New Osteoporosis Treatments

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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

% of days of disability due to different types of fractures

Results from FIT II
Cummings et al., JAMA 2006

We need drugs that...

• Maintain or promote bone formation
• Strengthen cortical bone → reduce Non-VFx
• Are convenient for patient
• Are cost-effective
• Are safe

Disclosures

Advisory Board: Merck, Eli Lilly, Radius
Research funding: Merck, Amgen
Consulting fees: Acceleron Pharma, Agnovos
New treatments, new mechanisms of action

- Cathepsin K inhibitors
  - Odanacatib (ODN)
- Anti-sclerostin antibody
  - Romozosumab
- 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 #↑

Osteoclasts have a dual function

Pharmacologic inhibition of CathepsinK

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

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>IC50 (nM)</th>
</tr>
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<tbody>
<tr>
<td>Cat K</td>
<td>0.2</td>
</tr>
<tr>
<td>Cat B</td>
<td>1,034</td>
</tr>
<tr>
<td>Cat L</td>
<td>2,995</td>
</tr>
<tr>
<td>Cat S</td>
<td>60</td>
</tr>
</tbody>
</table>

IC50 = 50% inhibitory concentration; Cat = cathepsin.

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

Human Osteoclasts

Effects of reducing activity of CatK in the osteoclast

- Same or increased number of osteoclasts
- Shallow resorption pits

Leung et al. Bone, 2011

ODN treatment increases avg. cortical thickness in femur of OVX monkeys

Cortical Thickness, mm

Central Femur

† p = 0.08 vs VEH

Proximal Femur

4.0

3.6

3.2

0

VEH

ODN, mg/kg

63

0

Cortical Thickness, mm

Femoral Neck

1.6

1.4

1.2

0

†

VEH

ODN, mg/kg

63

0


Human trials

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

Langdahl et al. JBMR 2012
**Lumbar spine BMD**

- **PBO/PBO (n=14)**
- **ODN 50 mg/PBO/PBO (n=14)**
- **ODN 50 mg/50 mg/50 mg (n=13)**

Mean % change from baseline (SE) = 11.9%

- Placebo
  - Mean % change from baseline = 0.8%
  - Mean % change from baseline = -0.4%

**Femoral neck BMD**

- **PBO/PBO (n=14)**
- **ODN 50 mg/PBO/PBO (n=14)**
- **ODN 50 mg/50 mg/50 mg (n=13)**

Mean % change from baseline (SE) = 9.8%

- Placebo
  - Mean % change from baseline = 1.6%

**ODN: Bone turnover markers**

- **CTX**
  - Mean % change from baseline = 3.03
  - Mean % change from baseline = -42.56

- **P1NP**
  - Mean % change from baseline = -1.99
  - Mean % change from baseline = -11.06

* P<0.001 vs PBO

**Phase 3 Fracture Trial - LOFT**

* Randomized, placebo-controlled
* ODN (50 mg/wk) vs PBO

- >16,000 subjects enrolled worldwide
  - Age > 65 yrs
  - Low hip BMD, with or without prior vertebral fx

Brixen et al, JCEM 2013 98:571-80

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Brixen et al, JCEM 2013 98:571-80
Fracture Reduction with Odanacatib
Presented at ASBMR, September 2014

Relative Risk
(vs PBO)

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Fx</td>
<td>↓47%</td>
</tr>
<tr>
<td>Non-Vert Fx</td>
<td>↓23%</td>
</tr>
<tr>
<td>Vert Fx (morphometric)</td>
<td>↓54%</td>
</tr>
<tr>
<td>Vert Fx (clinical)</td>
<td>↓72%</td>
</tr>
</tbody>
</table>

McClung et al, ASBMR 2014

Safety and adverse events: odanacatib
ASBMR Sept 2014

- Evidence of greater incidence of morphea-like skin reactions (<0.1%), which resolved after discontinuing drug
- Additional adjudication for cardiovascular events, atypical femoral fractures and other AE’s is ongoing
- Benefit: risk profile will be better defined with additional efficacy & safety data that are being acquired in blinded extension study

McClung et al, ASBMR 2014

New treatments, new mechanisms of action

- Cathepsin K inhibition
  Odanacatib (ODN)

- Anti-sclerostin antibody
  Romozosumab

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

Li et al, JBMR 2008
Treatment of rats & monkeys with Sclerostin Antibody

SHAM  VEH  OVX + VEH  OVX + SclAb

Li et al, JBMR 2009

Vertebral Strength

OMinsky et al, JBMR 2011

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

Phase 2 Study Design

McClung et al, NEJM 2014

Phase 2 Study Design

McClung et al, NEJM 2014
Lumbar spine BMD

Percentage Change From Baseline

Placebo ALN TPTD Romosozumab 210 mg QM

Romosozumab
TPTD ALN PBO

McClung et al, NEJM 2014

Total hip and femoral neck BMD

Percentage Change From Baseline

Placebo ALN TPTD Romosozumab 210 mg QM

Total Hip Femoral Neck

McClung et al, NEJM 2014

% Change in serum bone turnover markers: P1NP and CTX

P1NP CTX

McClung et al, NEJM 2014

Romozosumab: Phase III fracture trials

- FRAME (n ~ 6600) – placebo controlled
  - Blinded (0-12 mo): Romozosumab vs PBO
  - Open label (12-24 mo): Both groups transition to dmab
  - 1st outcome: Vertebral Fracture (12, 24 mo)
  - 2nd outcomes: Any fracture and BMD change (12, 24 mo)

- ARCH (n ~ 4100) – ALN active comparator
  - Blinded (0-12 mo): Romo + PBO (oral) vs ALN + PBO (inj)
  - Open label (12 – 24 mo): Both groups transition to ALN
  - 1st outcome: Vertebral or any clinical fracture (~ 24 mo)
  - 2nd outcomes: Any fracture, BMD change (12, 24 mo)
Press Release, Feb 21 2016

- FRAME met the co-primary endpoints by reducing the incidence of new vertebral fracture through months 12 and 24 in postmenopausal women with osteoporosis treated with romosozumab
  - 73% reduction in the risk of a vertebral fracture @ 12 mo's vs. pbo
  - 75% reduction in the risk of a vertebral fracture @ 24 mo's vs. pbo
- The study also met the secondary endpoint of reducing the incidence of clinical fractures (composite of vertebral and non-vertebral fractures) through 12 months.
  - 36 percent reduction through 12 months vs. placebo
- However, the secondary endpoint of reducing the incidence of non-vertebral fractures through months 12 and 24 was not met.

Press Release, Feb 21 2016...(continued)

- The percentage of patients with adverse events and serious adverse events in the 12-month double-blind period and 24-month study period were balanced overall between the treatment groups.
- There were two positively adjudicated events of osteonecrosis of the jaw in the romosozumab treatment group, one after completing romosozumab dosing and the other after completing romosozumab treatment and receiving the initial dose of denosumab.
- There was one positively adjudicated event of atypical femoral fracture after three months of romosozumab treatment.

New treatments, new mechanisms of action

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

Abaloparatide (BA058): Introduction

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

<table>
<thead>
<tr>
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<th>hPTH</th>
<th>hPTHrP</th>
<th>ABL</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>22</td>
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<td></td>
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<tr>
<td>34</td>
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<tr>
<td>38% hPTHrP</td>
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Abaloparatide 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

Phase 2 Clinical Study: Hip BMD

Bone Formation Markers

Bone Resorption Markers

* p-value < 0.05 vs. baseline

* Lower rise in CTX with BA058 compared with teriparatide
**Phase 3: Fracture trial study design**

**ACTIVE Study: Abaloparatide Comparative Trial in Vertebral Endpoints**

<table>
<thead>
<tr>
<th>Screening</th>
<th>Pretreatment (Ca &amp; Vit D)</th>
<th>Placebo</th>
<th>Abaloparatide 80µg</th>
<th>Teriparatide 20 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 subjects</td>
<td>800 subjects</td>
<td>800 subjects</td>
<td>800 subjects</td>
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<thead>
<tr>
<th>2 months</th>
<th>18 months</th>
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**Key Endpoints**

**Primary:**
- Reduction in new vertebral fractures for ABL vs. placebo at 18 months
- Reduction in new non-vertebral fractures for ABL vs. placebo at 18 months
- Difference in spine, total hip and femoral neck BMD for ABL vs. FORTEO®
- Difference in hypercalcemia rates in ABL vs. FORTEO®

**Secondary:**
- Reduction in new vertebral fractures for ABL vs. placebo at 18 months
- Difference in spine, total hip and femoral neck BMD for ABL vs. FORTEO®
- Difference in hypercalcemia rates in ABL vs. FORTEO®

**Summary: new therapies on the horizon**

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

- **Sclerostin inhibition (romozosumab)**
  - Potent anabolic with mild anti-resorptive effect, monthly SC
  - Large gains in BMD, bone formation return to BL by 6 mo
  - Large, international Ph III fracture studies ongoing

- **PTH Analog (abaloparatide)**
  - PTH-like anabolic with less hypercalcemia, less resorption
  - Daily SC dosing
  - Reduces vertebral, non-vertebral and clinical fractures

**ACTIVE study, Ph III Fracture trial (18 mo)**

n=690 abaloparatide, 711 placebo, 717 TPTD

<table>
<thead>
<tr>
<th></th>
<th>Vertebral Fx</th>
<th>Non-vert Fx</th>
<th>Clinical Fx</th>
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<tbody>
<tr>
<td>Abaloparatide</td>
<td>&lt;80% (p=0.001)</td>
<td>&lt;43% (p=0.049)</td>
<td>&lt;45% (p=0.01)</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>&lt;80% (p&lt;0.001)</td>
<td>&lt;18% (p=0.22)</td>
<td>&lt;29% (p=0.11)</td>
</tr>
</tbody>
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Miller et al, Endocrine Society Mtg, Mar 2015