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## **Prospective Comparison of Sham vs. Placebo Injections: Data from a Trial of Lorecivivint, a Wnt Pathway Inhibitor for Knee Osteoarthritis**

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**Background:** Intra-articular (IA) placebo (PBO) comparators in knee osteoarthritis (OA) trials demonstrate durable improvements in patient-reported outcomes (PROs) over baseline. Controversy exists over whether responses to IA saline represent true PBO effects versus physiological benefits. IA vehicle PBO effects were compared to sham in a 24-week phase 2b study of lorecivivint (SM04690), a Wnt pathway inhibitor in development as a potential disease-modifying knee OA drug.

**Methods:** Subjects with knee OA, Kellgren-Lawrence grades 2-3, and Pain Numeric Rating Scale (NRS)  $\geq 4$  and  $\leq 8$  in the target knee and  $< 4$  in the contralateral knee were randomized to a single, 2 mL, IA injection of vehicle (PBO, 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 saline), sham (dry needle), or lorecivivint at baseline. Patient-reported outcomes (PROs) included change from baseline in weekly average of daily target knee pain by NRS, WOMAC Pain, WOMAC Function, and Patient Global Assessment. Baseline-adjusted analysis of covariance was used to estimate change-over-time differences in PBO and sham outcomes compared to baseline.

**Results:** 207 of 233 PBO and sham subjects completed the 24-week study. Both PBO and sham subjects showed clinically relevant improvements ( $>10\%$ ) in all PROs from baseline at first post-baseline measurement that persisted through Week 24. No clinically meaningful or statistically significant differences were evident between the two groups at any time point (Figure).

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

**Figure:** Observations over time depicting mean change from baseline of PBO and sham injections. A) Pain NRS, B) WOMAC Pain, C) WOMAC Function, and D) Patient Global Assessment; in all subjects

