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A 52 Week Randomized, Double-Blind Phase 2 Study of Intra-Articular, Wnt Pathway Inhibitor (SM04690) for Osteoarthritis

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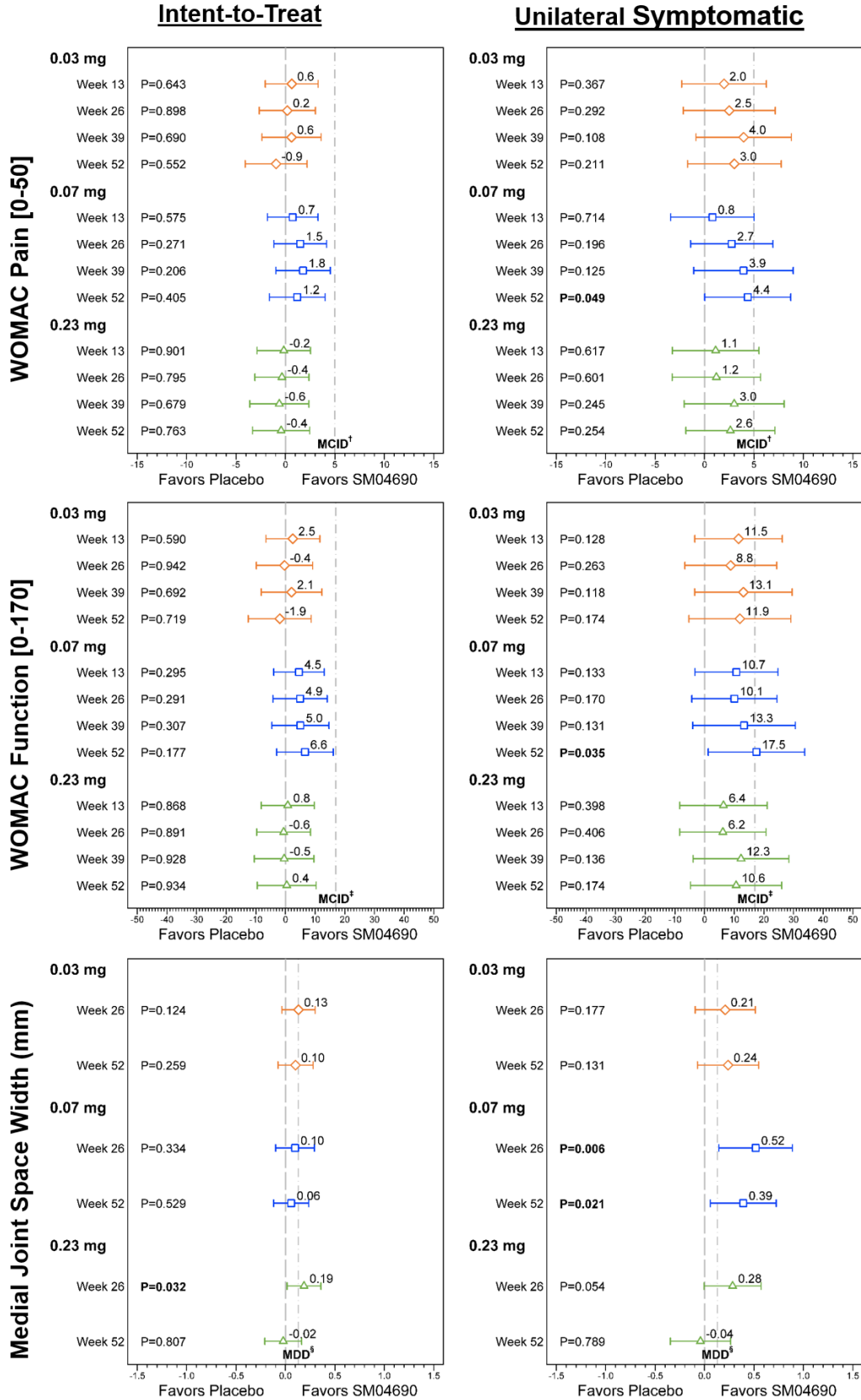
Purpose: Wnt signaling is upregulated in osteoarthritis (OA) and involved in cartilage degradation. SM04690 is a small molecule Wnt pathway inhibitor in development as a disease modifying osteoarthritis drug for knee OA. A phase 2a study was conducted to identify a target population and optimize dose. Primary endpoint was change from baseline in WOMAC Pain at Week 13. Secondary endpoints included change from baseline in WOMAC Pain, Function, and change in radiographic medial compartment joint space width (mJSW) at Week 52.

Methods and Materials: Kellgren-Lawrence (KL) grades 2-3 knee OA subjects received a single 2 mL injection of SM04690 0.03 mg, 0.07 mg, 0.23 mg or saline (PBO) in target (most painful) knees. WOMAC Pain and Function subscores were measured at Weeks 0, 4, 13, 26, and 52. Knee radiographs (PA, weight-bearing, positioned) were taken at Weeks 0, 26, 52. Analysis of covariance adjusted for baseline with multiple imputation in the intent-to-treat (ITT) population and a pre-specified subgroup analysis of subjects with unilateral symptoms (US subgroup) were performed.

Results: 455 subjects (mean age 60.3 [\pm 8.7], BMI 29.9 [\pm 4.6] kg/m², female 58.9%, KL 3 [64.4%], US [36.0%]) were enrolled. SM04690 was well tolerated and adverse events numbers were similar to PBO. In ITT, minimally clinically important differences from baseline were seen in all WOMAC subscores at all timepoints, but these differences were not significant compared to PBO. In the US subgroup (n=164), 0.07 mg SM04690 showed statistically significant improvements in WOMAC Pain (-4.4, $P=0.049$), WOMAC Function (-17.5, $P=0.035$) and mJSW (0.39 mm, $P=0.021$) at Week 52 compared to PBO (Figure).

Conclusion: While the primary endpoint was not met, a target population of subjects with unilateral symptoms was identified. Further investigation in the 0.07 mg SM04690 unilateral symptomatic population is warranted based upon significant improvements in WOMAC Pain, Function and mJSW demonstrated at Week 52 compared to PBO.

Improvement of SM04690 over Placebo



†Minimal clinically important difference (MCID) defined as 10% of WOMAC Pain scale, or 5 points. ‡MCID defined as 10% of WOMAC Function scale, or 17 points. §Minimum detectable difference (MDD) defined as 0.13 mm of mJSW.