SM04690, a small molecule Wnt pathway inhibitor appeared to have no deleterious effects on bone, joint and tissue health in knee OA models

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Background
- Wnt signaling plays a major role in maintaining articular cartilage and bone homeostasis and is involved in OA pathogenesis.1
- SM04690 is a small-molecule Wnt pathway inhibitor in development as a potential disease-modifying knee OA drug (DMOAD).2,3
- Systemic Wnt pathway inhibitors have shown deleterious effects on bone.4
- Animal and human data from SM04690 were reviewed to determine its effects on bone, joint, and tissue health.

Methods
- Vehicle or SM04690 (0.3, 1 µg) was intra-articularly (IA) injected in a rat surgical knee OA model (anterior cruciate ligament transaction + partial medial meniscectomy [ACLT + pMMx]).
  - Osteoblast markers were evaluated by qPCR at Week 5.
  - Subchondral bone and total volume (BV/TV) ratios were evaluated at Week 13 (Image J software).
- In healthy dogs, inflammation was scored (0: normal; 1: minimal; 2: mild; 3: moderate; 4: marked) and joint histology (cartilage, meniscus, subchondral bone, synovium) semiquantitatively evaluated (Mankin score).5,6
  - Acutely, 1 day and 10 days after single injection of vehicle or SM04690 (70, 1750, 35000 µg).
  - Subchronically, at 3 months after 3 repeat monthly injections of vehicle or SM04690 (12, 36, 116 µg) and after 28 days recovery.
  - Chronically, at 9 months after 9 repeat monthly injections of vehicle or SM04690 (12, 36, 116 µg) and after 28 days recovery.
- In a human phase 1 trial (n=61) of single IA knee injection of SM04690 or placebo (PBO):3
  - Bone mineral density (BMD) was measured by quantitative computed tomography (qCT) at baseline, Week 12, and Week 24 in ITT (all randomized subjects).
  - Bone marrow edema (BME) was assessed with magnetic resonance imaging (MRI) at baseline and Week 24 in the modified ITT population (all randomized subjects according to actual treatment received).
  - Bone health serum biomarkers were collected at baseline and Week 24 in the safety analysis set (all subjects exposed to study product).

Results
- There were no significant changes in BMD in SM04690-treated compared with untreated knees in a phase 1 trial

Figure 3. a) Medial and b) lateral subchondral qCT in the target vs. non-target knees.3

Table 1. MRI safety findings: BME (n=58)

<table>
<thead>
<tr>
<th></th>
<th>None (N[%])</th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.23 mg</th>
<th>PBO</th>
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<tr>
<td>ALPL</td>
<td>1 (6.7%)</td>
<td>2 (12.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (6.3%)</td>
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<tr>
<td>BGLAP</td>
<td>1 (6.3%)</td>
<td>2 (12.5%)</td>
<td>0 (0%)</td>
<td>1 (6.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>RUNX2</td>
<td>1 (6.3%)</td>
<td>2 (12.5%)</td>
<td>0 (0%)</td>
<td>1 (6.3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Table 2. Summary of OA serum biomarkers at baseline and Week 24 (n=60)

<table>
<thead>
<tr>
<th></th>
<th>COMP [ng/ml]</th>
<th>PTNP [mcg/L]</th>
<th>β-CTX [pg/ml]</th>
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<tr>
<td>Baseline Mean (SD)</td>
<td>267.0 (191.9)</td>
<td>45.7 (13.5)</td>
<td>40.4 (12.4)</td>
</tr>
<tr>
<td>Week 24 Mean (SD)</td>
<td>267.0 (191.9)</td>
<td>45.7 (13.5)</td>
<td>40.4 (12.4)</td>
</tr>
</tbody>
</table>

Conclusions
- SM04690 appeared generally safe and well-tolerated in preclinical and clinical studies.
- SM04690 had no appreciable bone, joint, or tissue health effects compared with baseline or vehicle at pharmacologically active or higher dose equivalents.

References