Addressing the Needs of Patients with Severe Osteoporosis: Emerging Therapies

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Disclosures

• Within the last two years, I have received:
  • Speaking, consulting, advisory board fees, grant funds and/or medication
    • *Eli Lilly, Amgen*
  • Advisory Board and/or Consulting Fees
    • *Merck, Radius, and Tarsa*
Objectives

- Osteoporosis Treatment Gap:
  - Patients who have had fractures
  - Patients with more severe osteoporosis
  - Patients with spine fractures

- Limitations of Current Therapeutic Armamentarium

- New Agents with Recent Phase 3 Studies Published
  - Romosozumab
  - Abaloparatide

- Goal Directed Therapy
  - How do the New Agents Fit in?
Treatment Gap in Osteoporosis

• Prior fracture is the most important risk factor for another fx
  - Risk is highest within first few years
  - Suggests an urgency to treatment
• Most patients (25%) with major osteoporotic fractures are not treated with osteoporosis medication
• Spine fractures are usually not diagnosed
  - NOF Guidelines for Screening Vertebral Imaging\(^1\)
    • Women ≥65 and men ≥70 with T-Score ≤-1.5
    • Women ≥70 and men ≥80 with T-Score ≤ -1
    • Women and Men 50 plus with adulthood fractures, height loss, glucocorticoid use

\(^{1}\)Cosman et al OI 2014
Current AR Agents Have Limited Efficacy

- At best, 40-50% reduced risk of hip fracture
  - Lesser risk reductions for all nonvert fractures (20-25%)
- Longterm efficacy of potent AR therapies on fx unclear
  - With denosumab, continued increase in BMD years 3-10
    - associated with low fracture rates but no pbo comparison
  - With Bisphosphonates, BMD plateaus after 3-4 years
    - if BMD remains ≤-2.5, patients still at risk for fx
    - Late effect on fx inconsistent at best
  - Longterm Potent AR Therapy is associated with duration dependent adverse events (ONJ, AFF)

Cosman et al JCEM 2014

AR, Antiresorptive
Fx, Fracture
PBO, Placebo group
AFF, Atypical Femur Fracture
ONJ, Osteonecrosis of the Jaw
Current Agents Have Limited Efficacy (cont)

- Currently only one anabolic therapy (Teriparatide)
  - Effect on nonvertebral fracture takes almost a year\(^1\)
  - Use limited to \(\leq 2\) years
  - Has limited impact on hip BMD
    - Lesser Hip BMD Increase if previously treated with BPs\(^2\)-\(^3\) or denosumab\(^4\)
- Additional Anabolic Approaches Needed
  - To improve structure and mass
    - For more rapid and substantial bone strengthening
  - To bridge between courses of AR therapy
  - To allow multiple courses of different anabolic therapies

\(^1\)Neer et al NEJM 2001 \(^2\)Cosman et al JCEM 2009 \(^3\)Cosman et al Current Osteop Reports 2015
\(^4\)Leder et al Lancet 2016
New Anabolic Therapies

- Romosozumab
- Abaloparatide
Romosozumab Treatment in Postmenopausal Women with Osteoporosis

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ASBMR; Atlanta, GA; September 16–19, 2016; Cosman F et al
NEJM September 19, 2016 (on line); October 2016 (print)
Romosozumab Background

- Monoclonal antibody that binds and inhibits sclerostin
- Sclerostin inhibition has dual effect on bone
  - Stimulates bone formation by promoting osteoblast number and activity
  - Reduces bone resorption by inhibiting RANK ligand expression
- In a phase 2 study of postmenopausal women with low bone mass, 1 year of romosozumab markedly increased BMD at the spine and hip\(^1\)
- FRAME is a phase 3, randomized, placebo-controlled FRActure study in postmenopausal woMen with ostEoporosis

Romosozumab FRAME Study Design

Double Blind
- Romosozumab 210 mg SC QM (N = 3,589)
- Placebo SC QM (N = 3,591)

Open Label
- Denosumab 60 mg SC Q6M

1:1 Randomization

Month
- 0\(^a\)
- 6
- 12
- 18
- 24

Spine x-rays
- \(\uparrow\)
- \(\uparrow\)
- \(\uparrow\)
- \(\uparrow\)

Clinical fracture assessment

Loading dose of 50,000–60,000 IU vitamin D

ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al
NEJM September 19, 2016 (on line); October 2016 (print)
### Inclusion Criteria
- Postmenopausal women age 55–90 years
- BMD T-score ≤ –2.5 at the total hip or femoral neck

### Exclusion Criteria
- BMD T-score ≤ –3.5 at the total hip or femoral neck
- History of hip fracture or any severe or more than two moderate vertebral fractures
- Recent osteoporosis therapy

### Co-Primary Endpoints
- Subject incidence of new vertebral fracture through 12 and 24 months

### Secondary Fracture Endpoints
- Subject incidence of clinical fracture, nonvertebral fracture, and other fracture categories through 12 and 24 months
Statistical Testing Sequence

**New vertebral fracture through Month 12**
- Co-Primary: Need statistical significance (≤ 0.05) on both to proceed

**Clinical fracture through Month 12**
- Secondary: Test at α = 0.05

**Nonvertebral fracture through Month 12**
- Secondary: Controlled by Hochberg procedure; if both p-values ≤ 0.05, claim statistical significance on both; if larger p-value > 0.05, test smaller one at α = 0.025

**New vertebral fracture through Month 24**

**Nonvertebral fracture through Month 24**

**Clinical fracture through Month 24**
- Additional endpoints tested in sequence

**Co-Primary**
- New vertebral fracture through Month 12
- New vertebral fracture through Month 24

**Secondary**
- Clinical fracture through Month 12
- Nonvertebral fracture through Month 12
- Nonvertebral fracture through Month 24


ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al
NEJM September 19, 2016 (on line); October 2016 (print)
Study Enrollment Geographic Region
(Total N = 7,180)

- North America: 2.7%
- Central and Eastern Europe: 29.2%
- Western Europe, Australia/New Zealand: 13.6%
- Asia Pacific: 11.5%
- Latin America: 43.0%

ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al NEJM September 19, 2016 (on line); October 2016 (print)
<table>
<thead>
<tr>
<th>Baseline Characteristics and Subject Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
</tr>
<tr>
<td>BMD T-score, mean (SD)</td>
</tr>
<tr>
<td>Lumbar spine</td>
</tr>
<tr>
<td>Total hip</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, %</td>
</tr>
<tr>
<td>Number of prevalent vertebral fractures, %</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>≥ 2</td>
</tr>
<tr>
<td>Most severe vertebral fracture grade, %</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Prior nonvertebral fracture on or after age 45, %</td>
</tr>
<tr>
<td>Completed 12-month double-blind period, %</td>
</tr>
<tr>
<td>Completed 24-month study period, %</td>
</tr>
</tbody>
</table>

N = Number of subjects randomized. Percentages based on number of subjects randomized. Vertebral fracture grade based on Genant semiquantitative scale.
Percent Change in Serum P1NP and CTX with Romosozumab Relative to Placebo Through Month 12

P1NP, romosozumab n = 62, placebo n = 62; CTX, romosozumab n = 61, placebo n = 62. Data presented as bootstrapped median treatment difference and 95% CI

ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al NEJM September 19, 2016 (on line); October 2016 (print)
P1NP, romosozumab n = 62, placebo n = 62; CTX, romosozumab n = 61, placebo n = 62. Data presented as bootstrapped median treatment difference and 95% CI
Lumbar Spine and Total Hip BMD Through Month 12

*\( p < 0.001 \) compared with placebo. Data are least square means (95% CI) adjusted for relevant baseline covariates.

\[ \text{Percent Change From Baseline} \]

\[ \text{Study Month} \]

Placebo (N = 61)  
Romosozumab (N = 65)

Placebo (N = 62)  
Romosozumab (N = 66)

\[ \text{ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al NEJM September 19, 2016 (on line); October 2016 (print)} \]
**New Vertebral Fracture Incidence Through Month 12 (Co-Primary Endpoint)**

- **Placebo (N = 3,591)**
  - Through Month 6: 0.8%
  - Through Month 12: 1.8%

- **Romosozumab (N = 3,589)**
  - Through Month 6: 0.4%
  - Through Month 12: 0.5%

**RRR** = 73%

\( p = < 0.001 \)

**RRR** = 46%

\( p = 0.056 \)

\( n/N1 = \frac{\text{number of subjects with fractures}}{\text{number of subjects in the primary analysis set for vertebral fractures}} \)

\( p \)-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture

ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al NEJM September 19, 2016 (on line); October 2016 (print)
Time to First Clinical Fracture Through Month 12

Nonvertebral and symptomatic vertebral fracture. Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures.

Kaplan Meier curve based on data through month 24. \( n \) = number of subjects at risk for event at time point of interest. \( P \)-value based on RRR.

Placebo (\( N = 3,591 \))

Romosozumab (\( N = 3,589 \))

RRR = 36%

\( p = 0.008 \)
Other Key Fracture Endpoints Through Month 12

Nonvertebral fractures excludes fractures of the skull, facial bones, metacarpals, fingers, and toes, pathologic fractures and fractures associated with high trauma.

Major osteoporotic fractures: clinical vertebral, hip, forearm, and humerus, excluding pathologic fractures.

*Osteoporotic fracture p-value not adjusted as not part of the testing sequence. n = number of subjects with fractures.
Nonvertebral Fracture Incidence Through Month 12 in Latin America vs Rest-of-World

<table>
<thead>
<tr>
<th></th>
<th>Latin America</th>
<th>Rest-of-World*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.2%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Romosozumab</td>
<td>1.5%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

RRR = 42%

$p = 0.012$

RRR = −25%

$p = 0.47$

Treatment-by-subgroup interaction ($p = 0.041$)

n/N1 = number of subjects with fractures/number of subjects in the full analysis set

*Regions excluding Latin America grouped post hoc

ASBMR; Atlanta, GA; September 16–19, 2016; Cosman F et al NEJM September 19, 2016 (on line); October 2016 (print)
Key Fracture Endpoints Through Month 12 in Subjects Outside Latin America

- **New Vertebral**: Placebo (N = 2,057) - 2.3%, Romosozumab (N = 2,039) - 0.6%, RRR = 74%
- **Clinical**: Placebo (N = 2,057) - 3.4%, Romosozumab (N = 2,039) - 1.6%, RRR = 52%
- **Nonvertebral**: Placebo (N = 2,057) - 2.7%, Romosozumab (N = 2,039) - 1.6%, RRR = 42%
- **Major Osteoporotic**: Placebo (N = 2,057) - 2.4%, Romosozumab (N = 2,039) - 1.0%, RRR = 58%
- **Hip**: Placebo (N = 2,057) - 0.5%, Romosozumab (N = 2,039) - 0.2%, RRR = 59%

**Key Fracture Endpoints**

**Placebo**
- New Vertebral: 43/1892
- Clinical: 69/2057
- Nonvertebral: 56/2057
- Major Osteoporotic: 50/2057
- Hip: 10/2057

**Romosozumab**
- New Vertebral: 11/1857
- Clinical: 33/2039
- Nonvertebral: 32/2039
- Major Osteoporotic: 21/2039
- Hip: 4/2039

**p-values**
- New Vertebral: < 0.001
- Clinical: < 0.001
- Nonvertebral: 0.012
- Major Osteoporotic: < 0.001
- Hip: 0.12
Serum P1NP and CTX Levels Through Month 24

Data are median and interquartile range. Placebo-to-denosumab n = 62; romosozumab-to-denosumab n = 62 (P1NP), n = 61 (CTX)

ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al NEJM September 19, 2016 (on line); October 2016 (print)
Lumbar Spine and Total Hip BMD Through Month 24

Placebo-to-denosumab (N = 61)
Romosozumab-to-denosumab (N = 65)

Lumbar Spine

Placebo vs romosozumab
Open-label denosumab

Percent Change From Baseline

Study Month

0 5 10 15 20

-5

9.7%*
13.3%*
15.1%*
17.6%*

0.4%
0.0%
3.3%
5.0%

0 5 10 15 20

-5

7.8%*
8.7%*
9.7%*

0.4%
0.0%
1.6%
2.9%

0 5 10 15 20

-5

* p < 0.001 compared with placebo (M6 and M12) or placebo/denosumab (M18 and M24)
Data are least square mean (95% CI) adjusted for relevant baseline covariates

Total Hip

Placebo vs romosozumab
Open-label denosumab

Percent Change From Baseline

Study Month

0 5 10 15 20

-5

4.7%*
6.8%*
8.4%*
8.8%*

0.4%
0.0%
1.6%
2.9%

0 5 10 15 20

-5

0.4%
0.0%
1.6%
2.9%

ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al
NEJM September 19, 2016 (on line); October 2016 (print)
Subject Incidence of New Vertebral Fracture Through Month 24 (Co-Primary Endpoint)

RRR = 73%  
$p < 0.001$

RRR = 81%  
$p < 0.001$

RRR = 75%  
$p < 0.001$

n/N1 = Number of subjects with fractures/number of subjects in the primary analysis set for vertebral fractures

$p$-value based on logistic regression model adjusted for age (< 75, ≥ 75) and prevalent vertebral fracture

ASBMR; Atlanta, GA; September 19, 2016; Cosman F et al NEJM September 19, 2016 (on line); October 2016 (print)
Time to First Clinical and Nonvertebral Fracture Through Month 24

Clinical Fractures

- Placebo-to-denosumab (N = 3,591)
- Romosozumab-to-denosumab (N = 3,589)

Nonvertebral Fractures

- Placebo-to-denosumab (N = 3,591)
- Romosozumab-to-denosumab (N = 3,589)

RRR = 33%
Adjusted $p = 0.096$
Nominal $p = 0.002$

RRR = 25%
Adjusted $p = 0.057$
Nominal $p = 0.029$

Nonvertebral fractures comprised the majority (more than 85%) of clinical fractures. $n =$ number of subjects at risk for event at time point of interest. $P$-value based on RRR.
**Romosozumab Safety Overview**

<table>
<thead>
<tr>
<th>Double-Blind Period</th>
<th>Placebo (N = 3,576) n (%)</th>
<th>Romosozumab (N = 3,581) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Incidence of All Adverse Events&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2850 (79.7)</td>
<td>2806 (78.4)</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>312 (8.7)</td>
<td>344 (9.6)</td>
</tr>
<tr>
<td>Adjudicated cardiovascular events&lt;sup&gt;b&lt;/sup&gt;</td>
<td>41 (1.1)</td>
<td>44 (1.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>23 (0.6)</td>
<td>29 (0.8)</td>
</tr>
<tr>
<td>Adjudicated cardiovascular deaths&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15 (0.4)</td>
<td>17 (0.5)</td>
</tr>
<tr>
<td>Events Leading to Study Discontinuation</td>
<td>50 (1.4)</td>
<td>44 (1.2)</td>
</tr>
<tr>
<td>Events of Interest&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0 (0.0)</td>
<td>1 (&lt; 0.1)</td>
</tr>
<tr>
<td>Hypersensitivity&lt;sup&gt;d&lt;/sup&gt;</td>
<td>245 (6.9)</td>
<td>242 (6.8)</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>104 (2.9)</td>
<td>187 (5.2)</td>
</tr>
<tr>
<td>Atypical femoral fracture&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0 (0.0)</td>
<td>1 (&lt; 0.1)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw&lt;sup&gt;b,e&lt;/sup&gt;</td>
<td>0 (0.0)</td>
<td>1 (&lt; 0.1)</td>
</tr>
<tr>
<td>Subject Incidence of Anti-romosozumab Antibody Formation&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding antibodies</td>
<td>NA</td>
<td>646 (18.0)</td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>NA</td>
<td>25 (0.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Occurring in ≥ 10% of subjects in either group: arthralgia (placebo, 12.0%; romosozumab, 13.0%), nasopharyngitis (placebo, 12.2%; romosozumab, 12.8%), back pain (placebo, 10.6%; romosozumab, 10.5%).

<sup>b</sup>Includes adverse events adjudicated positive by an independent adjudication committee. For cardiovascular deaths, includes fatal events adjudicated as cardiovascular-related or undetermined (presumed cardiac-related).

<sup>c</sup>Event of Interest identified by prespecified MedDRA search strategy.

<sup>d</sup>Occurring in ≥ 10% of subjects in either group: Hypersensitivity (placebo, 4.6%; romosozumab, 3.0%).

<sup>e</sup>One event also occurred in the open-label period after receipt of denosumab.

<sup>f</sup>Antibody positive postbaseline through month 15 with a negative or no result at baseline. NA = only assessed in romosozumab subjects.
Summary FRAME Trial Results

• Romosozumab for 12 months compared with placebo (RRR):
  – New vertebral fracture: 73% \( (p < 0.001) \)
  – Clinical fracture: 36% \( (p = 0.008) \)
  – Nonvertebral fracture: 25% \( (p = 0.096) \)
  • Among subjects outside of Latin America (Rest of the world grouped post hoc): 42% \( (p = 0.012) \)

• Over 24 months, romosozumab-to-denosumab compared with placebo-to-denosumab (RRR):
  – New vertebral fracture: 75% \( (p < 0.001) \)
  – Clinical fracture: 33% (nominal \( p = 0.002 \); adjusted \( p = 0.096 \))
  – Nonvertebral fracture: 25% (nominal \( p = 0.029 \); adjusted \( p = 0.057 \))
Abaloparatide Background

• Abaloparatide is 34–amino acid osteoanabolic peptide
  - Synthetic Analogue of PTH related Peptide
• In Preclinical and clinical studies:
  - BMD increases
  - Bone microarchitecture is improved
  - Bone strength is increased
• Unique mechanism of action at the PTH1 receptor
  - Stimulates bone formation
  - Results in Limited calcium mobilization and bone resorption
  - Optimized osteoanabolic profile

Doyle et al. ASBMR 2014; Bahar et al. ENDO 2015.
ACTIVE STUDY DESIGN

• ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints)
  - 18 months of abaloparatide-SC compared with placebo and open-label teriparatide
  - Multicenter, multinational, double-blind, placebo-controlled
  - 2463 postmenopausal women aged 49 to 86 were enrolled
    • With prior radiographic vertebral or recent (< 5 yrs prior) nonvertebral fracture
      • T-score ≤ -2.5 at spine or femoral neck and age ≤ 65
      • T-score ≤ -2.0 if age >65
      • No prior fracture required if age >65 and T-score ≤ -3.0

ACTIVE Trial Design

- Placebo (n=821)
- Abaloparatide-SC 80 μg daily (n=824)
- Teriparatide 20 μg daily SC (n=818)

N=2463

Months

## ACTIVE: Baseline Characteristics

<table>
<thead>
<tr>
<th>ITT population N=2463</th>
<th>Placebo (n=821)</th>
<th>Abaloparatide-SC (n=824)</th>
<th>Teriparatide (n=818)</th>
<th>Overall (N=2463)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (mean)</td>
<td>68.7</td>
<td>68.9</td>
<td>68.8</td>
<td>68.8</td>
</tr>
<tr>
<td>Age groups (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>19.6</td>
<td>18.4</td>
<td>18.5</td>
<td>18.8</td>
</tr>
<tr>
<td>65 to &lt;75 years</td>
<td>62.4</td>
<td>62.7</td>
<td>61.5</td>
<td>62.2</td>
</tr>
<tr>
<td>≥75 years</td>
<td>18.0</td>
<td>18.8</td>
<td>20.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Baseline prevalent vertebral fracture (%)</td>
<td>22.9</td>
<td>21.5</td>
<td>26.9</td>
<td>23.8</td>
</tr>
<tr>
<td>Prior nonvertebral fracture history* (%)</td>
<td>50.7</td>
<td>49.2</td>
<td>45.4</td>
<td>48.4</td>
</tr>
<tr>
<td>Patients with no history of prior fracture (%)</td>
<td>37.4</td>
<td>37.0</td>
<td>37.7</td>
<td>37.4</td>
</tr>
<tr>
<td>Lumbar spine BMD T-score (mean)</td>
<td>-2.9</td>
<td>-2.9</td>
<td>-2.9</td>
<td>-2.9</td>
</tr>
<tr>
<td>Total hip BMD T-score (mean)</td>
<td>-1.9</td>
<td>-1.9</td>
<td>-1.9</td>
<td>-1.9</td>
</tr>
<tr>
<td>Femoral neck BMD T-score (mean)</td>
<td>-2.2</td>
<td>-2.2</td>
<td>-2.1</td>
<td>-2.1</td>
</tr>
</tbody>
</table>

*Nonvertebral fracture within prior 5 years

ACTIVE: BMD Changes at Spine and Hip

ITT Population N=2463

A. Lumbar Spine BMD

B. Total Hip BMD

C. Femoral Neck BMD

*P<.001 compared with placebo; †P<.01 compared with teriparatide.

ACTIVE: Risk of New Vertebral Fractures

Modified ITT Population* N=2118

Proportion (%) of patients with new vertebral fractures

- Placebo
  - n=711
  - 4.22% (n=30)

- Abaloparatide-SC
  - n=690
  - 0.58% (n=4)

- Teriparatide
  - n=717
  - 0.84% (n=6)


*Includes all ITT patients who had pretreatment and postbaseline evaluable radiologic assessments. †P<.0001 vs placebo.
ACTIVE: Risk of Nonvertebral Fractures

ITT Population N=2463

Proportion (%) of patients with nonvertebral fractures

Placebo: 4.0% (n=33)
Abaloparatide-SC: 2.2% (n=18)
Teriparatide: 2.9% (n=24)

-43%* NS†

*P= 0.049 vs placebo.
†NS vs placebo and abaloparatide-SC,

ACTIVE: Time to First Nonvertebral Fractures

ITT Population N=2463

Kaplan-Meier Curve

- Placebo
- Teriparatide
- Abaloparatide-SC

Proportion (%) of patients with nonvertebral fracture vs time to event (days)

Logrank P-value = .049

Abaloparatide-SC vs placebo

ACTIVE: Major Osteoporotic Fractures

ITT Population N=2463

-70%*  
-55%†

Placebo  
n=821  
4.1% (n=34)

Abaloparatide-SC  
n=824  
1.2% (n=10)

Teriparatide  
n=818  
2.8% (n=23)

*P=0.0004, abaloparatide-SC vs placebo  
†P=0.031, abaloparatide-SC vs teriparatide; teriparatide NS vs placebo.

ACTIVE: Time to First Major Osteoporotic Fracture

ITT Population N=2463

- Abaloparatide-SC
  - Logrank P-value = .0004 vs placebo
  - Logrank P-value = .031 vs teriparatide

- Placebo

Proportion (%) of patients with major osteoporotic fracture

Time to event (days)

ACTIVE Subgroup Analysis: Study Overview

Objective: To determine whether the effect of abaloparatide-SC compared to placebo on fracture and BMD was consistent among different risk subgroups

• Prespecified subgroups were defined categorically
  – BMD T-score (-2.5 and -3.0 cutpoints)
  – Fracture history (nonvertebral and prevalent vertebral)
  – Age (<65, 65-75, >75)

• Treatment effects assessed in subgroups using
  – Forest Plots and
  – Tests for qualitative and quantitative treatment-by-subgroup interactions

Cosman et al JBMR 2016
ACTIVE Subgroup Analysis: Results

- Consistent fracture reductions in all risk subgroups for both new morphometric vertebral and nonvertebral fractures
- Consistent improvements in BMD of the lumbar spine, total hip, and femoral neck
- No meaningful interactions seen between baseline risk factor subgroups and treatment effects
ACTIVE and ACTIVExtend Trial Design

ACTIVE N=2463

ACTIVEExtend N=1139
Representing 92% of patients eligible to enroll

6-month planned interim analysis

Randomization

Placebo (n=821)
Abaloparatide-SC 80 μg daily (n=824)
Teriparatide 20 μg daily SC (n=818)

Months

6
12
18

Alendronate 70 mg QW

Full duration of extension, 24 months

19*
25†

*1-month gap in treatment was allowed for rollover from ACTIVE to ACTIVExtend. †Investigators and patients remained blinded to original treatment assignment for the initial 6 months of the extension study.

Cosman et al Mayo Clinic Proceedings 2016
ACTIVExtend: New Vertebral Fractures

Modified ITT Population N=1112*

Proportion (%) of patients with new vertebral fractures

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/Alendronate n=568</td>
<td>1.2%</td>
<td>(n=7)</td>
</tr>
<tr>
<td>Abaloparatide-SC/Alendronate n=544</td>
<td>0%</td>
<td>(n=0)</td>
</tr>
</tbody>
</table>

ACTIVE + ACTIVExtend Cumulative Incidence at 25 Months

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/Alendronate n=568</td>
<td>4.4%</td>
<td>(n=25)</td>
</tr>
<tr>
<td>Abaloparatide-SC/Alendronate n=544</td>
<td>0.55%</td>
<td>(n=3)</td>
</tr>
</tbody>
</table>

-87%†

All patients from the ACTIVE mITT population who had a postbaseline Month 25 (Visit 3 in ACTIVExtend) evaluable radiologic assessments. mITT population was the primary population used for the analyses of vertebral fracture. †P<.0001 vs pbo

Cosman et al Mayo Clinic Proceedings 2016
ACTIVExtend: Nonvertebral Fractures

ITT Population N=1139

ACTIVExtend first 6 months

Proportion (%) of patients with nonvertebral fractures

Placebo/Alendronate n=581
1.2% (n=7)

Abaloparatide-SC/Alendronate n=558
0.5% (n=3)

ACTIVE + ACTIVExtend
Cumulative Incidence at 25 Months

Placebo/Alendronate n=581
5.5% (n=32)

Abaloparatide-SC/Alendronate n=558
2.7% (n=15)

*P=0.017 vs placebo/alendronate.

Cosman F et al Mayo Clinic Proceedings 2016
ACTIVExtend First 6 Months: Time to First Nonvertebral Fractures

ITT Population N=1139

Kaplan-Meier Curve

Proportion (%) of patients with nonvertebral fracture

Time to event (months)

Treatment with alendronate began

Placebo/Alendronate

Abaloparatide-SC/Alendronate

Logrank P-value = .017

Cosman F et al Mayo Clinic Proceedings 2016
ACTIVExtend BMD Summary at 25 Months

ITT Population N=1139

*P<.0001 vs Placebo/Alendronate.

Cosman F et al Mayo Clinic Proceedings 2016
Conclusions: How do the New Agents Fit In?

- New Agents Target high risk patients and could help bridge treatment gap in osteoporosis
  - Agents have distinct mechanisms of action and
  - Each agent could play a role in treatment in one individual across her/his lifespan (in addition to teriparatide)
  - Both Romosozumab and Abaloparatide
    - Rapid reduction in fracture risk
    - Can help achieve BMD treatment goals
Conclusions: How do New Agents Fit In?

- Sequential monotherapy
  - can maximize benefits and minimize risks at each stage of life
  - Minimize exposure to pharmacology
- Use anabolic first line for more severe patients to reduce fracture risk quickly and/or to provide foundation for greater strengthening effect and BMD improvement
- Use Non-Bisphosphonate AR second line
  - To help achieve fracture free interval of 3-5 years
  - To help achieve BMD goals (T-Scores above -2.5)
Conclusions: How do New Agents Fit In?

• If use nonBP medications
  - If treatment is stopped, BMD is lost rapidly
  - Either continue these agents indefinitely or switch to Maintenance therapy

• Maintenance Therapy
  - Low dose intermittent bisphosphonates
    • eg. zoledronic acid infusion
    • repeat treatment when/if needed
  - Monitor Fx/BMD/biochemical turnover markers
    • Repeat sequential monotherapy as needed