

# Challenges of Osteoporosis Treatment

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## Endo2021 - Hot Topics in Osteoporosis

- ▶ Treating patients with osteoporosis during Covid-19 pandemic
- ▶ The role of anabolic therapy in the management of osteoporosis and fracture
- ▶ Sclerostin inhibition for the treatment of osteoporosis
- ▶ Osteoporosis medication holidays
- ▶ Treatment options in osteoporosis across the spectrum of fracture risk



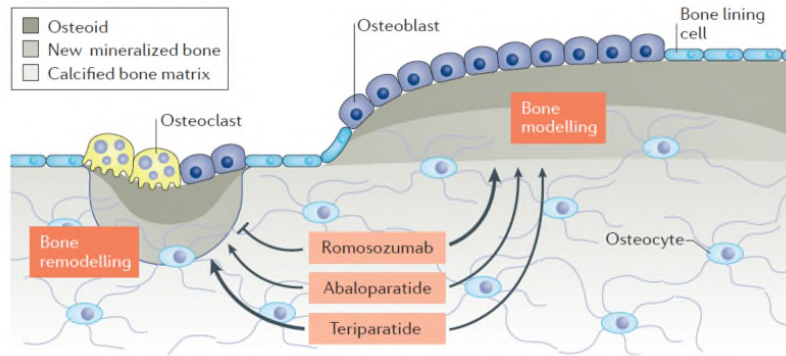
## Osteoporosis Management in the Era of Covid-19 (1)

- ▶ Social distancing strategies have introduced challenges in the management of many chronic medical conditions
- ▶ Paucity of data to provide evidence-based clinical recommendations
- ▶ Fracture risk stratification (FRAX), BMD testing may be delayed
- ▶ Standard pretreatment laboratory studies postponed
  - Excl. fluctuating renal function
  - Excl. higher risk of developing hypocalcemia (malabsorptive disorders, hypoparathyroidism, advanced CKD)

## Osteoporosis Management in the Era of Covid-19 (2)

- ▶ Pharmacologic osteoporosis treatment
  - Should not be delayed in patients at high risk for fractures (i.e. recent fracture, chronic high-dose GCs)
  - Initiation via non-face-to-face visit (telemedicine) using oral regimens
  - Hospitalized patients should receive medication initiation while hospitalized
  - No evidence that any osteoporosis therapy increases the risk or severity of Covid-19 infection: continue ongoing therapy
  - In case of temporary disruption of osteoporosis treatment
    - IV BP: delays of several months are unlikely to be harmful
    - DMAb short-term (<2 yrs) : Sequential treatment mandatory with oral BP
    - DMAb long-term (>2 yrs): Sequential treatment mandatory with oral BP, switch to ZOL asap
    - TPT: Sequential treatment mandatory, but delay of transition to oral BP of 2-3 months acceptable

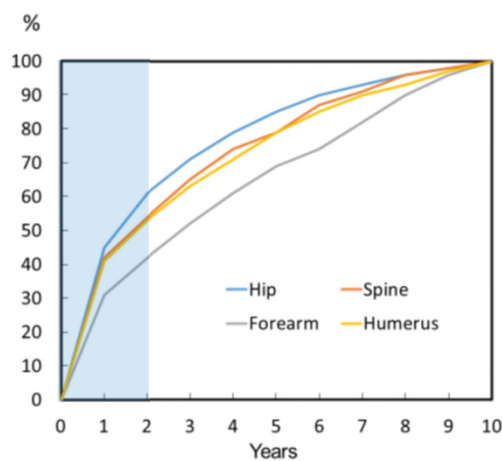
## Differential Effects of Bone-forming Agents on Bone Surfaces



Ferrari S, Nat Rev Rheumatol 2018, 14:128



## «Imminent Fracture Risk» Identification of Patients at Very High Fracture Risk



Increased RR of 2nd fracture within first 2 yrs after 1st fracture

40-60% of recurrent fractures will occur within first 2 yrs

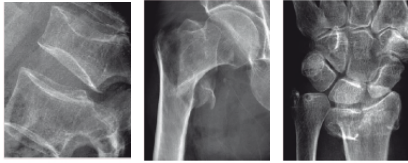
Kanis J et al, Osteoporos Int 2018, 29: 1747

Reykjavik Study (fracture registry)  
Time course of recurrent fractures following individual sentinel fractures (expressed as a percentage of all those experiencing recurrent fractures)

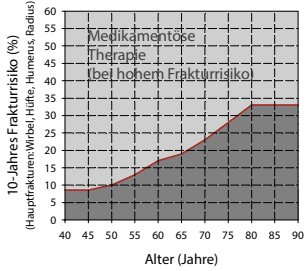


### Osteoporosis Treatment Initiation Recommendations in Switzerland (SVGO 2015)



Low trauma fracture



High fracture risk (FRAX)



www.svgo.ch

### Treatment Recommendations by Level of Fracture Risk

Low → Moderate → High → Very High → Imminent

Vert. fract.

Hip fract.

All MOF

Life Style measures, VitD ± Ca,

SERMS  
Oral BPs

DMAb BPs  
TPT (VFx, T<-3.5)

TPT ROMO



ZOL DMAB  
ROMO

ROMO BPs  
DMAB

DXA after 5-10 yrs

DXA after 2 yrs

Ferrari S, Meier C, et al, Swiss Med Wkly, 2020,150:w20352

## Fracture Risk Stratification

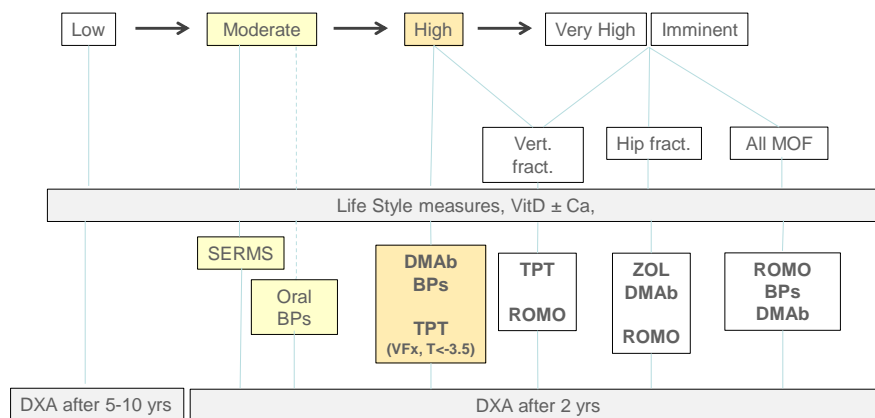
- ▶ **Imminent Risk (i.e. >10% fracture risk within 2 yrs)**
  - Recent (<2 yrs) clinical vertebral fracture or hip low-trauma fracture
  - Any recent MOF after the age of 65 yrs
  
- ▶ **Very high fracture risk**
  - 10-yr probability of MOF by FRAX at least 20% above the intervention threshold at any age (i.e. FRAX ~45% after age of 70 yrs)
  
- ▶ **High risk**
  - Previous MOF (>2 yrs) and/or FRAX probabilities above the intervention threshold but less than 20% above that limit
  - GC-therapy, ablative hormone therapies (if BMD T-score <-1.5 SD)

Ferrari S, Meier C, et al, Swiss Med Wkly, 2020,150:w20352

MOF=major osteoporotic fracture



## Treatment Recommendations by Level of Fracture Risk

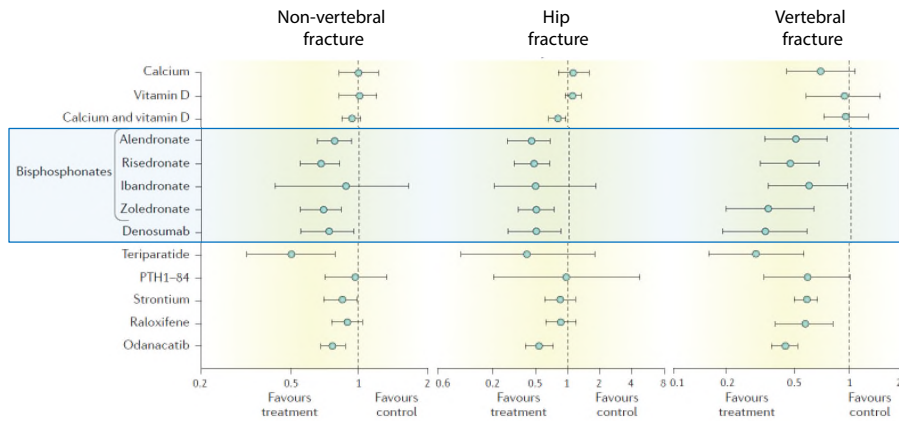


Ferrari S, Meier C, et al, Swiss Med Wkly, 2020,150:w20352



## Anti-fracture Efficacy of Osteoporosis Treatment

### Fracture Prevention by Osteoporotic Agents (RCTs)



Eastell R et al, Nature Rev 2016, 102: 1

OR (95% CI)



## Potential Candidates for «First-line» rhPTH Treatment



Review article | Published 4 June 2014, doi:10.4454/SMW.2014.13952  
 Cite this as: Swiss Med Wkly, 2014;144:w13952  
 The role of teriparatide in sequential and combination therapy of osteoporosis

**Table 2: Potential candidates for first-line treatment with teriparatide.**

Patients with high fracture risk, including

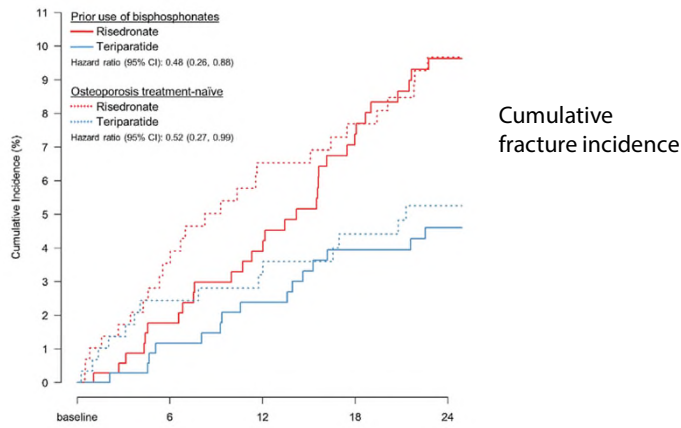
- Low BMD (T-score <-2.5 SD) and prevalent vertebral (≥2 vertebral fractures, Genant grade 2 and 3) or hip fracture
- Low BMD (T-score <-3.0 SD) and additional risk factors (i.e., advanced age, glucocorticoid treatment)
- Low BMD (T-score <-3.5 SD)

BMD = bone mineral density; SD = standard deviation

Meier C et al, Swiss Med Wkly 2014, 144:w13952



## 1st and 2nd-line Treatment with Teriparatide and Fracture Incidence (VERO Study)

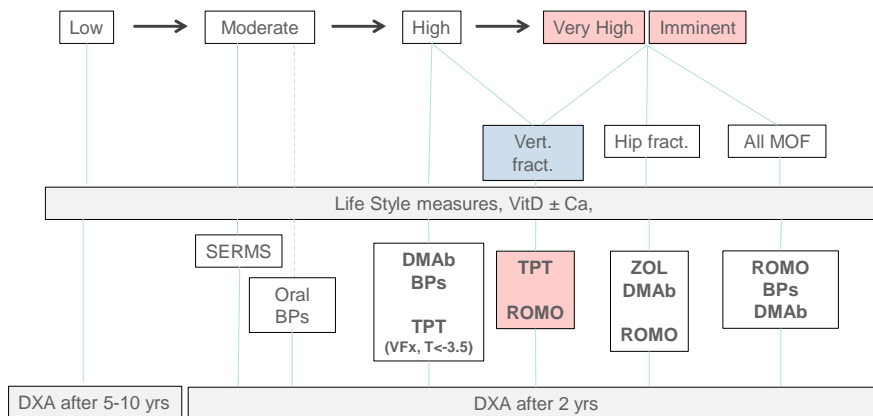


N=1360 with severe osteoporosis, TPD vs RIS for 24 mts  
 At least 2 moderate or one severe Vfx  
 (mean LS T-score -2.3 SD; age 72 yrs)  
 Previous AR drugs 60%, median duration 3.3 yrs; GC use 9%

Kendler D et al, Lancet 2018, 391: 230



## Treatment Recommendations by Level of Fracture Risk



Ferrari S, Meier C, et al, Swiss Med Wkly, 2020,150:w20352



## Effect of Teriparatide and Risedronate on Fracture Incidence in Postmenopausal Osteoporosis (VERO)

	Teriparatide group (n=680)	Risedronate group (n=680)
<b>Age (years)</b>		
<50	7 (1%)	2 (<1%)
50 to <65	144 (21%)	162 (24%)
65 to <80	382 (56%)	405 (60%)
≥80	147 (22%)	111 (16%)
Mean (SD)	72.6 (8.77)	71.6 (8.58)
<b>Race</b>		
White	670 (99%)	653 (96%)
Black or African American	5 (1%)	15 (2%)
Asian	4 (1%)	8 (1%)
Other	1 (<1%)	4 (1%)
Mean height (cm; SD)	154.7 (7.2)	155.0 (7.4)
Mean body mass index (kg/m <sup>2</sup> ; SD)	26.9 (4.61)	27.1 (4.64)
<b>Geographical region*</b>		
North America	91 (13%)	100 (15%)
South America	142 (21%)	159 (23%)
Europe	447 (66%)	421 (62%)
<b>Mean bone mineral density (SD)</b>		
Lumbar spine (g/cm <sup>3</sup> )	0.86 (0.15)	0.86 (0.15)
T score†	-2.27 (1.24)	-2.29 (1.22)
Femoral neck (g/cm <sup>3</sup> )	0.66 (0.11)	0.67 (0.11)
T score†	-2.27 (0.76)	-2.24 (0.74)
Total hip (g/cm <sup>3</sup> )	0.74 (0.11)	0.74 (0.12)
T score†	-1.95 (0.87)	-1.95 (0.82)

<b>Prevalent fractures</b>		
<b>Vertebral fractures†</b>		
≥1	679 (100%)	679 (100%)
1	231 (34%)	240 (35%)
2	178 (26%)	174 (26%)
3	104 (15%)	101 (15%)
4	60 (9%)	62 (9%)
≥5	106 (16%)	102 (15%)
<b>Grade of the most severe vertebral fracture‡</b>		
SQ2	73 (11%)	67 (10%)
SQ3	606 (89%)	612 (90%)
<b>Non-vertebral fractures</b>		
<b>Patients older than 40 years with ≥1 fracture</b>		
1	166 (24%)	164 (24%)
2	80 (12%)	81 (12%)
3	40 (6%)	21 (3%)
4	6 (1%)	11 (2%)
≥5	6 (1%)	7 (1%)

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Kendler D et al, Lancet 2018, 391: 230



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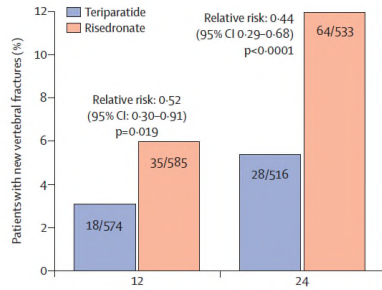
Kendler D et al, Lancet 2018, 391: 230



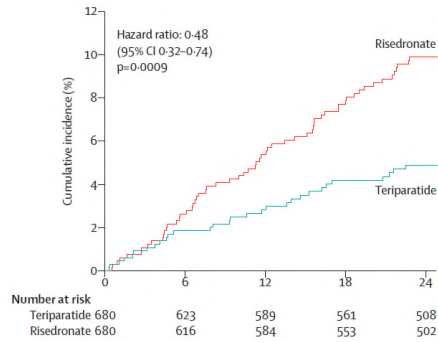


## Effect of Teriparatide and Risedronate on Fracture Incidence in Postmenopausal Osteoporosis (VERO)

Incidence of new vertebral fractures



First clinical fracture



N=1360 with severe osteoporosis, TPD vs RIS for 24 mts  
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Kendler D et al, Lancet 2018, 391: 230



## Effect of Teriparatide and Risedronate on Fracture Incidence in Postmenopausal Osteoporosis (VERO)

	Teriparatide group	Risedronate group	Effect size (95% CI)*	p value
<b>Primary endpoint</b>				
New vertebral fracture†	28 (5%)	64 (12%)	0.44 (0.29-0.68)	<0.0001
<b>Secondary gated endpoints</b>				
New and worsened vertebral fracture†	31 (6%)	69 (13%)	0.46 (0.31-0.68)	<0.0001
Pooled clinical fracture‡§	30 (5%)	61 (10%)	0.48 (0.32-0.74)	0.0009
Non-vertebral fragility fracture§	25 (4%)	38 (6%)	0.66 (0.39-1.10)	0.10
Major non-vertebral fragility fracture§	18 (3%)	31 (5%)	0.58 (0.32-1.05)	0.06
<b>Secondary non-gated endpoints</b>				
New moderate (SQ2) or severe (SQ3) vertebral fracture†	26 (5%)	63 (12%)	0.42 (0.27-0.65)	<0.001
New multiple vertebral fracture†	2 (<1%)	12 (2%)	0.16 (0.04-0.74)	0.007
Pooled fragility and traumatic non-vertebral fracture§	40 (7%)	57 (9%)	0.70 (0.46-1.05)	0.08

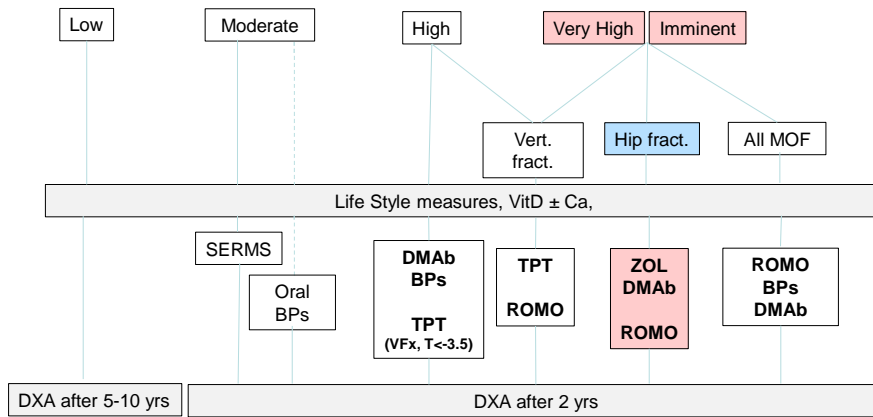
AE with TPT: dizziness, limb pain, hypercalcemia; no ONJ or AFF

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## Treatment Recommendations by Level of Fracture Risk

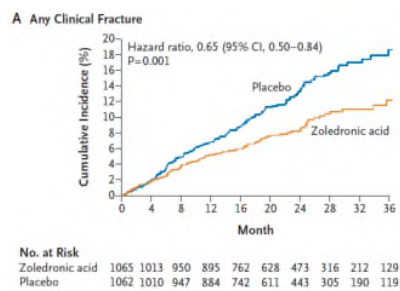


Ferrari S, Meier C, et al, Swiss Med Wkly, 2020,150:w20352



## Treatment Options in High Fracture Risk Patients

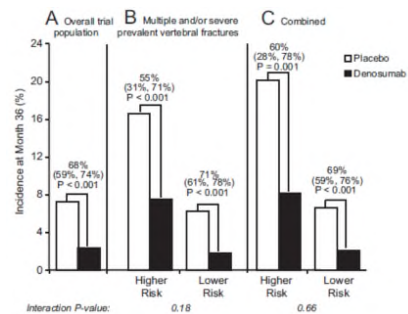
### Zoledronate (Hip Study)



RCT pcd; ZOL vs PBO  
 2127 **with hip fx**

Lyles KW et al, NEJM 2007, 357: 18

### Denosumab (FREEDOM posthoc)

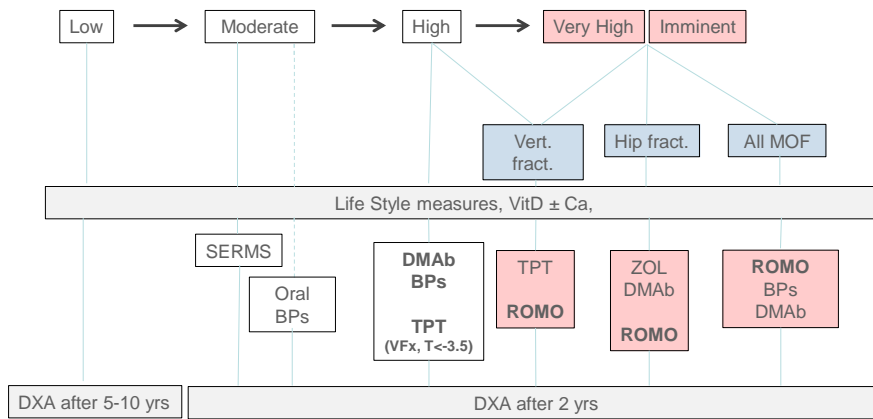


RCT pcd; DmAb vs PBO  
 n=7808 pmp women, T <-2.5 SD, 24% Fx

Boonen S et al, J Clin Endocrinol Metab 2011, 96: 1727



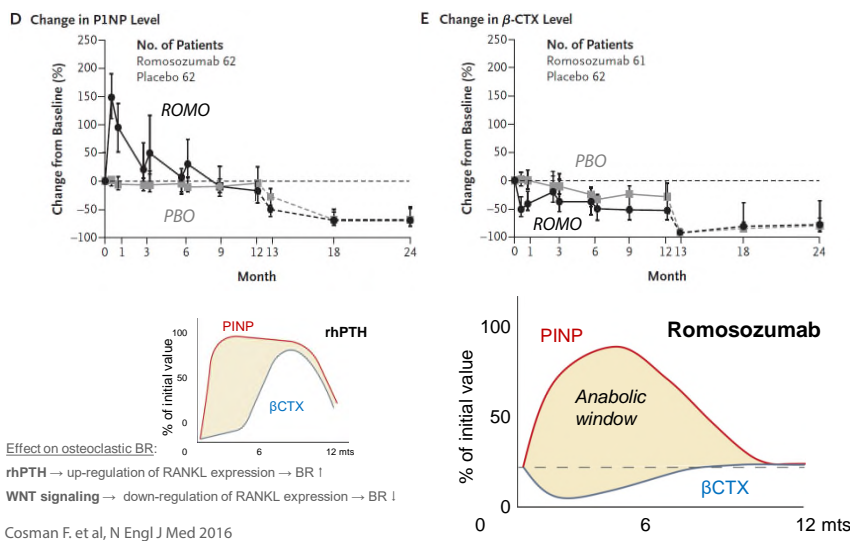
## Treatment Recommendations by Level of Fracture Risk



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## Uncoupling of Bone Formation and Bone Resorption during Romosozumab Therapy



Cosman F et al, N Engl J Med 2016



## Romosozumab vs Teriparatide in Postmenopausal Women with Osteoporosis transitioning from Oral BPs

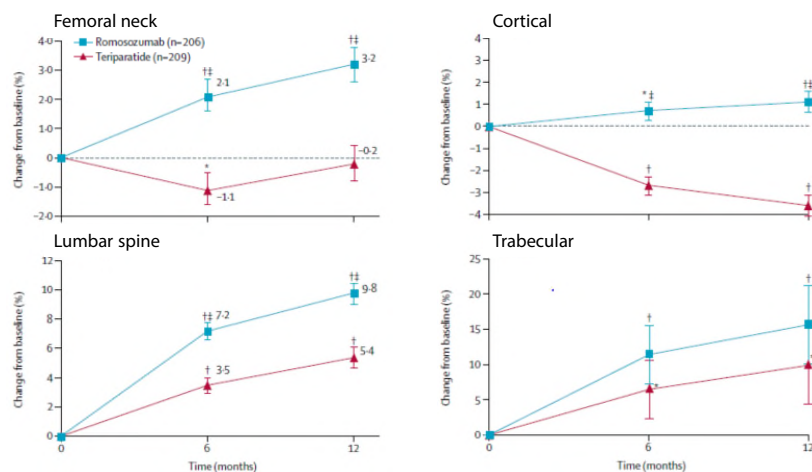
	Romosozumab (n=218)	Teriparatide (n=218)
Age (years)	71.8 (7.4)	71.2 (7.7)
Race		
White	191 (88%)	196 (90%)
Other	23 (11%)	18 (8%)
American Indian or Alaska native	4 (2%)	1 (<1%)
Asian	0	2 (1%)
Multiple	0	1 (<1%)
Oral bisphosphonate use in the 3 years before screening	218 (100%)	218 (100%)
Alendronate in the year before screening	218 (100%)	216 (99%)
Duration of previous bisphosphonate use (years)	6.2 (2.9)	6.2 (2.9)
Duration of previous alendronate use (years)	5.5 (3.2)	5.8 (3.1)
Alendronate use in the 3 years before the study	192 (88%)	202 (92%)
BMD T score		
Total hip	-2.27 (0.75)	-2.21 (0.72)
Femoral neck	-2.49 (0.67)	-2.43 (0.66)
Lumbar spine	-2.83 (1.10)	-2.87 (1.04)
Serum CTX (pmol/L)*	982 (654-1348)	1012 (732-1378)
Serum P1NP (µmol/L)†	0.33 (0.24-0.45)	0.33 (0.27-0.44)
Previous fracture	218 (100%)	217 (<100%)
Total hip cortical volumetric BMD by QCT (mg/cm³)	472.8 (64.3)	475.8 (57.5)
Total hip integral volumetric BMD by QCT (mg/cm³)	194.9 (38.9)	194.5 (34.4)
Hip strength under fall loading conditions (N)	2892 (494)	2923 (506)

Phase III RCT, open label (STRUCTURE Trial)  
 436 pmp op, , oral BP for at least 3 yrs  
 T-Score <-2.5 SD at any site and prevalent fracture

Langdahl B et al, Lancet 2017, 390: 1585



## Romosozumab vs Teriparatide in Postmenopausal Women with Osteoporosis transitioning from Oral BPs



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