Reducing the Risk of Fracture in Postmenopausal Women: Guidance for Family Physicians

Please complete the preassessment before the session starts.
Sponsorship and Support

This educational activity is jointly provided by the North Carolina Academy of Family Physicians (NCAFP) and Spire Learning.

This activity is supported by educational funding provided by Amgen.
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• Read the objectives and other introductory CME information
• Complete the preassessment *prior to the start* of the activity
• Participate in the postmenopausal osteoporosis presentation
• Complete the postassessment and evaluation *at the conclusion* of the activity
Faculty and Disclosures

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Disclosure Statement:
Advisory Board: Amgen Inc; Eli Lilly and Company; Radius Health, Inc
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Faculty and Disclosures (Cont.)

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Disclosure Statements:

Association Board Member: National Osteoporosis Foundation; International Society for Clinical Densitometry; Osteoporosis Foundation of New Mexico
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Speaker’s Bureau: Alexion Pharmaceuticals Inc.; Radius Health, Inc.
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This educational activity may contain discussion of published and/or investigational uses of romosozumab for the management of postmenopausal osteoporosis that are not indicated by the FDA.

Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings. Further, participants should appraise the information presented critically and are encouraged to consult appropriate resources for any product or device mentioned in this program.
# Levels of Evidence

<table>
<thead>
<tr>
<th>Recommendation Grade</th>
<th>Description</th>
</tr>
</thead>
</table>
| **A**                | • Homogeneous evidence from multiple, well-designed, randomized, controlled trials with sufficient statistical power  
• Homogeneous evidence from multiple, well-designed, cohort-controlled trials with sufficient statistical power  
• ≥1 conclusive level 1 publications demonstrating benefit >> risk |
| **B**                | • Evidence from ≥1 well-designed clinical trial, cohort- or case-controlled analytic study, or meta-analysis  
• No conclusive level 1 publications; ≥1 conclusive level 2 publications demonstrating benefit >> risk |
| **C**                | • Evidence based on clinical experience, descriptive studies, or expert consensus opinion  
• No conclusive level 1 or 2 publications; ≥1 conclusive level 3 publications demonstrating benefit >> risk  
• No conclusive risk at all and no conclusive benefit demonstrated by evidence |
| **D**                | • Not rated  
• No conclusive level 1, 2, or 3 publications demonstrating benefit >> risk  
• Conclusive level 1, 2, or 3 publications demonstrating risk >> benefit |

Learning Objectives

At the conclusion of this live activity, learners should be better able to:

• Identify patients at risk of fracture using prior fracture history, vertebral imaging, DXA, and FRAX®.
• Select appropriate therapies for osteoporosis based on an assessment of the patient’s imminent or long-term fracture risk.
• Compare the efficacy, adverse effects, and mechanism of action for available and emerging pharmacotherapies for the management of osteoporosis.
• Employ goal-directed therapy, sequential therapy, and drug holidays to achieve treatment goals.
Definition of Osteoporosis

• A chronic progressive skeletal disorder characterized by
  – **Compromised bone strength** predisposing to an **increased risk** of fracture

• Bone strength reflects the integration of two main features:
  – Bone density
  – Bone quality

• Risk Factors:
  – **Estrogen deficiency and aging**
  – Genetics: family history, ethnicity
  – Chronic diseases and medications
  – Lifestyle: nutrition, exercise, smoking, alcohol

2000 NIH Consensus Development Conference.
Health Consequences of Osteoporosis

• Osteoporosis-related fractures
  – Fractures in people >50 years of age that occur in the setting of trauma equal to or less than a fall from standing height
  – Exceptions are fingers, toes, face, and skull

• Lifetime osteoporosis-related fracture risk
  – 1 in 2 women
  – Up to 1 in 4 men

• Each year in the US
  – 500,000 vertebral fractures
  – 400,000 wrist fractures
  – 300,000 hip fractures
  – 150,000 pelvic fractures
  – 700,000 other fractures (humerus, rib, patella, clavicle, etc.)
Consequences of Hip Fracture

• Hip fractures require surgical repair and hospitalization
• 25% mortality in the year following the fracture
  – 65,000 deaths in the US each year
• 20% require at least temporary stay in nursing home
• Over 50% permanently disabled
• Over 2-fold risk of becoming destitute

Consequences of Vertebral Fracture

- Acute back pain in 25%-30%
- Increased risk of mortality
- Chronic back pain
- Height loss/kyphosis
- Disability related to poor ambulation, loss of balance, and high falling risk
- Pulmonary symptoms related to restrictive lung disease
- Abdominal symptoms

Vertebral Fracture Identification

Most spine fractures do not come to clinical attention at the time of the event (75%).

Proactive targeted screening spine imaging recommended to identify those with spine fractures

Prevalence of Spine Fractures by Age

Overall prevalence is 5.4%

![Graph showing prevalence of spine fractures by age and gender.](chart.png)

History of Self-Reported Spine Fracture Compared to VFA Diagnosis

- Of those reporting a history of spine fracture
  - 21% (95% CI 8.1 - 39.4) had a positive VFA
- Of those diagnosed with spine fracture by VFA
  - 8.2% (3.3, 16.3) reported a history of fracture

*Numbers in figure are unweighted.
VFA, vertebral fracture assessment.
Diagnosis of Osteoporosis
Osteoporosis Can Be Diagnosed by Presence of Fracture and/or BMD Criteria

Osteoporosis can be diagnosed by*:

- Occurrence of a low-trauma hip fracture¹-³
- Occurrence of a low-trauma spine, humerus, or pelvis fracture in a person with osteopenia¹-³
- BMD T-score ≤-2.5 spine, total hip, femoral neck¹-³
  - T-score compares an individual’s BMD with the mean value for young adults and expresses the difference as a standard deviation score⁴,⁵
    - Normal -1.0 and above
    - Low bone mass (osteopenia) -1.0 to -2.5
    - Osteoporosis -2.5 and below
- ?? Elevated fracture risk, e.g., by FRAX¹-³
  - This approach is being applied in many countries where the osteoporosis intervention threshold is based on fracture risk

*Grade B
BMD, bone mineral density.
Who Should Have a Bone Density Test?

<table>
<thead>
<tr>
<th>AAFP(^1) and NOF(^2) Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women age 65 and older</td>
</tr>
<tr>
<td>Men age 70 and older</td>
</tr>
<tr>
<td>Postmenopausal women and men ages 50-69 with clinical risk factors</td>
</tr>
<tr>
<td>Adults who have a fracture after age 50</td>
</tr>
<tr>
<td>Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids) associated with low bone mass or bone loss</td>
</tr>
</tbody>
</table>

AAFP, American Academy of Family Physicians; NOF, National Osteoporosis Foundation.

### Who Should Have a Vertebral Fracture Assessment?

<table>
<thead>
<tr>
<th>Age and T-score Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women age ≥70 and men age ≥80 if BMD T-score is ≤-1.0 at the spine, total hip, or femoral neck</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Women age 65-69 and men age 70-79 if BMD T-score is ≤-1.5 at the spine, total hip, or femoral neck</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Postmenopausal women and men age ≥50 with specific risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>• Low trauma fracture during adulthood (age 50+)</td>
<td></td>
</tr>
<tr>
<td>• Historical height loss of 1.5 inches or more (4 cm)</td>
<td></td>
</tr>
<tr>
<td>• Prospective height loss of 0.8 inches or more (2 cm)</td>
<td></td>
</tr>
<tr>
<td>• Recent or ongoing long-term glucocorticoid treatment</td>
<td></td>
</tr>
<tr>
<td><strong>If bone density testing is not available, vertebral imaging may be considered based on age alone</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

#### Questionnaire:

1. Age (between 40-90 years) or Date of birth
   - Age: 63
   - Date of birth: 11/8/2000

2. Sex
   - Male

3. Weight (kg) 58.87

4. Height (cm) 160.02

5. Previous fracture
   - Yes

6. Parent fractured hip
   - No

7. Current smoking
   - No

8. Glucocorticoids
   - No

9. Rheumatoid arthritis
   - No

10. Secondary osteoporosis
    - No

11. Alcohol 3 or more units per day
    - No

12. Femoral neck BMD (g/cm²)
    - T-score: -2.3

#### Weight Conversion

- Pounds to kg
  - 132 pounds

#### Height Conversion

- Inches to cm
  - 63 inches

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### Results

**BMI 23.4**

<table>
<thead>
<tr>
<th>With BMD</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major osteoporotic</td>
<td>19</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>3.5</td>
</tr>
</tbody>
</table>

**T-score:** -2.3

- Previous fracture: Yes (11)
- General fracture: 2.0
Limitations of FRAX®

- Not valid to monitor patients on treatment
- Only femoral neck BMD considered
- Risk is “yes/no” without consideration of “dose” (e.g., glucocorticoids, smoking)
- Not all risk factors included (e.g., risk of falling)
- Many diseases and medications not included
- No consideration of time from fracture
- No consideration for multiple fractures
- Do patients with high FRAX® scores benefit from medication? (Unknown)
Many Patients With Fractures Do Not Have “Osteoporosis” by BMD Criteria

Rotterdam Study

Women
- Nonvertebral fractures
  - 44% Osteoporosis
  - 13% Normal BMD
  - 43% Low BMD

Men
- Nonvertebral fractures
  - 21% Osteoporosis
  - 18% Normal BMD
  - 61% Low BMD

Women
- Hip fractures
  - 31% Osteoporosis
  - 31% Normal BMD
  - 64% Low BMD

Men
- Hip fractures
  - 39% Osteoporosis
  - 58% Normal BMD
  - 3% Low BMD

Patients With Prior Fractures Are High Risk

- Prior fracture is the most important risk factor for another fracture¹

<table>
<thead>
<tr>
<th>Previous fracture site</th>
<th>Any bone</th>
<th>Hip</th>
<th>Spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior fracture</td>
<td>2.19</td>
<td>2.02</td>
<td>2.93</td>
</tr>
<tr>
<td>1 fracture</td>
<td>1.81</td>
<td>1.60</td>
<td>2.16</td>
</tr>
<tr>
<td>2 fractures</td>
<td>2.98</td>
<td>2.95</td>
<td>3.97</td>
</tr>
<tr>
<td>≥3 fractures</td>
<td>4.80</td>
<td>3.66</td>
<td>9.05</td>
</tr>
</tbody>
</table>

- Approximately 60% of hip fracture patients have a prior fracture by history (often spine, wrist)²
  - Target these patients at a younger age after the first fracture to prevent hip fractures
- Risk is highest within first few years after first fracture¹
  - Suggests an urgency for treatment

Absolute Risk of Recurrent Fracture

377,561 women >50 years with first clinical fracture (excluding fingers, toes, face, skull) identified from Medicare Database

Years 3-5:
Annualized rates all fx: 4.3%/year
Annualized rates hip fx: 1.6%/year

Fx, fracture.
Management of Osteoporosis
## 2014 Universal Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counsel on the risk of fractures</td>
</tr>
<tr>
<td>Eat a diet rich in fruits and vegetables and calcium (supplemented if necessary) to a total calcium intake of:</td>
</tr>
<tr>
<td>• 1000 mg per day for men 50-70</td>
</tr>
<tr>
<td>• 1200 mg per day for women ≥51</td>
</tr>
<tr>
<td>• 1200 mg per day for men ≥71</td>
</tr>
<tr>
<td>Vitamin D intake should be 800-1000 IU per day (age ≥50), supplemented if necessary</td>
</tr>
<tr>
<td>Regular weight-bearing and muscle-strengthening exercise</td>
</tr>
<tr>
<td>Fall prevention evaluation and training</td>
</tr>
<tr>
<td>Cessation of tobacco use and avoidance of excessive alcohol intake</td>
</tr>
</tbody>
</table>

Whom to Treat: NOF Guidelines 2014

- Women ≥65 and men ≥70 (younger with risk factors)
  - T-score between -1.0 and -2.5
  - T-score ≤-2.5 in the lumbar spine, total hip, or femoral neck
  - Hip or spine fracture (clinical or radiographic)

**DXA test**

- YES
  - T-score ≤-2.5 in the lumbar spine, total hip, or femoral neck
  - Hip or spine fracture (clinical or radiographic)
  - Candidate for TREATMENT

- T-score between -1.0 and -2.5
  - FRAX 10-y fracture risk
  - ≥3% for hip fracture
  - ≥20% for major osteoporotic fractures

Pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce risk for hip and vertebral fractures in women with known osteoporosis

<table>
<thead>
<tr>
<th>Treat osteoporotic women with pharmacologic therapy for 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD screening not recommended during the 5-year treatment period for osteoporosis in women</td>
</tr>
<tr>
<td>Menopausal estrogen therapy ± progesterone therapy or raloxifene not recommended for the treatment of osteoporosis in women</td>
</tr>
<tr>
<td>Consider treatment in osteopenic women ≥65 years of age who are at high risk for fracture based on patient preferences, fracture risk profile, and benefits, harms, and costs of medications</td>
</tr>
</tbody>
</table>

**Limitations**
- No treatments without specific hip fracture efficacy were included
- Recommends a treatment holiday for denosumab
- No discussion of long-term treatment decisions beyond 5 years
- Anabolic therapy not included

The 2017 ACP guidelines are endorsed by the AAFP.

*Expert opinion.
ACP, American College of Physicians.
AACE/ACE Guidelines for Treatment

Prior fragility fractures or indicators of higher fracture risk*

- Denosumab, teriparatide, zoledronic acid**
- Alternate therapy: alendronate, risedronate

Reassess at least yearly for response to therapy and fracture risk

Denosumab
Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

Teriparatide for up to 2 years
Sequential therapy with oral or injectable antiresorptive agent

Zoledronic acid
- If stable, continue therapy for 6 years***
- If progression of bone loss or recurrent fractures, consider switching to teriparatide

*Indicators of higher fracture risk in patients with low BMD would include advanced age, frailty, glucocorticoids, very low T-scores, or increased fall risk.

**Medications are listed alphabetically.

***Consider a drug holiday after 6 years of IV zoledronic acid. During the holiday, another agent such as teriparatide or raloxifene could be used.

ACE, American College of Endocrinology; AACE, American Association of Clinical Endocrinologists; IV, intravenous.
Different Treatments for Patients at Different Risk Levels

• Moderate-risk patients
  – Patients with bone density in the mild osteoporosis range who have not had osteoporosis-related fractures do not need anabolic therapy
  – Could be served with antiresorptive therapy*

• High-risk patients
  – People with radiographic vertebral fracture
  – People with a history of any clinical osteoporosis-related fracture, especially if recent (high imminent risk)
  – People with very low BMD (high long-term risk)
  – Consider anabolic therapy versus antiresorptive therapy

*Expert opinion.
## Evidence for Fracture Reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vertebral Fracture</th>
<th>Nonvertebral Fracture</th>
<th>Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronate</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>Zoledronic acid</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Denosumab</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Abaloparatide</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
Overview Data for One Bisphosphonate and Other Potent Agents

- **Zoledronic Acid** (HORIZON Trial): Intravenous Bisphosphonate, administered once yearly
- **Denosumab** (FREEDOM Trial): Monoclonal Antibody to Rank Ligand, administered subcutaneously every 6 months
- **Teriparatide** (Fracture Prevention Trial): 1-34PTH, administered daily subcutaneously
- **Abaloparatide** (ACTIVE Trial): 1-34PTH-related peptide analogue, administered daily subcutaneously
- **Romosozumab*** (FRAME Trial): Monoclonal Antibody to Sclerostin, administered monthly subcutaneously

*Romosozumab is an investigational agent and is not approved by the FDA for the treatment of osteoporosis. PTH, parathyroid hormone.
Zoledronic Acid Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I)

*P<.0001, relative risk reduction vs placebo (95% confidence interval).
Zoledronic Acid Reduced Cumulative 3-Year Risk of Clinical Vertebral and Nonvertebral Fractures (Strata I + II)

*P=.0024, relative risk reduction vs placebo (95% confidence interval).
**Relative risk reduction vs. placebo.
Safety Information

• Contraindications:
  – Hypocalcemia
  – Creatinine clearance <35 mL
  – Acute renal impairment

• Adverse Reactions:
  – Pyrexia
  – Myalgia
  – Headache
  – Arthralgia
  – Pain in extremities
  – Flu-like symptoms
  – Nausea
  – Vomiting
  – Diarrhea
  – Eye inflammation

• Other Concerns:
  – Osteonecrosis of the jaw
  – Atypical femur fracture
  – Severe bone, joint, and muscle pain

US FDA. CDER. Zoledronic acid NDA 021817. Label 7/7/17.
Zoledronic Acid 5 mg Reduced Subsequent Fracture Risk Over Time

![Graph showing the reduction in fracture rates with Zoledronic Acid 5 mg compared to Placebo.](chart)

- **Clinical Fractures**: 13.9% (139/1062) Placebo vs. 8.6% (92/1065) Zoledronic Acid 5 mg, relative risk reduction 35%* (16%, 50%).
- **Nonvertebral Fractures**: 10.7% (107/1062) Placebo vs. 7.6% (79/1065) Zoledronic Acid 5 mg, relative risk reduction 27%† (2%, 45%).
- **Clinical Vertebral Fractures**: 3.8% (39/1062) Placebo vs. 1.7% (21/1065) Zoledronic Acid 5 mg, relative risk reduction 46%‡ (8%, 68%).
- **Hip Fractures**: 3.5% (33/1062) Placebo vs. 2.0% (23/1065) Zoledronic Acid 5 mg, relative risk reduction 30%NS (-2%, 59%).

*P=.0012; †P=.0338; ‡P=.0210, relative risk reduction vs. placebo; NS = not significant.

Values above bars are cumulative event rates based on Kaplan-Meier estimates at Month 24.

Zoledronic Acid 5 mg Reduced Risk of All-Cause Mortality by 28% Over Time

Hazard Ratio, 0.72 (95% CI, 0.56-0.93)
P = 0.0117
Absolute Risk Reduction, 3.7%

No. at Risk
ZOL 5 mg | 1054 | 1029 | 987 | 943 | 806 | 674 | 507 | 348 | 237 | 144
Placebo | 1057 | 1028 | 993 | 945 | 804 | 681 | 511 | 364 | 236 | 149

Effects of Denosumab Treatment on Lumbar Spine BMD and New Vertebral Fractures Through 10 Years

![Graph showing percentage change from baseline in lumbar spine BMD and yearly incidence of new vertebral fractures.](image)

BMD data are LS means and 95% confidence intervals. 

- aP<0.05 vs FREEDOM baseline. 
- bP<0.05 vs FREEDOM and Extension baselines. 
- cPercentage change while on denosumab treatment. 
- dAnnualized incidence: (2-year incidence) /2. 

Lateral radiographs (lumbar and thoracic) were not obtained at years 4, 7, and 9 (years 1, 4, and 6 of the Extension). 

Effects of Denosumab Treatment on Total Hip BMD and Nonvertebral Fractures Through 10 Years

BMD data are LS means and 95% confidence intervals. Percentages for nonvertebral fractures are Kaplan-Meier estimates. 

*P*<0.05 vs FREEDOM baseline. *P*<0.05 vs FREEDOM and Extension baselines. C Percentage change while on denosumab treatment. 

Safety Information

• Contraindications:
  – Hypocalcemia

• Adverse Reactions:
  – Back pain
  – Pain in extremities
  – Hypercholesterolemia
  – Musculoskeletal pain
  – Cystitis

• Other Concerns:
  – Skin rash
  – Osteonecrosis of the jaw
  – Atypical femur fracture
  – Multiple vertebral fractures upon withdrawal

Effects of Teriparatide on Vertebral and Nonvertebral Fractures

ARR, absolute risk reduction; RRR, relative risk reduction.


ARR = 2.9%

RRR = 53%

*P* ≤.05 vs placebo
Abaloparatide Background

- Abaloparatide is a 34-amino acid osteoanabolic peptide
  - Synthetic analogue of PTH-related peptide
- In preclinical and clinical studies:
  - Improved BMD, microarchitecture and strength increased
- Unique mechanism of action at the PTH1 receptor
  - Stimulates bone formation with limited calcium mobilization and bone resorption
  - Optimized osteoanabolic profile

ACTIVE: Risk of New Vertebral Fractures

Modified ITT Population* N=2118

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo n=711</td>
<td>-86%†</td>
</tr>
<tr>
<td>Abaloparatide n=690</td>
<td>-80%†</td>
</tr>
<tr>
<td>Teriparatide n=717</td>
<td>0.58% (n=4)</td>
</tr>
<tr>
<td></td>
<td>0.84% (n=6)</td>
</tr>
</tbody>
</table>

*Includes all ITT patients who had pretreatment and post-baseline evaluable radiologic assessments.
†P<.001 vs placebo
ITT, intention-to-treat.
ACTIVE: Time to First Nonvertebral Fracture

ITT Population N=2463

**Kaplan-Meier Curve**

- **Placebo**
  - Log-rank P value = .22 vs placebo
- **Teriparatide**
  - Log-rank P value = .22 vs placebo
- **Abaloparatide**
  - Log-rank P value = .049 vs placebo

Safety Information for Teriparatide and Abaloparatide

- Rodent Osteosarcoma
- Hypercalcemia
- Hypercalciuria
- Hyperuricemia
- Orthostatic Hypotension
- Adverse Reactions
  - Arthralgia
  - Pain
  - Nausea

Full ACTIVExtend Study (3.5 years)

- Compared to the placebo/alendronate group, the abaloparatide/alendronate group experienced at both 6 months and 24 months into the extension study:
  - Sustained reduced risk for vertebral, nonvertebral, clinical, and major osteoporotic fractures
  - Similar incidence of adverse effects, no cases of AFF or ONJ

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
  – Increases BMD markedly
• FRAME is a phase 3, randomized, placebo-controlled FRActure study in postmenopausal woMen with osteoporosis¹
  – 1 year blinded denosumab vs placebo and then transition to
    1 year denosumab in all patients

New Vertebral Fracture Incidence Through Month 12 (Co-Primary Endpoint)

- **Placebo (N=3591)**: 0.8% through Month 6, 1.8% through Month 12
- **Romosozumab (N=3589)**: 0.4% through Month 6, 0.5% through Month 12

RRR = 73%
P = < 0.001

RRR = 46%
P = 0.056

n/N1 = number of subjects with fractures/number of subjects in the primary analysis set for vertebral fracture.
P value based on logistic regression model adjusted for age (<75, ≥75) and prevalent vertebral fracture.
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.
Nonvertebral Fracture Incidence Through Month 12 in Latin America vs. Rest of the World

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

Subject Incidence (%)

n/N1 = 19/1534 24/1550 56/2057 32/2039

RRR = 42%
P = 0.012

RRR = -25%
P = 0.47

Treatment-by-subgroup interaction (P = 0.041)

*Regions excluding Latin America grouped post hoc.
n/N1 = number of subjects with fractures/number of subjects in the full analysis set.
Adverse Reactions

- No significant difference in the incidence of osteoarthritis, hyperostosis, cancer, hypersensitivity, and serious cardiovascular events
- Hypersensitivity reactions observed over the 12-month period in the romosozumab group
- Mild injection-site reactions observed in the romosozumab group (5.2%) and placebo group (2.9%)
- ONJ was reported in 2 patients from the romosozumab group

Limitations of Antiresorptives for the High-Risk Patient

• Nonvertebral fracture risk reductions for antiresorptives
  – At best 20%-25%
  – Takes 3 years to see significant decline

• Long-term efficacy of antiresorptives is unclear
  – With bisphosphonates
    • Effect on fractures beyond 3-4 years inconsistent
    • BMD plateaus after 3-4 years
      – If BMD remains <-2.5, patients still at risk

Limitations of Antiresorptives for the High-Risk Patient (Cont.)

• With denosumab
  – Continued increase in BMD years 3-10\textsuperscript{1}
  – Low fracture rates during the extension study years (but no long-term placebo group)\textsuperscript{1,2}
  – Hip BMD attained during denosumab treatment is predictive of lower risk of subsequent incident nonvertebral fracture\textsuperscript{2}

• Rare but significant long-term safety risks for both BPs and Denosumab (AFFs, ONJ)\textsuperscript{1}

\textsuperscript{2} Ferrari S. Abstract presented at: ASBMR 2017; Sept 10, 2017; Denver, CO. Abstract 1073.
Fracture Outcome Comparison Studies: Anabolic vs. Antiresorptive Agents

• In glucocorticoid-induced osteoporosis:
  – Teriparatide reduced vertebral fractures by 90% compared to alendronate over 18 months\(^1\)
• In patients with acute symptomatic vertebral fractures:
  – Teriparatide reduced vertebral fractures by 50% compared to risedronate\(^2\)
• In patients with prevalent vertebral fracture (VERO):
  – Teriparatide reduced vertebral and all clinical fractures vs. risedronate over 2 years\(^3\)
• In patients with prevalent spine (or hip) fracture (ARCH)\(^4\):
  – Romosozumab reduced risk of vertebral, clinical, nonvertebral, and hip fractures with romosozumab compared to alendronate
  – Potential safety issues (cardiovascular serious AEs) have resulted in delay of approval

Rationale for Anabolic Therapy First Line

• If imminent fracture risk is high
  – Anabolic agents provide fastest protection against fractures
    (12 to 18 months for both vertebral and nonvertebral risk reductions)
• If very low BMD (T-score <-3) even without prior fracture
  – Best initial treatment is still anabolic
    • Increased skeletal mass and improved microarchitecture
    • Largest effects when anabolic followed by antiresorptive

TPTD, teriparatide.


---

**Table 1. Hip BMD Effect of Switching From Potent Antiresorptive Therapy to TPTD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Treatment paradigm</th>
<th>% Change in total hip BMD during TPTD/PTH treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ettinger et al.</td>
<td>33</td>
<td>Alendronate (mean 29.3 mo) → TPTD (18 mo)</td>
<td>-1.8% -1.0% +0.3% -</td>
</tr>
<tr>
<td>Boonen et al.</td>
<td>107</td>
<td>Alendronate (median 29.2 mo) → TPTD (24 mo)</td>
<td>-1.2% -0.6% +0.6% +2.1%</td>
</tr>
<tr>
<td>Boonen et al.</td>
<td>59</td>
<td>Risedronate (median 23.4 mo) → TPTD (24 mo)</td>
<td>-1.6% -0.4% +0.9% +2.9%</td>
</tr>
<tr>
<td>Miller et al.</td>
<td>158</td>
<td>Risedronate (mean 37.2 mo) → TPTD (12 mo)</td>
<td>-1.2% -0.3% - -</td>
</tr>
<tr>
<td>Miller et al.</td>
<td>166</td>
<td>Alendronate (mean 38.0 mo) → TPTD (12 mo)</td>
<td>-1.9% -1.7% - -</td>
</tr>
<tr>
<td>Cosman et al.</td>
<td>50</td>
<td>Alendronate (mean 45.7 mo) → TPTD (18 mo)</td>
<td>-0.8% +0.9% - -</td>
</tr>
<tr>
<td>Leder et al.</td>
<td>27</td>
<td>Denosumab (24 mo) → TPTD (24 mo)</td>
<td>-1.7% -2.7% -1.7% -0.7%</td>
</tr>
</tbody>
</table>

mo = months.
In some cases, numbers are estimated by extrapolation from graph in article.

Langdahl et al² 218 Oral Bisphosphonate (mean 6.2 yr), Alendronate (mean 5.8 yr)* → TPTD (12 mo) -0.8% -0.5% - -
Potential Treatment Targets for Osteoporosis Treatment Targets Are the Inverse of Treatment Indications

• Remain free of fracture (first or recurrent) for 5 years
  – For recurrent fracture, fracture-free duration target might vary based on site of initial fracture
    • After incident spine or hip fracture, possibly a longer target
  – Must include assessment of vertebral fracture
    • Vertebral imaging needed at beginning and ‘end’
• Attain BMD T-scores above osteoporosis range
• Reduce fracture probabilities to below treatment indications

Treatment Targets Affect Selection of Initial Treatment and Treatment Sequence

• For highest-risk patients, especially those at high imminent risk (e.g., those with recent fractures)
  – Produce rapid reduction in osteoporosis-related fracture
  – Provide foundation for greater strengthening effect and BMD improvement
  – Growing consensus that anabolic therapy should be given first line for high-risk patients

• Use non-bisphosphonate antiresorptive (denosumab) second line
  – To help achieve fracture-free interval of 3-5 years
  – To help achieve BMD goals (T-scores above -2.5)

Treatment Targets Affect Treatment Sequence Decisions and Decisions About Drug Holidays

• If using non-bisphosphonate medications
  – When treatment is stopped, BMD is lost rapidly
  – Either continue these agents indefinitely or switch to maintenance therapy

• Maintenance therapy
  – Use bisphosphonates at end of treatment sequence
  – If treatment goals met, consider medication holiday
  – Intermittent bisphosphonates can be used to maintain BMD*
    • e.g., single zoledronic acid infusion
    • Repeat treatment when/if needed
  – Monitor fractures/BMD/biochemical turnover markers*
    • Repeat sequential monotherapy as needed

• Sequential monotherapy^  
  – Can minimize exposure to pharmacology while maximizing benefits on strength and BMD

*Grade A.
^Grade A for teriparatide followed by an antiresorptive agent.
Take-Home Messages

• Osteoporosis is a common disease with serious consequences due to fractures
  – Fracture numbers are expected to hit crisis range
• Tools to diagnose osteoporosis and identify patients for pharmacological therapy are available—cheap and without risk
• Pharmacological agents reduce fracture risk
  – Treatment decisions for initiating and continuing therapy should be individualized based upon the expected benefit and potential risk for each patient
  – Different medications are appropriate at different ages and stages of disease
• Secondary fracture prevention should be a priority
Questions?
Thank You!

Please complete the *post assessment and evaluation* for this session.
Appendix
## FDA-Approved Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Postmenopausal</th>
<th>Glucocorticoid-induced</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevent</td>
<td>Treat</td>
<td></td>
</tr>
<tr>
<td>Estrogen/HT/BZD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin (Miacalcin®)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene (Evista®)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ibandronate (Boniva®)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate (Actonel®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate (Atelvia®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronate (Reclast®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Denosumab (Prolia™)</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Abaloparatide (Tymlos™)</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

## Denosumab: Exposure-Adjusted Subject Incidence of Adverse Events (Rates per 100 Subject-Years)

<table>
<thead>
<tr>
<th></th>
<th>Extension Years 1–7</th>
<th>Freedom Years 1–3</th>
<th>Extension Years 1–7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cross-over Denosumab (N = 2206)</td>
<td>Long-term Denosumab (N = 2343)</td>
<td>Placebo (N = 3883)</td>
</tr>
<tr>
<td>Year</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Serious infections</td>
<td>1.6</td>
<td>1.5</td>
<td>1.1</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1.9</td>
<td>1.7</td>
<td>2.1</td>
</tr>
</tbody>
</table>

ACTIVE: BMD Changes at Spine and Hip

ITT Population N=2463

*P<.001 compared with placebo; †P<.01 compared with teriparatide.
Missing BMD was imputed using last observation carried forward.
ACTIVE and ACTIVExtend Trial Design

ACTIVE N=2463
ACTIVExtend N=1139
Representing 92% of patients eligible to enroll

Randomization

Placebo (n=821)
Abaloparate 80 µg daily (n=824)
Teriparate 20 µg daily SC (n=818)

Teriparatide 20 µg daily SC (n=818)

Alendronate 70 mg QW (n=581)
Alendronate 70 mg QW (n=558)

6-month planned interim analysis

19* 25† 43

Months 6 12 18

Full duration of extension, 24 months

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

**ACTIVExtend: New Vertebal Fractures**

**Modified ITT Population N=1112***

<table>
<thead>
<tr>
<th></th>
<th>Proportion (%) of Patients With New Vertebral Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACTIVExtend first 6 months</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo/Alendronate  n=568</td>
<td>1.2% (n=7)</td>
</tr>
<tr>
<td>Abaloparatide/Alendronate n=544</td>
<td>0% (n=0)</td>
</tr>
<tr>
<td><strong>ACTIVE + ACTIVExtend</strong></td>
<td></td>
</tr>
<tr>
<td>Placebo/Alendronate  n=568</td>
<td>4.4% (n=25)</td>
</tr>
<tr>
<td>Abaloparatide/Alendronate n=544</td>
<td>0.55% (n=3)</td>
</tr>
</tbody>
</table>

*All patients from the ACTIVE mITT population who had Month 25 evaluable radiologic assessments.

†P<.001 vs. placebo/alendronate.

# ACTIVE: Safety and Adverse Events

<table>
<thead>
<tr>
<th>Table 3. Safety and Adverse Events*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>All treatment-emergent adverse events</strong></td>
</tr>
<tr>
<td>725 (89.4)</td>
</tr>
<tr>
<td><strong>Serious treatment-emergent adverse events</strong></td>
</tr>
<tr>
<td>90 (4.7)</td>
</tr>
<tr>
<td><strong>Creatin</strong></td>
</tr>
<tr>
<td><strong>Adverse events leading to discontinuation</strong></td>
</tr>
<tr>
<td>81 (9.9)</td>
</tr>
<tr>
<td><strong>Discontinuation due to &gt;7.0% BMD decrease</strong></td>
</tr>
<tr>
<td>3/230 (0.5)</td>
</tr>
<tr>
<td><strong>Most frequently observed adverse events</strong></td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Nonspecific symptoms</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Pain in extremity</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td><strong>Hypercalcemia (prespecified safety end point)</strong></td>
</tr>
<tr>
<td>28/820 (3.4)</td>
</tr>
<tr>
<td><strong>Adverse events of special interest</strong></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Neoplasms, benign, malignant, and unspecified</td>
</tr>
<tr>
<td>20 (2.4)</td>
</tr>
<tr>
<td>Fall</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
</tr>
<tr>
<td>Renal impairment</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
</tbody>
</table>

### Table 2. Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>12 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=3576)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Romosozumab (N=3581)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>number of patients (percent)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event during treatment †</td>
<td>2850 (79.7)</td>
<td>2806 (78.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>429 (12.0)</td>
<td>467 (13.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>438 (12.2)</td>
<td>459 (12.8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>378 (10.6)</td>
<td>375 (10.5)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>312 (8.7)</td>
<td>344 (9.6)</td>
</tr>
<tr>
<td>Adjudicated serious cardiovascular event;‡</td>
<td>41 (1.1)</td>
<td>44 (1.2)</td>
</tr>
<tr>
<td>Death</td>
<td>23 (0.6)</td>
<td>29 (0.8)</td>
</tr>
<tr>
<td>Adjudicated cardiovascular death;‡</td>
<td>15 (0.4)</td>
<td>17 (0.5)</td>
</tr>
<tr>
<td>Event leading to discontinuation of trial regimen</td>
<td>94 (2.6)</td>
<td>108 (2.9)</td>
</tr>
<tr>
<td>Event leading to discontinuation of trial participation</td>
<td>50 (1.4)</td>
<td>44 (1.2)</td>
</tr>
<tr>
<td><strong>Event of interest;‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Hypersensitivity †</td>
<td>243 (6.9)</td>
<td>242 (6.8)</td>
</tr>
<tr>
<td>Injection-site reaction †</td>
<td>104 (2.9)</td>
<td>187 (5.2)</td>
</tr>
<tr>
<td>Hyperostosis</td>
<td>27 (0.8)</td>
<td>19 (0.5)</td>
</tr>
<tr>
<td>Cancer</td>
<td>69 (1.9)</td>
<td>59 (1.6)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>315 (8.8)</td>
<td>281 (7.8)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw;‡</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Atypical femoral fracture‡</td>
<td>0</td>
<td>1 (&lt;0.1)</td>
</tr>
</tbody>
</table>