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Saline-Based Placebo and Sham Injections Demonstrated Equivalent Improvements on Knee Osteoarthritis Symptoms in a Randomized Controlled Trial, Suggesting a Strong Contextual Response

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Teaser Summary: Trials of injectable knee osteoarthritis therapies show robust placebo responses, leading to the hypothesis that saline-based placebo injections provide therapeutic benefits. This prospective comparison of intra-articular placebo to dry needle sham injections suggested that improved patient-reported outcomes resulted from contextual instead of physiological effects.

Background: Intra-articular (IA) placebo 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 placebo or physiological effects. IA placebo and sham injections were prospectively compared in a 24-week Phase 2b trial of lorecivivint (LOR), a Wnt pathway modulator in development as a potential knee OA treatment.

Methods: Knee OA subjects were randomized to receive a single 2 mL IA injection of vehicle placebo (0.5% carboxymethylcellulose sodium, 0.05% polysorbate 80 in pH 7.4 saline), sham (dry needle), or LOR at baseline. Captured PROs included weekly average target-knee pain by NRS, WOMAC Pain, WOMAC Function, and Patient Global Assessment. Baseline-adjusted analysis of covariance estimated change-over-time differences in placebo and sham outcomes over baseline.

Results: 207/233 placebo and sham subjects completed the trial. Both placebo and sham subjects showed clinically relevant improvements (>10%) in all PROs from baseline at the first timepoint persisting through Week 24. No clinically meaningful or statistically significant differences were evident between the groups at any timepoint.

Conclusion: No differences were observed in PROs of knee OA subjects who received IA placebo or sham injections over 24 weeks. These data suggested that the effects were “contextual,” meaning that they resulted from the injection procedure rather than from direct therapeutic placebo effects in the joint. Therefore, IA knee OA drugs that are in development should achieve statistically/clinically meaningful improvements in PROs over placebo to establish therapeutic benefit.

Significance/Clinical Relevance: The improvements in patient-reported outcomes observed after placebo injection in knee osteoarthritis trials appear to be contextual. Knee osteoarthritis therapies should show meaningful symptomatic improvements over placebo to establish therapeutic benefit.