Radiographic Outcomes Were Associated with Pain and Function Responses: Post-Hoc Analysis of Results from a Phase 2 Study in a Small Molecule Wnt Inhibitor, SM04690, for Knee Osteoarthritis Treatment

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Background

• Osteoarthritis (OA) is characterized by pain, disability, and joint deformity due to articular cartilage degradation and bone remodeling.

• The Wnt pathway is a major family of signaling molecules that regulate cell development and tissue regeneration.

• Wnt signaling affects OA by modulating inflammation, cartilage breakdown, and bone/cartilage formation. Increased Wnt signaling induces differentiation of mesenchymal stem cells into osteoblasts, whereas inhibition induces chondrogenesis.

• Evidence suggests that joint space narrowing (JSN) is associated with pain and loss of function in knee OA.

• SM04690 is a small molecule, intra-articular Wnt pathway inhibitor developed as a potential disease modifying OA drug (DMOAD). Results of a randomized, double-blind, phase 2 trial are presented elsewhere (abstract 958). This post-hoc analysis evaluated associations of JSN with changes in pain and function.

Methods

• 455 subjects received a 2 ml SM04690 injection (0.03, 0.07, 0.23 mg) or saline placebo (PBO) in the target (most involved) knee at Week 0.

• Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain [0–50] and Function [0–10] subscores were assessed (Weeks 0, 4, 13, 26, 39, 52) and target knee radiographs taken (Weeks 0, 26, 52).

• JSN was assessed by analysis of covariance adjusted for baseline medial joint space width (mJSW) with multiple imputation.

• A pre-specified unilateral symptomatic knee OA subgroup was investigator defined by history and examination.

• An examination of the impact of widespread pain as measured at baseline by the Widespread Pain Index was also pre-specified.

• A post-hoc subgroup analysis of unilateral symptomatic subjects without widespread pain, was identified to exclude non-discriminatory pain (Widespread Pain Index ≤ 5 and Symptom Severity Score ≤ 2).

• Responders were defined as subjects who achieved both WOMAC Pain and Function improvement of ≥50% and ≥20 [scaled to 100 points], similar to an OMERACT-OARSI response23, but with both pain and function criteria met.

• Receiver operator characteristic curves (ROC) were generated following logistic regression analyses to assess statistical correlation between baseline JSN and AUC-ROC.

• Area Under the Curve (AUC) was calculated to establish concordance. AUC > 0.7 was defined as "acceptable" and AUC > 0.8 as "excellent" discrimination3 (concordance) between change in mJSW and responders.

Table 1. SM04690-02 Demographics (ITT)

<table>
<thead>
<tr>
<th>N</th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.23 mg</th>
<th>PBO</th>
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<tbody>
<tr>
<td>Age at Consent (Years) [Mean (SD)]</td>
<td>65.6 (9.9)</td>
<td>64.8 (9.8)</td>
<td>65.0 (9.8)</td>
<td>65.7 (9.8)</td>
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<tr>
<td>BMI (kg/m²) [Mean (SD)]</td>
<td>27.4 (4.8)</td>
<td>27.2 (4.8)</td>
<td>27.3 (4.8)</td>
<td>27.3 (4.8)</td>
</tr>
<tr>
<td>Female [%]</td>
<td>59 (3%)</td>
<td>59 (3%)</td>
<td>60 (3%)</td>
<td>60 (3%)</td>
</tr>
<tr>
<td>African-American</td>
<td>18 (16.1%)</td>
<td>14 (12.9%)</td>
<td>12 (10.9%)</td>
<td>10 (8.6%)</td>
</tr>
<tr>
<td>Asian</td>
<td>11 (10.9%)</td>
<td>12 (10.9%)</td>
<td>12 (10.9%)</td>
<td>10 (8.6%)</td>
</tr>
<tr>
<td>Kellgren-Lawrence Grade 3 [%]</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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</tr>
<tr>
<td>0.03 mg</td>
<td>0.07 mg</td>
<td>0.23 mg</td>
<td>PBO</td>
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<tr>
<td>WOMAC Pain and Function Response [%]</td>
<td>46 (44%)</td>
<td>46 (44%)</td>
<td>46 (44%)</td>
<td>46 (44%)</td>
</tr>
<tr>
<td>Baseline mJSW [mm] [Mean (SD)]</td>
<td>2.92 (2.92)</td>
<td>2.92 (2.92)</td>
<td>2.92 (2.92)</td>
<td>2.92 (2.92)</td>
</tr>
<tr>
<td>Week 2 mJSW Change from Baseline</td>
<td>0.10 (0.09)</td>
<td>0.10 (0.09)</td>
<td>0.10 (0.09)</td>
<td>0.10 (0.09)</td>
</tr>
<tr>
<td>Week 2 mJSW Change compared to PBO*</td>
<td>0.03 (0.03)</td>
<td>0.03 (0.03)</td>
<td>0.03 (0.03)</td>
<td>0.03 (0.03)</td>
</tr>
<tr>
<td>Placebo</td>
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Table 2. Clinical Outcomes by Treatment Group

Results

• Radiographic outcomes from this study demonstrated that treatment with all doses of SM04690 maintained or increased mJSW compared to PBO at Week 52 (Table 2).

• Unilateral symptomatic subjects were pre-specified to investigate subject discrimination of symptoms between target and non-target knees. In addition to this, the unilateral symptomatoc without widespread pain subgroup further excluded chronic pain syndromes.

• In unilateral symptomatic subjects treated with SM04690 0.07 mg, changes in mJSW were concordant (AUC=0.78) with WOMAC Pain and Function response at Week 52 (Fig. 1B).

• In unilateral symptomatic subjects without widespread pain, PBO, SM04690 0.03 mg and 0.23 mg doses showed no concordance between WOMAC and WOMAC Pain and Function response at Week 52 (AUC < 0.7, Fig. 1C). However, subjects treated with SM04690 0.07 mg showed excellent concordance between change in mJSW and WOMAC Pain and Function response (AUC=0.83).

• In a targeted population of unilateral symptomatic knee OA subjects without widespread pain, change in mJSW was concordant with a pain and function response in a post-hoc analysis.

• This post-hoc analysis demonstrated concordance could be established between radiographic mJSW change and clinical outcomes when investigating potential DMOAD treatments in knee OA.

Discussions

• Concordance between change in mJSW and Clinical Response

• No group achieved acceptable concordance as all AUC<0.7 in ITT (Fig. 1A).

• Acceptable concordance (AUC>0.8) was observed in unilateral symptomatic subjects treated with SM04690 0.07 mg (Fig. 1B).

• Excellent concordance (AUC>0.83) was seen in unilateral symptomatic subjects without widespread pain treated with SM04690 0.07 mg (Fig. 1C).

Conclusions

• Concordance between change in mJSW and Clinical Response

References


Poster 1204

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