Denosumab Therapy for Osteoporosis

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Disclosures

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Outline

• Mechanism of action
• Effect on fracture risk
• Effect on bone turnover and BMD
• Long term treatment: BMD and fractures
• Safety & treatment cessation

Excess RANK Ligand Increases Bone Resorption

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Denosumab Binds RANK Ligand

Denosumab binds to RANK ligand (RANKL), inhibiting osteoclast formation, function, and survival. It decreases osteoclast number and function, leading to inhibited bone resorption and increased bone formation.

BPs and denosumab act differently

Bisphosphonates bind to bone mineral and are taken up by mature osteoclasts at sites of bone resorption. They cause loss of resorptive function, but ‘disable’ osteoclasts.

Denosumab blocks osteoclast formation, function and survival, leading to inhibited bone resorption and increased bone formation.
PK and PD properties of Denosumab 60 mg Q 6

Denosumab: fully human IgG2 antibody with very high affinity and specificity for RANK ligand


Change (%) From Baseline

Mean ± SE

Denosumab Q 6 Month and Alendronate: Serum C-telopeptide (Phase II Study)

Denosumab is a more potent but reversible inhibitor of bone resorption than is alendronate

Outline

• Mechanism of action

• Effect on fracture risk

Denosumab FREEDOM Trial:
Pivotal Phase III Study

Study Month

<table>
<thead>
<tr>
<th>Study Month</th>
<th>1</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Denosumab 60 mg SC Q6M n = 3,902
- Calcium and vitamin D
- Placebo n = 3,906

Study population
- 7,888 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
**FREEDOM Trial: Pivotal Phase III Study**

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Denosumab 60 mg Q6M (n=3902)</th>
<th>Placebo (n=3906)</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 (BMI) (SD)</td>
<td>26.0 (4.1)</td>
<td>26.0 (4.2)</td>
</tr>
<tr>
<td>Mean serum 25 OH-vitamin D ng/ml (SD)</td>
<td>23.1 (11.7)</td>
<td>22.9 (11.3)</td>
</tr>
<tr>
<td>Mean lumbar spine T-score (SD)</td>
<td>-2.82 (0.70)</td>
<td>-2.84 (0.69)</td>
</tr>
<tr>
<td>Mean total hip T-score (SD)</td>
<td>-1.89 (0.81)</td>
<td>-1.91 (0.81)</td>
</tr>
<tr>
<td>Mean femoral neck T-score (SD)</td>
<td>-2.15 (0.72)</td>
<td>-2.17 (0.71)</td>
</tr>
<tr>
<td>Prevalent vertebral fracture, N (%)</td>
<td>929 (23.8)</td>
<td>915 (23.4)</td>
</tr>
<tr>
<td>Completed study, N (%)</td>
<td>3272 (84)</td>
<td>3206 (82)</td>
</tr>
<tr>
<td>Received all doses of study medication, N (%)</td>
<td>3093 (80)</td>
<td>2886 (75)</td>
</tr>
</tbody>
</table>

Denosumab treatment reduces fracture risk over 3 years

*Crude incidence
†Kaplan-Meier estimate of incidence
**Denosumab Treatment Reduced Vertebral Fracture Risk**

*Phase 3: The FREEDOM Trial*

**Vertebral fracture risk reduction within 12 months**

- **Placebo**
  - 0-12 Months: 2.2% 
  - 0-24 Months: 5.0% 
  - 0-36 Months: 7.2%
- **Denosumab**
  - 0-12 Months: 0.9% 
  - 0-24 Months: 1.4% 
  - 0-36 Months: 2.3%

RRR 61% *P* < 0.0001


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

*Phase 3: The FREEDOM Trial*

**Strong trend in reduction of hip fracture risk within 12 months**

- **Placebo**
  - Month 0: 0.0%
  - Month 6: 0.4%
  - Month 12: 0.8%
  - Month 18: 1.2%
  - Month 24: 1.8%
  - Month 30: 2.4%
  - Month 36: 3.0%

- **Denosumab 60 mg Q6M**
  - Month 0: 0.0%
  - Month 6: 0.4%
  - Month 12: 0.8%
  - Month 18: 1.2%
  - Month 24: 1.8%
  - Month 30: 2.4%
  - Month 36: 3.0%

RRR 40% *P* = 0.04


**Number of patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n</th>
<th>Denosumab, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0</td>
<td>3,906</td>
<td>3,902</td>
</tr>
<tr>
<td>Month 6</td>
<td>3,799</td>
<td>3,796</td>
</tr>
<tr>
<td>Month 12</td>
<td>3,672</td>
<td>3,676</td>
</tr>
<tr>
<td>Month 18</td>
<td>3,538</td>
<td>3,566</td>
</tr>
<tr>
<td>Month 24</td>
<td>3,430</td>
<td>3,477</td>
</tr>
<tr>
<td>Month 30</td>
<td>3,311</td>
<td>3,397</td>
</tr>
<tr>
<td>Month 36</td>
<td>3,221</td>
<td>3,311</td>
</tr>
</tbody>
</table>
Denosumab effective in reducing hip fractures in high risk subgroups

**Phase 3: The FREEDOM Trial**

Incidence represents Kaplan-Meier estimate at month 36

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence at Month 36 (%)</th>
<th>Placebo</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>1.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Femoral Neck BMD T-score ≤ -2.5</td>
<td>47% (8%, 70%)</td>
<td>2.8%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td></td>
<td>62%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>


Outline

- Mechanism of action
- Effect on fracture risk
- Effect on bone turnover and BMD
Switching From Bisphosphonates to Denosumab

Data are least-squares means and 95% confidence intervals. *p < 0.0001 denosumab vs BP.
Discontinuing Denosumab: BMD
Phase 2 Study in Women With Low BMD


Discontinued Treatment

Lumbar Spine

Total Hip

Percent Change (LS Mean ± SE)

Months

Placebo

210 mg Q6M

Open-label alendronate

Serum CTx

BSAP

Median ng/mL (Q1, Q3)

Median mcg/L (Q1, Q3)

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

Outline

- Mechanism of action
- Effect on fracture risk
- Effect on bone turnover and BMD
- Long term treatment: BMD and fractures

FREEDOM Extension Study Design
International, multicenter, open-label, single-arm study

Key Inclusion Criteria for the Extension:
- Completed the FREEDOM study (completed the 3-year visit, did not discontinue investigational product, and did not miss > 1 dose)
- Not receiving any other osteoporosis medications
Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cross-over DMAb Treatment</th>
<th>Long-term DMAb Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extension Subjects</td>
<td>Extension Subjects</td>
</tr>
<tr>
<td></td>
<td>N = 2207</td>
<td>N = 2343</td>
</tr>
<tr>
<td>Age (years)</td>
<td>FREEDOM Baseline 71.8</td>
<td>FREEDOM Baseline 71.9</td>
</tr>
<tr>
<td></td>
<td>Extension Baseline 74.8</td>
<td>Extension Baseline 74.9</td>
</tr>
<tr>
<td>Age groups (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>93.7%</td>
<td>94.3%</td>
</tr>
<tr>
<td></td>
<td>97.4%</td>
<td>97.9%</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>28.3%</td>
<td>28.3%</td>
</tr>
<tr>
<td></td>
<td>52.2%</td>
<td>53.7%</td>
</tr>
<tr>
<td>Prevalent vertebral fractures (%)</td>
<td>22.0%</td>
<td>23.9%</td>
</tr>
<tr>
<td></td>
<td>25.0%</td>
<td>24.5%</td>
</tr>
<tr>
<td>LS BMD T-score</td>
<td>-2.84</td>
<td>-2.83</td>
</tr>
<tr>
<td></td>
<td>-2.81</td>
<td>-2.14</td>
</tr>
<tr>
<td>TH BMD T-score</td>
<td>-1.85</td>
<td>-1.85</td>
</tr>
<tr>
<td></td>
<td>-1.93</td>
<td>-1.50</td>
</tr>
<tr>
<td>sCTX* (ng/mL)</td>
<td>0.555</td>
<td>0.505</td>
</tr>
<tr>
<td></td>
<td>0.568</td>
<td>0.182</td>
</tr>
<tr>
<td>P1NP* (µg/L)</td>
<td>55.81</td>
<td>46.17</td>
</tr>
<tr>
<td></td>
<td>48.80</td>
<td>17.25</td>
</tr>
</tbody>
</table>

N = number of subjects enrolled in the Extension. Data are means unless otherwise noted.

*Median values; from the BTM substudy.

Effects of Denosumab Treatment on Bone Turnover Markers Through 10 Years

Concentrations of the predose bone turnover markers sCTX and P1NP in subjects included in the BTM substudy. Dashed lines represent the premenopausal reference ranges: 0.20–0.90 ng/mL for sCTX and 17.4–61.6 µg/L for P1NP. Data are medians and interquartile ranges. Time points: baseline, month 1, and years 0.5, 1, 2, 3, 3 (day 10), 3.5, 4, 5, 6, 7, 8, 9, and 10.

Effects of Denosumab Treatment on BMD Through 10 Years

- **Lumbar Spine**
  - FREEDOM Extension: 21.7%
  - Lumbar spine percentage change from baseline.

- **Total Hip**
  - FREEDOM Extension: 9.2%

BMD data are LS means and 95% confidence intervals. *P < 0.05 vs FREEDOM baseline. *P < 0.05 vs FREEDOM and Extension baselines.

*Percentage change while on denosumab treatment.*


Effects of Denosumab Therapy on Total Hip BMD Through 10 Years

- **Total Hip BMD**
  - FREEDOM Extension: 9.2%

Effects of Therapy on Total Hip BMD Through 10 Years

**Total Hip BMD**

- **FREEDOM**
- Long-term Denosumab
- Alendronate 10 mg/d
- Zoledronic acid 5 mg/yr

### Percentage Change From Baseline

- **Study Year**
  - 0 1 2 3 4 5 6 7 8 9 10

- **Percentage Change From Baseline**
  - 9.2%
  - 10.5%
  - 6.8%
  - 5.6%


### Long-term Denosumab

**FREEDOM Extension**

- Yearly Incidence of New Vertebral Fractures (%)

- **Study Year**
  - 1 2 3 4 5 6 7 8

- **Years of Denosumab Treatment**
  - 1/2 4/5 7/8 9/10


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

**Lumbar Spine**

- Placebo
- Long-term Denosumab
- Cross-over Denosumab

### Percentage Change From Baseline

- **Study Year**
  - 0 1 2 3 4 5 6 7 8 9 10

- **Percentage Change From Baseline**
  - 21.7%
  - 20.3%
  - 15.5%

Virtual Twin Placebo

- A simulation method was used to estimate expected fracture rates in a hypothetical cohort of long-term placebo controls ("virtual twins") since all subjects in the Extension study received denosumab treatment.
  - Models were developed using actual FREEDOM data on BMD, fracture history, BMI, age, and smoking status for subjects who received placebo during the 3 years of FREEDOM and enrolled in the Extension.
  - Models then predicted fracture outcomes for the denosumab-treated women who entered the Extension had they received placebo for 3 years in FREEDOM and 7 years in the Extension ("virtual twins").

Cumulative Subject Incidence of New Vertebral and Nonvertebral Fractures: Long-term Denosumab Group

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Long-term Denosumab</th>
<th>Virtual Twin Placebo</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Vertebral</td>
<td>7.2</td>
<td>2.3</td>
<td>0.62 (0.47–0.80)</td>
<td></td>
</tr>
<tr>
<td>Nonvertebral</td>
<td>11.5</td>
<td>7.0</td>
<td>0.54 (0.43–0.69)</td>
<td></td>
</tr>
</tbody>
</table>

Yearly Subject Incidence of Nonvertebral Fractures: Long-term Denosumab Group

<table>
<thead>
<tr>
<th>Year</th>
<th>ARR in FREEDOM was 1.5% over 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 4</td>
<td>1.1%</td>
</tr>
<tr>
<td>Year 5</td>
<td>1.6%</td>
</tr>
<tr>
<td>Year 6</td>
<td>1.0%</td>
</tr>
<tr>
<td>Year 7</td>
<td>1.5%</td>
</tr>
<tr>
<td>Year 8</td>
<td>2.5%</td>
</tr>
<tr>
<td>Year 9</td>
<td>2.4%</td>
</tr>
<tr>
<td>Year 10</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Relationship Between Total Hip T-score and Non-vertebral Fracture Risk

Outline

- Mechanism of action
- Effect on fracture risk
- Effect on bone turnover and BMD
- Long term treatment: BMD and fractures
- Safety & treatment cessation
Denosumab Ph III study: Safety and Tolerability

- Overall, no increased risk of adverse events or serious adverse events in clinical trials
- Increased incidence of
  - skin rash (3.0% vs 1.7%)
  - cellulitis (12/3808 vs 1/3805)
- No renal or cardiovascular effects noted
- Deaths: 90 in placebo group; 70 with DMab (p=0.06)
- Less than 1% of patients developed binding antibodies over 2-8 years; none have developed neutralizing antibodies


### Exposure-adjusted Subject Incidence of Adverse Events (Rates per 100 Subject-years)

<table>
<thead>
<tr>
<th></th>
<th>FREEDOM Years 1–3</th>
<th>Extension Years 1–7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 3883)</td>
<td>Cross-over Denosumab (N = 2206)</td>
</tr>
<tr>
<td>All AEs</td>
<td>156.1</td>
<td>96.8</td>
</tr>
<tr>
<td>Infections</td>
<td>30.7</td>
<td>20.7</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Eczema</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>10.4</td>
<td>10.1</td>
</tr>
<tr>
<td>Infections</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Cellulitis or erysipelas</td>
<td>&lt; 0.1</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Atypical femoral fracture</td>
<td>0</td>
<td>&lt; 0.1</td>
</tr>
</tbody>
</table>

N = number of subjects who received ≥ 1 dose of investigational product. Treatment groups are based on the original randomized treatments received in FREEDOM. AEs coded using MedDRA v13.0. Cumulative osteonecrosis of the jaw cases: 6 cross-over, 7 long-term. Cumulative atypical femoral fracture cases: 1 cross-over, 1 long-term.

Osteonecrosis of the Jaw and Atypical Fractures with Denosumab

- Very few cases of ONJ (13) and AFF (2) were reported in the FREEDOM Extension trial to 10 years (>50,000 patient-years exposure)
- Rare cases of AFF in patients receiving denosumab in clinical practice have been described: most had received previous bisphosphonate therapy
- There are too few cases of ONJ and AFF to know whether these events are related to denosumab therapy or the duration of therapy

Discontinuing Denosumab After 8 Years

Lumbar Spine BMD

McClung M et al. Osteoporos Int. 2017;28:1723-32
Vertebral Fractures After Discontinuing Denosumab Therapy

- At least 24 patients have been reported who experienced vertebral fractures within 3-18 months after discontinuing denosumab therapy. (1)
- Many or most have had multiple and/or severe fractures
- Raised concern about “rebound” risk of fracture
- Similar to rapid loss of fracture protection when estrogen therapy is discontinued (2,3)

1. Anastasilakis AD et al. J Bone Miner Res. 2017 Feb 27
2. Heiss G et al. JAMA 299:1036–45

Case Reports of Clinical Vertebral Fractures Following Denosumab Discontinuation

- Anecdotal Case of Multiple Fractures following discontinuation of denosumab
  - 51 y.o. PMO 5 yrs., T score LS -2.5, no vertebral frx by xray
  - 2/2012 Rx Denosumab 60mg q 6 for 3 years., last Rx 8/2014
  - 2/2015 T score LS -1.8
  - 4/2015 Severe back pain bending to pull drawer of refrigerator, 8 months after last denab Rx
    - MRI found 3 incident Vertebral Frxns T12, L1, and L3

MRI of the Spine with Incident vertebral fractures and Change in Bone Turnover Markers

Vertebral Fractures After Discontinuing Denosumab or Placebo in FREEDOM Study

- Vertebral fracture risk was assessed in patients who discontinued either placebo or denosumab in the FREEDOM study or who stopped denosumab in the FREEDOM Extension study and who had a follow-up at least 7 months after their last dose.
- Fracture risk increased upon stopping denosumab but not to levels greater than seen in those who stopped placebo.

Brown JP et al. ASBMR Abstract #1100, 2016
Discontinuing Denosumab

Other Information

• Bone loss and rise in serum CTX is attenuated in patients who stop denosumab but who took bisphosphonates before denosumab therapy.
  
  Ferrari S et al. ECTS 2016

• Bone loss after stopping denosumab is attenuated in patients who then receive anti-remodeling agents
  
  McClung M et al. Osteoporos Int. 2017;28:1723-32

Recommendations

• If treatment with denosumab is discontinued, there may be an increase in bone turnover, bone mass loss and increased risk of vertebral fracture. Therefore
  
  • Consider switching to another anti-resorptive agent like a bisphosphonate
  • Studies with less potent antiresorptive agents may work (SERM, calcitonin, estrogen) however need to be tested.
  • Discuss with the potent patients the risk of increased fracture with discontinuation of treatment
Conclusions

- Mechanism of action
  - Rapid and potent effect
- Effect on fracture risk
  - Reduction in fracture risk, greatest effect at the spine
- Effect on bone turnover and density
  - Greater than oral alendronate
- Long-term effect on bone density
  - Continued effects to 10 years
- Safety
  - Cellulitis; a few cases of ONJ, AFF; transient hypocalcaemia (avoided by administration of calcium and vitamin D supplements), and if discontinuing Denosumab- consider treatment with another anti-resorptive agent for a few years.
Summary

- Denosumab treatment for up to 10 years was associated with:
  - persistent reduction of bone turnover
  - continued increases in BMD without therapeutic plateau
  - low incidence of new vertebral and nonvertebral (including hip) fracture
  - no evidence of resistance to therapy
  - no new adverse events with long-term therapy

Conclusions

- Long-term therapy to treat patients with osteoporosis is necessary and important for many patients
- Discontinuing therapy results in rapid loss of gains
- There is rarely a need to discontinue denosumab therapy
  - *Certainly no need for a “drug holiday”*
- Denosumab is effective in elderly patients
- The benefit/risk profile for denosumab in an aging population of postmenopausal women remains favorable
risk of Incident Fracture after Discontinuation

• Discontinuation of Dmab was not associated with an increase in incident osteoporotic fractures in Phase 2 and 3 studies. However, they were short term and underpowered for incident fractures
• Studies on increased hip fracture risk have been reported after estrogen treatment in an observational study (Yates) Odds Ratio: 1.65
• No reports of increased incident fracture risk after discontinuation of Bisphosphonates

Denosumab and Alendronate (DAPS Trial)
Cross-over Treatment after 12 Months

Switching from denosumab to alendronate, bone loss did not occur

Freemantle N et al. Osteoporos Int. 2012;23:317-26
Discontinuing Denosumab
Change in Prescribing Information

- A new caution has been added to Prolia label:
  - Multiple vertebral fractures have been reported following Prolia discontinuation.
  - Consider transitioning to another antiresorptive agent if Prolia is discontinued.

Long-term Denosumab Therapy
Summary

- There are very few reasons to consider stopping denosumab therapy
  - intolerance or side effect
  - reaching a treatment “target”

- If therapy is stopped after a year or more, consider options to prevent rapid bone loss and fracture risk

- At present, the most appealing strategy would be to treat with a bisphosphonate for 1-2 years, re-evaluating the patient at regular intervals

McClung MR. Cancel the denosumab holiday. Osteoporos Int. 2016;27:1677-82
AACE Osteoporosis Treatment Guidelines - 2016

Effects of Therapy on Total Hip BMD Through 10 Years

1. Bone HG et al. ASBMR; Seattle, WA; October 12, 2015; #LB-1157
Fracture Risk after Stopping Denosumab

- Subgroup of 797 subjects (470 placebo, 327 denosumab), who discontinued study drug in FREEDOM after 2-5 doses.
- During the off-treatment period (median 0.8 years per subject), 42% versus 28% of placebo- and denosumab-treated subjects, respectively, initiated other therapy.

Following discontinuation, similar percentages of subjects in both groups sustained a new fracture (9% placebo, 7% denosumab)

Fracture rate per 100 subject-years of 13.5 for placebo and 9.7 for denosumab
Hazard ratio [HR] 0.82; 95% confidence interval [CI], 0.49–1.38, adjusted for age and total hip BMD T-score at baseline.

There was no apparent difference in fracture occurrence pattern between the groups during the off-treatment period.

Vertebral Fractures After Discontinuing Denosumab or Placebo in FREEDOM Study

- Vertebral fracture risk was assessed in patients who discontinued either placebo or denosumab in the FREEDOM study or who stopped denosumab in the FREEDOM Extension study and who had a follow-up at least 7 months after their last dose
- Fracture risk increased upon stopping denosumab but not to levels greater than seen in those who stopped placebo
- Prevalent vertebral fracture was main risk factor for vertebral fracture after stopping therapy

Brown JP et al. ASBMR Abstract #1100, 2016
Fracture Risk after Stopping Denosumab

- Protection from vertebral fractures is quickly lost upon stopping denosumab

**BUT**

- There is no apparent excess or rebound in vertebral fracture risk upon stopping therapy

Discontinuing Denosumab

**Other Information**

- Bone loss and rise in serum CTX is attenuated in patients who stop denosumab but who took bisphosphonates before denosumab therapy.

  Ferrari S et al. ECTS 2016

- Bone loss after stopping denosumab is attenuated in patients who then receive anti-remodeling agents

  McClung M et al. Osteoporos Int. 2017;28:1723-32
Long-term Denosumab Therapy

Safety

Long-term Denosumab Therapy


Table: Number of participants and adverse events

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Combined denosumab groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>Year 2</td>
<td>Year 3</td>
</tr>
<tr>
<td>Number of participants</td>
<td>3893</td>
<td>3687</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All adverse events</td>
<td>359.5</td>
<td>356.3</td>
</tr>
<tr>
<td>Infections</td>
<td>38.6</td>
<td>33.9</td>
</tr>
<tr>
<td>Malignancies</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>-0.1</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>11.7</td>
<td>11.5</td>
</tr>
<tr>
<td>Infections</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Cellulitis or abscesses</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatal adverse events</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Analyses were based on the original randomized treatment groups in FREEDOM. Data include all participants who received at least one dose of investigational product in FREEDOM or the extension. Placebo data are for all participants who received at least one dose of placebo during FREEDOM. Denosumab data are for all participants who received at least one dose of denosumab during FREEDOM or the extension. Data are shown for each year of exposure, thus a long-term participant could have up to 10 years of exposure and a crossover participant could have up to 7 years of exposure to denosumab. All adverse and serious adverse events were coded using Medical Dictionary for Regulatory Activities version 13.0.


Long-term Denosumab Therapy

Bone Mineral Density

Persistent inhibition of turnover; no evidence of loss of effect with therapy to 10 years

Long-term Denosumab Therapy

**Bone Mineral Density**

Persistent inhibition of turnover; no evidence of loss of effect with therapy to 10 years


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Long-term Denosumab Therapy

**Bone Turnover Markers**

Persistent inhibition of turnover; no evidence of loss of effect with therapy to 10 years

Long-term Denosumab Therapy

Vertebral Fractures

Persistent reduction in vertebral fracture risk

Non-vertebral Fractures

Persistent reduction in non-vertebral fracture risk

Long-term Denosumab Therapy

**Hip Fractures**

Persistent reduction in hip fracture risk

![Graph showing hip fracture rates over years of treatment](image)


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Long-term Denosumab Therapy

**Fractures: Virtual Twin Placebo Comparison**

Virtual twin matched for age, BMD and baseline fracture history

![Graph showing cumulative fractures](image)

Effects of Denosumab on Total Hip Integral and Cortical BMD

Data are LS means and 95% CIs.

†P < 0.02 for denosumab compared with baseline and placebo.

Effects of Denosumab on Total Hip Cortical Thickness and Cortical Mass

Data are LS means and 95% CIs.

†P < 0.02 for denosumab compared with baseline and placebo. ‡One subject had a non-evaluable scan.
Effects of Denosumab on Total Hip Integral and Cortical Strength

FEA Total Hip Integral Strength

FEA Total Hip Cortical Strength

Placebo Denosumab

Percentage Change From Baseline at 36 Months

-16 -12 -8 -4 0 4 8 12 16

n=14 n=26 n=12 n=10

< 75 years ≥ 75 years

* P < 0.02 for denosumab compared with baseline. † P < 0.02 for denosumab compared with placebo.

Data are LS means and 95% CIs.

Porosity Throughout the Hip Cortex

% Change From Baseline at 36 Months

Cortex Compact Cortex Outer Transitional Zone Inner Transitional Zone

Placebo (n=22) DMAB (n=28)

p=0.0001 p=0.0009 p=0.0008 p=0.0002

Percentage Change From Baseline (LS Means and 95% CIs)

n=number of subjects with available data at baseline and 36 months.