Denosumab to Reduce Fracture Risk in Postmenopausal Women with Osteoporosis

Steven Boonen, MD, PhD

Professor of Medicine
Leuven University Center for Metabolic Bone Diseases and Division of Geriatric Medicine
Effect of Denosumab on Fracture Incidence in Women With Osteoporosis

The FREEDOM Trial
Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months
Study Design

*Phase 3: The FREEDOM Trial*

**Study population**
- 7,808 postmenopausal women
- T-score < −2.5 at the lumbar spine or total hip and not < −4.0 at either site

**Primary endpoint**
- New vertebral fracture over 36 months

**Secondary endpoints**
- Time to nonvertebral fracture
- Time to hip fracture

**International, placebo-controlled study**

SC = subcutaneously; Q6M = once every 6 months

Data depicts patients included in the efficacy analysis, which excludes data from 60 patients at one study center (29 randomized to placebo, 31 randomized to denosumab) because participation of the study center was discontinued due to issues regarding study procedures and data reliability.

### Baseline Characteristics

**Phase 3: The FREEDOM Trial**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 3,906)</th>
<th>Denosumab 60 mg Q6M (n = 3,902)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>72.3 (5.2)</td>
<td>72.3 (5.2)</td>
</tr>
<tr>
<td>Mean body mass index (SD)</td>
<td>26.0 (4.2)</td>
<td>26.0 (4.1)</td>
</tr>
<tr>
<td>Mean 25 (OH) vitamin D level, ng/mL (SD)</td>
<td>22.9 (11.3)</td>
<td>23.1 (11.7)</td>
</tr>
<tr>
<td>Mean lumbar spine T-score (SD)</td>
<td>−2.84 (0.69)</td>
<td>−2.82 (0.70)</td>
</tr>
<tr>
<td>Mean total hip T-score (SD)</td>
<td>−1.91 (0.81)</td>
<td>−1.89 (0.81)</td>
</tr>
<tr>
<td>Mean femoral neck T-score (SD)</td>
<td>−2.17 (0.71)</td>
<td>−2.15 (0.72)</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, n (%)</td>
<td>915 (23.4)</td>
<td>929 (23.8)</td>
</tr>
</tbody>
</table>
The Percent Change in Bone Turnover Markers Over 36 Months With Denosumab

*Phase 3: The FREEDOM Trial*

**Bone Turnover Markers Substudy**

\[ n = 160 \]

- **Serum CTx-1**
  - Placebo
  - Denosumab 60 mg Q6M

- **P1NP**

\[ *P < 0.001 \text{ for denosumab vs placebo} \]

\[ \dagger \text{ denosumab group relative decrease vs placebo at month 36} \]

CTx-1 = type 1 C-telopeptide; P1NP = intact N-terminal propeptide of type I procollagen

The Percent Change in Bone Mineral Density Over 36 Months With Denosumab

Phase 3: The FREEDOM Trial

Bone Mineral Density Substudy
n = 441

Intent-to-treat, last observation carried forward analysis
*P < 0.001 for denosumab vs placebo
† denosumab group relative increase in BMD vs placebo at month 36

The Effect of Denosumab on Fracture Risk at 36 Months

*Phase 3: The FREEDOM Trial*

**Incidence at Month 36 (%)**

- **New Vertebral**: Placebo 7.2%, Denosumab 2.3%, RR = 68%, \( P < 0.001 \)
- **Nonvertebral**: Placebo 8.0%, Denosumab 6.5%, RR = 20%, \( P = 0.01 \)
- **Hip**: Placebo 1.2%, Denosumab 0.7%, RR = 40%, \( P = 0.04 \)

RR = risk reduction

The Effect of Denosumab on New Vertebral Fractures At Month 12, 24, and 36

Phase 3: The FREEDOM Trial

Intention-to-treat, last observation carried forward analysis

Data on file, Amgen.
The Effect of Denosumab on Time to First Nonvertebral Fracture Through 36 Months

**Phase 3: The FREEDOM Trial**

- Nonvertebral fractures were reduced by 20% (95% CI: 0.67, 0.95) *P* = 0.01

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Month</th>
<th>Placebo</th>
<th>Denosumab 60 mg Q6M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, n</td>
<td>0</td>
<td>3,906</td>
<td>3,902</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3,750</td>
<td>3,759</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3,578</td>
<td>3,594</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>3,410</td>
<td>3,453</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>3,264</td>
<td>3,337</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>3,121</td>
<td>3,228</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3,009</td>
<td>3,130</td>
</tr>
</tbody>
</table>

†Nonvertebral fractures were reduced by 20% (95% CI: 0.67, 0.95)

The Effect of Denosumab on Time to First Hip Fracture Through 36 Months

*Phase 3: The FREEDOM Trial*

- **Placebo**, n = 3,906
  - Month: 0, 6, 12, 24, 30, 36
  - Cumulative Incidence (%): 0.0, 0.4, 0.8, 1.2

- **Denosumab 60 mg Q6M**, n = 3,902
  - Month: 0, 6, 12, 24, 30, 36
  - Cumulative Incidence (%): 0.0, 0.4, 0.8, 1.2

- Hip fractures were reduced by 40% (95% CI: 0.37, 0.97)

- *P = 0.04

### Adverse Events Over 36 Months

**Phase 3: The FREEDOM Trial**

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>Placebo (n = 3,876)</th>
<th>Denosumab 60 mg Q6M (n = 3,886)</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>3,607 (93.1)</td>
<td>3,605 (92.8)</td>
<td>0.91</td>
</tr>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>972 (25.1)</td>
<td>1,004 (25.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>Deaths</td>
<td>90 (2.3)</td>
<td>70 (1.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>81 (2.1)</td>
<td>93 (2.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>AEs leading to discontinuing the study drug</td>
<td>202 (5.2)</td>
<td>192 (4.9)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

AEs = adverse events

## Adverse Events Over 36 Months (continued)

### Phase 3: The FREEDOM Trial

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>Placebo (n = 3,876)</th>
<th>Denosumab 60 mg Q6M (n = 3,886)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2,108 (54.4)</td>
<td>2,055 (52.9)</td>
</tr>
<tr>
<td>Cancer</td>
<td>166 (4.3)</td>
<td>187 (4.8)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>26 (0.7)</td>
<td>33 (0.8)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Delayed fracture healing</td>
<td>4 (0.1)</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>Femoral shaft fracture</td>
<td>3 (0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Humerus nonunion fracture</td>
<td>1 (0.03)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw (ONJ)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Adverse events occurring with ≥ 2% incidence and $P \leq 0.05$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>65 (1.7)</td>
<td>118 (3.0)</td>
</tr>
<tr>
<td>Fall*</td>
<td>219 (5.7)</td>
<td>175 (4.5)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>53 (1.4)</td>
<td>84 (2.2)</td>
</tr>
</tbody>
</table>

*Excludes falls occurring on the same day as a fracture.

### Phase 3: The FREEDOM Trial

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>Placebo (n = 3,876)</th>
<th>Denosumab 60 mg Q6M (n = 3,886)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>133 (3.4)</td>
<td>159 (4.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cancer</td>
<td>125 (3.2)</td>
<td>144 (3.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>178 (4.6)</td>
<td>186 (4.8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Stroke</td>
<td>54 (1.4)</td>
<td>56 (1.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>39 (1.0)</td>
<td>47 (1.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>30 (0.8)</td>
<td>31 (0.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29 (0.7)</td>
<td>29 (0.7)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Serious adverse events occurring with ≥ 0.1% incidence and P ≤ 0.01</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis (includes erysipelas)</td>
<td>1 (&lt; 0.1)</td>
<td>12 (0.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Concussion</td>
<td>11 (0.3)</td>
<td>1 (&lt; 0.1)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Reversibility of the Effect of Denosumab on Bone Remodeling in Women With Low Bone Density

The AMG 162 Bone Loss Study
Study Design

*Phase 2: Postmenopausal Women With Low BMD*

**Eligibility criteria**
- Postmenopausal women with T-score of –1.8 to –4.0 at the lumbar spine or –1.8 to –3.5 at either the femoral neck or total hip

**Primary endpoint**
- Percent change from baseline to month 12 in the BMD of the lumbar spine for the placebo and denosumab arms

**Additional analysis**
- Percent change in BMD at total hip, distal 1/3 radius, and lumbar spine over 4 years, actual values of BTMs at 4 years, and safety

BTMs = bone turnover markers.

Discontinuation of Treatment at 24 Months

*Phase 2: Postmenopausal Women With Low BMD*

Patients in the denosumab 210-mg Q6M group and alendronate group discontinued treatment for the last 24 months of the study.
Serum CTx and BSAP Levels After Discontinuation of Denosumab Treatment

*Phase 2: Postmenopausal Women With Low BMD*

**Serum CTx**
- Placebo
- 210 mg Q6M
- Open-label alendronate

**BSAP**
- Placebo
- 210 mg Q6M
- Open-label alendronate

*P < 0.001 at month 36 vs placebo
^P = 0.05 at month 48 vs placebo.
†P = 0.008 at month 36 vs placebo.

Changes in Lumbar Spine and Total Hip BMD After Discontinuation of Denosumab Treatment

*Phase 2: Postmenopausal Women With Low BMD*

**Lumbar Spine**

- Placebo: 210 mg Q6M
- Open-label alendronate

**Total Hip**

- Placebo: 210 mg Q6M
- Open-label alendronate

Patients in the 30-mg group discontinued treatment for 12 months, then were re-treated with denosumab 60 mg Q6M for 12 months.
Denosumab Re-treatment and Changes to Serum CTx and BSAP Levels

*Phase 2: Postmenopausal Women With Low BMD*

**Serum CTx**
- **Discontinued Treatment**
- **Re-treatment 60 mg Q6M**

**BSAP**
- **Discontinued Treatment**
- **Re-treatment 60 mg Q6M**

Denosumab Re-treatment and Changes in Lumbar Spine and Total Hip BMD

*Phase 2: Postmenopausal Women With Low BMD*

**Lumbar Spine**

<table>
<thead>
<tr>
<th>Months</th>
<th>-6</th>
<th>-4</th>
<th>-2</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total Hip**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adherence of Postmenopausal Women Taking Denosumab or Alendronate

The DAPS Trial

Denosumab Adherence Preference Satisfaction
Adherence in Postmenopausal Women Taking Denosumab or Weekly Alendronate

The DAPS Trial

Persistence Probability vs Time (weeks)

- Denosumab (N=126)
- Alendronate (N=124)

Kendler et al. Osteoporos Int. 2010