Joint Space Width Criteria Can Reduce Knee Osteoarthritis Trial Heterogeneity: Phase 2 Post-Hoc Data from Wnt Pathway Inhibitor, SM04690

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## Disclosures

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<thead>
<tr>
<th>Name</th>
<th>Relationship</th>
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Background

• Kellgren-Lawrence (KL) radiographic grading of knee osteoarthritis (OA) subjects:
  – Standard baseline knee OA disease classification in trials
  – Subjective evaluation of joint space narrowing and osteophyte formation
  – Leads to trial population with varied baseline joint space width (JSW), reducing structural measurement responsiveness and ability to detect change

• A more objective baseline measure may reduce JSW heterogeneity compared with KL grading and increase measurement responsiveness
  – Previous Osteoarthritis Initiative (OAI) analysis suggested improved responsiveness for structural measurement in subjects with baseline medial JSW 2-4 mm¹

Radiographic joint space width distribution in KL 0 males and females in the OAI

Distribution of rJSW values for all KL0 knees (3,440 knees in total)

Lower 95% threshold is about 0.5 mm thicker for males than females – used 4 mm for both for convenience – a knee below 4 mm rJSW is likely to already fall outside healthy range

2 year change for all 3 measures using bins from baseline rJSW dataset = whole OAI with radiographic measures ~ 6500 knees

- Mean 2 year changes were greatest for the categories of 2-3 and 3-4 mm baseline rJSW
- Notably little change in knees with rJSW <2 mm for rJSW
  - This is why we set the lower boundary to 2 mm (in common with most clinical trials)
- Best pragmatic compromise is that baseline rJSW should be >2 mm, and <4 mm for maximum responsiveness

Does selecting subjects with baseline mJSW 2-4 mm improve responsiveness in a clinical trial setting?

- SM04690, a Wnt pathway inhibitor and potential disease modifying knee OA treatment in development was tested in a phase 2a trial (N=455)
- Knee OA subjects (KL grades 2-3) were randomized and received a single intra-articular injection of SM04690 (0.03 mg, 0.07 mg, or 0.23 mg) or placebo (PBO)
- Radiographs (PA, QuAP™ positioned) were taken at Weeks 0 and 52; mJSW was assessed using a blind read, fixed landmark-based technology
- A post-hoc, exploratory analysis of subjects with baseline mJSW [2-4] mm was compared between groups (ITT, KL 2, KL 3, mJSW [2-4] mm) to assess effects on radiographic measurement responsiveness
Post-hoc analysis methodology

• Baseline heterogeneity of each group (ITT, KL 2, KL 3, mJSW [2-4] mm) was assessed with ‘box-and-whisker’ plots

• Standardized response means (SRMs) were calculated:
  – Week 52 mJSW mean change from baseline compared with PBO divided by standard error

• Baseline-adjusted ANCOVA used to compare SM04690 with PBO for mJSW at Week 52

• Multiple imputation was employed to account for missing data
Selecting mJSW [2-4] mm group resulted in reduced heterogeneity compared with other groups

Post-hoc analysis

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<tr>
<th>N per group</th>
<th>SM04690</th>
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<tr>
<td></td>
<td>0.03 mg</td>
</tr>
<tr>
<td>ITT</td>
<td>112</td>
</tr>
<tr>
<td>KL 2</td>
<td>38</td>
</tr>
<tr>
<td>KL 3</td>
<td>74</td>
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<tr>
<td>mJSW [2-4] mm</td>
<td>56</td>
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mJSW [2-4] mm group showed increased SRMs compared with most other groups

*Ladder plots from baseline-adjusted ANCOVA comparing treatment with placebo at Week 52 with standardized response means (SRMs) reported as favoring SM04690. ‡0.13mm is radiographic minimal detectable difference. (Dupuis, et al. (2003) OAC.) δ:SRM
This post-hoc analysis demonstrated:

- Week 52 mJSW changes compared with PBO were beyond minimal detectable difference (>0.13 mm)\(^1\) for 0.03 mg and 0.07 mg SM04690 doses in the mJSW [2-4] mm group, and 0.03 mg dose in the KL 2 group.

- mJSW [2-4] mm group increased SRMs for mJSW measurements compared with most other groups, and with reduced subject numbers compared with ITT.

- A less heterogenous baseline mJSW can potentially increase responsiveness, reducing the knee OA trial population size needed to detect mJSW changes, while maintaining statistical power.

- Radiographic mJSW [2-4] mm should therefore be considered as an inclusion criterion in knee DMOAD trials.

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Thank you