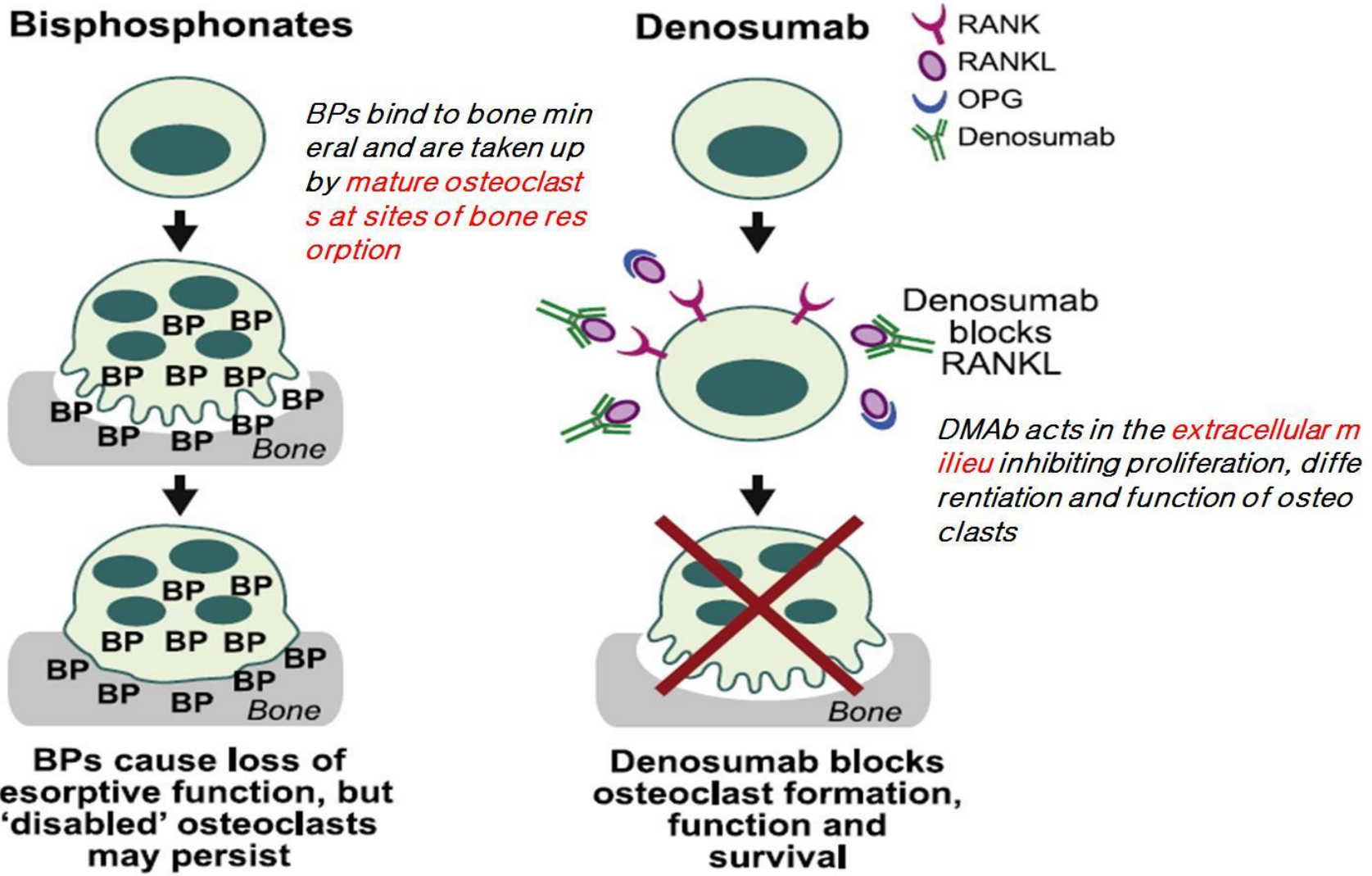


Switching from ALN to BPs vs Denosumab



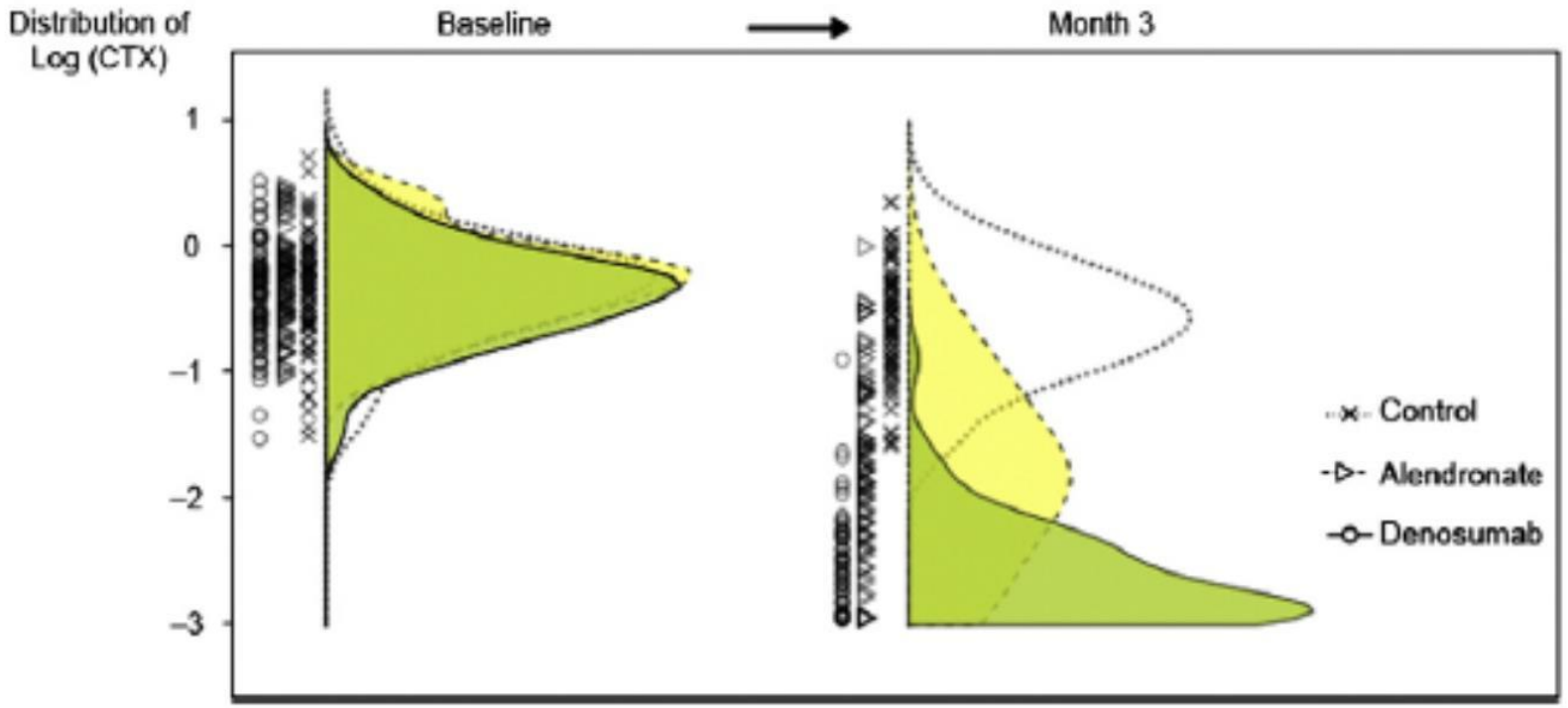
(1) TTR (2) TTI (3) STAND (4) TTZ * P<0.001 denosumab vs BP

Bisphosphonate and Denosumab: Different Mechanism of Action



Initial closure of remodeling space

Differing effect of Dmab and ALD on cortical and trabecular bone

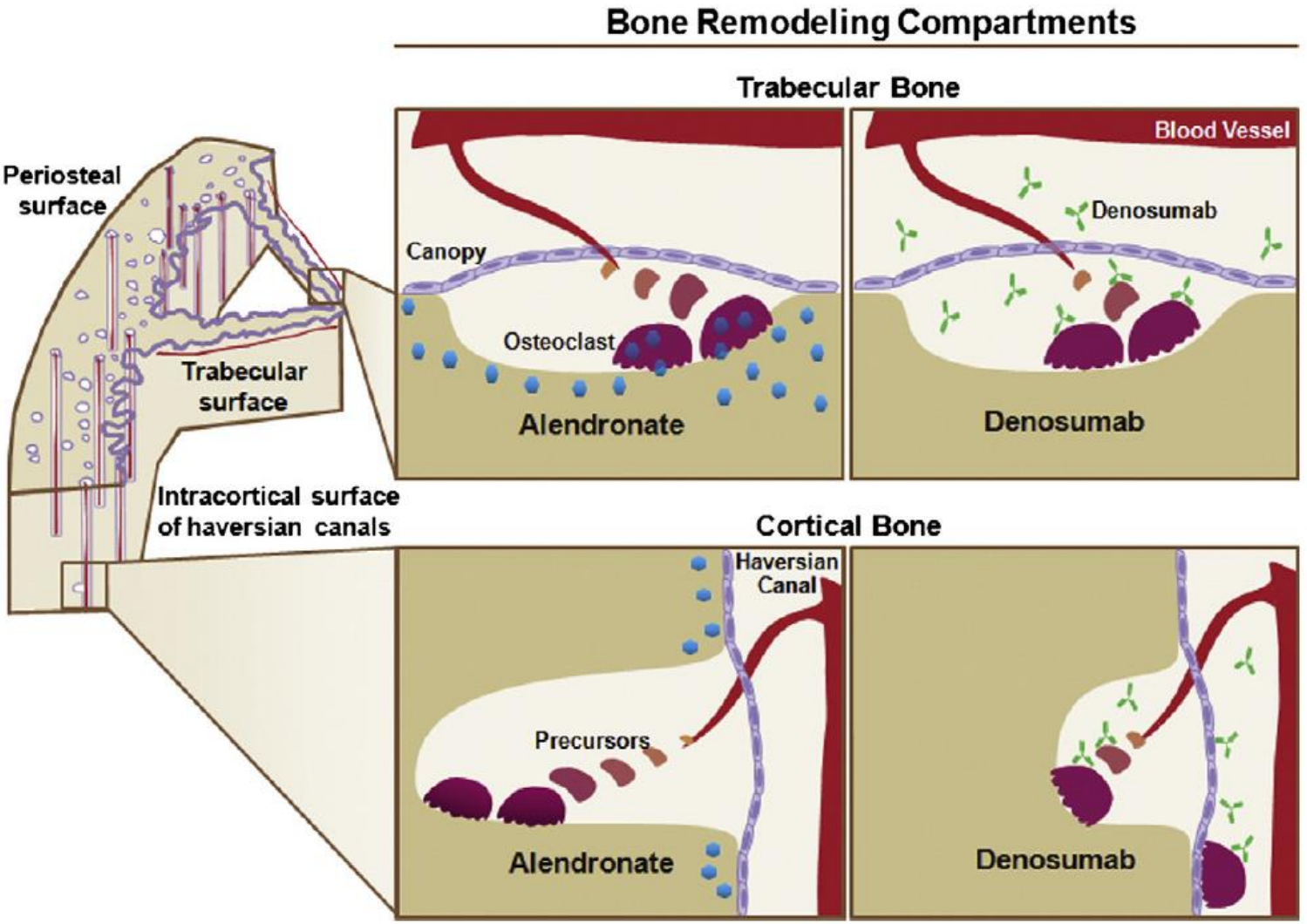


denosumab reduced remodeling more rapidly and more completely than alendronate as assessed by serum CTX

Zebaze RM et al. Bone. 2014 Feb;59:173-9.

Initial closure of remodeling space

Differing roles between alendronate and denosumab in bone remodelling



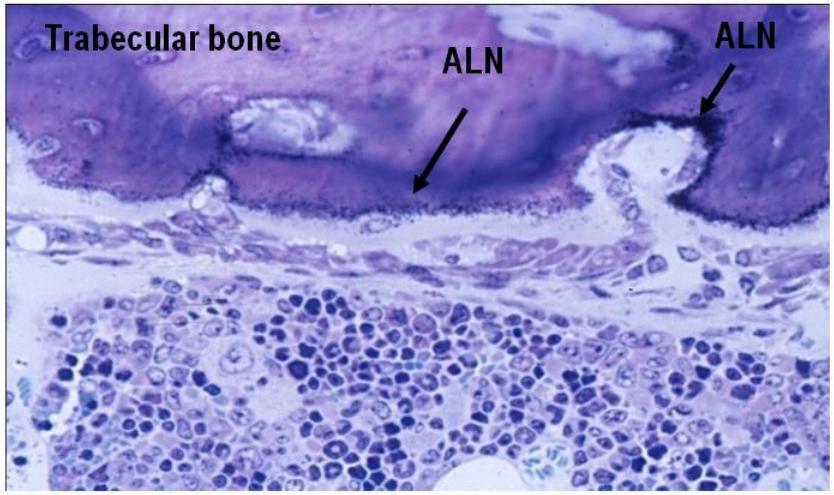
Zebaze RM et al. Bone. 2014 Feb;59:173-9.

Bisphosphonates and denosumab are distributed differently

Bisphosphonates are rapidly absorbed to bone surfaces at sites of bone turnover, thought to act primarily on trabecular bone[1-3]

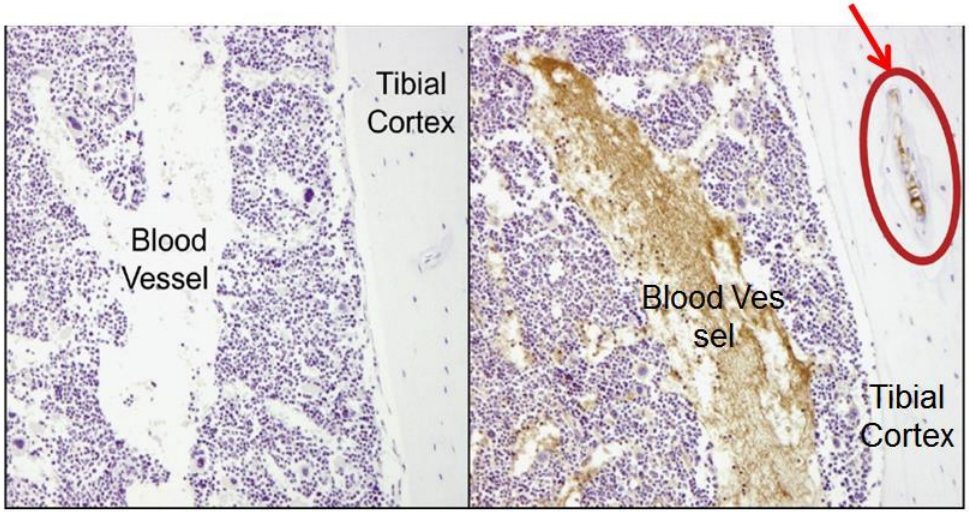
Denosumab circulates in blood and extracellular fluid including bone tissue, can reach both trabecular and cortical bone[1,4]

ALN on bone surfaces at 24 hrs



Control

Denosumab



1. Baron R et al, *Bone* 2011;48: 677-692. 2. Kimmel DB *J Dent Res 2007;*86:1022-1033
3. Masarachia P, et al. *Bone* 1996;19:281-290. 4. Kostenuik PJ, et al. *J Bone Miner Res* 2009;24:182-195

Properties of ideal osteoporosis treatment

- **Anti-fracture efficacy** at various skeletal sites, begins within months of starting therapy
- persists with **Long –term therapy**
- Mode of administration and treatment interval translate into **patient's adherence**
- **High safety margin**, both skeletal and extra skeletal

- But, …. wane when treatment is stopped….even with BPs

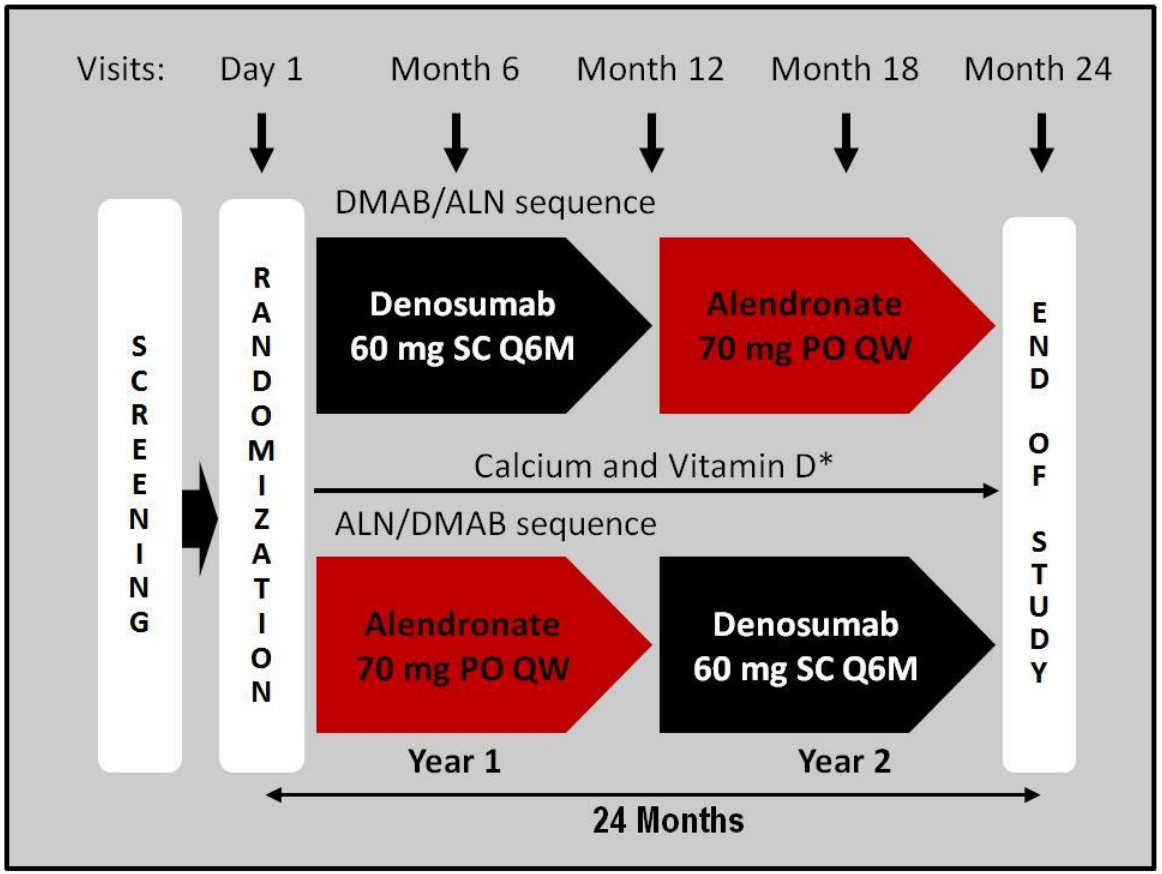
Clinical Research Summary

STUDY/CITATION	STUDY DESIGN	STUDY POPULATION	ENDPOINTS & KEY RESULTS
PREFERENCE, SATISFACTION AND ADHERENCE			
DECIDE/STAND Preference Pooled post-hoc analysis Kendler DL, *et al.* *Osteoporos Int* 2010;21:837-46.	• Patient Satisfaction Questionnaires (PSQ) were completed by subjects in STAND (N=504) and DECIDE (N=1189): double-blinded phase 3 head-to-head randomised controlled trials comparing Prolia 60mg SC Q6M with oral alendronate 70mg QWK • Patients were asked to complete the PSQ after 12 months of treatment or upon study discontinuation	• **DECIDE inclusion criteria** – Postmenopausal women with BMD T-score of ≤ -2.0 at lumbar spine or total hip • **STAND inclusion criteria** – Postmenopausal women previously treated with ALN 70 mg QW or equivalent for ≥6 months – BMD T-score of ≤ –2.0 to ≥ –4.0 at lumbar spine or total hip	• **Patient preference as assessed by the PSQ:** – Significantly more patients preferred the 6-month injection (65% of Prolia treated group; 63% of alendronate treated group) vs. weekly tablet • **Satisfaction:** – Significantly more patients in both the Prolia (64% vs 16%) and alendronate (63% vs 16%) treated groups were more satisfied with the 6-month injection vs the weekly tablet
DAPS Freemantle N, *et al.* *Osteoporos Int* 2012;23:317-26.	• 2 year, randomised, open-label, cross-over study of 250 postmenopausal women to compare compliance†, persistence‡ and adherence§ between Prolia 60mg SC Q6M and oral alendronate 70mg QWK • Patients received either Prolia or alendronate for 1 year, and were then switched over to the alternate therapy for another year	• **Inclusion criteria** – Postmenopausal women ≥ 55 years with BMD T-score of ≤ –2.0 to ≥ –4.0 at the spine, hip, or femoral neck	• **Adherence after 1st year:** – 88% vs 77% for Prolia and alendronate respectively (p=0.026) • **Persistence and preference after 2nd year:** – After cross-over at 24 months (all patients had received 12 months of denosumab and 12 months of alendronate), patients had a 91% lower relative risk of non-persistence with Prolia (p<0.001) • 92.4% of the 198 subjects who expressed a preference between treatments, expressed a preference for 6-monthly SC Prolia injection over once weekly alendronate tablets (p<0.001)

DECIDE, Determining Efficacy: Comparison of Initiating Denosumab versus Alendronate ;
STAND, Study of Transitioning from Alendronate to Denosumab; DAPS, Denosumab Adherence Preference Satisfaction.

DAPS Study Design

Denosumab Adherence Preference Satisfaction



Study population

- Postmenopausal women ≥ 55 years
- BMD –2.0 ≥ T-scores ≥ –4.0 at the spine, hip, or femoral neck

Objectives

- To evaluate adherence (including compliance and persistence)
- To also evaluate patient treatment beliefs, preference, satisfaction, and bother

Primary endpoint

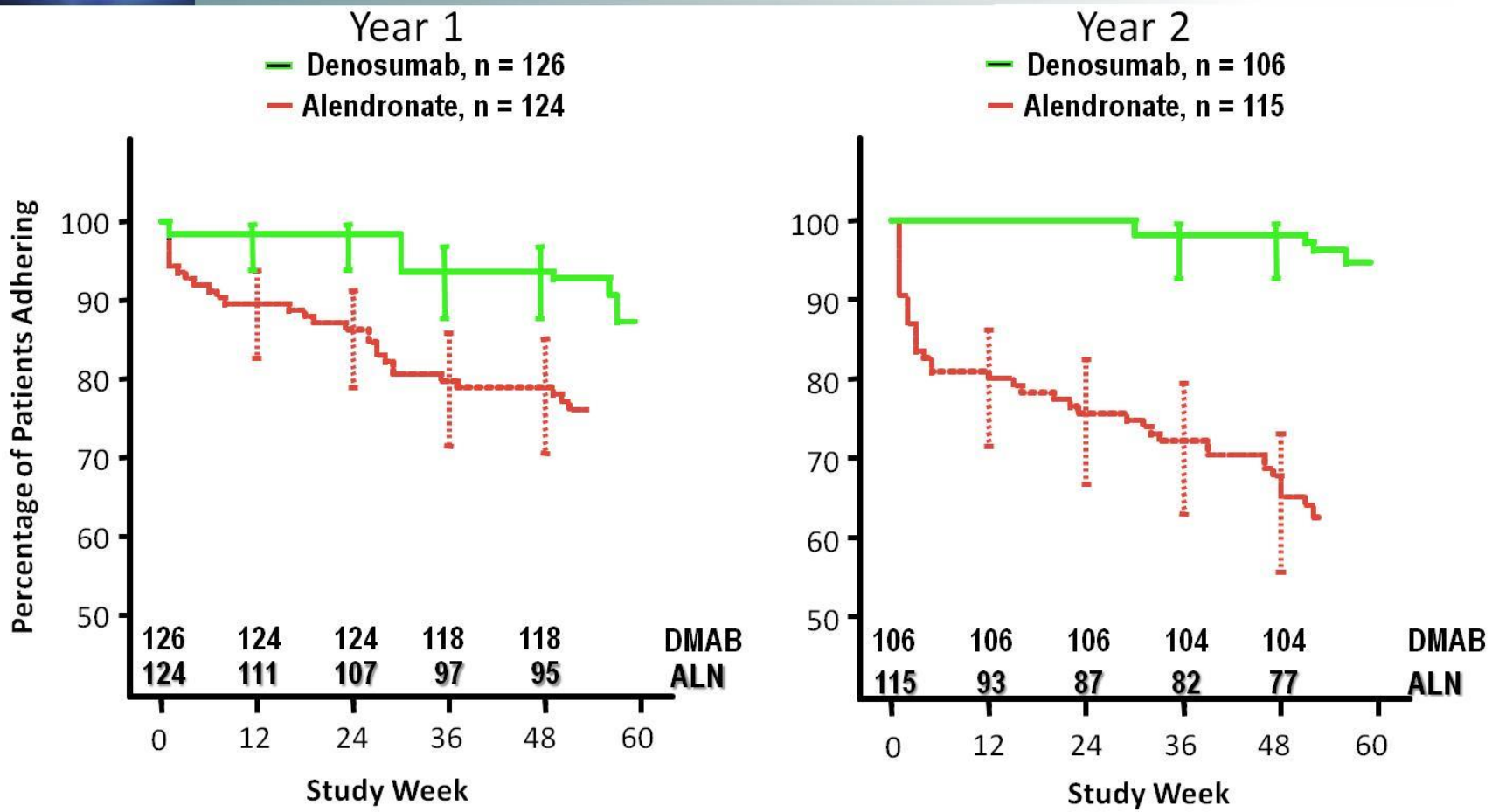
- Adherence during the first year

- **Open-label, randomized, cross-over study**

*All patients were instructed to take daily supplements of ≥ 1,000 mg calcium and ≥ 400 IU vitamin D.
DMAB = denosumab; ALN = alendronate; SC = subcutaneous; Q6M = once every 6 months; PO = by mouth ; QW = once a week; BMD = bone mineral density

Freemantle N, et al. *Osteoporos Int*. 2012;23:317-326.

DAPS : Time to Treatment Nonadherence



For each treatment group, time points with > 95% cumulated patients were excluded.

Adapted from: Freemantle N, et al. *Osteoporos Int.* 2012;23:317-326.

Properties of ideal osteoporosis treatment

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Effects of Denosumab on Fracture by Level of Kidney Function

Jamal SA et al., JBMR 2011

Effect on Fractures

	Stage 4 CKD by CG			Stage 3 CKD by CG			Stage 2 CKD by CG			Stage 1 CKD by CG		
	Placebo	DMAb	Odds ratio	Placebo	DMAb	Odds ratio	Placebo	DMAb	Odds ratio	Placebo	DMAb	Odds ratio
Vertebral	3/33	1/31	0.31 (0.02–5.08)	92/1309	38/1332	0.38 (0.26–0.59)	137/1952	34/1924	0.23 (0.15–0.34)	32/394	13/413	0.33 (−0.16–0.66)
Nonvertebral	2/37	1/36	0.51 (0.04–7.26)	106/1399	93/1418	0.88 (0.66–1.16)	157/2048	115/2021	0.69 (0.54 to 0.89)	28/418	29/424	0.89 (0.51–1.52)

Change in Serum Creatinine (mmol/L)

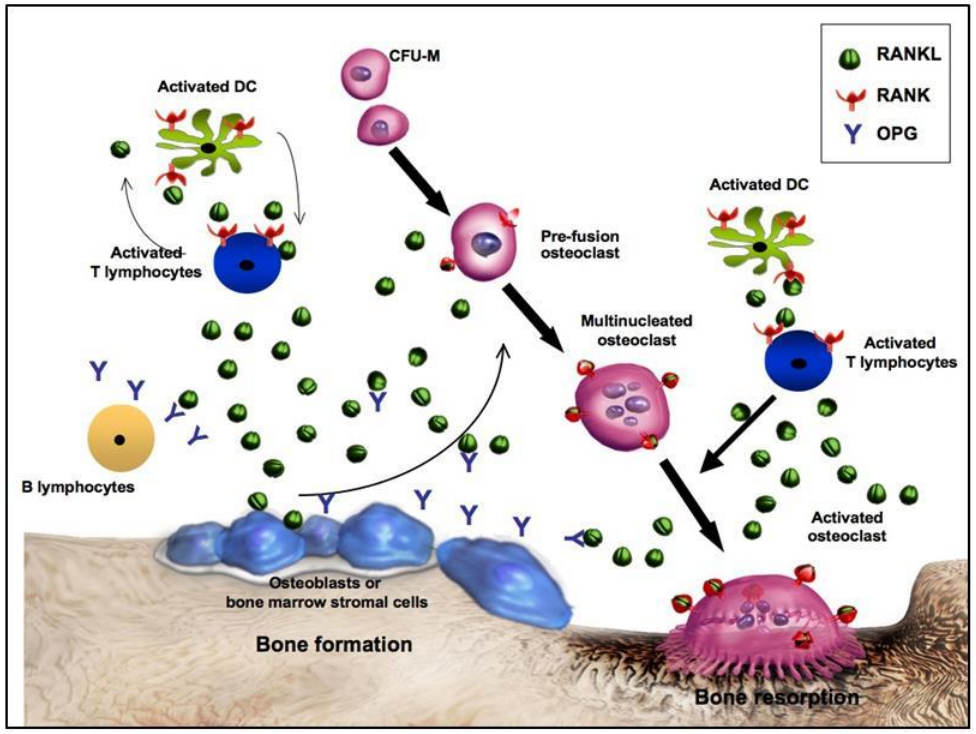
	Stage 4 CKD		Stage 3 CKD		Stage 2 CKD		Stage 1 CKD	
	Placebo	DMAb	Placebo	DMAb	Placebo	DMAb	Placebo	DMAb
Year 1	−6.9 (±22.9), $N=33$	−4.6 (±32.8), $N=28$	−2.3 (±11.4), $N=1280$	−2.3 (±10.7), $N=1302$	0.76 (±8.4), $N=1908$	0.76 (±7.6), $N=1896$	3.1 (±6.9), $N=387$	3.1 (±7.6), $N=404$
Year 2	1.53 (±32.0), $N=27$	6.1 (±33.6), $N=21$	1.53 (±11.4), $N=1176$	0.76 (±10.9), $N=1222$	2.3 (±7.6), $N=1792$	2.3 (±7.6), $N=1806$	3.81 (±6.1), $N=374$	5.34* (±7.6), $N=388$
Year 3	−8.4 (±23.6), $N=19$	−12.9 (±22.9), $N=16$	−3.1 (±12.9), $N=1104$	−1.53** (±12.9), $N=1141$	0.76 (±8.4), $N=1700$	1.53* (±8.4), $N=1732$	3.1 (±8.4), $N=357$	3.8 (±7.6), $N=372$

Incidence of Adverse Events

	Stage 4 CKD		Stage 3 CKD		Stage 2 CKD		Stage 1 CKD	
	Placebo, $N=37$	DMAb, $N=36$	Placebo, $N=1392$	DMAb, $N=1410$	Placebo, $N=2034$	DMAb, $N=2015$	Placebo, $N=410$	DMAb, $N=423$
Adverse events, *n* (%)	35 (94.6)	35 (97.2)	1307 (93.9)	1308 (92.8)	1875 (92.2)	1869 (92.8)	387 (94.4)	391 (92.4)
Serious adverse events, *n* (%)	13 (35.1)	15 (41.7)	351 (25.2)	392 (27.8)	509 (25)	502 (25.0)	99 (24.1)	95 (22.5)
Serious adverse events of infection, *n* (%)	1 (2.7)	4 (11.1)	49 (3.5)	60 (4.3)	66 (3.2)	79 (3.9)	17 (4.1)	16 (3.8)
Cardiovascular serious adverse events, *n* (%)	3 (8.1)	4 (11.1)	88 (6.3)	88 (6.3)	71 (3.5)	78 (3.9)	16 (3.9)	16 (3.8)

Adverse Events

Immune modulation ?
: increase risk of infection and malignancy



Common AEs
Back and extremity pain
Musculoskeletal pain
Hypercholesterolemia
Cystitis

Event	Denosumab (N=3886)	Placebo (N=3876)	P Value†
	no. (%)		
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of a study drug	192 (4.9)	202 (5.2)	0.55
Adverse events			
Infection	2055 (52.9)	2108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcemia	0	3 (0.1)	0.08
Osteonecrosis of the jaw	0	0	NA
Serious adverse events			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	178 (4.6)	0.74
Stroke	56 (1.4)	54 (1.4)	0.89
Coronary heart disease	47 (1.2)	39 (1.0)	0.41
Peripheral vascular disease	31 (0.8)	30 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Adverse events occurring in at least 2% of subjects‡			
Eczema	118 (3.0)	65 (1.7)	<0.001
Falling§	175 (4.5)	219 (5.7)	0.02
Flatulence	84 (2.2)	53 (1.4)	0.008
Serious adverse events occurring in at least 0.1% of subjects¶			
Cellulitis (including erysipelas)	12 (0.3)	1 (<0.1)	0.002
Concussion	1 (<0.1)	11 (0.3)	0.004

Exposure-adjusted Subject Incidence of Adverse Events
(Rates per 100 Subject-years)

	FREEDOM Years 1–3	Extension Years 1–7	
	Placebo (N = 3883)	Cross-over Denosumab (N = 2206)	Long-term Denosumab (N = 2343)
All AEs	156.1	96.8	97.0
Infections	30.7	20.7	19.9
Malignancies	1.6	2.0	2.0
Eczema	0.6	0.9	0.9
Hypocalcemia	< 0.1	< 0.1	< 0.1
Pancreatitis	< 0.1	< 0.1	< 0.1
Serious AEs	10.4	10.1	10.3
Infections	1.3	1.4	1.5
Cellulitis or erysipelas	< 0.1	< 0.1	< 0.1
Fatal AEs	0.8	0.8	0.8
Osteonecrosis of the jaw	0	< 0.1	< 0.1
Atypical femoral fracture	0	< 0.1	< 0.1

13 cases of ONJ and 2 atypical femoral fracture were reported through 10years

N = number of subjects who received ≥ 1 dose of investigational product. Treatment groups are based on the original randomized treatments received in FREEDOM. AEs co ded using MedDRA v13.0. Cumulative osteonecrosis of the jaw cases: 6 cross-over, 7 long-term. Cumulative atypical femoral fracture cases: 1 cross-over, 1 long-term.

JBMR®

Osteonecrosis of the Jaw in the United States Food and Drug Administration's Adverse Event Reporting System (FAERS)

Xiaoyan Zhang,[1]* Issam S Hamadeh,[2,3]* Shuang Song,[2] Joseph Katz,[4] Jan S Moreb,[5] Taimour Y Langaee,[2,3] Lawrence J Lesko,[1] and Yan Gong[2,3]

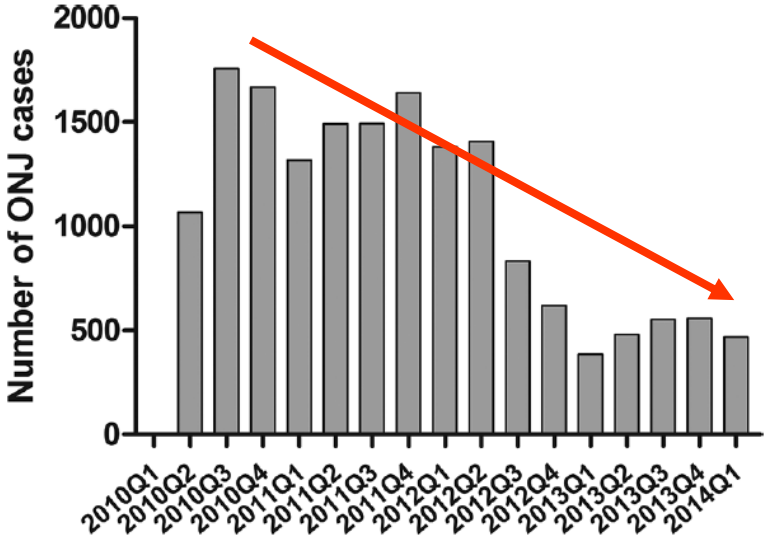


Fig. 1. The number of ONJ cases reported to FAERS by quarter from the first quarter of 2010 through the first quarter of 2014.

Table 2. Drugs Associated With ONJ and the Reporting Odds Ratios in FAERS

Drug	Drug class	OR	95% Confidence interval	*p* Value
Pamidronate	BP	498.9	(475.2–523.8)	<0.0001
Zoledronate	BP	171.7	(166.1–177.6)	<0.0001
Alendronate	BP	63.6	(61.6–65.7)	<0.0001
Clodronate	BP	33.0	(22.8–47.7)	<0.0001
Risedronate	BP	16.6	(15.4–17.8)	<0.0001
Denosumab	RANKL inhibitor	13.8	(13.0–14.7)	<0.0001
Sunitinib	Antiangiogenic	4.6	(4.2–5.1)	<0.0001
Bevacizumab	Antiangiogenic	4.5	(4.2–4.9)	<0.0001
Temsirolimus	m-TOR inhibitor	3.1	(2.2–4.6)	<0.0001
Sorafenib	Antiangiogenic	1.5	(1.2–1.9)	<0.0001
Everolimus	m-TOR inhibitor	1.4	(1.2–1.8)	0.0008
Pazopanib	Antiangiogenic	1.3	(0.7–2.5)	0.38
Axitinib	Antiangiogenic	0.8	(0.4–1.5)	0.49

OR = reporting odds ratio; BP = bisphosphonates; RANKL = human monoclonal antibody to the receptor activator of nuclear factor-κB ligand; m-TOR inhibitor = mammalian target of rapamycin inhibitor.

Incidence of atypical femur fractures

Incidence of atypical femur fractures in **naïve** patients
- **0.1 per 10,000** person-years (1 per 100,000 person-years)

Incidence of atypical femur fractures in patients on **BP** (Post-Marketing)
- **5.5 per 10,000** person-years (55 per 100,000 person-years)
- Incidence: rare

Incidence of atypical femur fractures in patients on **denosumab**
[2 cases in clinical trial, 4 post-marketing cases]
- **0.3 per 10,000** person-years (2.7 per 100,000 person-years)
- Incidence: very rare

Donnelly E et al. Curr Opin Support Palliat Care 2012, 6:348–354

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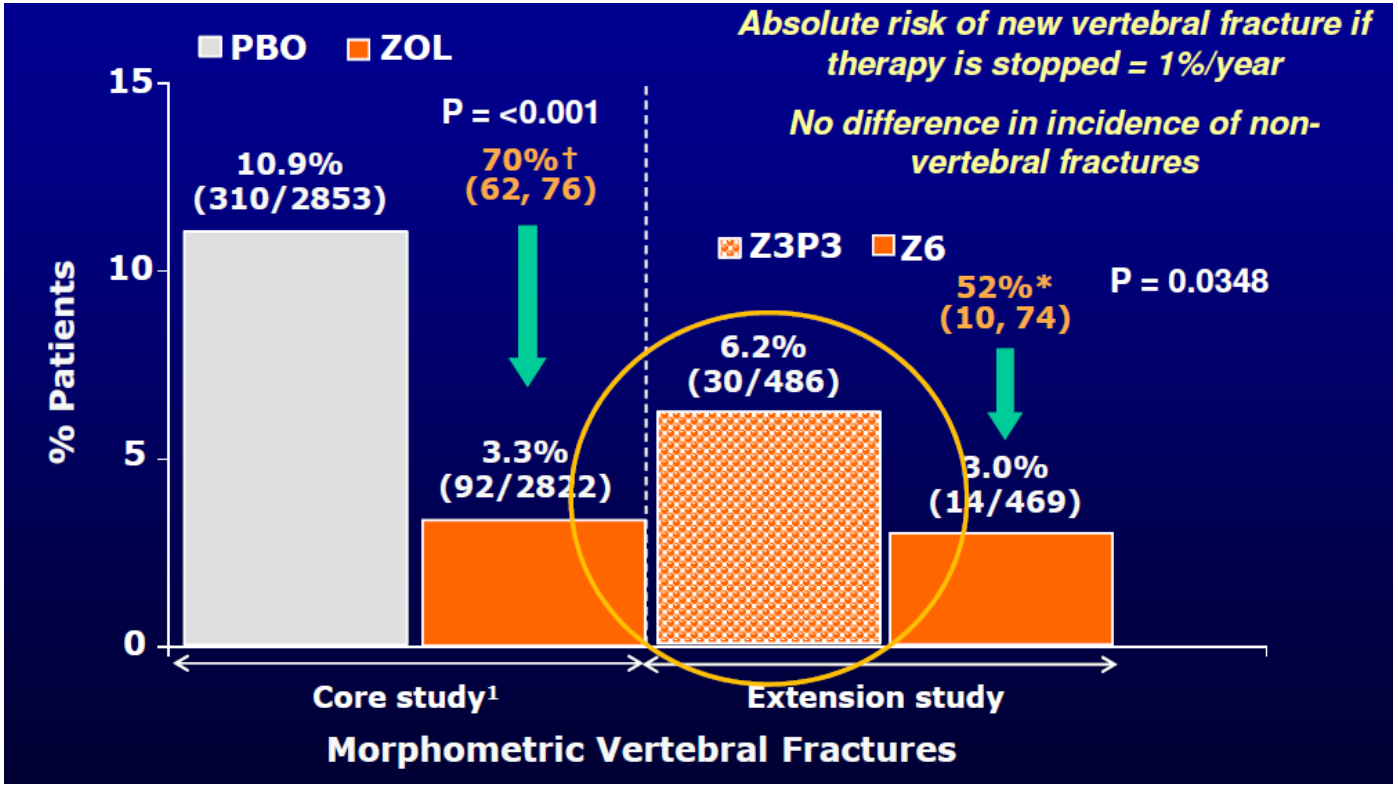
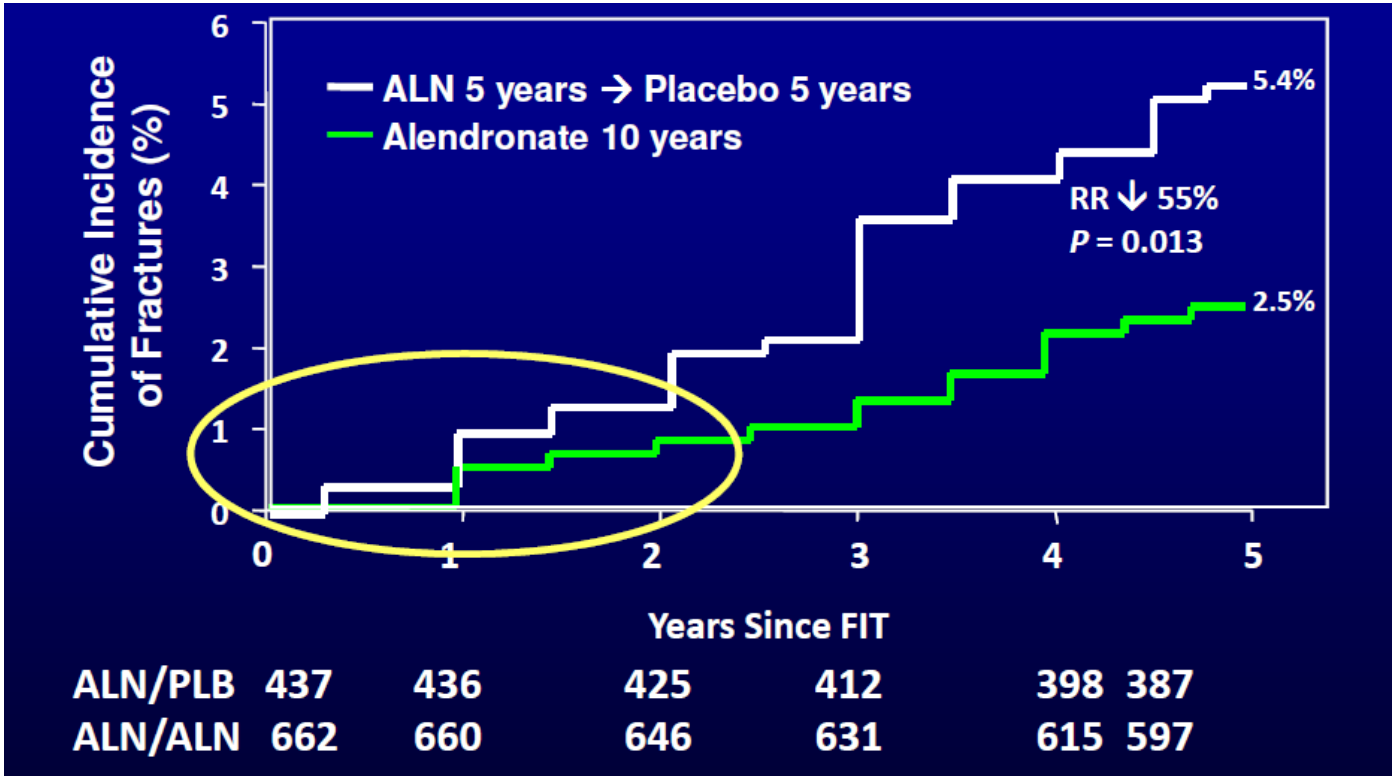
VFx after zoledronate stopping



Black DM et al. NEJM 2007

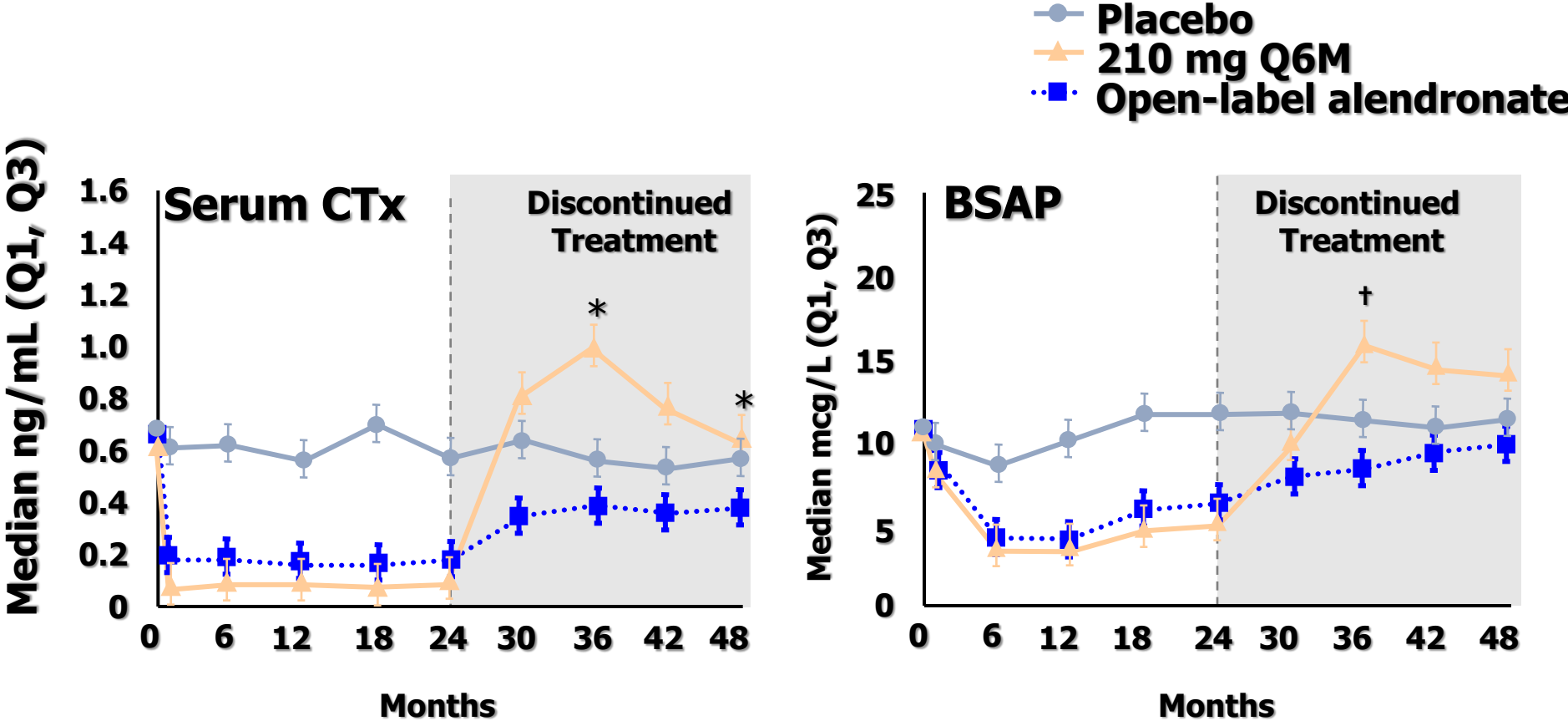
Clinical VFx in FLEX



Black DM et al. JAMA 2006

Discontinuing Denosumab: BTM

Phase 2 Study in Women With Low BMD

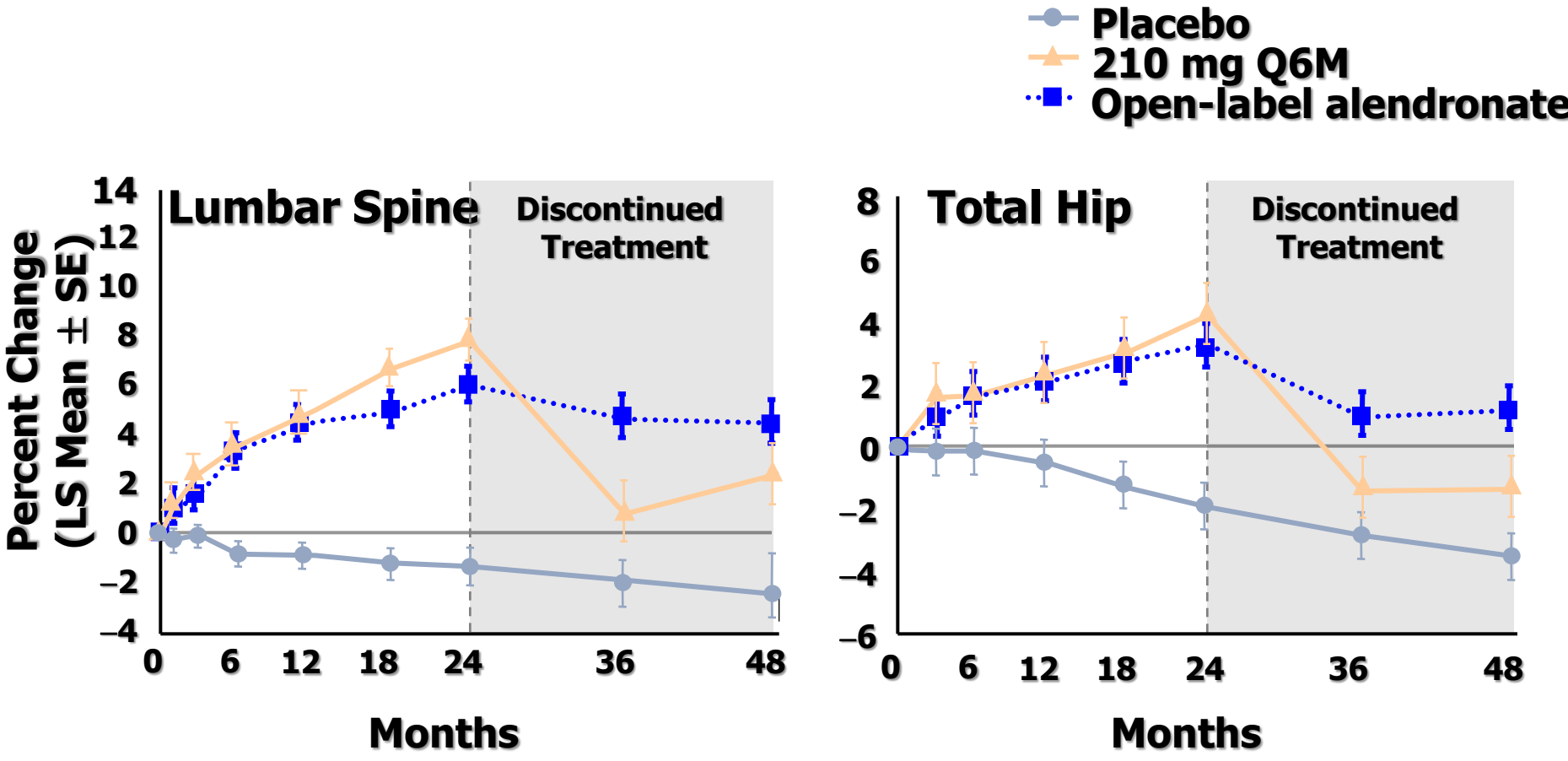


*P < 0.001 at month 36 and = 0.05 at month 48 vs placebo.
†P = 0.008 at month 36 vs placebo.

Adapted from Miller PD, McClung M et al. *Bone* 2008;43:222-29

Discontinuing Denosumab: BMD

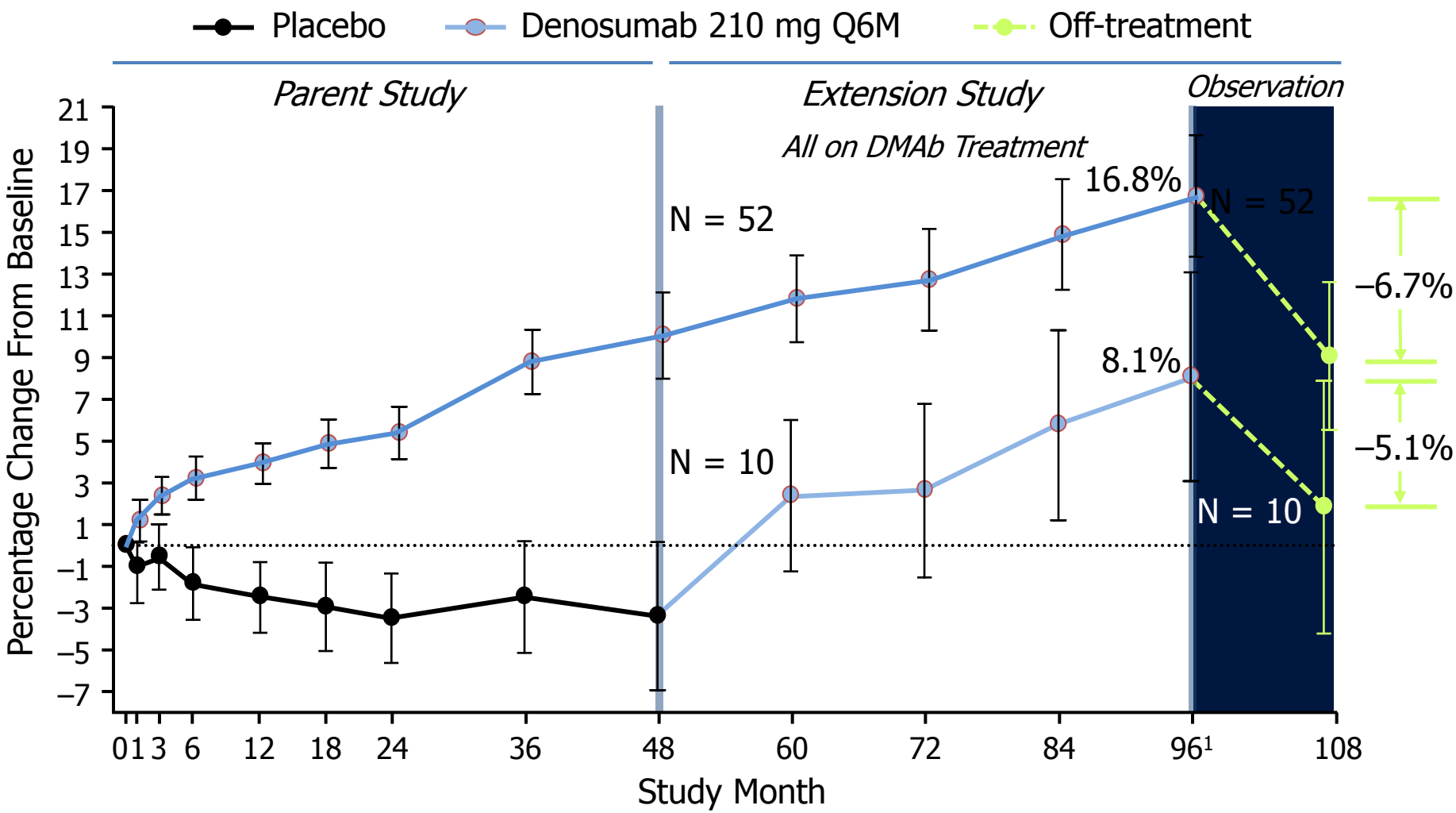
Phase 2 Study in Women With Low BMD



Adapted from Miller PD, McClung M et al. *Bone* 2008;43:222-29

Discontinuing Denosumab After 8 Years

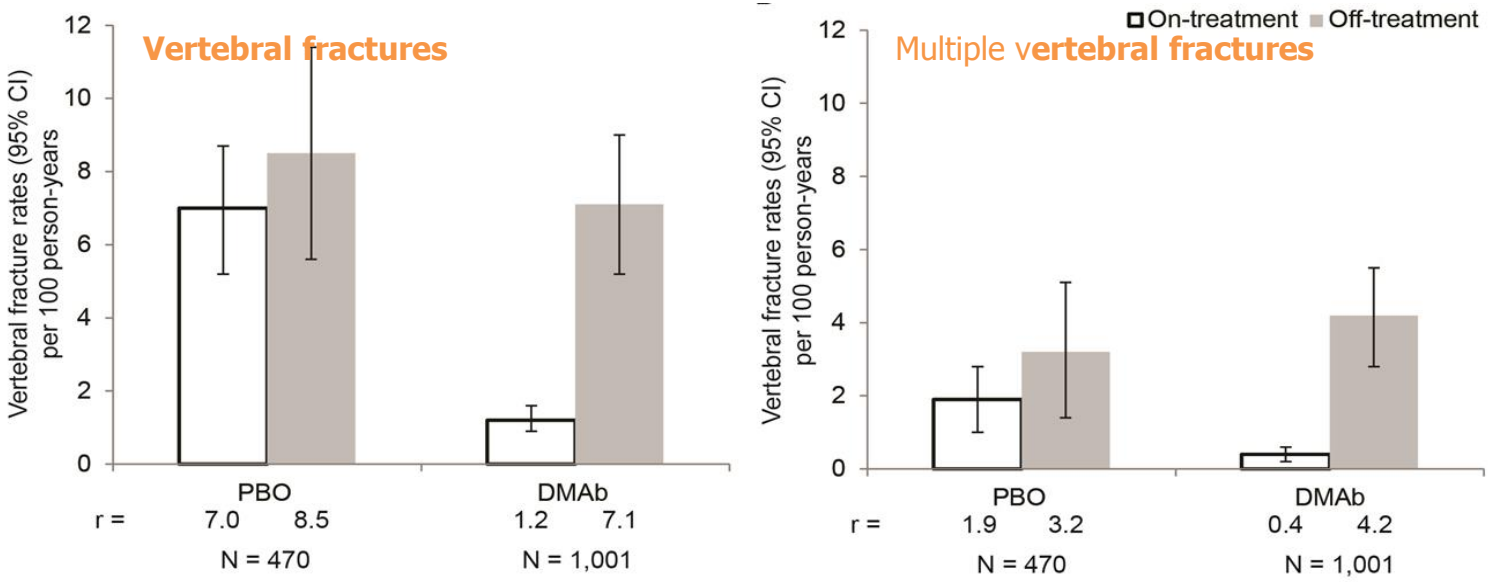
Lumbar Spine BMD



McClung M et al. *Osteoporos Int*. 2017 Jan 31. doi: 10.1007/s00198-017-3919-1

Vertebral Fractures After Discontinuing Denosumab or Placebo in FREEDOM Study

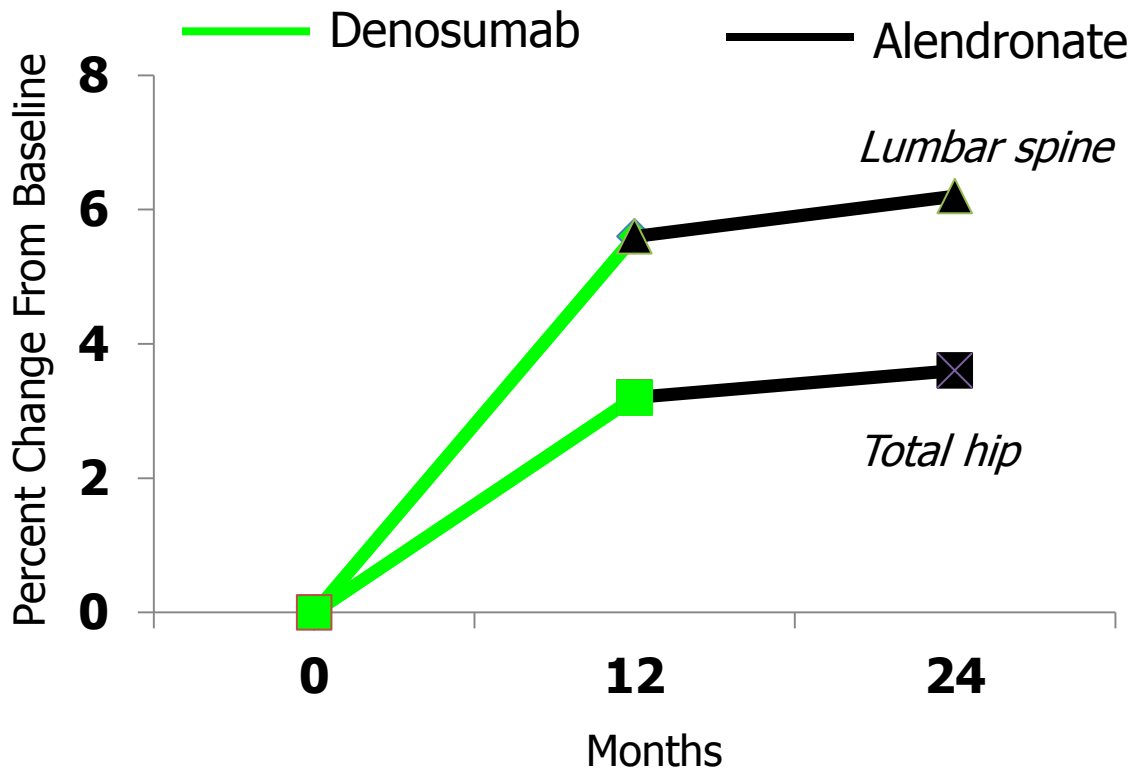
- Vertebral fracture risk was assessed in p**atients who discontinued either placebo or denosumab in the FREEDOM study or who stopped denosumab in the FREEDOM Extension study and who had a follow-up at least 7 months after their last dose**
- Fracture risk increased upon stopping denosumab but not to levels greater than seen in those who stopped placebo



Cummings SR et al. ASBMR Abstract, 2016

Denosumab and Alendronate (DAPS Trial)
Cross-over Treatment after 12 Months

Switching from denosumab to alendronate, bone loss did not occur



Freemantle N et al. *Osteoporos Int.* 2012;23:317-26

Long term Denosumab treatment

- When to consider discontinuation Dmab Tx
  - Intolerance or A/E
  - Reachinb a treatment "target"

- If therapy is stopped after a year4 or more, consider options to prevent rapid vone loss and fracture risk
- At present, the most appealing strategy would be to treat with a BP for 2 yr and then re-evaluate (McClung MR. Osteo Int 2016)

AACE/ACE 2016 Postmenopausal Osteoporosis Treatment Algorithm

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

No prior fragility fractures or moderate fracture risk**

- Alendronate, denosumab, risedronate, zoledronic acid***
- **Alternate therapy:** Ibandronate, raloxifene

Reassess at least yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to teriparatide if on injectable antiresorptive or at very high risk of fracture

Prior fragility fractures or indicators of higher fracture risk**

- Denosumab, teriparatide, zoledronic acid***
- **Alternate therapy:** Alendronate, risedronate

Reassess at least yearly for response to therapy and fracture risk

Denosumab

Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

Teriparatide for up to 2 years

Sequential therapy with oral or injectable antiresorptive agent

Zoledronic acid

- If stable, continue therapy for 6 years****
- If progression of bone loss or recurrent fractures, consider switching to teriparatide

* 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.

** Indicators of higher fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.

*** Medications are listed alphabetically.

**** Consider a drug holiday after 6 years of IV zoledronic acid. During the holiday, another agent such as teriparatide or raloxifene could be used.

Product information

효능효과

1. 폐경 후 여성 골다공증 환자의 치료
2. 남성 골다공증 환자의 골밀도 증가를 위한 치료
3. 안드로겐 차단 요법을 받고 있는 비전이성 전립선암 환자의 골 소실 치료
4. 아로마타제 저해제 보조요법을 받고 있는 여성 유방암 환자의 골 소실 치료

용법용량

이 약 1시린지(데노수맙 60mg)를 매 6개월마다 상완, 허벅지 위쪽 또는 복부에 피하 주사한다. 모든 환자는 칼슘 1000mg과 비타민D 400IU 이상을 매일 복용해야 한다.

정기 투여일에 투여하지 못했을 경우, 가능한 빨리 투여한다. 그 후, 마지막 투여일자로부터 매 6개월마다 투여한다.

보험기준

허가사항 범위 내에서 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 동 인정기준 이외에는 약값 전액을 환자가 부담토록 함.

가. 투여대상

중심골[Central bone : 요추, 대퇴(Ward's triangle 제외)]에서 이중에너지 방사선 흡수계측(Dual-Energy X-ray Absorptiometry: DEXA)을 이용하여 골밀도 측정 시 T-score가 -2.5이하인 경우로서, 다음의 경우에 해당하는 환자

(1) **Bisphosphonate 제제를 1년 이상 충분히 투여**했음에도 **새로운 골다공증성 골절이 발생**하거나, 1년 이상 투여 후 **골밀도 검사 상 T-score가 이전보다 감소한 경우**

(2) **신부전, 과민반응 등 Bisphosphonate 제제에 금기**인 경우

나. 투여기간: 1년 (2회)

추적검사에서 T-score가 -2.5이하이거나 골다공증성 골절이 발생하여 약제 투여가 계속 필요한 경우 추가 2년(4회)까지 인정함.

Reference 1. 보건복지부. 요양급여의 적용기준 및 방법에 관한 세부사항. 고시 제2017-0570.

Conclusion

- Denosumab was associated with a significant reduction in the risk of vertebral, hip, and nonvertebral fractures in men and postmenopausal women with osteoporosis - FREEDOM trial
- Treatment with denosumab increased BMD and decreased markers of bone turnover more than alendronate, both in women who were essentially treatment-naïve and in those who switched from alendronate to denosumab - DECIDE and STAND trial
- Rapid reversibility of it's anti-resorptive effect Taylor KH, Br J Oral Maxillofac Surg, 2010
- Discontinuation of denosumab results in loss of gains in BMD; BMD at the spine and total hip returned to preTx levels within 12 months of discontinuation. Bone HG, J Clin Endocrinol,Metab, 2011
- Greater adherence (subcutaneous injection every 6 months) over weekly alendronate at 12 months (p=0.043) Kendler DL, Osteoporos Int, 2010
- Suspected cases of ONJ in pts. on denosumab Aghaloo T, J Oral Maxillofac Surg, 2010