New Osteoporosis Treatments

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Research funding: Merck, Amgen

What we have today

• Treatments that reduce the risk of vertebral fractures by 50 to 80%
• Treatments that reduce the risk of non-vertebral fractures by 20-25%
  – Non-vertebral fracture remain major source of disability

We need drugs that...

• Maintain or promote bone formation
• Strengthen cortical bone —> reduce NVFx
• Are convenient for patient
• Are cost-effective

New treatments, new mechanisms of action

• Cathepsin K inhibitors
  Odanacatib (ODN)
• Anti-sclerostin antibodies
  Romozosumab
  Blozozumab
• Novel PTH Analogs
  Abaloparitide (BA-058)
Cathepsin K and Bone Resorption

- CatK is a lysosomal protease highly expressed in osteoclasts, where it is released during bone resorption.
- CatK is the major protease responsible for degradation of type I collagen.

Global deletion of Cathepsin K in mice decreases bone resorption but increases bone formation

How can cathepsin K inhibition lead to increased bone formation?

Revisiting the ‘coupled’ process of bone remodeling

Coupling of bone formation & resorption

- Direct effects on osteoblasts?
- Indirect effects via the osteoclasts and coupling?
Genetic deletion of CatK in osteoclasts

- Bone mass ↑
- Bone resorption ↓
- Bone formation ↑
- Osteoclast #


Pharmacologic inhibition of CathepsinK

Odanacatib

Odanacatib is a selective, and reversible nonbasic inhibitor of Cat K with minimal metabolism, which supports once weekly dosing in humans.

IC$_{50}$ (nM)

- Cat K 0.2
- Cat B 1,034
- Cat L 2,995
- Cat S 60

Duong LT. BoneKey Reports. 2012;1. Article no. 67.


Leung et al. Bone, 2011

Osteoclasts have a dual function

Bone Formation

Bone Resorption

Effects of reducing activity of CatK in the osteoclast

- Same or increased number of osteoclasts
- Shallow resorption pits

Human Osteoclasts

CON

ODN-treated

Leung et al. Bone, 2011
ODN treatment increases avg. cortical thickness in femur of OVX monkeys

Cortical Thickness, mm

<table>
<thead>
<tr>
<th>Veh</th>
<th>0.8</th>
<th>0.6</th>
<th>0.4</th>
<th>0.2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODN, mg/kg</td>
<td>6</td>
<td>30</td>
<td></td>
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</tr>
</tbody>
</table>

Proximal Femur

Central Femur

Femoral Neck

ODN increases periosteal bone formation in proximal femur of OVX monkeys

Proximal Femoral Periosteum (Rhesus monkeys @ 21-mo Tx)


Mineralized Surface, %

<table>
<thead>
<tr>
<th>Veh</th>
<th>50</th>
<th>40</th>
<th>30</th>
<th>20</th>
<th>10</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODN, mg/kg</td>
<td>6</td>
<td>30</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Mineral Apposition Rate, µm/d

<table>
<thead>
<tr>
<th>Veh</th>
<th>0.8</th>
<th>0.6</th>
<th>0.4</th>
<th>0.2</th>
<th>0</th>
</tr>
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<tr>
<td>ODN, mg/kg</td>
<td>6</td>
<td>30</td>
<td></td>
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</tbody>
</table>

Bone Formation Rate, µm/3y

<table>
<thead>
<tr>
<th>Veh</th>
<th>90</th>
<th>60</th>
<th>30</th>
<th>0</th>
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<tbody>
<tr>
<td>ODN, mg/kg</td>
<td>6</td>
<td>30</td>
<td></td>
<td></td>
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Randomized trial (phase 2b)

- Original: 2 year dose-ranging study
- Postmenopausal women 45-85 years (N=399)
- BMD T-score ≤ -2.0 but not < -3.5
- 50 mg odanacatib vs. placebo (once weekly, oral)
- After 2 years, randomly assigned to stop or continue to 5 years

**Study design**

Year 1 & 2 (N=399)
- PBO
- 3 mg
- 10 mg
- 25 mg
- 50 mg

Year 3 (N=189)
- PBO
- 3 mg
- 50 mg

Year 4 & 5* (N=141)
- PBO
- 50 mg

Women who entered the Year 4 to 5 extension
- n=13
- n=14
- n=14
- n=13
- n=12
- n=14
- n=14
- n=16
- n=14

*Year 6 to 10 extension in planning.

Langdahl B et al. J Bone Miner Res. Nov 2012

**Lumbar spine BMD**

Mean % change from baseline (SE)

<table>
<thead>
<tr>
<th>Month</th>
<th>PBO/PBO (n=14)</th>
<th>ODN 50 mg/50 mg/50 mg (n=13)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>11.9%</td>
<td>0.8%</td>
<td>-0.4%</td>
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</table>

Langdahl et al. JBMR 2012

**Femoral neck BMD**

Mean % change from baseline (SE)

<table>
<thead>
<tr>
<th>Month</th>
<th>PBO/PBO (n=14)</th>
<th>ODN 50 mg/50 mg/50 mg (n=13)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>9.8%</td>
<td>-1.6%</td>
<td>-0.5%</td>
</tr>
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</table>

Langdahl et al. JBMR 2012

**Effect of ODN on bone resorption markers**

uNTx/Cr ratio

<table>
<thead>
<tr>
<th>Month</th>
<th>PBO/PBO</th>
<th>ODN 50 mg/50 mg/50 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100</td>
<td>-100</td>
<td>100</td>
</tr>
</tbody>
</table>

Langdahl et al. JBMR 2012
ODN: Bone turnover markers

CTX

P1NP

* P<0.001 vs PBO

Brixen et al, JCEM 2013 98:571-80

Per-Protocol Population

Phase 3 Fracture Trial

- Randomized, placebo-controlled
- ODN (50 mg/wk) vs PBO
- >16,000 subjects enrolled
  - Age > 65 yrs
  - Low hip BMD, with or without prior vertebral fx

Phase 3 Fracture Trial: Updates

- July 2012: study stopped early
  "The study met its primary efficacy outcomes... and is being concluded early... Robust efficacy and a favorable benefit-risk profile... safety issues remain in certain selected areas"

- May 2014: press release
  "ODN reduced the risk of osteoporotic fractures vs. placebo, including vertebral, non-vertebral and hip fractures... Among adjudicated adverse effects associated with odanacatib, morphea was reported uncommonly (<0.2%), with improvement after discontinuation of treatment, and femoral shaft fractures of an atypical type were rare (<0.1%). Both were higher than placebo. There were no reported cases of osteonecrosis of the jaw."

- Plan to file for FDA approval in second half of 2014
New treatments, new mechanisms of action

- Cathepsin K inhibition
  Odanacatib (ODN)

- Anti-sclerostin antibodies
  Romozosumab
  Blozosumb

Sclerostin: Osteocyte-derived cytokine that inhibits bone formation

- Sclerosteosis, van Buchem’s disease
  -- Due to mutations in gene SOST

- Sclerostin: protein encoded by gene SOST
  -- Potent inhibitor of Wnt signaling & bone formation
  -- Deletion of SOST in mice: ↑bone mass
  -- Sclerostin expression localized to osteocytes

Treatment of rats & monkeys with Sclerostin Antibody

Phase 2 Study of Sclerostin Antibody (Romozosumab) in Postmenopausal Women with Low BMD
Phase 2 Study Design

McClung et al, NEJM 2014

Lumbar spine BMD

McClung et al. NEJM 2014

Total hip and femoral neck BMD

McClung et al. NEJM 2014
% Change in serum bone turnover markers: P1NP and CTX

**New treatments, new mechanisms of action**

- Cathepsin K inhibition
  - Odanacatib (ODN)
- Anti-sclerostin antibodies
  - Romozosumab
  - Blozozumb
- Novel PTH Analogs
  - Abaloparitide (BA-058)

**Abaloparitide (BA058): Introduction**

Abaloparitide is a novel analog of hPTHrP (1-34)

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

**Phase 2 Clinical Study: Spine BMD at 48 Weeks**

Mean (SE) % Change in Lumbar Spine BMD from Baseline (Ext. pop, N=55)
Phase 2 Clinical Study: Hip BMD

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

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

Bone Formation Markers

Percent Change in PINP from Baseline

* p-value < 0.05 vs. baseline

Bone Resorption Markers

Percent Change in CTX from Baseline

* Lower rise in CTX with BA058 compared with teriparatide

* p-value < 0.05 vs. baseline

Summary

- **Cathepsin K inhibition (odanacatib)**
  - Bone formation sparing anti-resorptive, weekly oral
  - Persistent gains in BMD over 5 yrs
  - Decreases hip and vertebral fracture risk

- **Sclerostin inhibition (romozosumab, blozosumab)**
  - Potent anabolic with mild anti-resorptive effect, monthly SC
  - Effect on bone formation marker CTX gone by 6 mo

- **PTH Analog (abaloparatide)**
  - PTH-like anabolic with less hypercalcemia, less resorption
  - Daily SC dosing