**Dose-Response Effects of Denosumab, A Novel Subcutaneous RANKL Inhibitor, on the Progression of Bone Erosion in Japanese Patients with Rheumatoid Arthritis Treated with Methotrexate**

**Results of Phase II DRIVE Study**
- A Twelve Months Placebo Controlled, Randomized, Double Blind Study

**Informed Consent**
- 28 days
- First administration
- 12 months

**Mechanism of Action**
- Denosumab inhibits osteoclast formation, function and survival

**Objective**
- **Background:** In spite of the recent advances in non-biologics treatment of RA, many patients continue to experience progressive joint damage
  - One published study of denosumab in RA patients
    - Patients with chronic phase RA in the USA and Canada (mainly Caucasians)
    - Evaluated the effect of denosumab doses of 60 mg Q6M and 180 mg Q6M

- **Objective:**
  - To evaluate the efficacy and safety of denosumab
    - Early phase RA in Japanese patients
    - To evaluate the effect of dosing-frequency (60 mg Q6M, Q3M or Q2M)

**Main Inclusion and Exclusion Criteria**

- **Main Inclusion Criteria:**
  - Diagnosis of RA (by 1987 ACR criteria)
  - RA disease duration 0.5 to < 5 years
  - Use of MTX for at least 6 weeks before the first investigational drug administration (at a stable dose for 4 weeks before the first administration)
  - Active RA (≥ 6 swollen joints)
  - At least one presence of
    - ≥ 2 erosions
    - C-reactive protein ≥ 1.0 mg/dL AND positive for CCP antibodies or RF > 20 IU/mL
    - ESR ≥ 28 mm/hr AND positive for CCP antibodies or RF > 20 IU/mL

- **Main Exclusion Criteria:**
  - Use of the biologic agent for RA treatment
  - Glucocorticoid use > 10 mg/day (prednisone or equivalent) within 4 weeks before the first administration
  - Administration of oral bisphosphonate ≥ 104 weeks

**Disclosures**
- This study was funded by Daiichi-Sankyo Co., Ltd.
- The presenters receive consulting fees and/or other remuneration and/or research grants:
  - T. Yoneda
  - N. Ishiguro
  - H. Yamanaka
  - D. van der Heijde

- **Study Design**
  - Stratification factor: Steroid use at screening, Rheumatoid Factor status
**Concomitant Therapy**

- All patients were receiving Calcium and Vitamin D.
- All patients were receiving background MTX.
- Bisphosphonate therapy was prohibited.
- Salazosulfapyridine, Bucillamine, and NSAIDs allowed at investigators’ discretion under the approved dosage in Japan.
- Glucocorticoid use (≤10 mg/day, prednisone or equivalent) is possible.

**Endpoints**

**Primary Endpoint:** Change from baseline in modified Sharp erosion score (ES ×) at month 12

**Secondary Endpoints:**
- Change from baseline in modified Sharp erosion score at month 6.
- Change from baseline in modified total Sharp score (TSS ×) at month 6 and month 12.

**Radiographic Scoring Method**

- Radiographs of the hands/wrists and feet were analyzed using the van der Heijde-modified Sharp method.
- Two well-trained readers read the images of all patients blinded for treatment, clinical data and time order of the radiographs.
- The scores of the 2 readers were averaged for the analysis.

**Patient Disposition**

- 350 patients randomized
- 6 patients never received the IP
- 6 discontinued 2 consent withdrawal 2 adverse event 1 disease progression 1 invasive dental treatment
- 82 patients completed the study
- 78 patients completed the study
- 86 patients completed the study
- 85 patients completed the study
- 79 patients completed the study

**Patient Demographics and Characteristics at Baseline**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=88)</th>
<th>Q3M (N=92)</th>
<th>Q2M (N=80)</th>
<th>Q1M (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>76 (86.4)</td>
<td>65 (75.5)</td>
<td>59 (72.5)</td>
<td>65 (77.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.9 ± 10.6</td>
<td>54.4 ± 10.6</td>
<td>53.0 ± 11.7</td>
<td>54.6 ± 10.5</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>54.9 ± 9.9</td>
<td>56.1 ± 12.0</td>
<td>58.6 ± 10.3</td>
<td>58.9 ± 10.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 ± 3.3</td>
<td>22.3 ± 3.6</td>
<td>22.2 ± 3.1</td>
<td>22.3 ± 3.5</td>
</tr>
<tr>
<td>Duration of RA (years)</td>
<td>2.31 ± 1.34</td>
<td>2.16 ± 1.31</td>
<td>2.26 ± 1.27</td>
<td>2.25 ± 1.40</td>
</tr>
<tr>
<td>RF status, n(%)</td>
<td>60 (68.2)</td>
<td>59 (63.4)</td>
<td>56 (62.5)</td>
<td>57 (67.1)</td>
</tr>
<tr>
<td>Anti-CCP antibodies, n(%)</td>
<td>66 (75.0)</td>
<td>70 (80.4)</td>
<td>64 (76.3)</td>
<td>65 (76.5)</td>
</tr>
<tr>
<td>MTX weekly dose (mg)</td>
<td>7.61 ± 1.75</td>
<td>7.58 ± 2.01</td>
<td>8.40 ± 2.19</td>
<td>8.25 ± 2.02</td>
</tr>
<tr>
<td>Glucocorticoid use, n (%)</td>
<td>37 (44.0)</td>
<td>36 (42.4)</td>
<td>37 (45.1)</td>
<td>37 (45.5)</td>
</tr>
<tr>
<td>NSAIDs use, n (%)</td>
<td>64 (72.7)</td>
<td>61 (71.8)</td>
<td>60 (73.2)</td>
<td>62 (80.0)</td>
</tr>
<tr>
<td>DMBARs use, n (%)</td>
<td>22 (25.0)</td>
<td>18 (21.2)</td>
<td>15 (18.3)</td>
<td>22 (27.5)</td>
</tr>
</tbody>
</table>

**Baseline Disease Activity**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=82)</th>
<th>Q3M (N=87)</th>
<th>Q2M (N=85)</th>
<th>Q1M (N=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>modified Sharp ES (0 - 280)</td>
<td>6.6 ± 10.3</td>
<td>6.4 ± 7.8</td>
<td>5.9 ± 6.8</td>
<td>7.4 ± 8.7</td>
</tr>
<tr>
<td>modified Sharp Jx5 Score (0 - 163)</td>
<td>6.9 ± 14.3</td>
<td>5.0 ± 6.3</td>
<td>4.1 ± 8.1</td>
<td>5.3 ± 8.7</td>
</tr>
<tr>
<td>modified total Sharp Score (0 - 440)</td>
<td>13.6 ± 24.0</td>
<td>11.4 ± 14.5</td>
<td>10.0 ± 14.0</td>
<td>12.7 ± 16.6</td>
</tr>
<tr>
<td>Seselijn joint count (0 - 66)</td>
<td>10.5 ± 5.9</td>
<td>8.9 ± 4.2</td>
<td>10.5 ± 4.6</td>
<td>10.2 ± 4.7</td>
</tr>
<tr>
<td>Tender joint count (0 - 66)</td>
<td>9.9 ± 9.7</td>
<td>8.0 ± 7.4</td>
<td>8.2 ± 7.3</td>
<td>8.3 ± 7.8</td>
</tr>
<tr>
<td>DAS28-CRP</td>
<td>4.0 ± 1.0</td>
<td>3.6 ± 1.0</td>
<td>3.8 ± 1.0</td>
<td>3.8 ± 0.9</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.75 ± 1.24</td>
<td>0.52 ± 0.92</td>
<td>0.61 ± 1.17</td>
<td>0.60 ± 1.08</td>
</tr>
<tr>
<td>Health assessment questionnaire disability index (HAQ-DI) (0 - 3)</td>
<td>0.47 ± 0.52</td>
<td>0.39 ± 0.45</td>
<td>0.32 ± 0.38</td>
<td>0.35 ± 0.39</td>
</tr>
</tbody>
</table>

**Value means Mean ± SD.**

*In a subset of patients who received ≥ 1 dose of investigational product and had a baseline and at least 2 postbaseline measurements of radiographic variables at any time point.*
Because the changed score of Q3M was not statistically significant, statistical comparison at month 6 between placebo and Q6M

Shirley

Missing values were imputed using linear extrapolation/interpolation.

Mean

N = Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 postbaseline measurement of radiographs.

Mantel-Haenszel test with 1-sided α = 0.025.  

ACR20 Response and DAS28-CRP

Probability Plots for Change from Baseline in Modified Sharp Erosion Score at 12 Months

Mean Change from Baseline in Modified Total Sharp Score at Month 6 and 12

Mean Change from Baseline in Modified Sharp Joint Space Narrowing Score at Month 6 and 12

Probability Plots for Change from Baseline in Modified Sharp Erosion Score at 12 Months

Summary of Adverse Events over 12 Months

n (%)  Placebo (N=88)  Q6M (N=85)  Q2M (N=82)  Q3M (N=85)  G2M (N=87)

All AEs

73 (83.0)  69 (80.2)  65 (76.5)  82 (94.3)

SAEs

9 (10.2)  4 (4.7)  6 (7.1)  8 (9.2)

Discontinued study due to adverse events

2 (2.3)  2 (2.3)  4 (4.7)  2 (2.3)

Related AEsa

16 (18.2)  16 (18.6)  12 (14.1)  18 (20.7)

Related SAEsa

2 (2.3)  1 (1.2)  2 (2.4)  0 (0.0)

Death

0 (0.0)  0 (0.0)  0 (0.0)  0 (0.0)

a: Number of patients who received ≥ 1 dose of investigational product and had a baseline and at least 1 postbaseline measurement of radiographs.

b: Safety set is investigational product exposure periods.

c: Number of patients reporting ≥ 1 event.

d: Events that the investigator indicated there was a causative possibility they may have been occurring investigational product.
Incidence of Adverse Events Occurring at ≥ 5% in Any Treatment Group over 12 Months

<table>
<thead>
<tr>
<th>Events</th>
<th>Placebo (N=88)</th>
<th>Denosumab 60 mg Q6M (N=86)</th>
<th>Q3M (N=85)</th>
<th>Q2M (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>23 (26.1)</td>
<td>21 (24.4)</td>
<td>20 (23.5)</td>
<td>28 (32.2)</td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>14 (15.9)</td>
<td>7 (8.1)</td>
<td>9 (10.5)</td>
<td>17 (19.5)</td>
</tr>
<tr>
<td>Upper respiratory tract inflammation</td>
<td>5 (5.7)</td>
<td>6 (7.0)</td>
<td>5 (5.9)</td>
<td>9 (10.3)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>7 (8.0)</td>
<td>7 (8.1)</td>
<td>4 (4.7)</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (2.3)</td>
<td>5 (5.8)</td>
<td>3 (3.5)</td>
<td>6 (7.0)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3 (3.4)</td>
<td>2 (2.3)</td>
<td>5 (5.9)</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (3.4)</td>
<td>3 (3.5)</td>
<td>5 (5.9)</td>
<td>4 (4.6)</td>
</tr>
<tr>
<td>Eczema</td>
<td>2 (2.3)</td>
<td>2 (2.3)</td>
<td>3 (3.5)</td>
<td>6 (7.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (3.4)</td>
<td>5 (5.8)</td>
<td>1 (1.2)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Periodontitis</td>
<td>2 (2.3)</td>
<td>0 (0.0)</td>
<td>5 (5.9)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>2 (2.3)</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

No hypocalcemia, osteonecrosis of the jaw or atypical femoral fracture were observed.

Summary

- Treatment with denosumab for 1 year showed a significant inhibition of the progression of the bone erosion in Japanese patients with RA. Numerically, greater suppression of bone erosion was confirmed with more frequent dosing.

- Neither significant differences in modified Sharp JSN score between denosumab and placebo nor differences in ACR response and DAS28-CRP were observed.

- No significant differences in the types and the overall incidences of AEs were observed among the placebo and denosumab groups. The more frequent dosing regimen of denosumab did not increase AE incidence.

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