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## **Prospective Comparison of Intra-articular Sham vs. Placebo Injections: Data from a Randomized Controlled Phase 2b Trial of SM04690, a Wnt Pathway Inhibitor for Knee Osteoarthritis**

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**Objectives:** Intra-articular (IA) placebo (PBO) comparators in knee osteoarthritis (OA) trials demonstrate consistent and durable symptom improvements over baseline. There is controversy concerning whether responses to IA saline represent a true PBO effect versus actual physiologic benefit.<sup>1</sup> To test if the effects are due to intrinsic saline properties, one arm of a 24-week phase 2b study of SM04690 (IA Wnt pathway inhibitor in development as a potential disease-modifying knee OA drug) compared effects of IA vehicle PBO to sham. Primary study results are presented separately.

**Materials and 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 receive a blinded, single, IA, 2 mL injection of vehicle (PBO, 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 saline), sham (dry needle), or SM04690 at baseline. Patient-reported outcomes (PROs) included change from baseline in weekly average of daily target knee pain by NRS, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Function, and Patient Global Assessment. Baseline-adjusted analysis of covariance was used to estimate change-over-time differences in outcomes between sham and PBO.

**Results:** 207 out of 233 PBO and sham subjects completed the 24-week study. Both PBO and sham subjects showed clinically relevant improvement ( $>10\%$ ) from baseline at first post-baseline measurement that persisted through Week 24.<sup>2</sup> However, no clinically meaningful or statistically significant differences were evident between the two groups at any time points (**Figure**).

**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 suggest that the observed effects were “contextual,” meaning that 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.
2. Devji T, et al. *BMJ Open.* 2017.

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

