Osteoporosis Update 2014: New Frontiers in Therapeutics

15th Asia-Oceana Congress of Endocrinology
Radisson Blu Hotel
Cebu City, Philippines
October 8-11, 2014

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• Relevant Financial Relationships: None

• Off-Label Usage: None
Objectives

• Review mechanisms by which new antiresorptive and anabolic therapies increase BMD and reduce fractures in postmenopausal and age-related osteoporosis
• Summarize available clinical trial data on new antiresorptive and anabolic therapies to treat postmenopausal and age-related osteoporosis
• Discuss when new antiresorptive and anabolic therapies should be used in treatment of postmenopausal and age-related osteoporosis
Why Are New Therapies Needed for Osteoporosis?

- Need for greater efficacy in treatment, especially for hip and nonvertebral fracture risk reduction
- Need for reduced risk profile
- Need for agents that can be used in patients with chronic kidney disease
- Need for therapies that can be applied in specific clinical situations
- Greater choices for individual patient
Bone Remodeling Cycle

- Four Stages of Bone Remodeling:
  - Recruitment and activation of osteoclasts
  - Osteoclast resorption of bone packets
  - Recruitment and activation of osteoblasts
  - Filling in of resorption pits
- Resorption and formation normally coupled
Osteoporosis: Basic Multicellular Unit

### Osteoporosis Treatment Options

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>RESORPTION</th>
<th>FORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-remodeling agents</strong></td>
<td><img src="down.png" alt="down" /></td>
<td><img src="down.png" alt="down" /></td>
</tr>
<tr>
<td>– bisphosphonates, SERMs,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcitonin, RANKL inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-resorptive agent</strong></td>
<td><img src="down.png" alt="down" /></td>
<td></td>
</tr>
<tr>
<td><strong>Bone activating agent</strong></td>
<td></td>
<td><img src="up.png" alt="up" /></td>
</tr>
<tr>
<td>– PTH and its analogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anabolic agent</strong></td>
<td></td>
<td><img src="up.png" alt="up" /></td>
</tr>
</tbody>
</table>
Challenges of Osteoporosis Treatment

- Success has been defined as the absence of fracture—which from a patient perspective is not very “exciting”
- Economic and non-economic treatment costs
- Uncertainty about the optimal duration of therapy
- Uncertainty about “treatment failure”
- Balancing the benefits and risks of treatment—and of no treatment
Pathogenesis of Osteoporosis

AGING

MENOPAUSE

OTHER RISK FACTORS

RESORPTION > FORMATION

Bone Loss

LOW PEAK BONE MASS

POOR BONE QUALITY

LOW BONE DENSITY

FRACTURES

FALLS

### FDA-Approved Therapeutic Options

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stops bone loss</td>
<td>Reduces vertebral fractures</td>
</tr>
</tbody>
</table>

#### Prevention
- Estrogen
- Alendronate
- Risedronate
- Ibandronate
- Zoledronic acid
- Raloxifene
- Conjugated estrogens/bazedoxifene

#### Treatment
- Calcitonin
- PTH (teriparatide)
- Denosumab
# Anti-Remodeling Agents: Clinical Trial Results

**Trials of Different Agents Cannot Be Compared Directly**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Spine</th>
<th>Non-spine</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Denosumab</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alendronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>+</td>
<td>§</td>
<td>-</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+ documented in randomized, controlled trial;  - effect not documented
§ effect documented only in a post hoc analysis of a high-risk sub-group (femoral neck T score < -3)
New Antiresorptive Agents

- Anti-RANKL Monoclonal Antibody: Denosumab (MK-0558)
- Cathepsin K Inhibitors: Odanacatib, ONO-5334, others
Denosumab

- First in class anti-receptor activator of nuclear factor κB (RANK) ligand (RANKL) monoclonal antibody
- Blocks RANKL secreted predominantly by osteocytes to stimulate osteoclast recruitment and activation
- FREEDOM phase III, randomized, double-blind, placebo-controlled clinical trial showed that denosumab reduced vertebral fractures by 68%, hip fractures by 40%, and nonvertebral fractures by 20%
Denosumab: FREEDOM Fracture Reduction Trial

- Fracture Reduction Trial
- Primary Endpoint: Reduction in New Vertebral Fracture
- Secondary Endpoints: Reduction in Hip and Nonvertebral Fractures
- 7,868 postmenopausal women
- Mean Age 72.3 years
- Entry L-spine or Total Hip BMD T-score: -2.5 to -4.0
- Denosumab 60 mg SQ q 6 months
- 3 years duration

68% Reduction

% Patients with Fracture

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PBO</th>
<th>DEN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vert Fx</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Denosumab: FREEDOM Fracture Reduction Trial

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• Primary Endpoint: Reduction in New Vertebral Fracture
• Secondary Endpoints: Reduction in Hip and Nonvertebral Fractures
• 7,868 postmenopausal women
• Mean Age 72.3 years
• Entry L-spine or Total Hip BMD T-score: -2.5 to -4.0
• Denosumab 60 mg SQ q 6 months
• 3 years duration
Denosumab: Long-Term Extension

Mechanism of Action of Cathepsin K Inhibitors


Key points

- Cathepsin K, a cysteine protease that is highly expressed in osteoclasts, degrades proteins present in the organic matrix of bone, and, therefore, has a fundamental role in bone resorption
- Loss-of-function mutations in the cathepsin K gene lead to pycnodysostosis, a disorder characterized by osteosclerosis, bone fragility, and decreased bone turnover
- In preclinical studies, cathepsin K inhibitors decreased bone resorption markers and prevented bone loss induced by ovariectomy
- The concerning off-target effects reported in early human clinical trials of cathepsin K inhibitors have not been observed with the newer, more-selective compounds currently in phase III trials
- Clinical trials have demonstrated that cathepsin K inhibitors are potent antiresorptive drugs that act exclusively on bone resorption without perturbing bone formation or osteoclast survival, and demonstrate rapid reversibility
Mechanism of Osteoclast-Mediated Bone Resorption

Odanacatib: Clinical Trials

• Odanacatib
  – a non-lysosomotropic selective inhibitor of cathepsin K

• Study design:
  – Phase 2: 3, 10, 25 or 50 mg once weekly vs placebo

  • Dose-dependent increase in BMD
  • Inhibition of resorption more than formation
  • Rapid “off” effect when treatment was stopped
  • No important safety issues noted over 5 years

Odanacatib: Bone Turnover Markers

Serum CTx (vs. baseline, %)

Mean Percent Change from Baseline

Month

-100 -50 0 50 100 150

Placebo/Placebo
50 mg/Placebo
50 mg/50 mg

Serum P1NP (vs. baseline, %)

Mean Percent Change from Baseline

Month

-100 -50 0 50 100

Placebo/Placebo
50 mg/Placebo
50 mg/50 mg

Odanacatib: Bone Mineral Density

Lumbar Spine BMD

Total Hip BMD

Odanacatib: Bone Mineral Density: 5 Years

Odanacatib: Clinical Trials

- Phase 3:
  - Event-driven, randomized, placebo-controlled, multi-center trial with spine and hip fracture as endpoints
  - >16,000 postmenopausal women with osteoporosis
  - Data and Safety Monitoring Board recommended stopping the trial because of “robust” efficacy
  - Results and regulatory filing anticipated in late 2014
Comparative Effects on Bone Turnover of Alendronate, Denosumab, and Odanacatib
Osteoporosis: Mechanism of Action of Anti-catabolic Agents

Decreased Bone Remodeling

- Refilling remodeling space
- Increase mineralization
- Positive remodeling balance
- Prevents microstructural damage
  a) Trabecular plate perforation
  b) Loss of trabeculae
  c) Resorption “Stress risers”

Increase BMD
Trabecular + to ++
Cortical 0 to +

Preservation of architecture

3 to 30% of effect
70 to 97% of effect

Decreased fractures
New Anabolic Agents

- Anti-Sclerostin Antibody (Romosozumab, Amgen; Blosozumab, Lilly)
- Anti-Dickkopf-1 Antibody (BHQ 880)
- Calcilytics (MK-5442)
- Endothelin-A Receptor Inhibitors (atrasentan)
- Activin A Inhibitors (ACE 011)
- Others
**Anabolic Therapies For Osteoporosis**
Canalis E. JCEM 2010;95:1496-1504.

- Potential Targets are BMP, Wnt, and IGF-1 signaling pathways that stimulate osteoblast differentiation and function.
- BMP and Wnt signaling cause mesenchymal cells to differentiate toward osteoblasts.
- IGF-1 enhances functions of mature osteoblasts.
- Regulatory proteins bind to these growth factors or their receptors to inhibit signaling pathways.
- Changes in expression or binding affinity of these regulatory proteins may cause increase or decrease in bone formation and bone mass.
Anabolic Therapies For Osteoporosis
Canalis E. JCEM 2010;95:1496-1504.

• Anabolic therapies may involve use of anabolic agents or neutralizing antagonists of these growth factors
• Therapies under investigation involve:
  – Neutralizing antibodies to Wnt antagonists
  – Enhancing BMP signaling by proteasome inhibitors
  – Use of activin soluble receptors, IGF-1, or PTH analogs
• Therapies need to target bone to avoid non-skeletal effects and ensure safety
Anabolic Therapies for Osteoporosis

• Current clinical investigative focus is on stimulating the Wnt signaling pathway in osteoblasts to cause new bone formation

• Monoclonal antibodies under development are directed against Wnt signaling inhibitors:
  – Anti-sclerostin antibody (Romosozumab/AMG 785 and Blosozumab/Lilly) targets sclerostin produced by osteocytes to inhibit new bone formation
  – Anti-Dkk1 antibody (DHQ 880) targets Dkk1 produced by osteocytes to inhibit new bone formation
Recombinant Parathyroid Hormone Analogues

- Teriparatide [rhPTH (1-34)] (Forteo) was first and only anabolic bone agent approved for treatment of osteoporosis in U.S. in 2002
- PTH 1-84 was approved for treatment of osteoporosis in Europe and other countries in 2006
- Other PTH analogues remain under development
- rhPTH (1-34) is very potent anabolic bone agent which increases bone density significantly and reduces vertebral fractures by 65% and non-vertebral fractures by 54%
- Causes significant increases in bone density
- Available only by daily SQ injection for 2 years in U.S.
**Teriparatide Prevents Vertebral Fractures**


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**Table 2. Radiographic Evidence of New Vertebral Fractures.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=448)</th>
<th>PTH, 20 µg (N=444)</th>
<th>PTH, 40 µg (N=434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of months at risk (randomization to final radiograph)</td>
<td>21±3</td>
<td>21±3</td>
<td>20±4</td>
</tr>
<tr>
<td>≥1 Fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of women (%)</td>
<td>64 (14)</td>
<td>22 (5)†</td>
<td>19 (4)†</td>
</tr>
<tr>
<td>Relative risk (95% CI) vs. placebo</td>
<td>—</td>
<td>0.35 (0.22–0.55)</td>
<td>0.31 (0.19–0.50)</td>
</tr>
<tr>
<td>Percent reduction in absolute risk</td>
<td>—</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>&gt;1 Fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of women (%)</td>
<td>22 (5)</td>
<td>5 (1)†</td>
<td>3 (&lt;1)†</td>
</tr>
<tr>
<td>Relative risk (95% CI) vs. placebo</td>
<td>—</td>
<td>0.23 (0.09–0.60)</td>
<td>0.14 (0.04–0.47)</td>
</tr>
<tr>
<td>Percent reduction in absolute risk</td>
<td>—</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>≥1 Moderate or severe fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of women (%)</td>
<td>42 (9)</td>
<td>4 (&lt;1)†</td>
<td>9 (2)†</td>
</tr>
<tr>
<td>Relative risk (95% CI) vs. placebo</td>
<td>—</td>
<td>0.10 (0.04–0.27)</td>
<td>0.22 (0.11–0.45)</td>
</tr>
<tr>
<td>Percent reduction in absolute risk</td>
<td>—</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. PTH denotes parathyroid hormone (1-34), and CI confidence interval.

†P≤0.001 for the comparison with placebo.
Teriparatide Prevents Nonvertebral Fractures
Potential Anabolic Osteoblast Targets

Developmental Signals Regulating Key Steps in Osteoblast Differentiation


Diagram:

- **Hedgehog signalling**
  - PTCH1 → SMO → GLI3 → GLI3* → GLI2 → GLI2*
  - γ-secretase → NICD
  - Generation of RUNX2*OSX* cells
  - HEY and HES transcription
  - Inhibition of RUNX2 activity
  - Inhibition of RUNX2*OSX* cell transition

- **Notch signalling**
  - Notch ligand → Notch
  - RBPjκ
  - RUNX2* to RUNX2*OSX* cell transition
  - RUNX2*OSX* cell to osteoblast transition

- **WNT signalling**
  - WNT → LRP5,6 → β-catenin
  - PKCδ
  - SMAD1,5,8
  - RunX2* to RUNX2*OSX* cell transition
  - Osteoblast function

- **BMP signalling**
  - BMP2,4 → BMPR → SMAD1,5,8
  - SMAD4
  - MAPK, PI3K, STAT1, PKC signalling
  - Preosteoblast proliferation
  - Osteoblast differentiation
  - Osteoblast function

- **FGF signalling**
  - FGF → FGFR
Wnt/β-Catenin Signaling via Canonical Pathway
Sclerostin Monoclonal Antibody Pharmacokinetic Study

N=54
Men and Postmenopausal Women
Aged 45-59
Hepatitis in 1 Pt
Enzymes 6-13X
Resolved d26
SCa decreased 4%,
PTH increased
Romosozumab Phase II Clinical Trial Results

Figure 1. Study Schema to 12 Months.
Alendronate and teriparatide were administered in an open-label fashion, whereas the administration of placebo and the various romosozumab doses was blinded.
# Romosozumab Phase II Clinical Trial Results


## Table 1. Baseline Characteristics of the Participants. *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pooled Placebo (N=52)</th>
<th>Alendronate (N=51)</th>
<th>Teriparatide (N=55)</th>
<th>Romosozumab 210 mg Monthly (N=52)</th>
<th>All Doses (N=261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>67.0±6.5</td>
<td>67.1±5.8</td>
<td>66.8±5.7</td>
<td>66.3±6.5</td>
<td>66.7±6.6</td>
</tr>
<tr>
<td>BMD T score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>-2.29±0.66</td>
<td>-2.08±0.69</td>
<td>-2.29±0.57</td>
<td>-2.33±0.57</td>
<td>-2.32±0.70</td>
</tr>
<tr>
<td>Total hip</td>
<td>-1.35±0.67</td>
<td>-1.55±0.68</td>
<td>-1.32±0.78</td>
<td>-1.45±0.65</td>
<td>-1.61±0.62</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-1.76±0.56</td>
<td>-1.91±0.61</td>
<td>-1.79±0.67</td>
<td>-1.87±0.58</td>
<td>-2.00±0.56</td>
</tr>
<tr>
<td>Distal third of the radius</td>
<td>-1.85±1.04</td>
<td>-2.08±0.99</td>
<td>-2.05±1.21</td>
<td>-2.03±0.99</td>
<td>-2.03±1.07</td>
</tr>
<tr>
<td>Serum P1NP (µg/liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>48</td>
<td>49</td>
<td>49</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Serum β-CTX (ng/liter)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>481</td>
<td>494</td>
<td>506</td>
<td>519</td>
<td>515</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. BMD denotes bone mineral density, P1NP procollagen type I N-terminal propeptide, and β-CTX β-isomer of the C-terminal telopeptide of type I collagen.
Romosozumab Phase II Clinical Trial Results

Figure 2. Percentage Change from Baseline in Bone Mineral Density.
Data are least-squares means, and I bars indicate 95% confidence intervals. The asterisk indicates P<0.05 for the comparison of the 210-mg monthly dose of romosozumab with placebo, the dagger P<0.02 for the comparison of the 210-mg monthly dose with alendronate, and the double dagger P<0.02 for the comparison of the 210-mg monthly dose with teriparatide.
Romosozumab: BMD Changes in Phase 2 Study

## Table 2. Percentage Change from Baseline in Bone Mineral Density at the Lumbar Spine at Month 12.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pooled Placebo (N = 50)</th>
<th>Alendronate (N = 51)</th>
<th>Teriparatide (N = 49)</th>
<th>Romosozumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants with available data</td>
<td>47</td>
<td>47</td>
<td>46</td>
<td>49</td>
</tr>
<tr>
<td>Mean change in bone mineral density at lumbar spine — % (95% CI)</td>
<td>-0.1 (-1.2 to 0.9)</td>
<td>4.1 (3.0 to 5.1)</td>
<td>7.1 (6.1 to 8.2)</td>
<td>5.4 (4.4 to 6.5)</td>
</tr>
<tr>
<td>P values</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comparison of romosozumab with pooled placebo</td>
<td>—</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Comparison of romosozumab with alendronate</td>
<td>—</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Comparison of romosozumab with teriparatide</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Data include all the participants who underwent randomization, had bone mineral density measured at baseline, and had at least one measurement of bone mineral density after baseline and on or before the 12-month visit. NS denotes not significant.
Romosozumab Phase II Clinical Trial Results

Figure 3. Percentage Change from Baseline in Bone-Turnover Markers.
Shown are median changes in the bone-formation marker serum procollagen type I N-terminal propeptide (PINP; Panel A) and the bone-resorption marker serum β-isomer of the C-terminal telopeptide of type I collagen (β-CTX; Panel B). I bars indicate interquartile ranges. Samples were not obtained from participants in the alendronate and teriparatide groups at week 1 and months 1 and 2. The asterisk indicates P<0.04 for the comparison of the 210-mg monthly dose of romosozumab with placebo.
# Romosozumab Phase II Clinical Trial Results


<table>
<thead>
<tr>
<th>Event</th>
<th>Pooled Placebo (N = 50)</th>
<th>Alendronate (N = 51)</th>
<th>Teriparatide (N = 54)</th>
<th>Romosozumab 210 mg Monthly (N = 51)</th>
<th>All Doses (N = 255)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>45 (90)</td>
<td>44 (86)</td>
<td>37 (69)</td>
<td>42 (82)</td>
<td>221 (87)</td>
</tr>
<tr>
<td>Injection-site reaction†</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>31 (12)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>7 (14)</td>
<td>4 (8)</td>
<td>5 (9)</td>
<td>5 (10)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>Event leading to study discontinuation</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Death‡</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

* Included are data from participants who received at least one dose of a study drug. Participants may have reported more than one event.

† Adverse events potentially associated with injection-site reactions included any of the following events occurring at the injection site: pain, hematoma, erythema, reaction, discomfort, hemorrhage, or rash.

‡ Deaths were due to colon cancer (in one participant in the placebo group) and complications after aortobifemoral-bypass surgery (in one participant in the group receiving the 70-mg monthly dose of romosozumab).
Teriparatide vs. Romosozumab

- Dosing: Daily
- Duration: 2 years
- Bone Formation: +60% at 3 months
- Bone Resorption: Increased (coupled)
- Bisphosphonate blunting of effect
- BMD: +5.3% at 3 months

- Dosing: q 1-3 months
- Duration: Not known
- Bone Formation: +180% at 1 month
- Bone Resorption: Stable to decreased (uncoupled)
- No Bisphosphonate blunting of effect
- BMD: +11.7% at 19 months
Abaloparatide (BA058): Analog of hPTHrP (1-34)

Abaloparatide was selected to achieve
- Potent and rapid bone anabolic activity
- Limited effect on bone resorption
- Room temperature stability

Comparison of Sequence Identity

- hPTH
- hPTHrP
- Abaloparatide (ABL)

100% hPTHrP
38% hPTHrP

Slide courtesy of Radius Health
**Abaloparatide Phase 2 Study: Hip BMD**

Mean (SE) % Change in Total Hip BMD from Baseline (ITT, N=221)

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>+0.4%</td>
<td></td>
</tr>
<tr>
<td>ABL 20 µg</td>
<td></td>
<td>+1.4%</td>
</tr>
<tr>
<td>ABL 40 µg</td>
<td></td>
<td>+2.0%</td>
</tr>
<tr>
<td>ABL 80 µg</td>
<td></td>
<td>+2.6%</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>+0.5%</td>
<td></td>
</tr>
</tbody>
</table>

Slide courtesy of Radius Health
Abaloparatide Phase 2: Spine BMD at 48 Weeks

Mean (SE) % Change in Lumbar Spine BMD from Baseline (Ext. pop, N=55)

<table>
<thead>
<tr>
<th>Group</th>
<th>% Change in BMD at Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>+0.7%</td>
</tr>
<tr>
<td>ABL 20 µg</td>
<td>+5.1%</td>
</tr>
<tr>
<td>ABL 40 µg</td>
<td>+9.8%</td>
</tr>
<tr>
<td>ABL 80 µg</td>
<td>+12.9%</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>+8.6%</td>
</tr>
</tbody>
</table>

Slide courtesy of Radius Health
Summary and Conclusions

- New agents are being developed that focus on both antiresorptive and anabolic mechanisms.
- Both types of new agents target key steps in osteoclast and osteoblast function.
- New agents have relatively mild effects on bone resorption or more potent effects on bone formation.
- These agents may allow uncoupling of bone resorption from bone formation, with a resultant anabolic window.
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