**Background**

- OA is the fastest growing chronic pain disease worldwide.
- Current treatments available for OA are at best for controlling pain. There is a need for new therapies, so-called Disease-Modifying Osteoarthritis Drugs (DMOADs) that can prevent joint structural degeneration.
- DMOADs are compounds that target key enzymes such as inflammatory cytokines.
- Preclinical and early clinical profile.

**Methods: Study Design**

- MIV-711: (activity in vitro and vivo) was a multi-centred, randomised, placebo-controlled, double-blind, three arm, parallel, Phase IIa study. All patients were permitted to remain on their current arthritic medication regimen.

**Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>100 mg</th>
<th>200 mg</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean</td>
<td>62.3</td>
<td>61.2</td>
<td>62.0</td>
</tr>
<tr>
<td>BMX (kg/m²)</td>
<td>Mean</td>
<td>32.49</td>
<td>31.98</td>
<td>32.02</td>
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<tr>
<td>female</td>
<td>NA</td>
<td>62 (80.5%)</td>
<td>66 (78.0%)</td>
<td>18 (13.6%)</td>
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<tr>
<td>Male</td>
<td>NA</td>
<td>15 (19.5%)</td>
<td>18 (22.0%)</td>
<td>13 (13.6%)</td>
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<tr>
<td>Exclusions</td>
<td>NA</td>
<td>8</td>
<td>20</td>
<td>28</td>
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<tr>
<td>Treatment</td>
<td></td>
<td>79</td>
<td>79</td>
<td>79</td>
</tr>
</tbody>
</table>

**Effect of MIV-711 on Symptoms: NRS Pain**

- No statistically significant effect by treatment (unadjusted p=0.41 for 200 mg and p=0.15 for 100 mg).
- Tendency to less pain in the MIV-711 treated arms compared to placebo.

**Effect of MIV-711 on Symptoms: WOMAC**

- The tendency of a treatment effect was more pronounced in WOMAC scales (including placebo across 12 weeks versus treatment arms).
- Both treatment arms showed a benefit on the attenuation of cartilage thinning in the central malleolar femoral region (%/6 months) compared to that of placebo (~4%/6 months). No significant effect was seen on the tibial side.
- Unadjusted p-value = 0.023 (100 mg) and 0.125 (200 mg).

**Effect of MIV-711 on Biomarkers: CTX-I and CTX-II**

- The reductions in both serum CTX-I and urine CTX-II were rapid and sustained over 26 weeks of treatment with a slight climb consistent with the literature.
- The biomarker data suggest robust target engagement with ca. 30% and 50% reductions for 100 mg and 200 mg groups, respectively, for both biomarkers.

**Effect of MIV-711 on Joint Structure: Bone Area**

- Pronounced attenuation with both doses on medial femur bone area progression (~<0.3%/6 months) compared to that of placebo (~1%/6 months).
- Unadjusted p-value = 0.002 (100 mg), 0.004 (200 mg).

**Effect of MIV-711 on Joint Structure: Cartilage Loss**

- Both treatment arms showed a benefit on the attenuation of cartilage thinning in the central malleolar femoral region (%/6 months) compared to that of placebo (~4%/6 months).
- No significant effect was seen on the tibial side.
- Unadjusted p-value = 0.023 (100 mg) and 0.125 (200 mg).

**Discussion**

- Despite substantial effects on medial femur bone area and cartilage loss over 6m, the length of time over which the observed effects on these markers need to be sustained to detect effects on patient-reported symptoms remains uncertain.
- Data from the OAI cohort indicate that changes in joint bone markers over 24 weeks are associated with radiographic and pain progression over 48 months (Hunter et al., Ann Rheum Dis. 2020. 79:1607-14).

**Conclusions**

- Primary endpoint of knee pain not met, however consistent tendency favors treated arms in all symptom measures.
- Analgesic use showed tendency to be lower in treated arms.
- Joint structure: NRI measures demonstrated joint protection after 6 months of treatment.
- DMOADs: Significant depressions of both CTX-I and CTX-II show clear target engagement.
- Safety & Tolerability: Acceptable safety and tolerability at both doses.

**Overall conclusion**

- Even with a short treatment period (6 m), MIV-711 demonstrated significant reductions in OA bone disease and cartilage disease (100 mg dose) progression in the femur.
- The treatment duration required to demonstrate a corresponding reduction in patient-reported symptoms was not reached.
- Further evaluation of MIV-711 in longer and larger OMAOD2 trials is therefore warranted.

**Safety & Tolerability**

- Overall safety summary:
  - MIV-711 showed acceptable tolerability; overall AEs were balanced across arms. A DMC gave go ahead of 4 expected and unblinded safety reviews.
  - Significant increase in number of patients reporting skin disorders (2.5%, 12.2%, 7.3%) infections (13.9%, 18.3%, 3.1%), and musculoskeletal events (18.3%, 25.2% in the placebo, 100 and 200 mg arms respectively).
  - Infections and skin events were generally mild to moderate and non-specific.
  - Three patients presented with allergic drug eruptions.
  - No instance of myocardial infarction.
  - Significant increase in number of patients with severe AEs and AEs leading to discontinuation in 3.2%, 10.6%, and 200 mg (5.4%) arms vs placebo (3.1%, 3.8%).
  - There were 9 SAEs in 6 patients: None were reported related to study medication.
  - Thrombo-embolic events (dVT).
  - 100 mg arm: xalralat, prinzemel, angina, pyelonephritis, compression fracture, contusion, haematomas (last 4 events all in one patient).
  - 100 mg: cholecystitis, cerebral infarction, DVT.
  - Independent experts assessed cases with atrial fibrillation and DVT as unrelated to treatment due to concomitant medications and pre-existing conditions.
  - Proremic effect was present in placebo and undisclosed condition diagnosed during study.
  - Transient shifts in calcium and parathyroid hormone (PTH) seen in line with the mode of action of study drug. These shifts however, did not appear to associate with any AEs or ECS changes. No other clinically significant changes in lab, vital, or ECGs.

**Overall Safety**

- **TEAEs Leading to early Discontinuation from Study**
  - All TEAEs
  - NMT 118: 118 (35.6%) N=118 (35.6%) N=118 (35.6%)
  - MODERATE: Treatment related TEAEs
    - MIV-711: Treated arms compared to placebo.
    - MIV-711 demonstrated a clear target engagement.
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