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Comparison of Intra-articular Sham and Vehicle Injections from a Phase 2b Trial of Lorecivint (SM04690), a Small-Molecule Wnt Pathway Inhibitor for Knee Osteoarthritis

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Background: Intra-articular (IA) saline, commonly used as a placebo (PBO) comparator in knee osteoarthritis (OA) trials, has consistently shown improvements from baseline in patient-reported outcomes (PROs).¹ These effects have been attributed to contextual and/or physiological benefits of saline, thus causing interpretation of potential IA therapeutics trial results to be questioned.^{2,3}

Objective: A prospective, randomized, controlled, 24-week phase 2b study compared effects of vehicle PBO to sham and SM04690 (an IA Wnt pathway inhibitor in development as a potential disease-modifying knee OA drug [DMOAD]) injections. Potential unblinding impact of PBO or sham was also tested. Primary study results are presented separately.

Methods: Knee OA subjects with Kellgren-Lawrence (KL) grades 2-3 and Pain Numeric Rating Scale (NRS) ≥ 4 and ≤ 8 in the target knee and < 4 in the contralateral knee were randomized to receive a single, blinded, IA injection of 2 mL vehicle (PBO, 0.5% carboxymethylcellulose sodium, 0.05% polysorbate 80 in pH 7.4 saline), sham (dry needle), or SM04690 in the target knee on Day 0. PROs included change from baseline in weekly average of daily pain in the target knee by NRS, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Physical Function, and Patient Global Assessment (PtGA). Subjects were asked which treatment assignment they thought they received; their accuracy was compared using Bang's Blinding Index (BBI), a method used to evaluate blinding across clinical trial treatment arms. The index scale is $-1 < 0 < +1$, with values toward -1 indicating more subjects incorrectly guessing treatment allocations, toward 0 indicating perfect blinding, and toward +1 indicating more subjects correctly identifying treatment allocations.

Results: In the full analysis set of PBO and sham subjects (N=233; 207 [89%] completed), both groups showed clinically relevant improvements ($>10\%$ of full scale⁴) from baseline at first measurement that persisted through Week 24. However, no clinically meaningful or statistically significant differences were evident between the two groups at any timepoints (**Figure**). BBI did not indicate unblinding.

Conclusion: Subjects with knee OA receiving a single IA injection of PBO reported no differences in changes from baseline in knee OA PROs compared to subjects who received sham injections. These data suggested the effects were “contextual,” meaning they resulted from the injection procedure rather than from direct therapeutic effects of PBO or saline in the joint.

References:

1. Altman RD et al. *Semin Arthritis Rheum.* 2016;46:151-9
2. Zou K et al. *Ann Rheum Dis.* 2016;75:1964–197
3. Bannuru R et al. *Ann Intern Med.* 2015;163(5):365-72
4. Devji, Tahira, et al. *BMJ open* 7.5 (2017):e015587

Figure: Observations over time depicting mean improvements (\pm 95% CI) of PBO compared to sham injection adjusted for baseline. A. Pain NRS, B. WOMAC Pain, C. WOMAC Function, and D. Patient Global; in all subjects.

