The Potential Clinical Relevance of Imaging Biomarker Data from Short-Term Interventional Trials in Osteoarthritis: A Comparison of the Cathepsin K Inhibitor MIV-711 Phase 2a MRI Knee Joint Data and KL-Matched 5577 Knee Control Data from the Osteoarthritis Initiative

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Background
- Osteoarthritis (OA) is the fastest growing chronic pain disease worldwide.
- Current treatments available for OA are aimed at controlling pain. There is a need for new therapies, so called Disease Modifying Osteoarthritis Drugs (DMOADs), that can prevent joint structural degeneration.
- New imaging biomarkers using supervised machine learning offer opportunities to demonstrate effects of potential DMOADs on joint structure in short, small trials based on superior reliability.
- MIV-711, a cathepsin K inhibitor, demonstrated substantial effects vs placebo on both joint bone area and cartilage thickness following 6 months’ treatment in the MIV-711-201 trial4. This study was the first to apply these highly sensitive imaging biomarkers in an interventional setting.
- Structural and clinical progression data from the Osteoarthritis Initiative (OAI) provide an opportunity to compare the outcome data from the MIV-711-201 trial with data on the natural history of OA from a large prospective cohort.

Methods
- MIV-711-201 (EudraCT no 2015-003320-26) was a multicentre, randomised, placebo-controlled, double-blind, three-arm, parallel, Phase 2a study.
- Key inclusion criteria for MIV-711-201 study patients:
  - ACR knee OA
  - KL classification grade 2 or 3 (local radiologist’s assessment based X-ray taken within the last 12 months)
  - Current average target knee pain 0-10 on a 0 to 10 NRS
- Patients were randomised to receive MIV-711 100 mg, MIV-711 200 mg or placebo once daily for 26 weeks. A total of 240 patients were included in the mITT population (placebo=77; MIV-711 100 mg=81, MIV-711 200 mg=82).
- 3D bone area of the medial femoral condyle (MF) and central medial femur (cMF) were measured using automated cartilage segmentation as used in the MIV-711-201 study and a baseline and 12 month image, using the same methods of bone and cartilage segmentation as used in the MIV-711-201 study.

Conclusions
- This comparison suggests that patients in the placebo arm of the MIV-711-201 study had a similar structural progression rate to untreated KL2/KL3 patients in the OA cohort.
- The effects of 6 months treatment with MIV-711 on bone area and cartilage thickness are relevant when compared to the natural progression seen over 12 months in OA Kl-1/3 patients, establishing the relevance of these endpoints for use in prospective interventional studies.
- Benefits on clinical symptoms could become manifest if MIV-711’s positive effects on joint structure can be maintained over time.

Demographics

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Placebo</th>
<th>100 mg</th>
<th>200 mg</th>
<th>KL0</th>
<th>KL2</th>
<th>KL3</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>77</td>
<td>82</td>
<td>81</td>
<td>2789</td>
<td>1870</td>
<td>918</td>
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<tr>
<td>Age (years) Mean</td>
<td>62.3</td>
<td>61.2</td>
<td>62.0</td>
<td>59.2</td>
<td>61.7</td>
<td>64.2</td>
</tr>
<tr>
<td>Female NA</td>
<td>62 (80.5%)</td>
<td>64 (78.0%)</td>
<td>58 (71.6%)</td>
<td>1542 (55.3%)</td>
<td>1182 (63.2%)</td>
<td>479 (52.2%)</td>
</tr>
<tr>
<td>Discontinuations NA</td>
<td>11</td>
<td>8</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
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</tr>
</tbody>
</table>

Patient flow overview MIV-711-201

- Treatment groups well-balanced overall in Study MIV-711-201 also including but not shown here; height, weight, ethnicity and race.
- The average BMI in the MIV-711-201 study was slightly higher than in the OA cohort. In addition, the MIV-711-201 study had a higher proportion of females compared to the OA cohort.

Effect of MIV-711 on Joint structure compared with the OA cohort: Bone Area

- In the MIV-711-201 quantitative MRI data, mean changes in MF bone area (mm²) were 13.4 (7.48, 19.28); 7.54 (4.67, 10.36) for the placebo, 100 mg and 200 mg groups respectively (95% CI). This is in good agreement with the corresponding published data based on manual segmentation1.
- OA KL2 KL3 bone area change (mm²) over 12 months was 4.26, 5.17, 10.09 (mm²) for KL0, 2 and 3 respectively (equates to 2.3, 4.59, 10.05 over 6 months assuming linear change).

Effect of MIV-711 on Joint structure compared with the OA cohort: Cartilage thickness

- In the MIV-711-201 quantitative MRI data cMF cartilage thickness (mm) mean changes were -0.042 (0.001, -0.085), -0.008 (0.034, -0.051), -0.007 (0.044, -0.058) for the placebo, 100 mg and 200 mg respectively (95% CI), also in good agreement with the data based on manual segmentation1.
- OA cMF cartilage change over 12 months was -0.005, -0.024, -0.060 (mm²) for KL0, 2 and 3 respectively (equates to -0.0025, -0.012, -0.03 over 6 months assuming linear change).

References