Comparison of Intra-articular Sham and Vehicle Injection from a Phase 2b Trial of SM04690, a Small-Molecule Wnt Inhibitor, for Knee Osteoarthritis

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Background

• Intra-articular (IA) saline or vehicle, used as placebo (PBO) comparators in knee osteoarthritis (OA) trials, have consistently demonstrated statistically significant and clinically meaningful improvements in patient-reported outcomes (PROs) from baseline
• IA “PBO” effects have been attributed to contextual or possible physiological benefits of IA saline.1 These effects have called into question the interpretation of study results from putative IA therapeutic agents
• In a prospective, randomized controlled, 24-week, phase 2b study, the relative effects of a vehicle PBO injection were compared to those of a sham injection and SM04690, an IA Wnt pathway inhibitor in development as a potential disease-modifying knee osteoarthritis drug (DMOAD)
• The potential unblinding impact of PBO or sham was tested
• Full primary study results are presented separately

Conclusions

• Subjects with knee OA receiving a single IA PBO injection reported no substantial differences in changes from baseline knee OA PROs compared to subjects who received a single IA sham injection
• Based on the BBI data, subjects appeared unable to discern which non-drug injection they received (either PBO or sham)
• While IA PBO injections often yield statistically and clinically meaningful improvements from baseline in knee OA study PROs, these data suggested the effects were “contextual,” meaning they resulted from the injection procedure rather than from a direct therapeutic effect of saline in the joint

Methods

• Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, and Pain Numeric Rating Scale (NRS) ≥4 to ≤6 in target knee and <4 in contralateral knee
• Subjects were randomized to receive a blinded, single, IA, 2 mL vehicle injection (PBO, 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline), sham injection (dry needle only), or a dose of SM04690 (0.03 mg, 0.07 mg, 0.15 mg, or 0.23 mg) in the target knee at Day 0
• PROs included change from baseline in weekly average of daily OA target knee pain by NRS [0-100] (PBO, either IA, 2 mL vehicle injection), adjusted to baseline
• In the Full Analysis Set population of PBO and sham groups versus an increased positive value for the SM04690 group at 24 weeks (Table 1)

Results

Figure 1. PROs: Change from baseline, sham compared to PBO over time

Table 1. Subjects’ treatment identification accuracy using BBI

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<tr>
<th>Visit</th>
<th>Planned Treatment</th>
<th>Subject Response</th>
<th>Total</th>
<th>Bang’s BI</th>
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<tr>
<td>Day 1</td>
<td>SM04690 Vehicle</td>
<td>Sham</td>
<td>Don’t Know</td>
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<td>695</td>
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<tr>
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<td>Sham</td>
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<tr>
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<td>39</td>
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</tbody>
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Table 1. Compared subjects’ treatment identification (PBO, sham, or SM04690) accuracy using Bang’s Blinding Index (BBI)

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References: