Advances in Osteoporosis

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No disclosures

Overview

- Calcium and vitamin D intake requirements
- Rationale behind bone loss and bone gain
- Bisphosphonate therapy
- Atypical femur fracture
- Bisphosphonate holiday or continuation
- Denosumab
- Osteonecrosis of the jaw
- New anabolic agents
  - Abaloparatide
  - Romosozumab
- Goal-directed treatment (“Treat-to-Target”)
- Sequential therapy according to fracture risk

Institute of Medicine 2011 Report: Dietary Reference intake (DRI) for US and Canadian Population

EAR = estimated average requirement
RDA = recommended daily allowance
UL = upper tolerable intake level (the level at which risk of harm begins)

25OHD Equivalents
EAR = 40 nmol/L
RDA = **50** nmol/L
UL = 125 nmol/L

DRIs for Calcium

Age years	EAR mg/d	RDA mg/d	UL mg/d
19-50	800	1,000	2,500
51-70 men	800	1,000	2,000
51-70 women	1,000	1,200	2,000
>70	**1,000**	**1,200**	2,000

DRIs for Vitamin D
(**based on minimal or no sun exposure**)

Age years	EAR IU/d	RDA IU/d	UL IU/d
9-70	400	600	4,000
>70	**400**	**800**	4,000

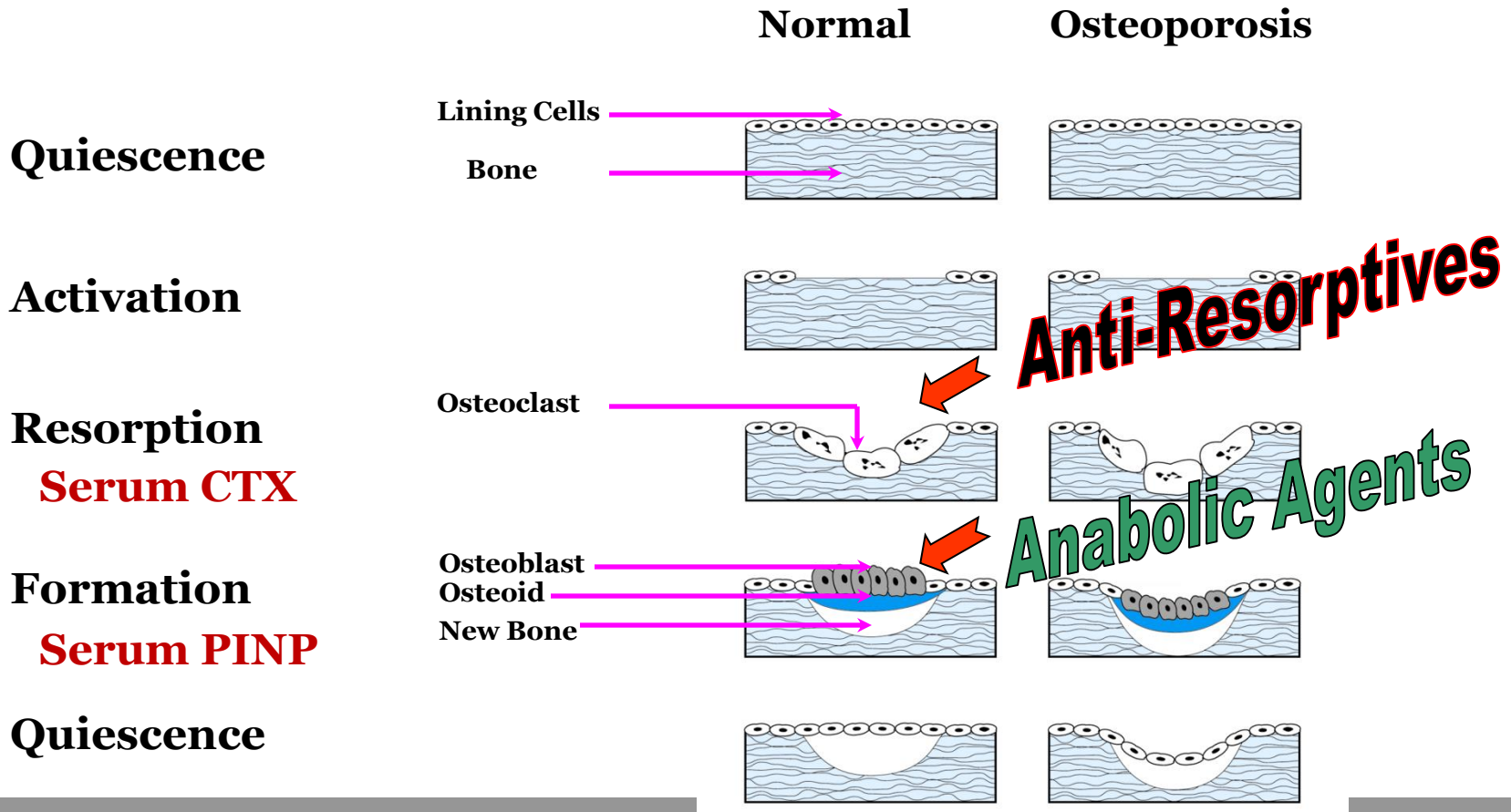
SACN, 2016: "25(OH)D … should not fall below 25 nmol/L at any time of year"+"10 µg/d (400 IU/d) … is the average amount needed by 97.5% "

Ross C, et al. J Clin Endo Metab 2011; 96: 53-58. Rosen C, et al. J Clin Endo Metab 2012; 97 :1146-1152.

Bone Remodelling Unit

Bone Turnover: replacing "old" bone with "new bone"

Bone Remodelling balance: explains "bone loss" & "bone gain"



Medications

Anti-resorptive agents

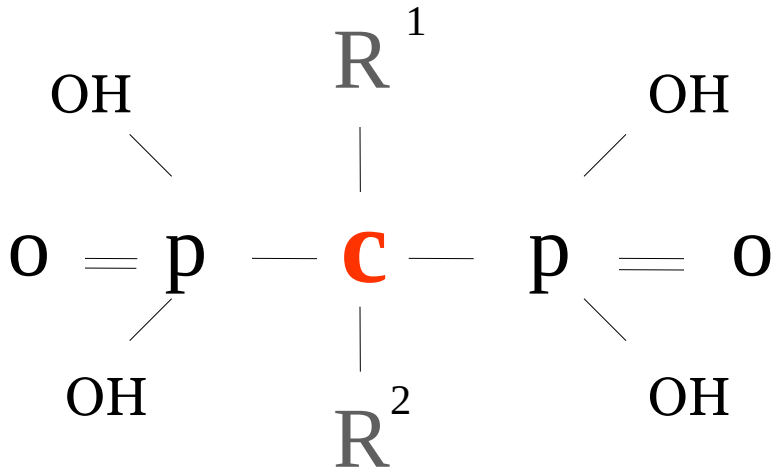
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Denosumab

Anabolic Agents

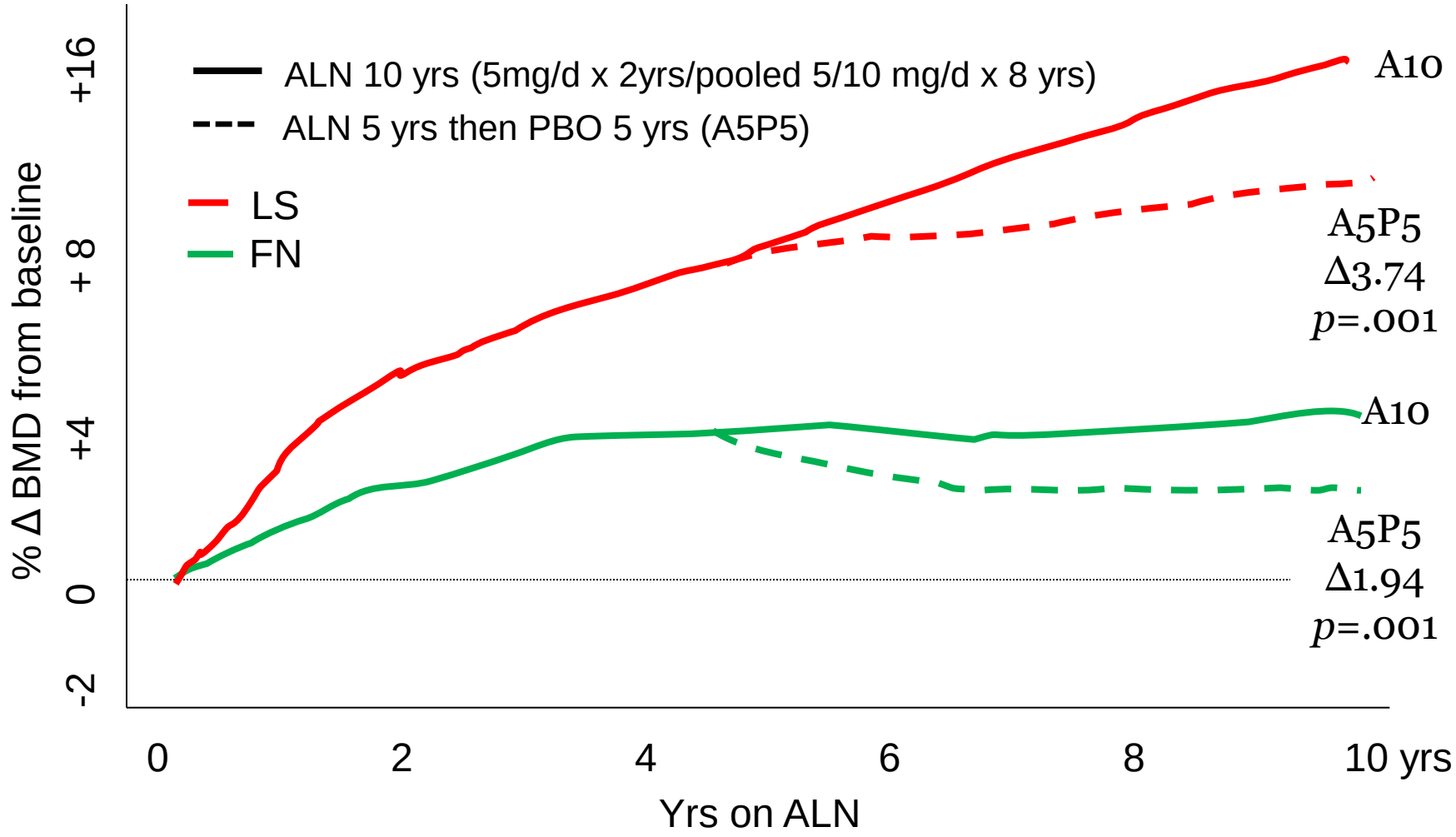
- Teriparatide
- New agents
  - Abaloparatide
  - Romosozumab

The Bisphosphonate Story

Bisphosphonic Acid



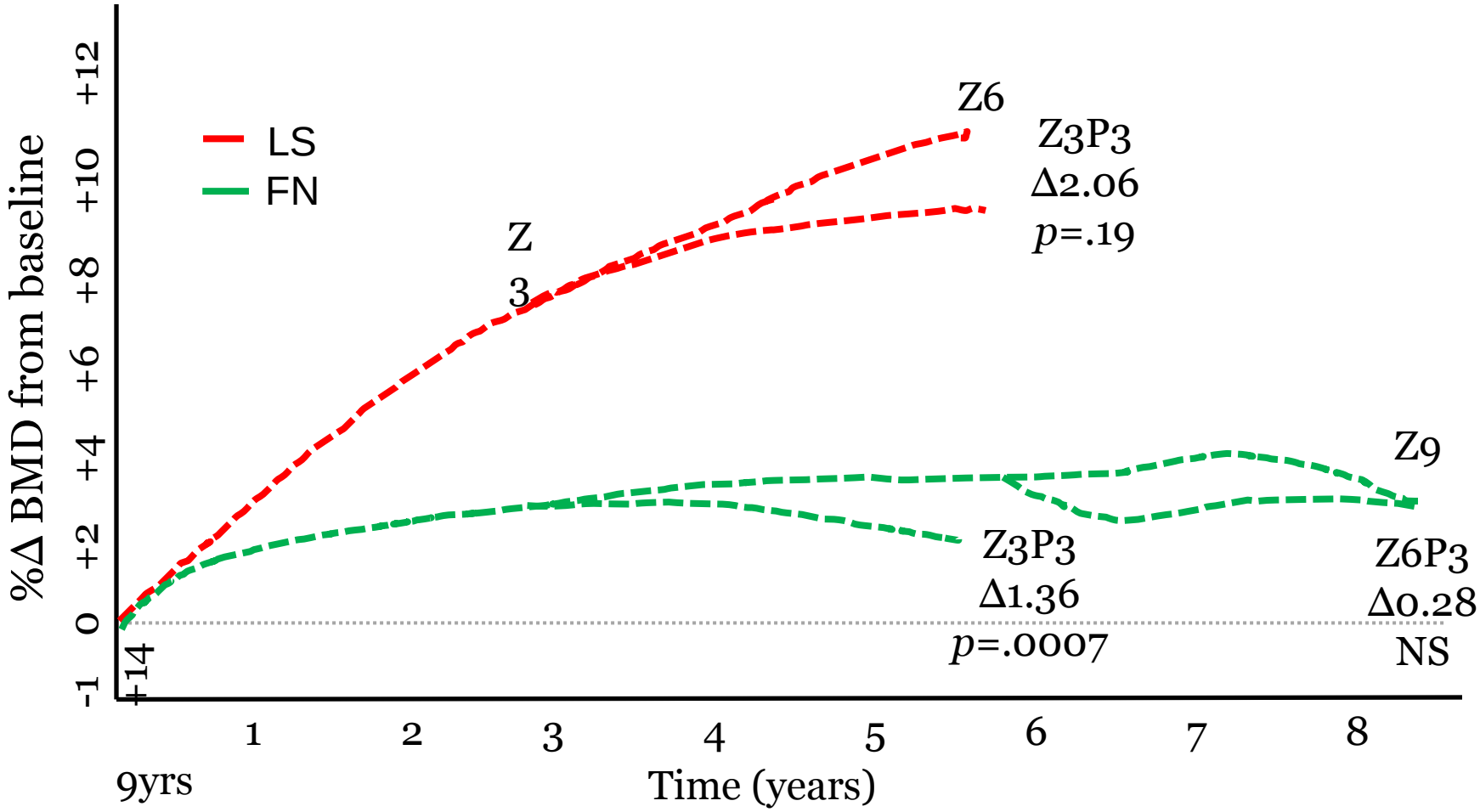
FLEX: Alendronate Extension Trial



n = 1099, at FLEX baseline average ALN duration was 5 yrs

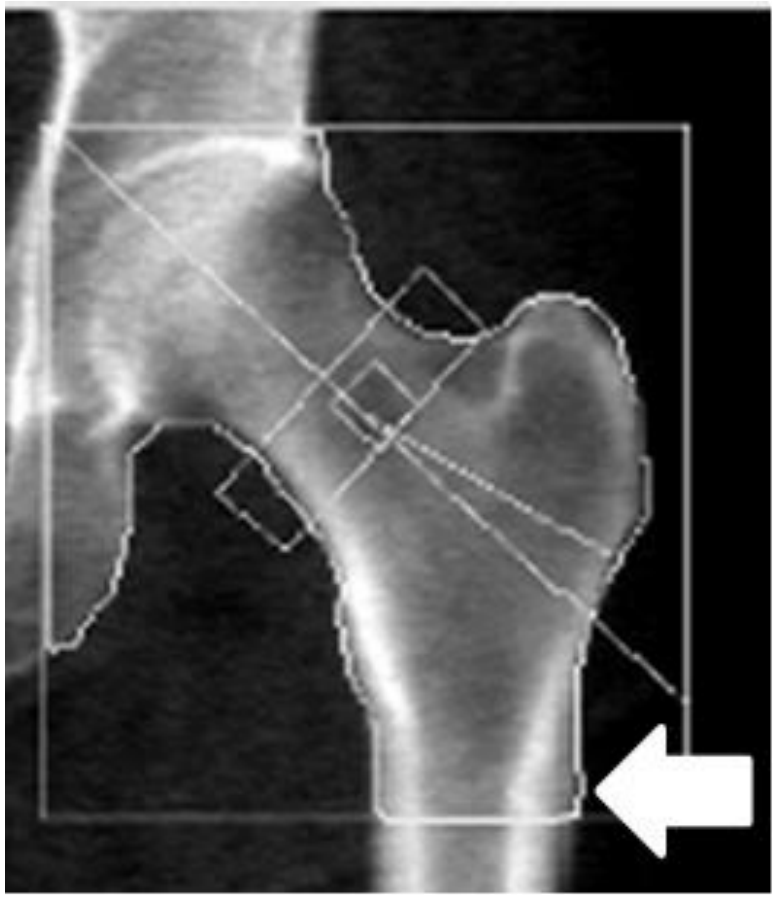
Black DM, et al. JAMA 2006 296;2927-38

HORIZON: Zoledronate Extension Trial



1. Black DM. NEJM 2007;356:1809-22, 2. Black DM. JBMR 2012;27:243-54, 3. Black DM. JBMR 2015;30:934-44

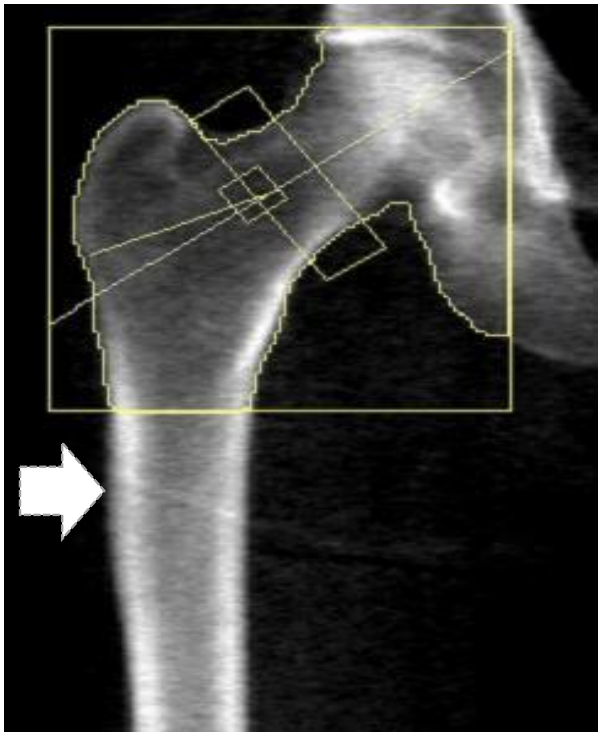
AFF: Potential role for DXA in early diagnosis
2011: 73 yo woman; Alendronate 10 years



McKiernan FE. 2010 Atypical femoral diaphyseal fractures documented by serial DXA. J Clin Densitom 13:102-103. McKenna MJ, et al. J Clin Densitom 2013; 16: 579-583.

Incomplete AFF diagnosed on DXA

46 yo woman; post renal transplant; bisphosphonate ≈ 10 years
Left and Middle Panels: DXA and X-ray image showing periosteal flare
Right Panel: Showing incomplete fracture after elective femur fixation



McKenna MJ, et al. Incomplete Atypical Femoral Fractures: Assessing the Diagnostic Utility of DXA by Extending Femur Length. J Clin Densitom 2013; 16: 579-583.

High-definition (HD) imaging of entire femur

Adapting feature for imaging spine

- If a DXA machine is capable of HD imaging of the lateral spine, then it can be adapted to conduct HD imaging of the femur (Hologic models with single-energy imaging)
- HD image is acquired immediately after acquiring DXA of femur, keeping the patient in the same position on the DXA table (rotating C-arm not required)

Comparing SE imaging to DXA imaging

- Superior image quality
- Full extent of femur is visualized
- Faster:
  - DXA image: 108 sec
  - SE image: 18 sec
- Separate examinations
  - No effect on BMD estimation

McKenna MJ, et al. Identifying Incomplete Atypical Femoral Fractures With Single-Energy Absorptiometry: Declining Prevalence. Journal of the Endocrine Society 2017; 1:211-220. https://doi.org/10.1210/js.2016-1118

Case study using DXA system to detect incomplete AFF

82 years old woman, who was taking an oral bisphosphonate therapy for 10 years, presented with 5 month history of right thigh pain

DXA image

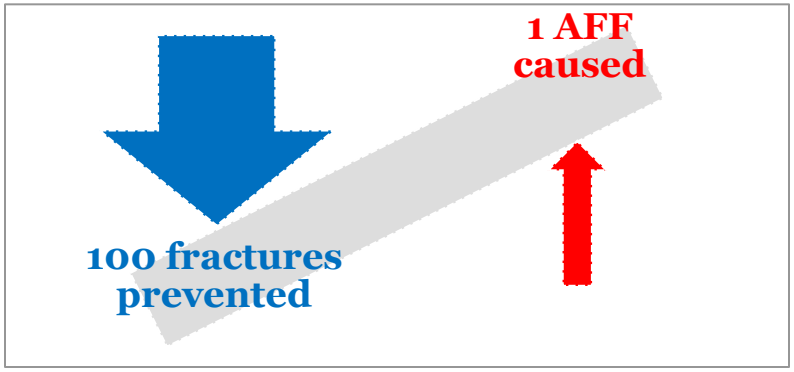
Single-energy HD image

X-ray image

Intramedullary nail

McKenna MJ, et al. Identifying Incomplete Atypical Femoral Fractures With Single-Energy Absorptiometry: Declining Prevalence. Journal of the Endocrine Society 2017; 1:211-220. https://doi.org/10.1210/js.2016-1118

Balancing Benefit & Harm



BP 5 years

Drug Holiday (from BP)

Review after 2 years

Alternative agent

Long-term BP

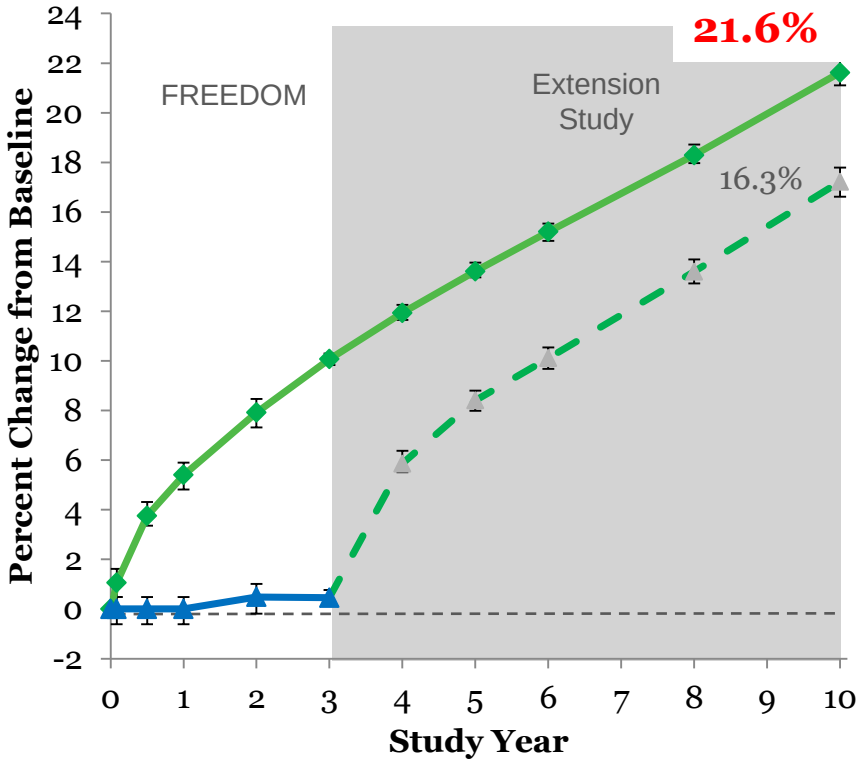
Screening for incomplete AFF

Black D, Rosen C. N Engl J Med 2016;374:254-62 . Adler RA, Fuleihan GE, *et al.* Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2016 Jan;31(1):16-35.

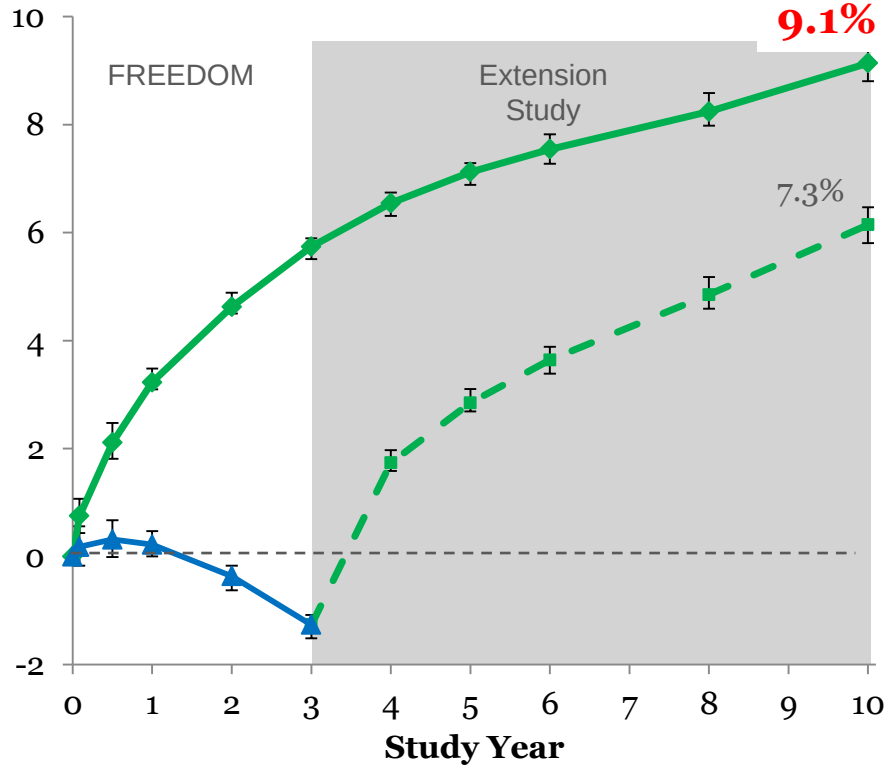
Ten Years of Denosumab Treatment in Postmenopausal Women With Osteoporosis: Results From the FREEDOM Extension Trial

Placebo — Cross-over Denosumab — Continued Denosumab

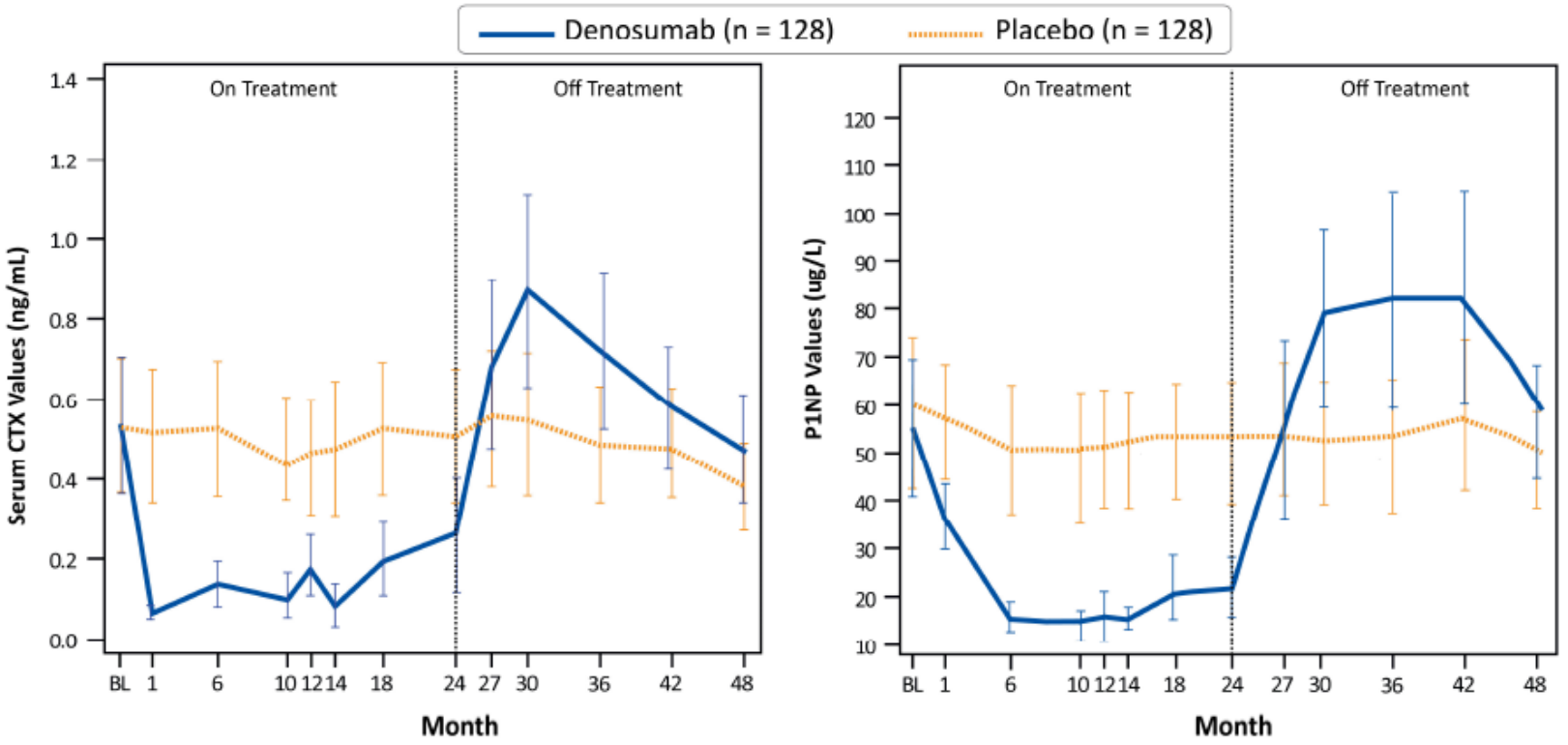
Lumbar Spine Bone Mineral Density



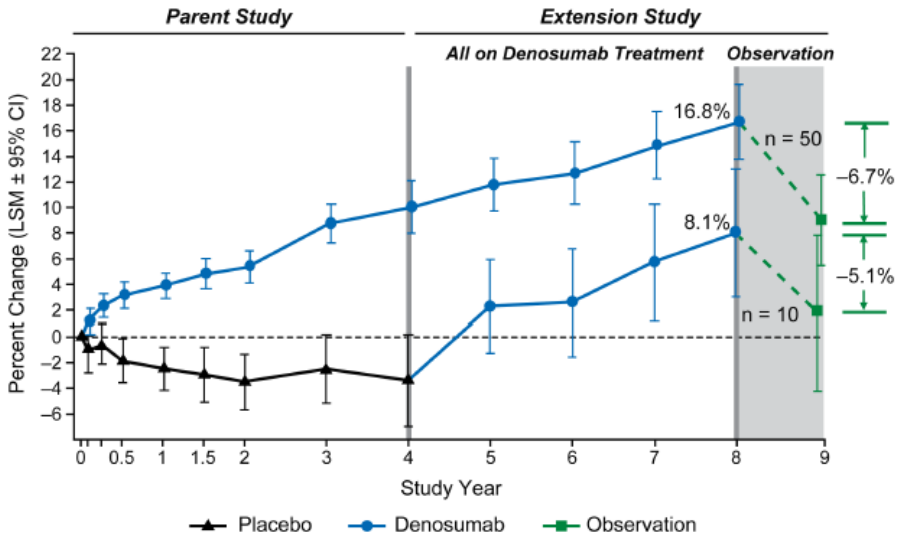
Total Hip Bone Mineral Density



Effect Denosumab Treatment and Discontinuation on Bone Turnover Markers

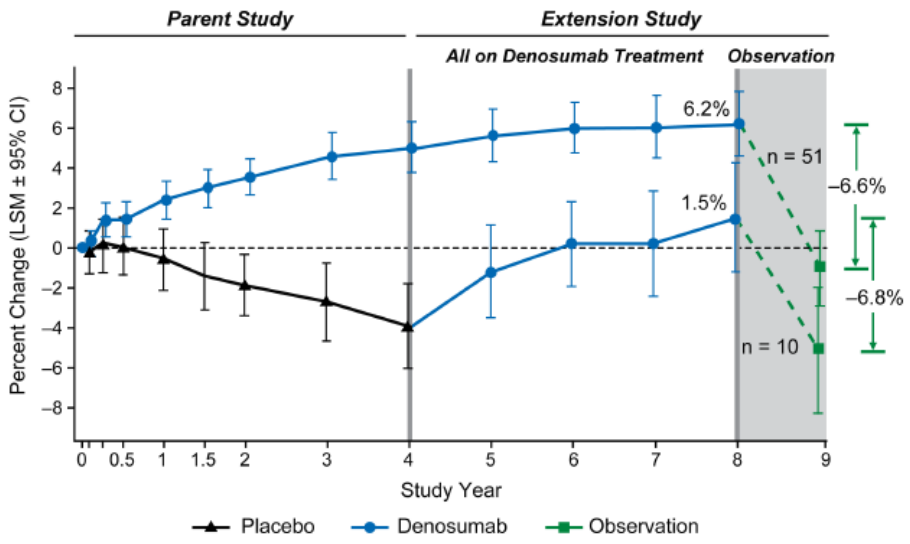


Effect of Denosumab discontinuation after up to 8 years treatment during 1 year observation



Lumbar Spine BMD

Total Hip BMD



McClung MR, et al. Osteoporos Int . Published online January 31, 2017 as doi 10.1007/s00198-017-3919-1

Anti-Resorptives' Profiles

Bisphosphonates

- BMD: plateau response
- Offset effect: Slow
- Sustained suppression in bone turnover
- BMD stable
- Anti-fracture efficacy
- Drug holiday

Denosumab

- BMD: steady rise
- Offset effect: Rapid
- Rebound remodelling activity
- BMD decline
- Loss of fracture efficacy
- "Cancel the holiday"[1]; consolidate with BP

[1]McClung M. OI 2016; 27:1677–1682

New Therapeutics Agents

Abaloparatide

Romosozumab

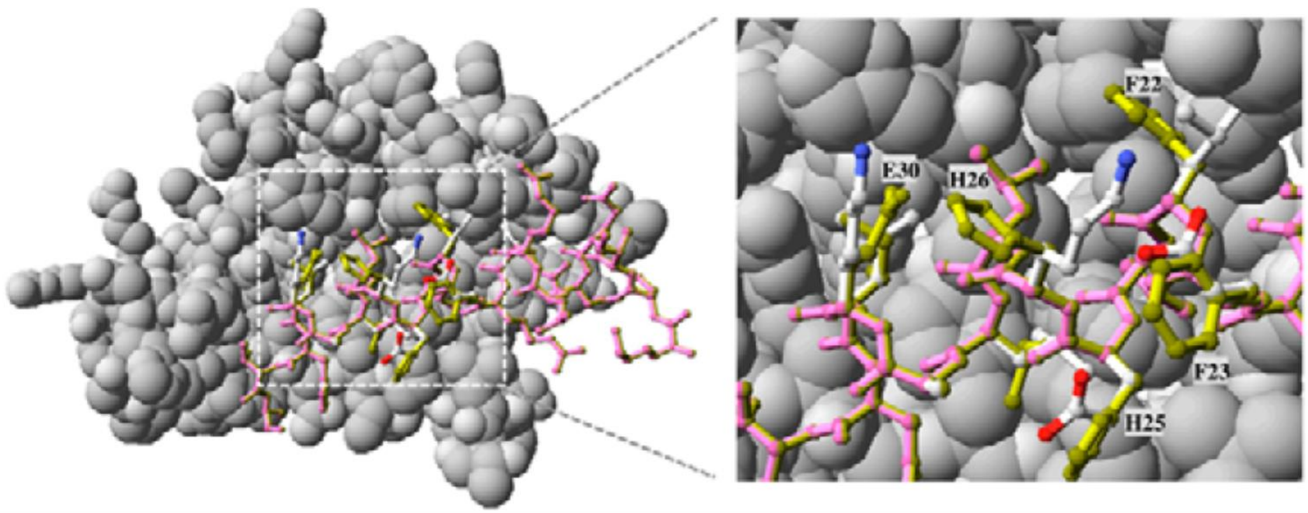
Abaloparatide

Parathyroid hormone related peptide (PTHrP) ligand analog

A

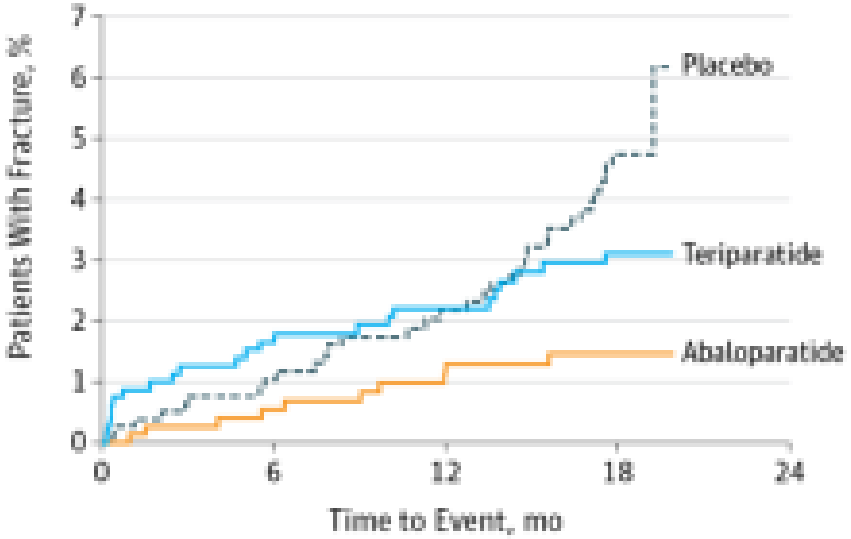
	1 34
PTH(1-34)	SVSEIQLMHNLGKHLNSMERVEWLRKKLQDVHNF-(NH_2)
PTHrP(1-36)	AVSEHQLLHDKGKSIQDLRRRFFLHHLIAEIHTAEI-(NH_2)
LA-PTH	AVAEIQLMHQRAKWIQDARRRAFLHKLIAEIHTAEI-(COOH)
ABL	AVSEHQLLHDKGKSIQDLRRRELLEKLLXKLHTA-(NH_2)

B



ACTIVE: Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial

Major Osteoporotic Fractures



Log-rank *P* value
<.001 Abaloparatide vs placebo
.14 Teriparatide vs placebo
.03 Abaloparatide vs teriparatide

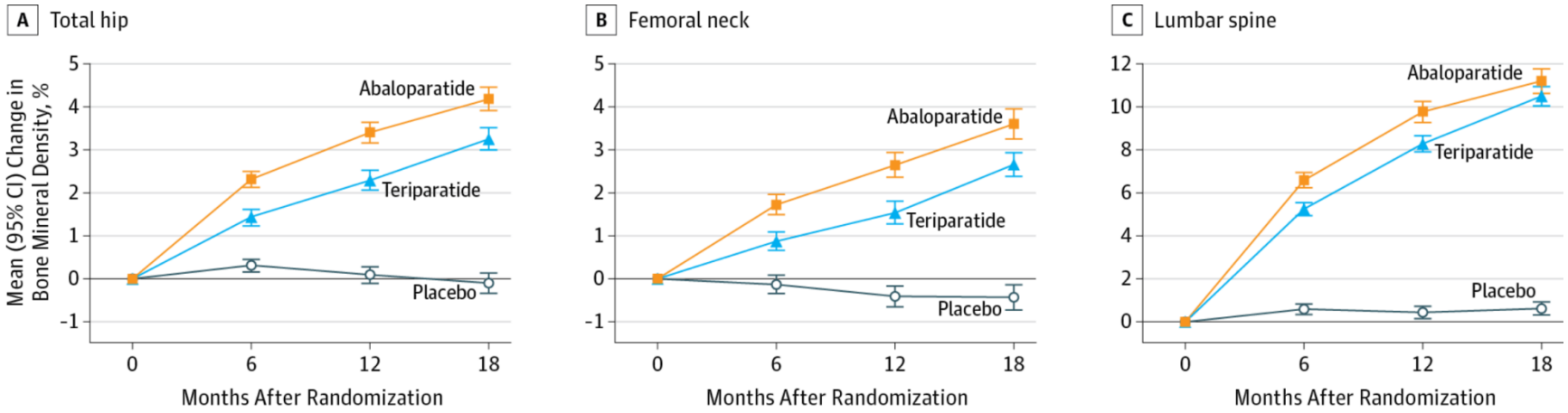
Median follow-up time, mo
18.93 Abaloparatide
18.93 Placebo
18.90 Teriparatide

No. at risk				
Abaloparatide	824	693	640	606
Placebo	821	728	671	616
Teriparatide	818	729	678	637
Cumulative No. with event				
Abaloparatide		4	9	10
Placebo		8	16	33
Teriparatide		13	17	23

FDA approval 28th April 2017
80 µg sc daily for 2 years
Same warnings as PTH1-34
Tymlos™

ACTIVE: Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial

BMD response

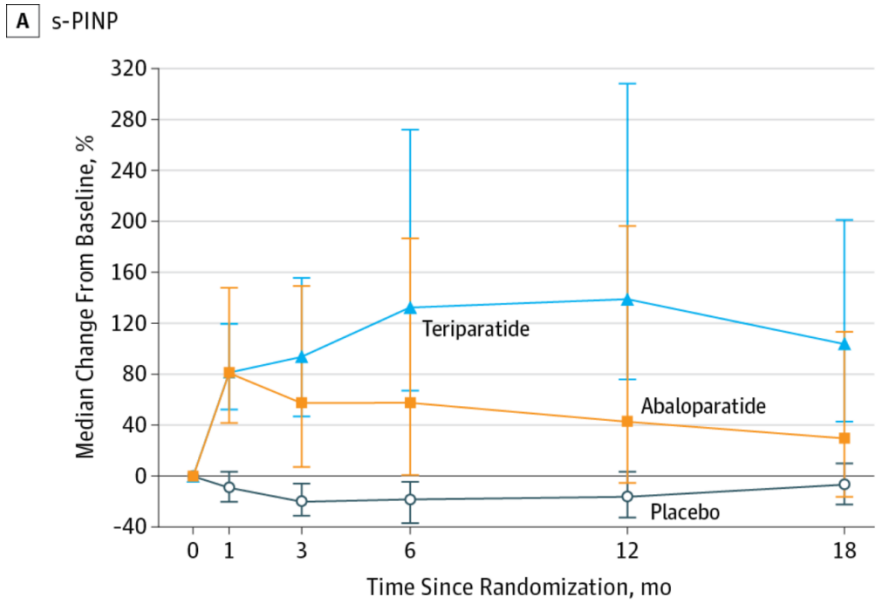


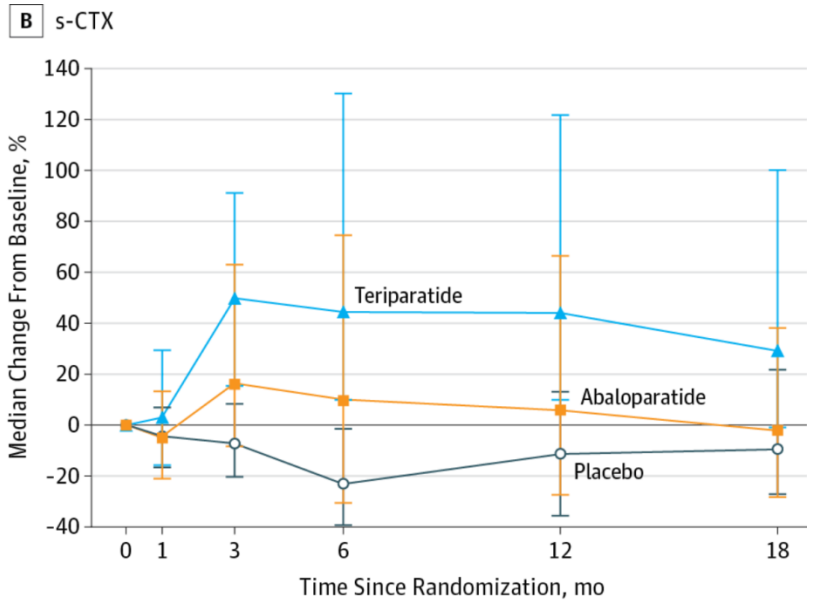
No. of participants evaluated

Abaloparatide	822	736	651	615	822	736	651	615	823	738	652	617
Placebo	820	762	693	651	820	762	693	651	821	764	694	650
Teriparatide	818	754	705	660	818	754	705	660	818	755	704	665

ACTIVE: Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial

Bone turnover marker response



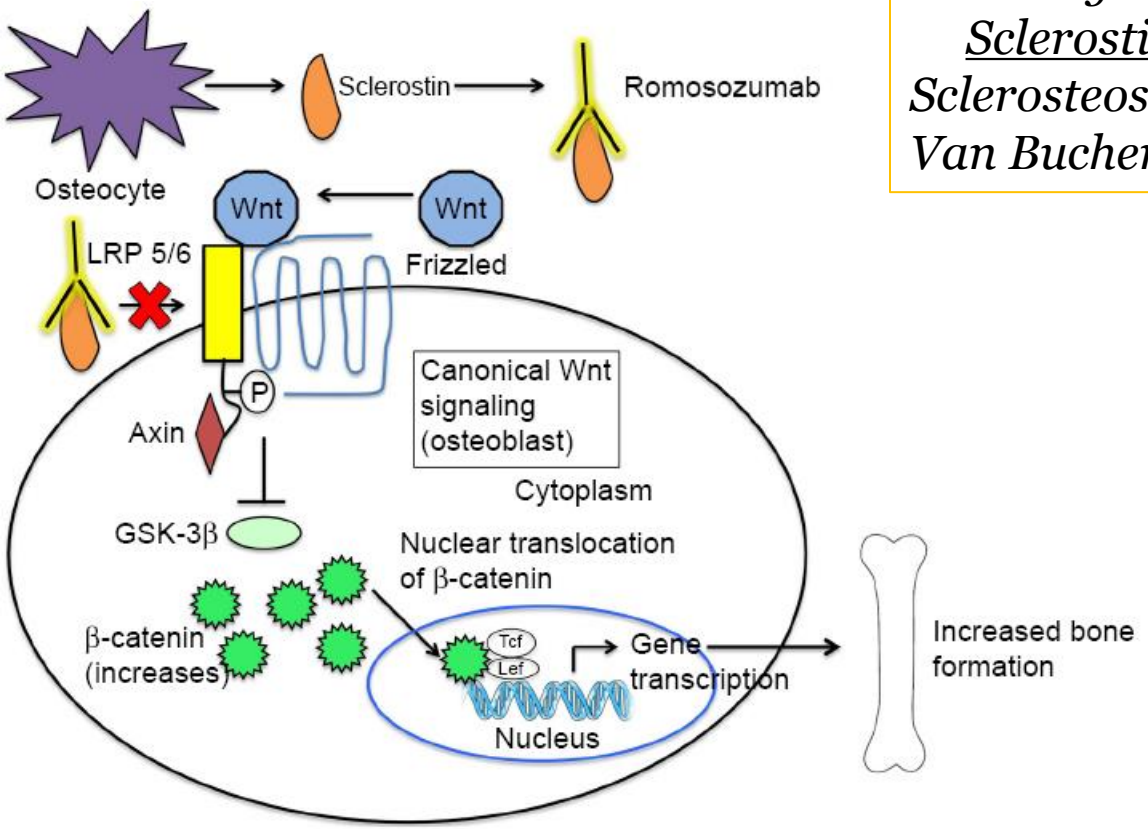


No. of participants evaluated						
Abaloparatide	189	187	187	189	189	189
Placebo	184	183	181	184	184	184
Teriparatide	227	227	227	227	227	227

	189	187	187	189	189	189
	184	183	181	184	184	184
	227	227	227	227	227	227

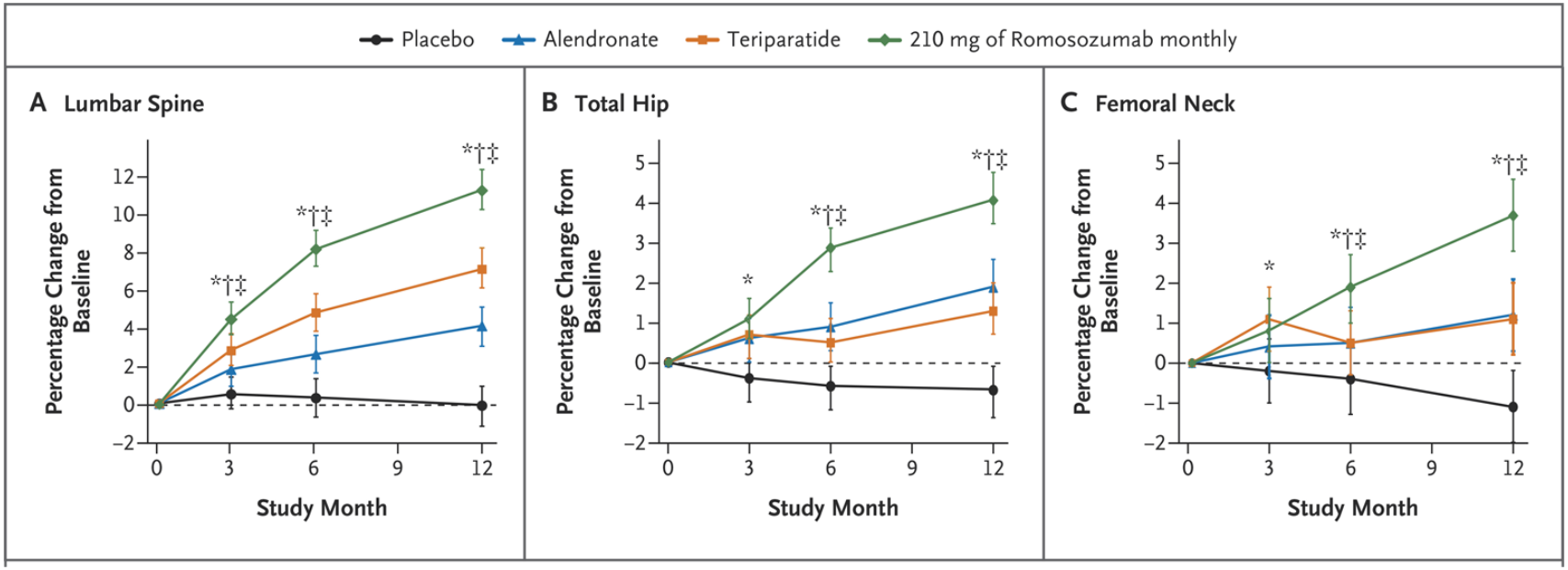
Romosozumab: Inhibition of Sclerostin

SOST gene mutations
Sclerostin deficiency
Sclerosteosis
Van Buchem's disease



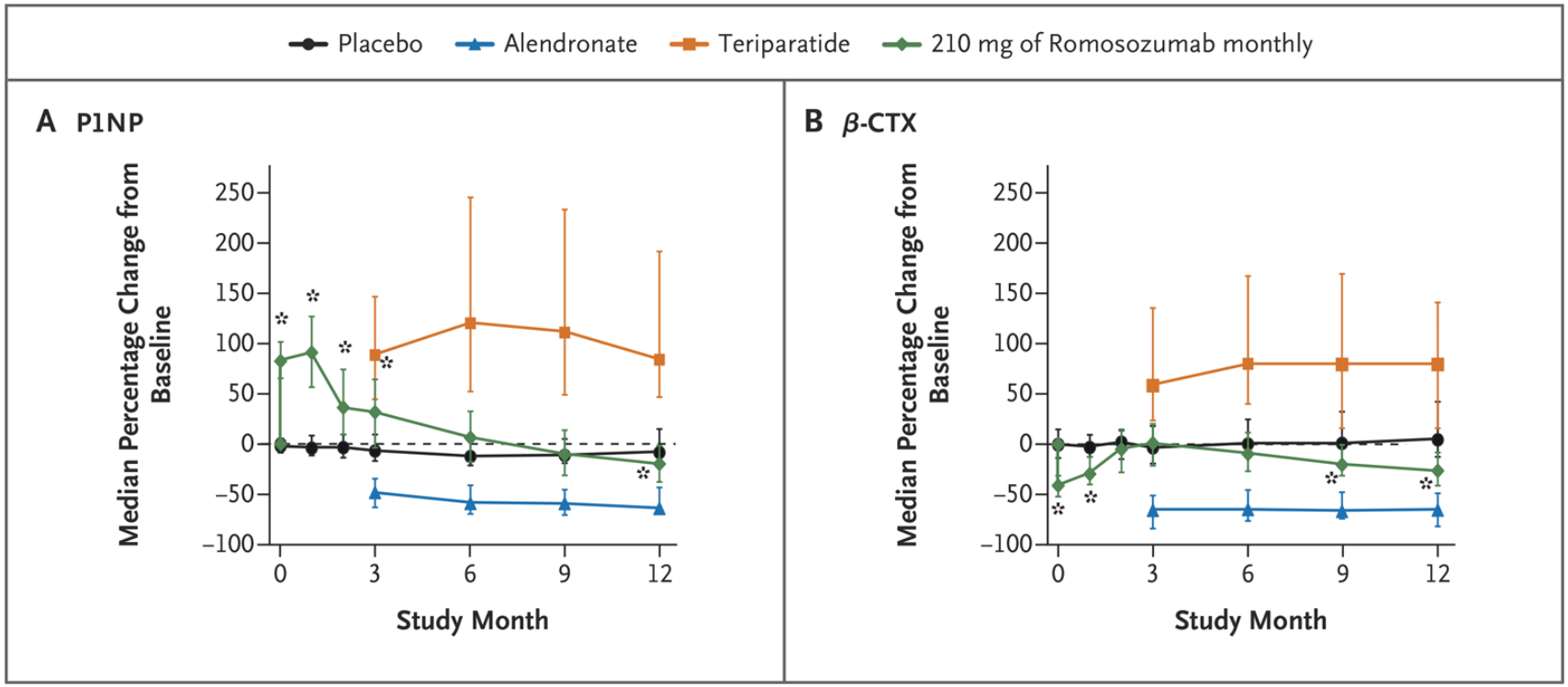
Romosozumab in Postmenopausal Women with Low Bone Mineral Density

Percentage Change from Baseline in Bone Mineral Density.

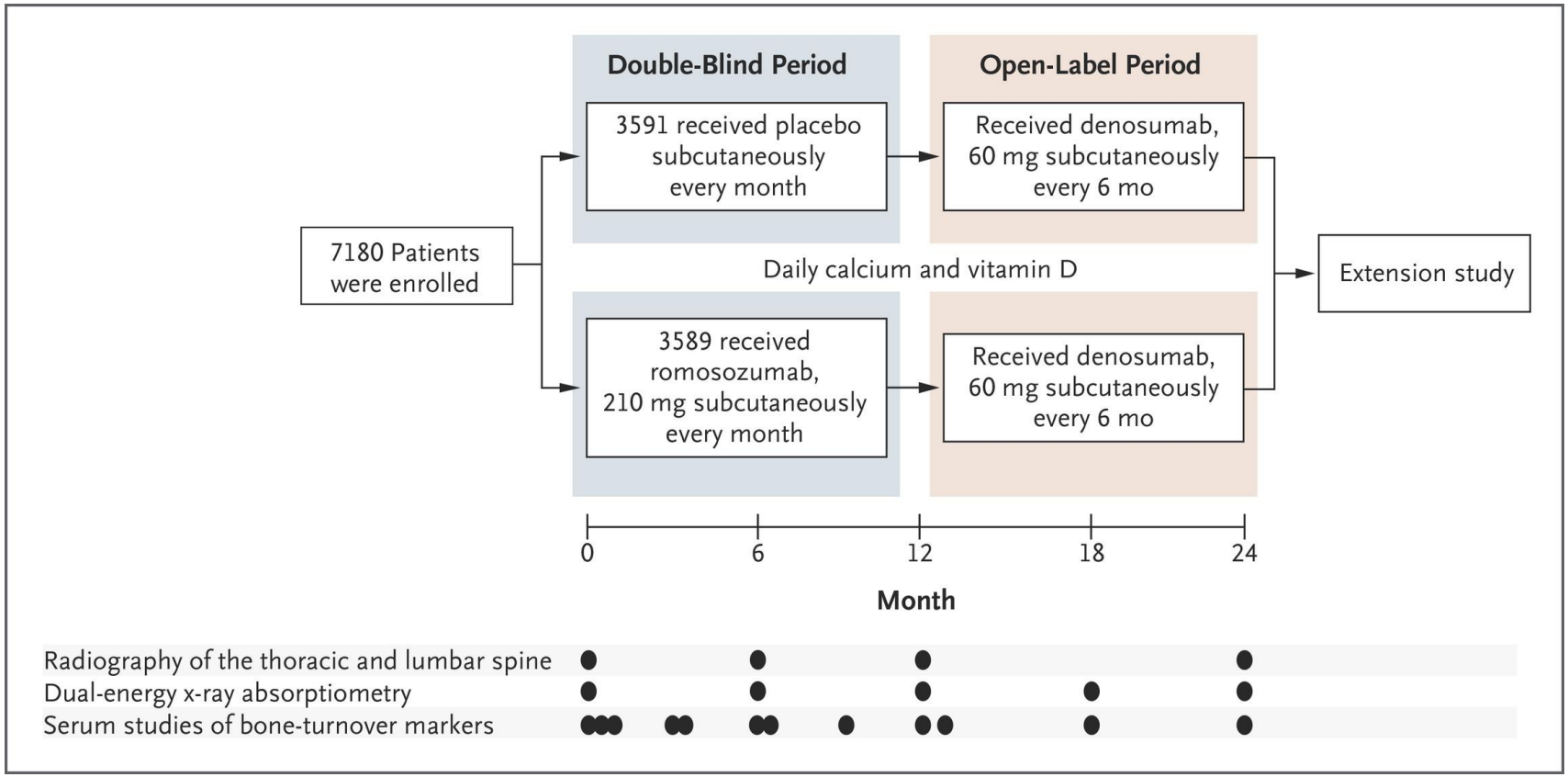


Romosozumab in Postmenopausal Women with Low Bone Mineral Density

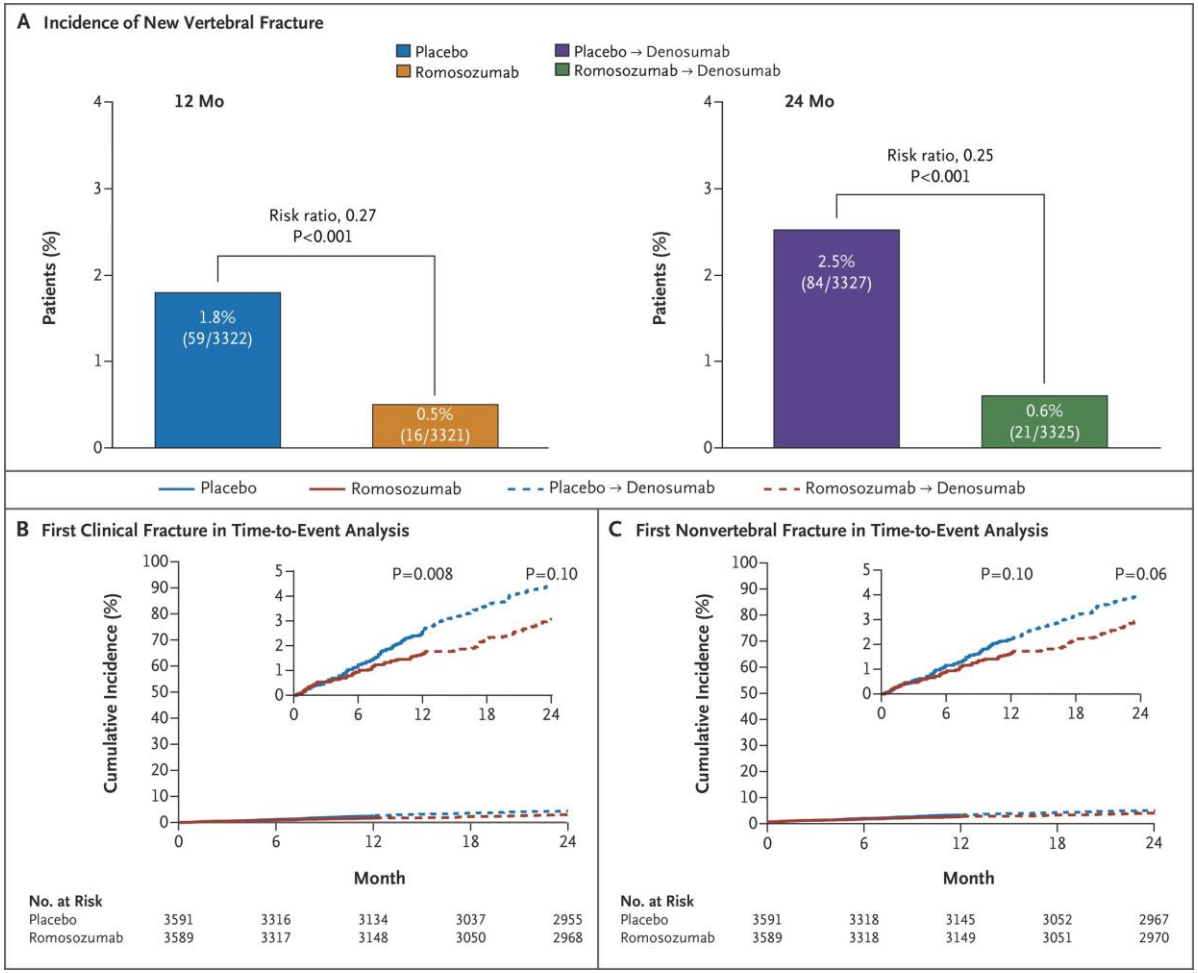
Percentage Change from Baseline in Bone-Turnover Markers.



Romosozumab Treatment in Postmenopausal Women with Osteoporosis: FRAME trial

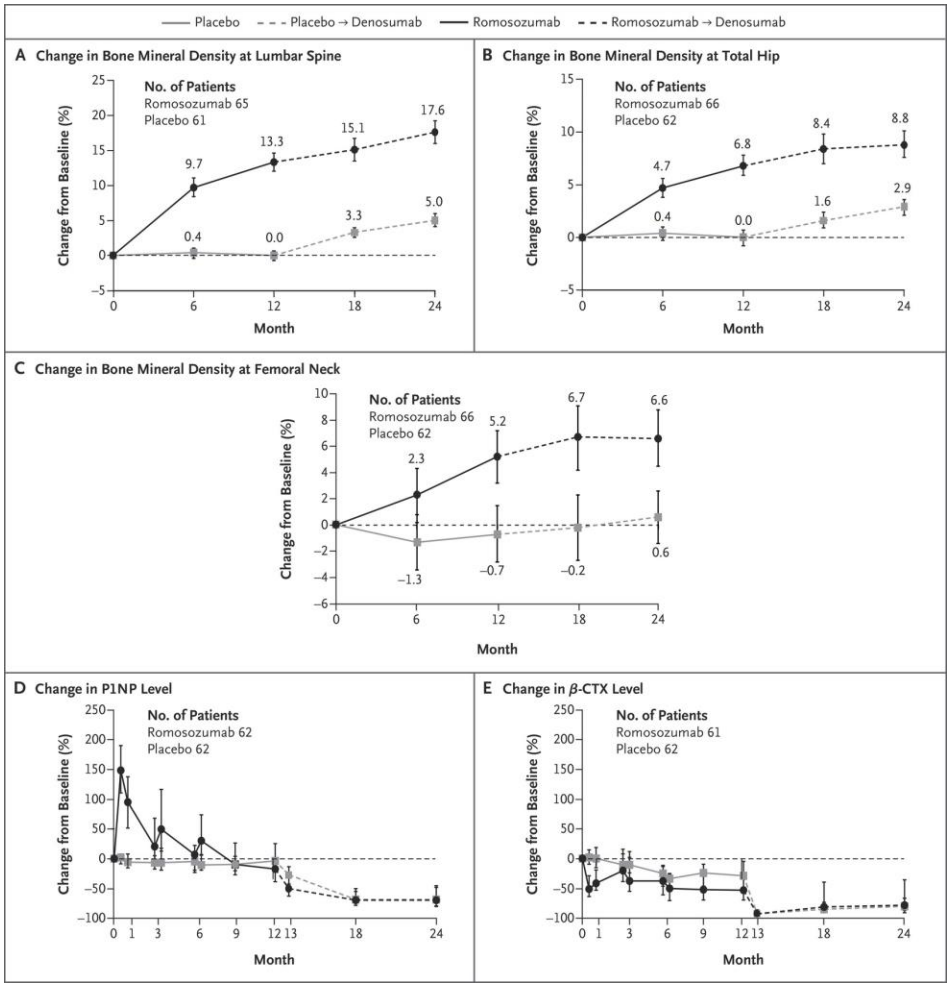


Romosozumab Treatment in Postmenopausal Women with Osteoporosis: FRAME trial



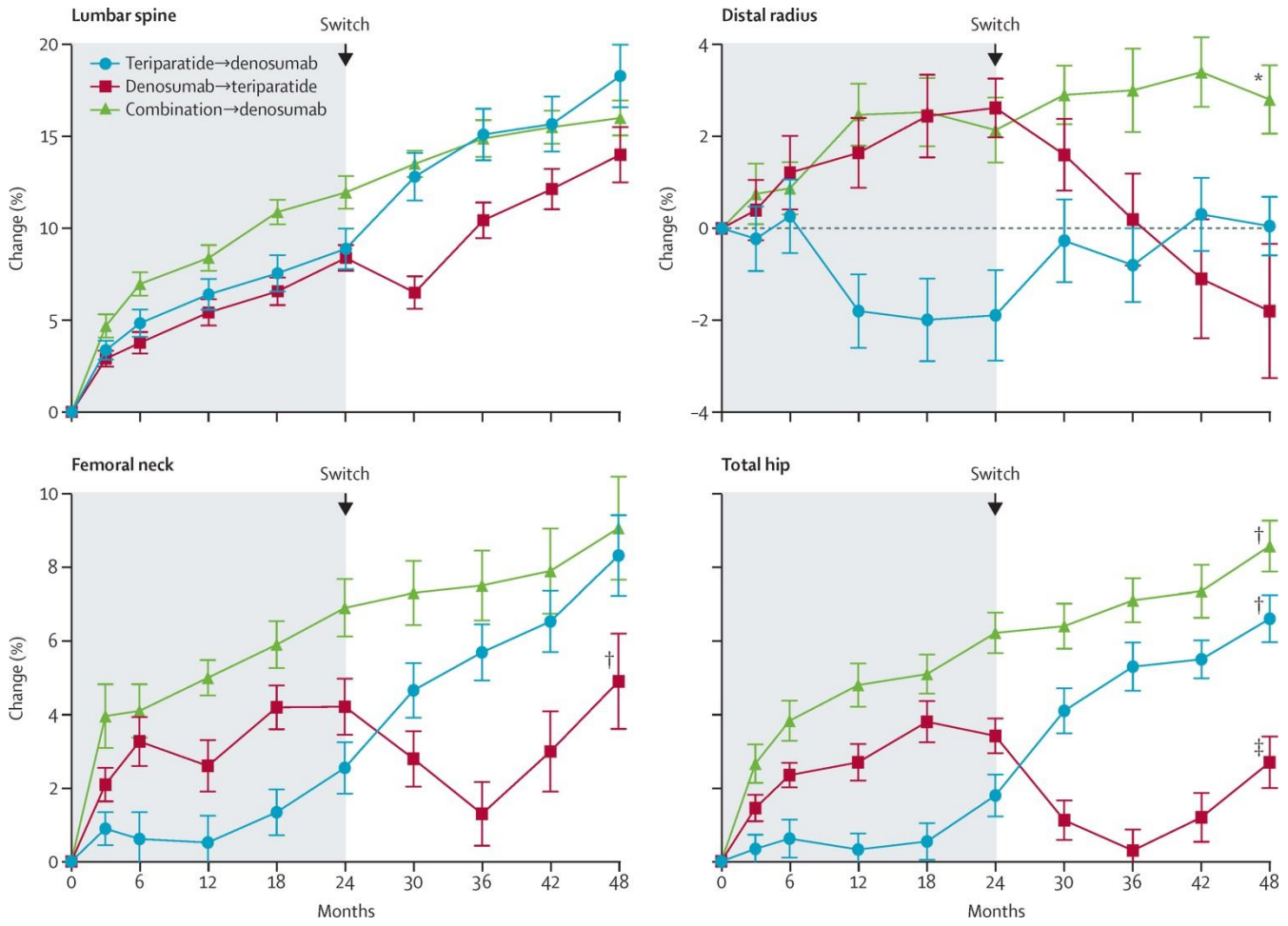
Romosozumab Treatment in Postmenopausal Women with Osteoporosis: FRAME trial

Percentage Change from Baseline in Bone Mineral Density and Levels of Bone-Turnover Markers.

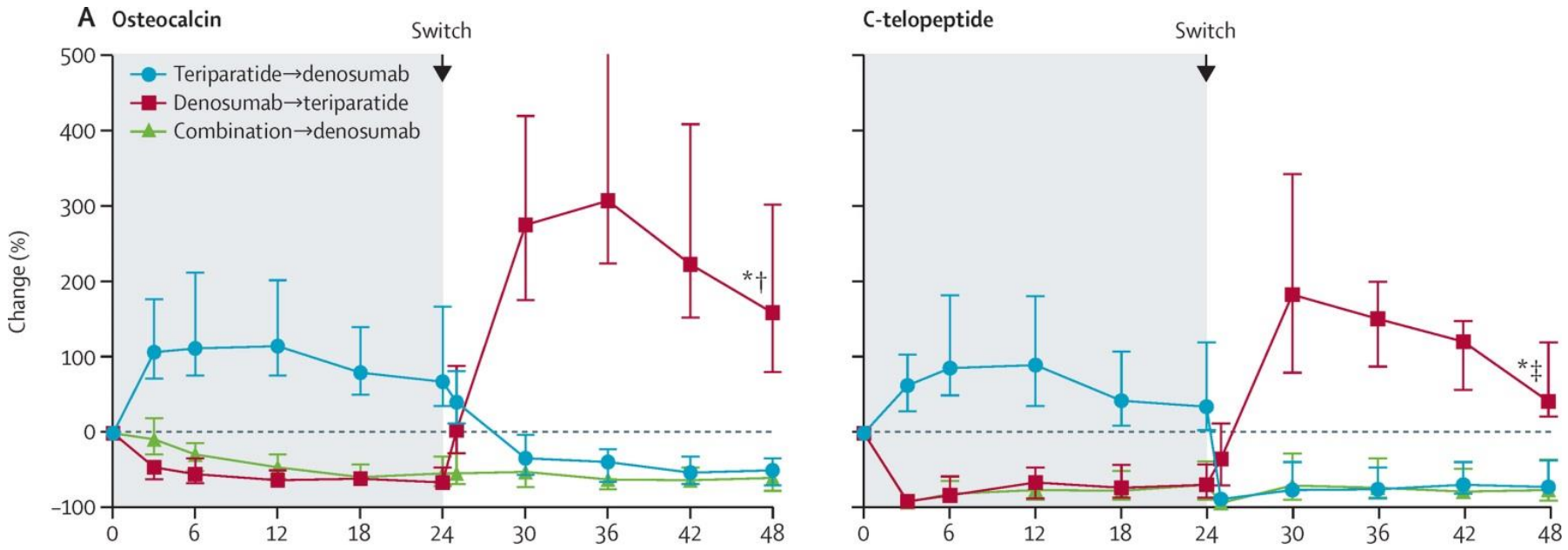


FDA decision is Expected 17th July 2017

Combination or Sequential Therapy? DATA-Switch study



Combination or Sequential Therapy? DATA-Switch study



Optimal Sequence of Therapy

Anabolic → **Antiresorptive**

Goal-Directed Treatment for Osteoporosis: ASBMR-NOF Working Group

- Remain free of fracture (either first or recurrent)
  - If incident non-vertebral fracture during trial, then higher risk of same type of fracture over next 3 years.
- Attain BMD T-scores above osteoporosis range
  - If T-score ≤-2.5; then higher rate of both non-vertebral and vertebral fracture
- Reduce fracture probabilities below Rx indications
  - Fracture risk assessment tools (FRAX) inadequate

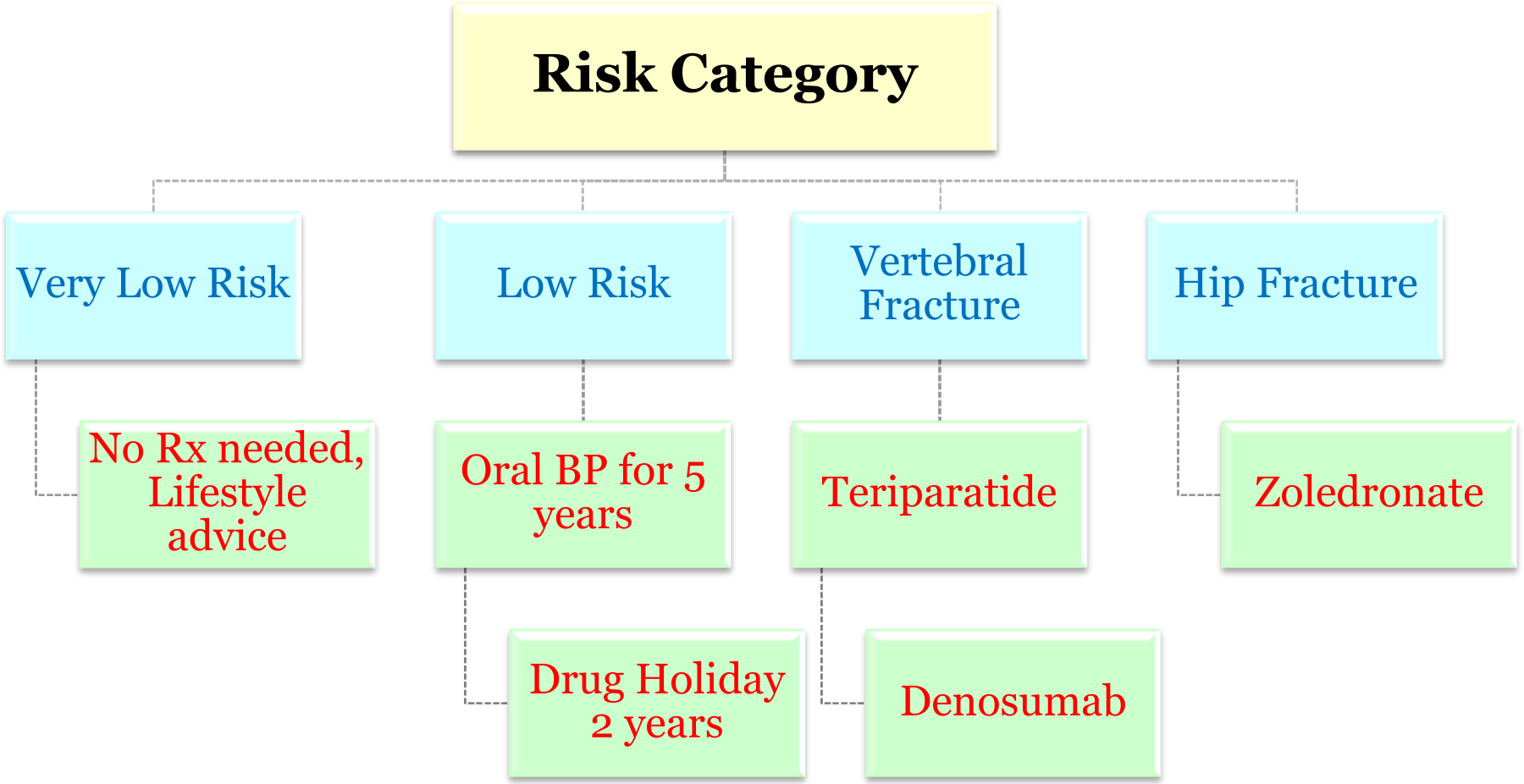
Cummings S, et al. J Bone Miner Res, 2017; 32: 3–10. Cosman F, et al. J Bone Miner Res, 2017; 32: 198–202

Limitations of Goal-Directed Treatment

- Evidence is dependent on post-hoc analysis of extension trials & on trials without fracture end-points.
- Feasibility with current medications.
- Assessing fracture risk in those on treatment.
- Evidence for continuing or withholding treatment is based on hip & femur neck BMD, not lumbar BMD.
- Lack of cost-benefit analysis (see additional slides)

Cummings S, et al. J Bone Miner Res, 2017; 32: 3–10. Cosman F, et al. J Bone Miner Res, 2017; 32: 198–202

My Approach to Sequential Therapy



Thank You

WNT Signalling: Bone Formation

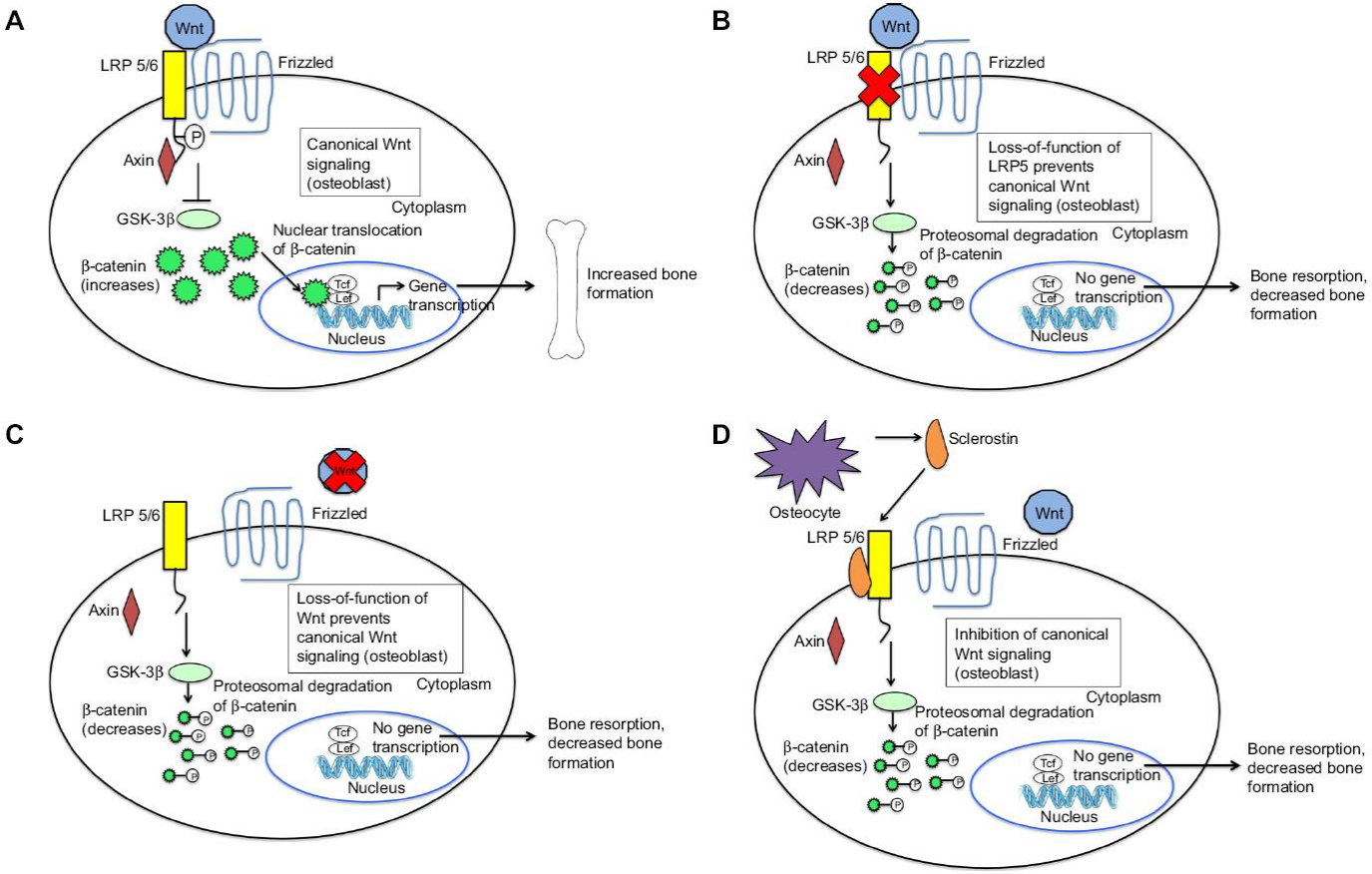


Figure 1 Wnt signaling pathways and the biology of sclerostin.

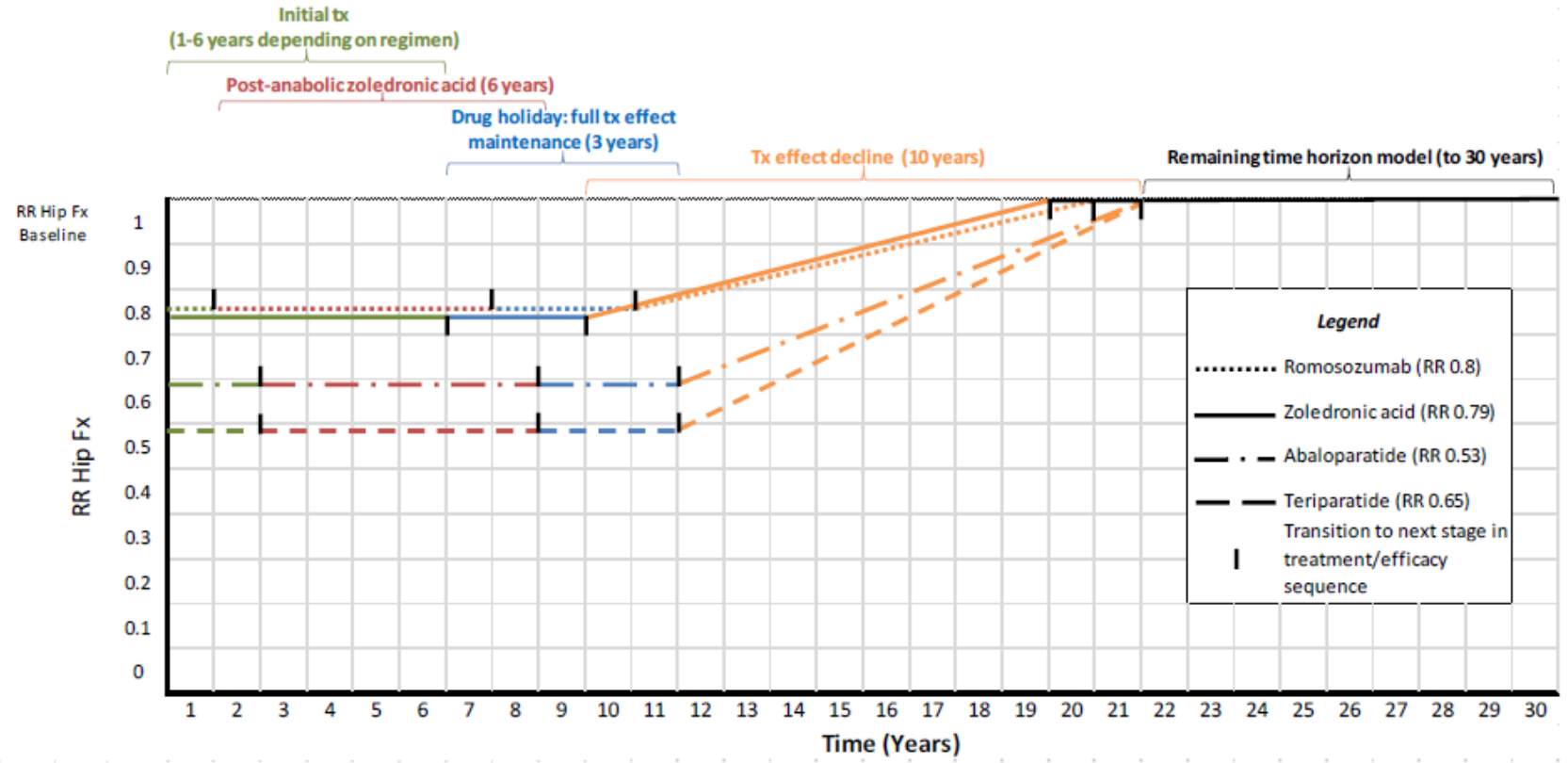
Notes: (**A**) Canonical Wnt signaling: in the absence of sclerostin, Wnt binds to LRP 5/6 and its co-receptor, frizzled. This results in phosphorylation of the cytoplasmic tail of LRP 5/6, which allows axin to bind the receptor complex. Axin binding leads to inhibition of GSK-3β, which normally functions to target β-catenin for degradation. Therefore, cytoplasmic levels of β-catenin increase and are translocated to the nucleus, where they bind to DNA binding proteins and activate target gene promoters. This results in osteoblast differentiation, proliferation and survival and hence, increased bone formation. (**B** and **C**) Loss-of-function of LRP5 and Wnt prevent canonical Wnt signaling: Loss-of-function of LRP5 and Wnt prevent formation of the active Wnt-LRP 5/6-frizzled complex and prevent Wnt signaling. The cytoplasmic tail of LRP 5/6 remains unphosphorylated. Therefore, axin does not bind the receptor complex. GSK-3β activity is uninhibited and therefore leads to phosphorylation of β-catenin, targeting it for degradation. Cytoplasmic levels of β-catenin decrease. Therefore, there is less translocation of the protein to the nucleus. Target gene promoters of the Wnt signaling pathway are not activated. This results in decreased bone formation and increased bone resorption and hence, skeletal fragility and fractures. (**D**) Inhibition of canonical Wnt signaling by sclerostin: sclerostin is secreted by osteocytes. It binds to LRP 5/6, which prevents Wnt from binding to LRP 5/6 and its co-receptor, frizzled. Therefore, Wnt signaling is inhibited. Through the mechanisms described above (**B** and **C**), this results in decreased bone formation and increased bone resorption.

Comparative Effectiveness:
Preventing Vertebral Fractures

Table 4. Network Meta-Analysis Results for the Relative Risk of Vertebral Fractures*

Abaloparatide (80 mcg)				
0.51 (0.13 – 1.52)	**Romosozumab (210 mg)**			
0.50 (0.14 – 1.34)	0.98 (0.48 – 1.92)	**Teriparatide (20 mcg)**		
0.49 (0.14 – 1.28)	0.96 (0.52 – 1.67)	0.98 (0.60 – 1.57)	**Zoledronic Acid (5 mg)**	
0.14 (0.04 – 0.36)	**0.27 (0.16 – 0.47)**	**0.28 (0.18 – 0.43)**	**0.29 (0.23 – 0.37)**	**Placebo**

Treatment Sequencing & Effect on Hip Fracture



Note: Each treatment line is color-coded to match the X-axis labels at the top of the chart; vertical black lines indicate transitions to the next stage in sequence/efficacy. Line placement is not exact.

Fx: fracture, RR: relative risk, Tx: treatment

Cost Effectiveness of Anabolic Agents: Comparator, Zoledronic Acid

Table 15. Base-Case Results

Regimen	Cost	QALYs	Life Years
Zoledronic acid	$17,851	8.953	12.202
Romosozumab	$37,100	8.957	12.202
Teriparatide	$56,298	8.989	12.205
Abaloparatide*	$40,522	9.028	12.208

QALY: quality-adjusted life year

Table 16. Pairwise Results for Anabolic Therapies Compared to Zoledronic Acid

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Abaloparatide	$22,671	0.075	0.006	$303,584
Teriparatide	$38,448	0.037	0.004	$1,052,824
Romosozumab	$19,249	0.004	<0.001	$4,388,095

ICER: incremental cost-effectiveness ratio, Incr.: incremental, LY: life year, QALY: quality-adjusted life year