Denosumab Safety
FDA Analysis

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Safety Review

• **Methods**
  – Review of verbatim terms and event coding
  – Review of subject narratives

• **ISS**
  – Modified database to include only the four primary studies (216, 132, 135, 138)
  – Safety Populations: PMO=8091 HA=1705
## Adverse Event Rates: Osteoporosis Trials

<table>
<thead>
<tr>
<th></th>
<th>Trial 216</th>
<th></th>
<th>Trial 132</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Denos</td>
<td>Placebo</td>
<td>Denos</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n, Safety</td>
<td>3876</td>
<td>3886</td>
<td>165</td>
<td>164</td>
</tr>
<tr>
<td>Deaths</td>
<td>90 (2)</td>
<td>70 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>972 (25)</td>
<td>1004 (26)</td>
<td>9 (6)</td>
<td>19 (12)</td>
</tr>
<tr>
<td>AE / trial withdrawal</td>
<td>81 (2)</td>
<td>93 (2)</td>
<td>2 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>AE / IP discontinue</td>
<td>203 (5)</td>
<td>192 (5)</td>
<td>6 (4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Any AE</td>
<td>3608 (93)</td>
<td>3605 (93)</td>
<td>157 (95)</td>
<td>156 (95)</td>
</tr>
</tbody>
</table>
# Adverse Event Rates: Hormone Ablation Trials

<table>
<thead>
<tr>
<th></th>
<th>Trial 135</th>
<th></th>
<th>Trial 138</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Denos</td>
<td>Placebo</td>
<td>Denos</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n, Safety</td>
<td>120</td>
<td>129</td>
<td>725</td>
<td>731</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>46 (6)</td>
<td>44 (6)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>11 (9)</td>
<td>19 (15)</td>
<td>222 (31)</td>
<td>253 (35)</td>
</tr>
<tr>
<td>AE / trial</td>
<td>5 (4)</td>
<td>1 (1)</td>
<td>44 (6)</td>
<td>51 (7)</td>
</tr>
<tr>
<td>withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE / IP</td>
<td>5 (4)</td>
<td>2 (2)</td>
<td>47 (6)</td>
<td>49 (7)</td>
</tr>
<tr>
<td>discontinue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>108 (90)</td>
<td>117 (91)</td>
<td>627 (86)</td>
<td>638 (87)</td>
</tr>
</tbody>
</table>
Deaths in the Phase 1/2 Studies

• Two deaths in the Phase 1 program (one MVA; one progression of breast cancer)
• Four deaths in Trial 223 (dose-finding), all received denosumab
  – Cerebrovascular accident (n = 1)
  – Neoplasms (n = 3)
    • Brain tumor
    • Adenocarcinoma (probable lung)
    • Adenocarcinoma (gastric)
• One additional death in the extension phase of 223
  – unknown cause
Deaths in the Primary Phase 3 Trials

• Postmenopausal Osteoporosis:
  – 90/4041 (2.2%) placebo; 70/4050 (1.7%) denosumab
  – Most common: Neoplasms, Cardiac disorders, Respiratory disorders, Nervous System disorders

• Hormone Ablation Trials:
  – 47/845 (5.6%) placebo; 45/860 (5.2%) denosumab
  – Most common: Cardiac disorders, Respiratory disorders, Nervous System disorders, Neoplasms

• No imbalances in deaths in any of the phase 3 trials
Serious Adverse Events: PMO Trials

- **Trial 216** (N=3876 plac, N=3886 denos; mean age 72 yr):
  - 972 (25.1%) placebo; 1004 (25.8%) denosumab
  - Increased in denosumab: Cardiac disorders, Musculoskeletal disorders, Infections, Neoplasms
  - Increased in placebo: Injuries (incl. fractures)

- **Trial 132** (N=165 plac, N=164 denos; mean age 59 yr):
  - 9 (5.5%) placebo; 19 (11.6%) denosumab
  - Most Common:
    - Infections: 1 (0.1%) placebo, 8 (4.9%) denosumab
    - Neoplasms: 1 (0.1%) placebo, 4 (2.4%) denosumab
Serious Adverse Events: Hormone Ablation

- **Trial 135** (N=120 plac, N=129 denos; mean age 59 yr):
  - 11 (9.2%) placebo; 19 (14.7%) denosumab
  - Most Common:
    - Musculoskeletal: 1 (0.8%) placebo, 4 (3.1%) denosumab
    - Neoplasms: 1 (0.8%) placebo, 3 (2.3%) denosumab

- **Trial 138** (N=725 plac, N=731 denos; mean age 75 yr):
  - 222 (30.6%) placebo; 253 (34.6%) denosumab
  - Most Common:
    - Cardiac: 75 (10.3%) placebo, 69 (9.4%) denosumab
    - Nervous system: 35 (4.8%) placebo, 50 (6.8%) denosumab
    - Neoplasms: 42 (5.8%) placebo, 37 (5.1%) denosumab
    - Infection: 33 (4.6%) placebo, 43 (5.9%) denosumab
### Most Common Adverse Events Leading to IP Discontinuation in the PMO Trials

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo N=4041</th>
<th>Denos N=4050</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE / IP discontinuation</td>
<td>209 (5.1)</td>
<td>197 (4.9)</td>
</tr>
<tr>
<td>breast cancer</td>
<td>10 (0.2)</td>
<td>20 (0.5)</td>
</tr>
<tr>
<td>back pain</td>
<td>10 (0.2)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>constipation</td>
<td>6 (0.1)</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>colon cancer</td>
<td>4 (0.1)</td>
<td>5 (0.1)</td>
</tr>
<tr>
<td>lumbar vertebral fracture</td>
<td>12 (0.3)</td>
<td>2 (&lt;0.1)</td>
</tr>
<tr>
<td>thoracic vertebral fracture</td>
<td>8 (0.2)</td>
<td>1 (&lt;0.1)</td>
</tr>
</tbody>
</table>
Adverse Events of Special Interest

- Infection
- New Malignancy
- Tumor Progression
- Dermatologic Events
- Pancreatitis
- Ocular Adverse Events
- Cardiovascular Adverse Events
- Hypocalcemia
- Osteonecrosis of the Jaw
- Hypersensitivity / Immunogenicity
- Bone Histomorphometry Findings
Infections
Infections: Reason for Concern

• **Biologic Plausibility**
  – Denosumab is an inhibitor of RANKL
  – RANKL in B- and T-cell differentiation
  – RANKL is also involved in dendritic (antigen-presenting) cell survival

• **Phase 1**: Three subjects, two of which were healthy subjects under the age of 35, required hospitalization for pneumonia after a single dose of denosumab

• **Phase 2, Trial 223**:  
  – Infection SAEs: 10/314 (3.2%) of denosumab cohort, 0/46 (0%) placebo, 0/46 (0%) alendronate
Infections

• **Serious Adverse Events**
  – 216: 133/3876 (3.4%) placebo; 159/3886 (4.1%) denos
  – 132: 1/166 (0.6%) placebo; 8/166 (4.9%) denosumab
  – 135: 1/124 (0.8%) placebo; 3/125 (2.3%) denosumab
  – 138: 33/725 (4.6%) placebo; 43/731 (5.9%) denosumab

• **Adverse Events**
  – Balanced across all treatment groups in the PMO trials
  – Increased in the denosumab groups in the hormone ablation trials

• **No imbalances in opportunistic infections**
Skin Infection SAEs – Trial 216

3/3876 placebo subjects
  – Cellulitis -1
  – Paronychia – 1
  – Subcutaneous abscess – 1

14/3886 denosumab subjects
  – Erysipelas – 7
  – Cellulitis – 6
  – Skin bacterial infection – 2
  – Infected skin ulcer -1
Infection SAEs of Concern

Serious ear infections in Trial 216:
- 0 / 3876 placebo subjects
- 5 / 3886 denosumab subjects
  - Labrynthitis - 4, Otitis media - 1

Serious UTIs in Trial 216:
- 17 / 3876 placebo subjects
  - Cystitis – 2, Kidney infection – 1, Pyelonephritis – 3, Renal abscess – 1, UTI – 10
- 28 / 3886 denosumab subjects
  - Cystitis – 6, Pyelonephritis – 7, UTI – 16
Endocarditis

Trial 216:

• 0 / 3876 placebo subjects
• 3 / 3886 denosumab subjects
  • 1 fatality
  • 1 valve replacement
  • Event occurred ~59-149 days from last dose
Infective Arthritis

Trial 216:

- **0 / 3876** placebo subjects
- **8 / 3886** denosumab subjects
  - Affected joints include: elbows, knee, hip, ankle, shoulder
  - None reported as serious
Infections - Summary

- There is an imbalance in the number of serious infections in the denosumab group.
- Most notable were infections of the skin, ear, and urinary tract.
- An imbalance in endocarditis was noted.
- An imbalance in infective arthritis was noted.
- There was no evident increase in opportunistic infections.
New Malignancies
New Malignancies: Reason for Concern

• Denosumab is specific to human and non-human primate RANKL and is not active in the rodent
• No carcinogenicity studies were performed due to a lack of an animal model
• Dose-finding trial (Trial 223) – 3 deaths due to neoplasms in 100 mg Q6months cohort
• Common AE leading to discontinuation in PMO trials
## New Malignancies: PMO Trials

<table>
<thead>
<tr>
<th>High Level Group Term</th>
<th>Placebo N=4041 n (%)</th>
<th>Denosumab N=4050 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event, Neoplasm SOC</td>
<td>285 (7.1)</td>
<td>316 (7.8)</td>
</tr>
<tr>
<td><strong>Malignant or unspecified neoplasm</strong></td>
<td><strong>168 (4.2)</strong></td>
<td><strong>192 (4.7)</strong></td>
</tr>
<tr>
<td>Gastrointestinal neoplasm malignant &amp; unspecified</td>
<td>24 (0.6%)</td>
<td>35 (0.9%)</td>
</tr>
<tr>
<td>Breast neoplasms malignant &amp; unspec</td>
<td>29 (0.7%)</td>
<td>35 (0.9%)</td>
</tr>
<tr>
<td>Reproductive neoplasms female malig &amp; unspec</td>
<td>9 (0.2%)</td>
<td>21 (0.5%)</td>
</tr>
<tr>
<td>Respiratory &amp; mediastinal neoplasms malignant &amp; unspecfied</td>
<td>24 (0.6%)</td>
<td>15 (0.4%)</td>
</tr>
</tbody>
</table>
New Malignancies, Summary

- No carcinogenicity studies were performed due to a lack of an animal model.
- Three subjects in a high dose denosumab group in the dose finding trial died of a new malignancy.
- In the primary PMO studies, there was an imbalance in the incidence of malignancies in the denosumab group, driven by breast, reproductive and gastrointestinal cancers.
Tumor Progression
Tumor Progression: Reason for Concern

• Hormone ablation trials not designed to evaluate cancer outcomes
• There was an imbalance in metastatic events:
  – In trial 135
    • placebo 5 (4.2%), denosumab 9 (7.0%)
  – In trial 138:
    • placebo 40 (5.5%), denosumab 60 (8.2%)
Dermatologic Adverse Events
## Dermatologic Adverse Events

- A significant imbalance was noted in adverse events related to skin and soft tissue disorders, **not** including skin infections.
- Not specific to the injection site.
- Mainly driven by epidermal and dermal conditions.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Placebo N=4041</th>
<th>Denosumab N=4050</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal and dermal conditions, all</td>
<td>340 (8.4)</td>
<td>447 (11.0)</td>
</tr>
<tr>
<td>Dermatitis and eczema</td>
<td>81 (2.0)</td>
<td>147 (3.6)</td>
</tr>
<tr>
<td>Pruritis, NEC</td>
<td>97 (2.4)</td>
<td>110 (2.7)</td>
</tr>
<tr>
<td>Rashes, eruptions, exanthems, NEC</td>
<td>89 (2.2)</td>
<td>116 (2.9)</td>
</tr>
</tbody>
</table>
Dermatologic Serious Adverse Events

- **Skin SAEs** occurred in 7 (0.2%) placebo subjects and 10 (0.3%) denosumab subjects
- In many of these cases, while denosumab could not be ruled out as the cause, subjects were noted to be on other medications that could also be the cause
- The four cases of “toxic skin eruptions” were reviewed and do not appear to be secondary to denosumab
Pancreatitis
## Pancreatitis: PMO Pooled Data

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Non-serious</th>
<th>Serious</th>
<th>Non-serious</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Pancreatitis acute</strong></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Pancreatitis chronic</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic pseudocyst</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total Events</strong></td>
<td>3 (0.1%)</td>
<td>1 (&lt; 0.1%)</td>
<td>0 (0%)</td>
<td>9 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=4041</th>
<th>Denos. N=4050</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>No. of Events</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

Total Pancreatitis events: 3 (0.1%) in Placebo, 1 (< 0.1%) in Denos.
Ocular Adverse Events
Ocular Adverse Events

• Reason for Concern
  – An imbalance in the incidence of cataracts in trial 20040138 (prostate)

<table>
<thead>
<tr>
<th></th>
<th>Trial</th>
<th>Placebo n (%)</th>
<th>Denosumab n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cataract AEs</strong></td>
<td>Trial 138</td>
<td>9 (1.2%)</td>
<td>34 (4.7%)</td>
</tr>
<tr>
<td></td>
<td>Trial 216</td>
<td>253 (6.3%)</td>
<td>229 (5.7%)</td>
</tr>
<tr>
<td><strong>Cataract SAEs</strong></td>
<td>Trial 138</td>
<td>0 (0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td></td>
<td>Trial 216</td>
<td>28 (0.7%)</td>
<td>21 (0.5%)</td>
</tr>
</tbody>
</table>
Cardiovascular Adverse Events
Cardiovascular: Reason for Concern

• Osteoprotegerin (OPG) is a cytokine in the TNF receptor superfamily. Its main function is inhibition of RANKL and osteoclast differentiation.

• Literature reports suggest an association between osteoprotegerin (OPG) levels and arterial wall calcification, cardiovascular disease, and mortality.

• There is a theoretical potential for elevated OPG levels with denosumab inactivation of RANKL, as it binds to the same target.
Cardiovascular Safety Analysis

- Deaths and Cardiovascular SAEs from studies 216 and 138 were adjudicated by an independent panel of cardiologists
  - There was a similar incidence of cardiac deaths, and SAEs in the treatment arms
- OPG levels were measured in the bone marker substudy of trial 216
  - OPG levels did not increase with denosumab use
- Abdominal aortic calcification scores were assessed using the x-rays collected for fracture analyses
  - No differences in the scores were seen
Hypocalcemia
Hypocalcemia

- Hypocalcemia is a well recognized adverse event with anti-resorptive therapy - essentially these therapies function to shut off bone as a reservoir for calcium
- All subjects in the primary phase 3 trials were supplemented with 1000 mg calcium and 400 – 800 IU vitamin D.
- Timing of the calcium measurements in the primary phase 3 trials missed the anticipated calcium nadir (8-11 days post-dose)
- One denosumab-treated subject in trial 138 reported an SAE of hypocalcemia
- In the phase 3 PMO trials, 1.6% of subjects had an asymptomatic calcium < 8.5 mg/dL. Calcium levels < 7.5 mg/dL were rare
Osteonecrosis of the Jaw
Osteonecrosis of the Jaw (ONJ)

- The etiology of ONJ is not clear, but may be associated with inhibition of bone remodeling.
- Potential cases of ONJ were adjudicated by an independent committee.
- There was a balanced distribution of potential ONJ cases, as identified by the search criteria, between arms in all studies.
- No cases met the definition of ONJ.
- Cases of ONJ are being reported in denosumab subjects in ongoing & completed advanced cancer trials.
Immunogenicity

• Any therapeutic protein has the potential to elicit an immune response

• A three-step process for detection of antibodies was used:
  – A screening immunoassay to detect binding antibodies
  – A second immunoassay to confirm binding antibodies
  – Cell-based bioassay to evaluate for neutralizing antibodies

• Most clinical studies from the denosumab program had evaluations of immunogenicity
### Binding Antibodies

<table>
<thead>
<tr>
<th>Population</th>
<th>Subjects</th>
<th>Pre-existing binding Ab</th>
<th>Binding Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects Exposed to Denosumab</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8113</td>
<td>12 (0.1%)</td>
<td>43 (0.5%)</td>
</tr>
<tr>
<td>PMO</td>
<td>6111</td>
<td>6 (0.1%)</td>
<td>28 (0.5%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1273</td>
<td>2 (0.2%)</td>
<td>7 (0.5%)</td>
</tr>
<tr>
<td>Other*</td>
<td>729</td>
<td>4 (0.5%)</td>
<td>8 (1.1%)</td>
</tr>
<tr>
<td><strong>Subjects Exposed to Placebo or Active Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5320</td>
<td>8 (0.2%)</td>
<td>16 (0.3%)</td>
</tr>
</tbody>
</table>

*Includes healthy population, rheumatoid arthritis and renal disease