What's Next on the Horizon:
Promising Therapies for Osteoporosis Treatment

Rachel Pessah Pollack, MD, FACE
Assistant Clinical Professor of Medicine
Icahn School of Medicine at Mount Sinai, New York
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Disclosures

- Industry support
  - Speaker for Boehringer Ingelheim/Lilly
- Off label drug use
  - None

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Objectives

- Understand the pathophysiology behind promising new bone treatment agents
- Identify data regarding the efficacy, risks, and benefits of potential anabolic and antiresoptive agents on the horizon

Available Options for Osteoporosis Treatment

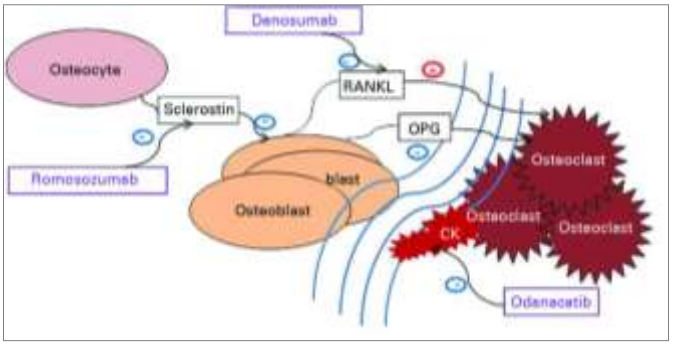
Inhibit Bone Resorption	Stimulate Bone Formation
Alendronate (Fosamax, generic)	Teriparatide (Forteo)
Risedronate (Actonel, Atelvia, generic)	PTH 1-84*
Ibandronate (Boniva, generic)	
Zoledronic acid (Reclast, generic)	
Denosumab (Prolia)	
Raloxifene (Evista, generic)	
Calcitonin (Miacalcin, Fortical)	
Estrogen (various)	
Strontium ranelate*	*not approved in the US for osteoporosis

What Are The Clinical Needs For More Osteoporosis Treatments?

- Oral medications without gastrointestinal side effects
- More anabolic options
- Medications not linked to rare side effects (Osteonecrosis of the jaw, atypical fractures)
- Convenient and cost-effective medications

Options on the Horizon

- Odanacatib – Cathepsin K Inhibitor
- Romosozumab – Sclerostin Inhibitor
- Abaloparatide – Recombinant PTHrP analogue



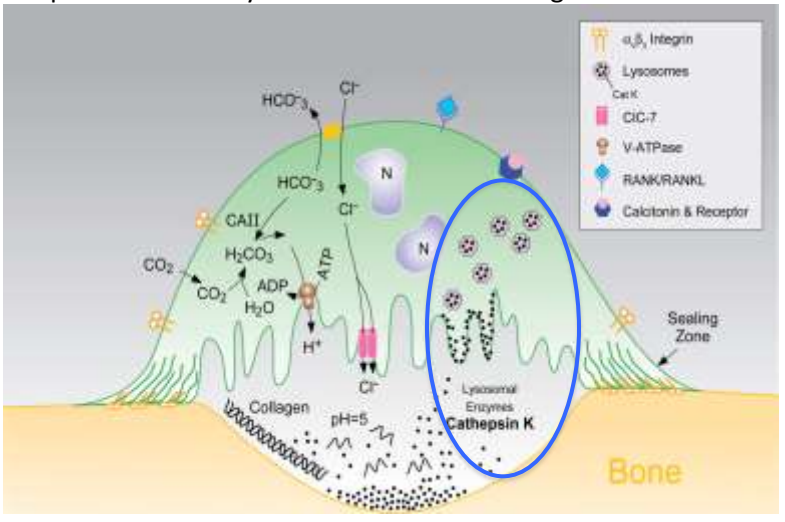
Farrier et al. *Bone Joint J.* 2016; Feb 98-B2

Options on the Horizon

- **Odanacatib – Cathepsin K Inhibitor**
- Romosozumab – Sclerostin Inhibitor
- Abaloparatide – Recombinant PTHrP analogue

Cathepsins are a Family of Cysteine Proteases

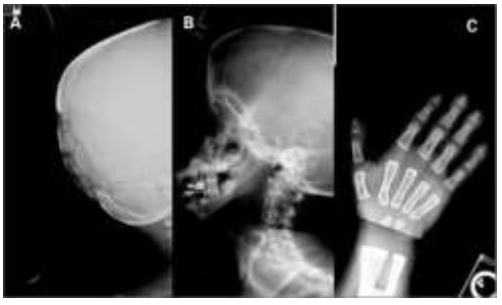
Cathepsin K stored in lysosomes and leads to degradation of bone



Rodan SB et al. IBMS Bonekey. 2008;5(1):16-24.

Pycnodysostosis Due to Genetic Deficiency of Cathepsin K

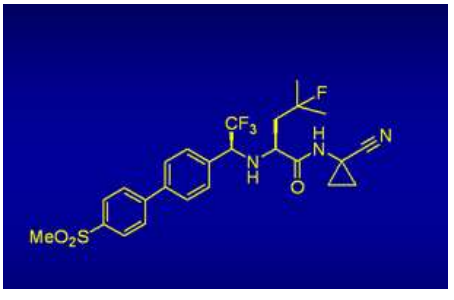
- Autosomal recessive
- Short stature, short fingers
- Abnormally dense but brittle bones
- Midface is flattened



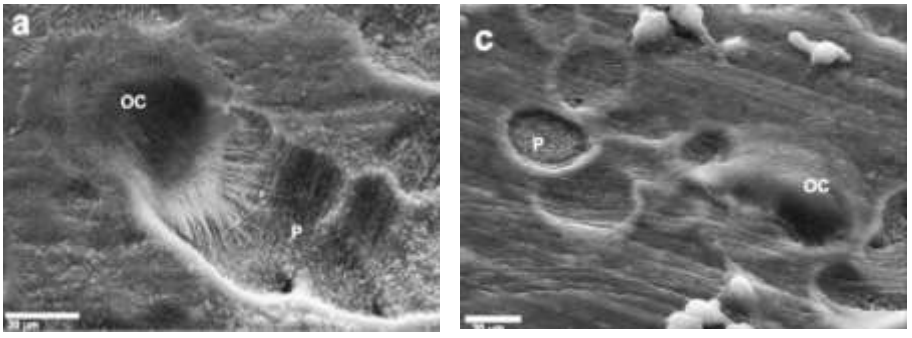
Henri de Toulouse-Lautrec (1864-1901)

Odanacatib is a Non-Basic, Selective Inhibitor of Cathepsin K

- Once weekly oral dosing
- Increased BMD in the spine and hip
- Reduced fractures in spine, hip, non-vertebral areas
- Not affected by food



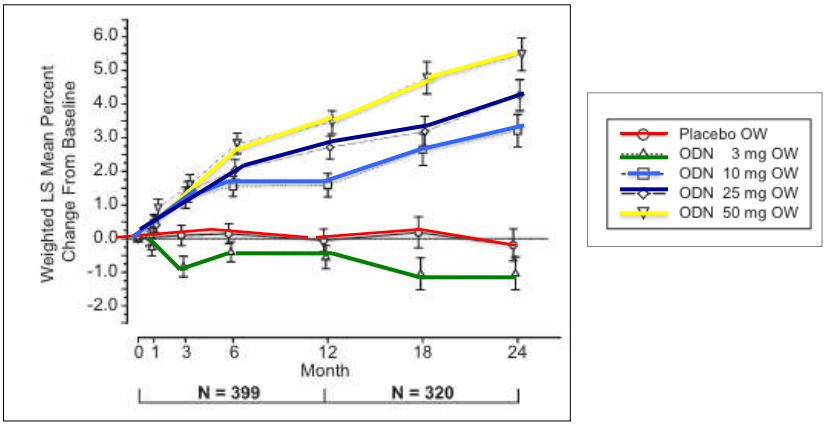
Odanacatib Treatment Results in Smaller, More Shallow Resorption Pits



Control **Odanacatib**

Leung P et al. Bone. 2011;49: 623-635

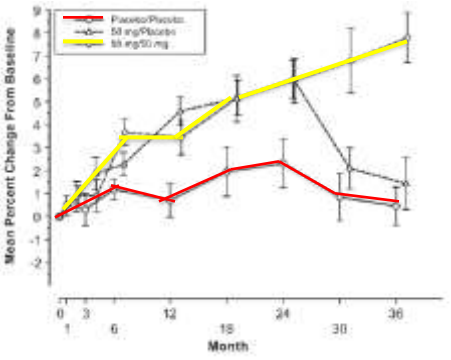
Dose Dependent Increases in Lumbar Spine BMD with Odanacatib Treatment



Bone H et al. *J Bone Miner Res*. 2010; 25(5): 937-947

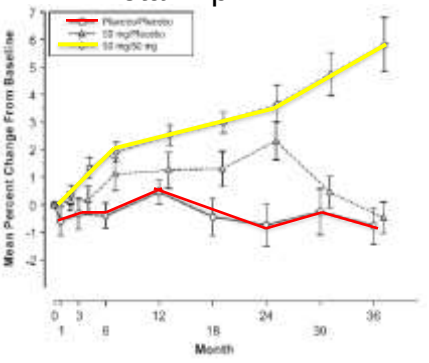
BMD Increases in Lumbar Spine and Total Hip in Odanacatib Phase II Trial

Lumbar Spine BMD



7.9% BMD increase at 36 months with 50 mg q week

Total Hip BMD



5.8% BMD increase at 36 months with 50 mg weekly dose

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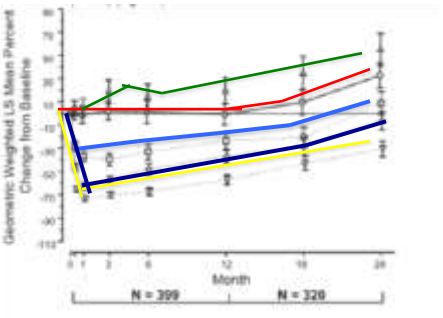
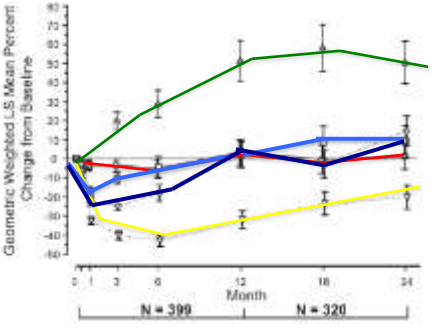
Eisman JA et al. *J Bone Miner Res*. 2011; 26: 242-251

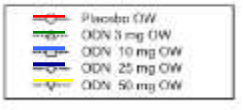
Bone Resorption and Formation Markers Influenced By Dose of Odanacatib Treatment

Serum C-Terminal Telopeptides of Type 1 Collagen (sCTx) ng/mL



Serum N-Terminal Propeptides of Type 1 Collagen (sP1NP) ng/mL





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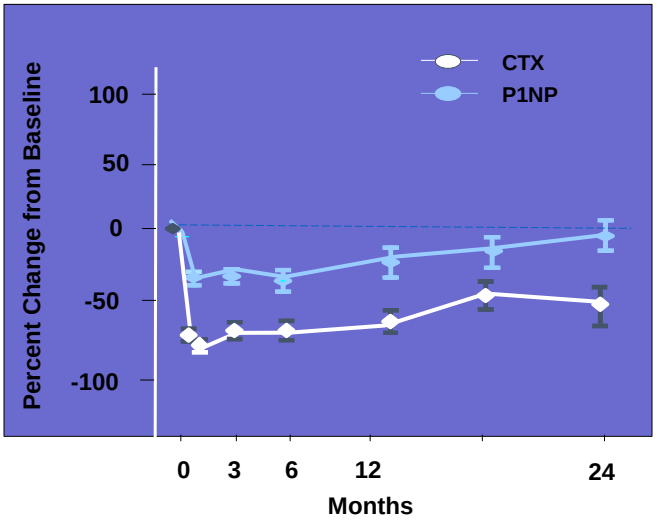
Bone H et al. *J Bone Miner Res*. 2010; 25(5): 937-947

Effect of Odanacatib on Bone Remodeling



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Courtesy of Michael McClung

Phase III Long-Term Odanacatib Fracture Trial (LOFT) Shows Fracture Reduction and BMD Improvement

Postmenopausal women ≥65 years of age with osteoporosis [BMD T-score ≤-2.5 total hip (TH) or femoral neck (FN), or prior vertebral fracture (Fx) and TH/FN T-score ≤-1.5]

- Randomized, placebo-controlled study
- ODN 50 mg weekly for ~3 years:
  - 54% RR reduction new and worsening morphometric vertebral Fx (P<0.001)
  - 47% RR reduction of clinical hip Fx (P<0.001)
  - 23% RR reduction of clinical non-vertebral Fx (p<0.001)
  - 72% RR reduction of clinical vertebral Fx (P<0.001)
- ODN 50mg weekly for 5 years:
  - 11.2% increase in lumbar spine BMD (p<0.001)
  - 9.5% increase in TH BMD (p<0.001)

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McClung and Papapoulos et al. ASBMR 2014

Adverse Effects With Odanacatib

- **Cardiovascular disease**
  - Slight increase in risk of atrial fibrillation and CVA events in odanacatib group
  - 109 patients (1.4%) CVA in drug arm, compared to 89 (1.1%) in the placebo arm
- **Skin**
  - Morphea-like skin lesions more frequent in odanacatib group compared to placebo (12 vs 3, p = 0.04)
- **Atypical Femoral Fractures (AFF)**
  - 5 AFF in odanacatib group (0.1% incidence, unrelated to duration of treatment); no cases in placebo (p = 0.02)
- **Osteonecrosis of the Jaw (ONJ)**
  - No cases of ONJ

McClung and Papapoulos et al. ASBMR 2014

Cardiovascular Events in LOFT Trial: Preliminary Analyses

Event	Odanacatib n (incidence)	Placebo n (incidence)	HR (95% CI)
Atrial fibrillation	92 (1.1%)	80 (1.0%)	NA
MACE	215	194	1.12 (0.93–1.36)
Stroke	109 (1.4%)	86 (1.1%)	1.28 (0.97–1.70)
Cerebrovascular events	305 (3.8%)	290 (3.6%)	1.06 (0.91–1.25)
Death	271	242	1.13 (0.95–1.35)

MACE = Major Adverse Cardiac Events

Papapoulos et al. ASBMR 2014

Odanacatib Summary

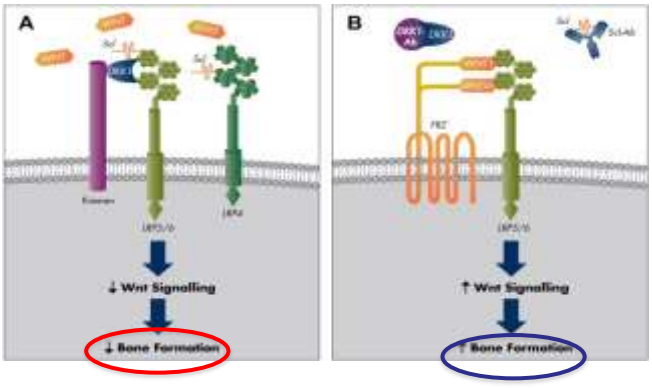
- Inhibiting Cathepsin K provides a potentially efficacious and unique mechanism of action to treat osteoporosis
- Generally safe but possible cardiovascular and other adverse effects noted
- Await further status on
  - Final adjudication of CV events
  - Follow-up of placebo-controlled results for a full 5 years

Options on the Horizon

- Odanacatib – Cathepsin K Inhibitor
- **Romosozumab – Sclerostin Inhibitor**
- Abaloparatide – Recombinant PTHrP analogue

Romosozumab is a Humanized Monoclonal Antibody Against Sclerostin

Sclerostin Inhibits Wnt Signaling | Abs to Sclerostin Stimulate Wnt Signaling



Ke HZ et al. *Endocrine Reviews*. 2012; 33: 747-783.

Numerous skeletal manifestations from disorders associated with Wnt signaling

Disorder	Skeletal manifestation	Gene affected
Sclerosteosis	Bone overgrowth	*SOST*
van Buchem syndrome	Bone overgrowth	*SOST*
High bone mass syndrome	Increased bone mass	*LRP5*
Osteoporosis–pseudoglioma syndrome	Osteoporosis, fractures	*LRP5*
Cenani–Lenz syndactyly	Abnormal limb development	*LRP4*
Osteogenesis imperfecta	Osteoporosis, fractures	*WNT1*

Canalis E. *Nature Reviews Endocrinology* **9**, 575-583; 2013

Sclerosteosis Results in Skeleton Resistant to Trauma

- Autosomal recessive
  - Less than 100 people described
- Mutation in SOST gene leads to genetic deficiency of sclerostin
- High bone mass and increased bone strength
  - No known fracture among affected individuals
- Neurologic complications in homozygotes from bone compression; none in heterozygotes

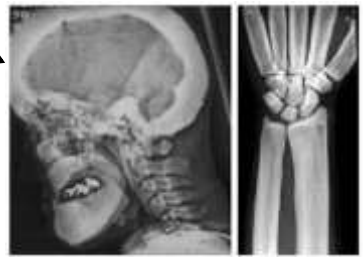
S. Larsson / Injury, Int. J. Care Injured 47 S1 (2016) S31–S35

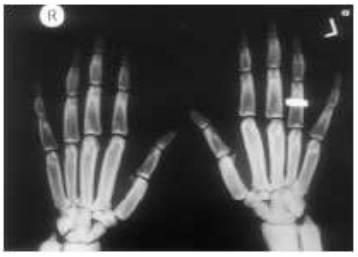
Chronology of a patient with Sclerosteosis

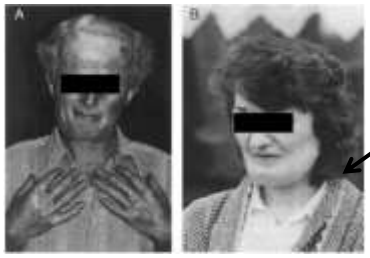
Epstein S et al. *S Afr Med Journal. 1979*

Sclerosteosis and Van Buchem Disease

skull overgrowth



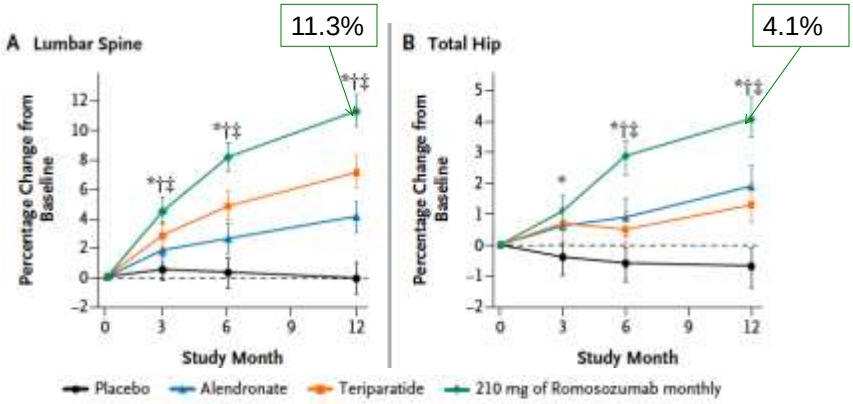




mandible prominence

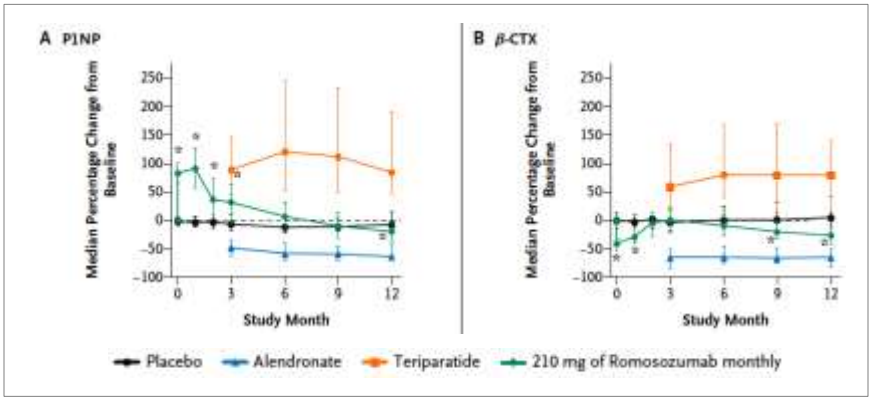
Romosozumab Results in Significant Improvement in Lumbar Spine and Total Hip BMD

- Romo increased BMD superior to Teriparatide and Alendronate
- Similar adverse reactions to placebo except injection site reactions
  - 4% PBO, 12% Romo



McClung MR et al. N Engl J Med. 2014;370:412-420.

Romosozumab Results in Increase in Bone Formation Markers; Decreased Bone Resorption



- Phase III fracture prevention studies ongoing

McClung MR et al. N Engl J Med. 2014;370:412-420.

FRActure study in postmenopausal woMen with ostEoporosis (FRAME) – preliminary data

- Multi-center, international, RCT, double-blind, romo 12 months vs placebo, followed by 12 months denosumab
- Reduced incidence new vertebral fracture 12 and 24 months (primary endpoint)
  - 73% RR vertebral fx 12 mos c/w placebo
  - Transitioned to denosumab and through 24 mos, RR new vertebral fx reduction 75%
  - Reduction in incidence of clinical fractures 36% - composite of vertebral and non-vertebral fractures through 12 months (secondary endpoints)
- Did not meet secondary endpoint of reduction in incidence of non-vertebral fractures 12, 24 months
- Data analysis ongoing

Amgen Press Release Feb 2016

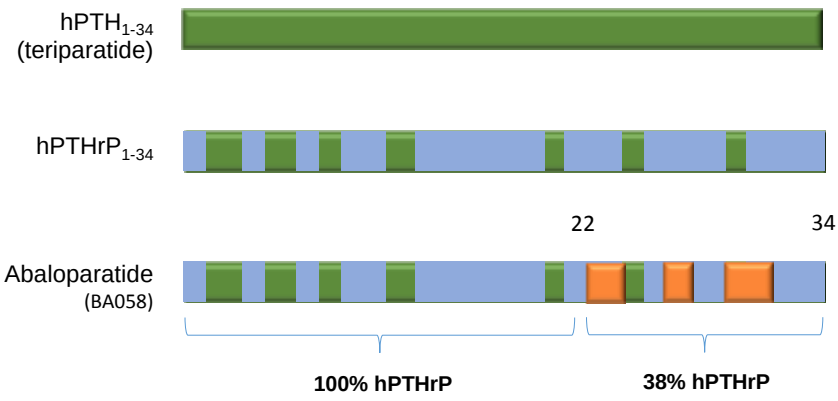
Romosozumab Summary

- Romosozumab increases BMD at the lumbar spine, total hip and femoral neck
- Bone formation markers with rapid transitory increase and bone resorption markers decreased
- Phase III fracture trials (BRIDGE and FRAME) ongoing with completion expected in 2016

Options On the Horizon

- Odanacatib – Cathepsin K Inhibitor
- Romosozumab – Sclerostin Inhibitor
- **Abaloparatide – Recombinant PTHrP analogue**

Abaloparatide Has a Novel Amino Acid Sequence



Functionally important amino acid replacements at positions between residues 22-34

*Courtesy of Paul Miller, Endo San Diego, March 2015

Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE) is a Phase 3 Fracture Prevention Trial

- Objective: assess efficacy and safety 18-months abaloparatide vs. placebo or teriparatide in postmenopausal women with osteoporosis
  - Multicenter, multinational, double-blind, placebo-controlled
  - Healthy, ambulatory postmenopausal women aged 50 to 85; postmenopausal ≥5 years
  - T-score ≤ -2.5 spine or hip with prior vertebral or low-trauma fracture
- 2,463 patients enrolled and randomized to 18-months of daily sc abaloparatide 80 µg, placebo, or teriparatide 20 µg

Baseline Characteristics of Study Population

	Placebo (N=821)	Abaloparatide (N=824)	Teriparatide (N=818)	Overall (N=2463)
Age (years)	68.1	68.9	68.8	68.8
Age groups (%)				
< 65 years	19.6	18.4	18.5	18.8
65 to 74	62.4	62.7	61.5	62.2
> 74	18	18.8	20.0	19.0
Baseline Vertebral Fractures (%)	44.6	43.2	46.0	44.6
Baseline Non-Vertebral Fractures (%)	48.8	47.3	44.1	46.8
LS BMD T-score	-2.9	-2.9	-2.8	-2.9
TH BMD T-score	-1.9	-1.9	-1.8	-1.9
FN BMD T-score	-2.2	-2.2	-2.1	-2.1

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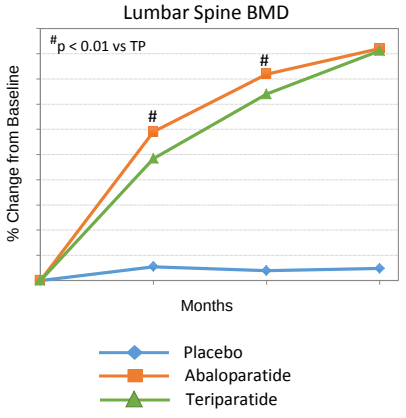
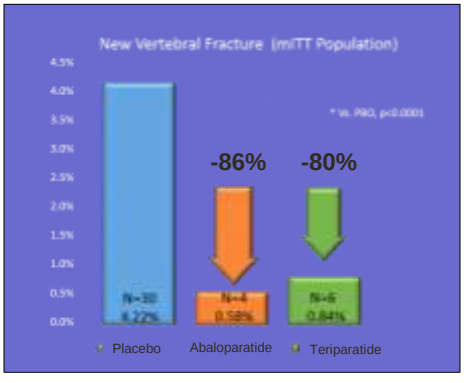
Vertebral Fractures Decreased With Abaloparatide and Teriparatide Versus Placebo





86% reduction in new vertebral fracture on Abaloparatide

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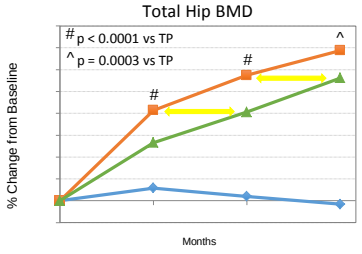
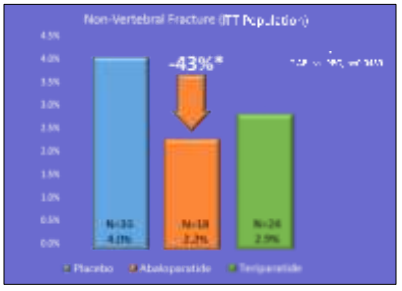
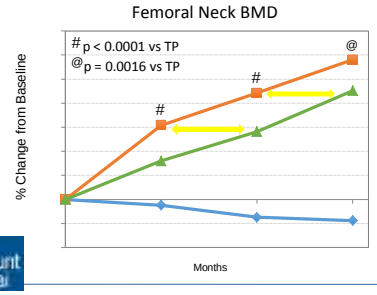
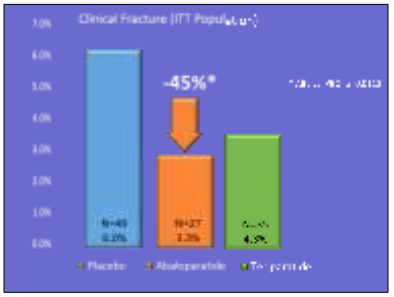
BMD Response to Abaloparatide Greater in Both Spine and Hip Than Teriparatide









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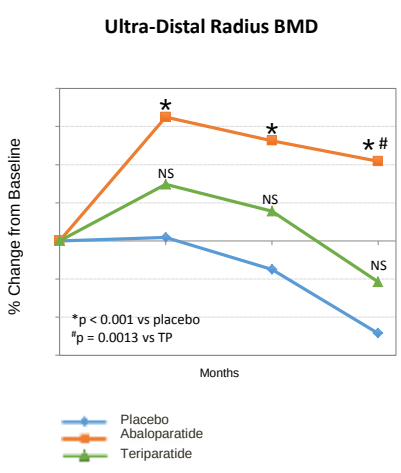
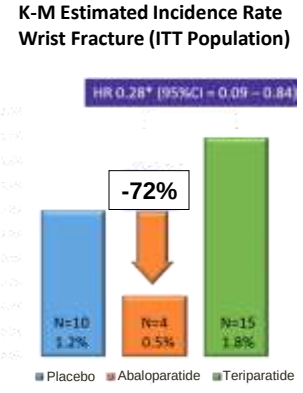
Courtesy of Paul Miller, Endo San Diego, March 2015

Incidence of Wrist Fracture Lower in Abaloparatide Group versus Teriparatide





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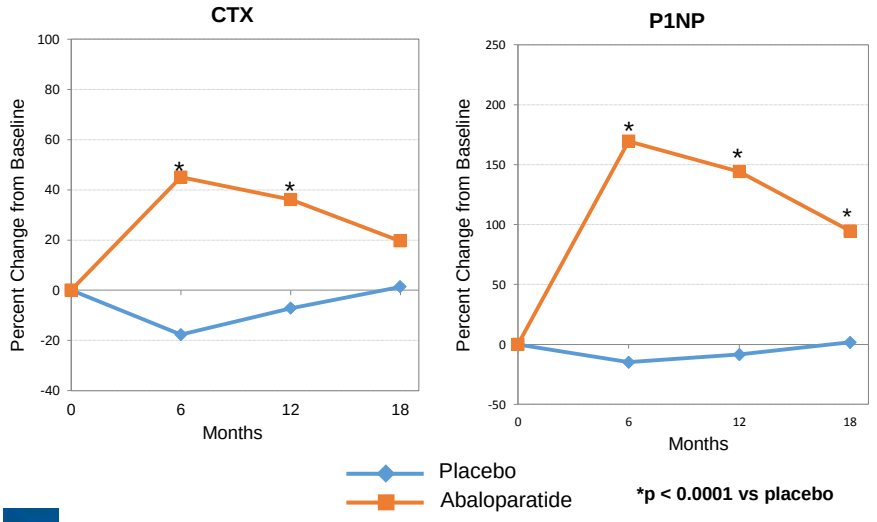
Courtesy of Paul Miller, Endo San Diego, March 2015

Increase in Bone Resorption and Formation Markers on Abaloparatide



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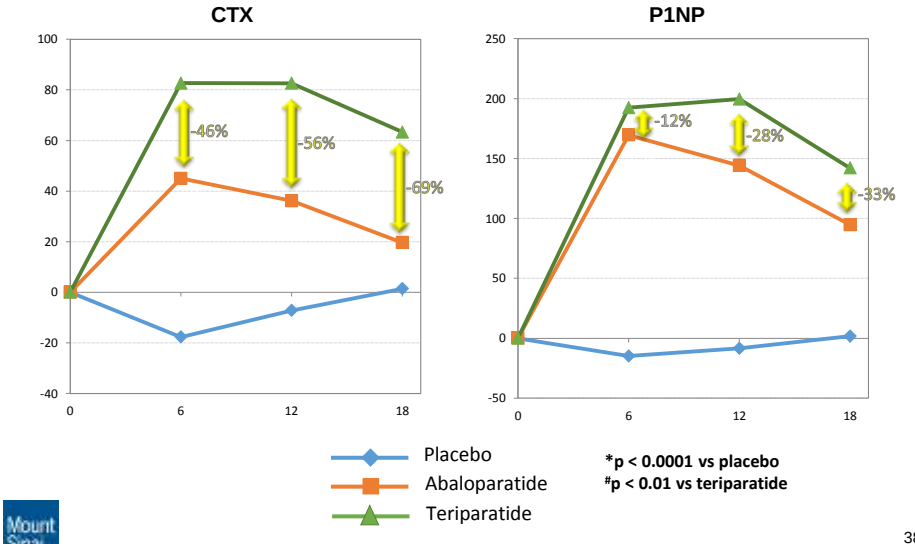
Courtesy of Paul Miller, Endo San Diego, March 2015

Modest Rise in Bone Resorption and Formation Markers With Abaloparatide Versus Teriparatide



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Courtesy of Paul Miller, Endo San Diego, March 2015

Abaloparatide With Few Side Effects and Less Hypercalcemia Compared with Teriparatide

Safety Population (N=2460)

Most Frequently Observed Events	Placebo (N=820)	Abaloparatide-SC (N=822)	Teriparatide (N=818)
Back Pain	10.0%	8.6%	7.2%
Arthralgia	9.8%	8.5%	8.6%
Upper respiratory tract infection	8.9%	9.0%	9.8%
Hypercalciuria	8.9%	10.9%	12.5%
Dizziness	6.1%	10.0%	7.3%

Hypercalcemia (lab values > 10.7 mg/dL at any time point)	Placebo (N=820)	Abaloparatide-SC (N=822)	Teriparatide (N=818)
Hypercalcemia event rate (primary analysis based on albumin corrected serum calcium)	0.37%	3.41%*	6.36%*

* ABL vs. TPTD, p=0.0055

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Abaloparatide Summary

- Significant reduction in incidence of new vertebral fractures and non-vertebral fractures compared with placebo
- Slightly more efficacious than teriparatide (increased BMD total hip and femoral neck)
- Safety profile similar to teriparatide; less hypercalcemia noted
- Pivotal trial data in peer-review

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Several Agents Show Promising Results for Osteoporosis Treatment in the Future

- **Cathepsin-K inhibitor** (odanacatib), is a weekly oral antiresorptive agent with BMD improvement over five years and decreased hip and vertebral fracture risk
- **Sclerostin inhibitor** (romosozumab) is a monthly agent with potent anabolic effects, mild antiresorptive effects
- **PTH-like analogue** (abaloparatide), is a daily sc anabolic agent with less hypercalcemia and less bone resorption than teriparatide

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Stay Tuned…

Acknowledgements:
- Pauline Camacho, MD
- Paul Miller, MD
- Michael McClung, MD
- Steve Petak, MD

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