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Results from a 52-Week Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Wnt Pathway Inhibitor (SM04690) for Knee Osteoarthritis Treatment

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Problem statement: Wnt signaling is upregulated in osteoarthritis (OA) and is involved in cartilage degradation. SM04690, a small molecule Wnt pathway inhibitor, is in development as a potential disease-modifying OA drug (DMOAD) for knee OA. A phase 2, multicenter, 52-week, placebo (PBO)-controlled trial was conducted to identify a target population, determine optimal dose, and assess safety.

Methods: Knee OA subjects, Kellgren-Lawrence (KL) grades 2-3, received a single 2-mL injection of SM04690 (0.03 mg, 0.07 mg, 0.23 mg) or PBO in their target (most painful) knee. WOMAC Pain and Function were assessed (Weeks 0, 4, 13, 26, 39, 52) and fixed flexion radiographs (QuAP™ positioned; Weeks 0, 26, 52) assessed medial joint space width (mJSW). Analysis of covariance adjusted for baseline with multiple imputation in the intent-to-treat (ITT) population and pre-specified subgroup analyses of subjects with unilateral symptoms with or without widespread pain (UNI and UNI WP-, respectively) were performed.

Results: 455 subjects (mean age 60.3 [±8.7] years, BMI 29.9 [±4.6] kg/m^2, female 58.9%, KL grade 3 [64.4%], unilateral symptomatic OA [36.0%]) were enrolled. SM04690 appeared well-tolerated, and incidence of adverse events was similar in treatment and PBO groups.

In ITT, minimum clinically important differences (>10% full range) in WOMAC Pain and Function compared with baseline were seen in all groups at all timepoints. In 0.07 mg UNI, at 52 weeks, WOMAC Pain (4.4; P=0.049), and Function (17.5, P=0.035) were significantly improved compared with PBO. In 0.07 mg UNI WP-, at Weeks 26, 39, and 52, WOMAC Pain (4.6, P=0.039; 5.9, P=0.042; and 5.6, P=0.025, respectively) and Function (16.3, P=0.027; 19.7, P=0.035; and 22.8, P=0.017, respectively) were significantly improved compared with PBO (Figure).

At 26 and 52 weeks, 0.07 mg UNI (0.5 mm, P=0.006 and 0.4 mm, P=0.021, respectively) and 0.07 mg UNI WP- (0.5 mm, P=0.016 and 0.4 mm, P=0.032, respectively) demonstrated significant increases from baseline in mJSW compared with PBO (Figure).

Conclusion: A target subgroup of unilateral symptomatic knee OA subjects was identified. Findings support SM04690 as a potential DMOAD, especially at the 0.07 mg dose in unilateral symptomatic subjects without WP.

Disclosures: Y. Yazici, C. Swearingen, A. DiFrancesco, and J. Tambiah are shareholders and employees of Samumed, LLC.

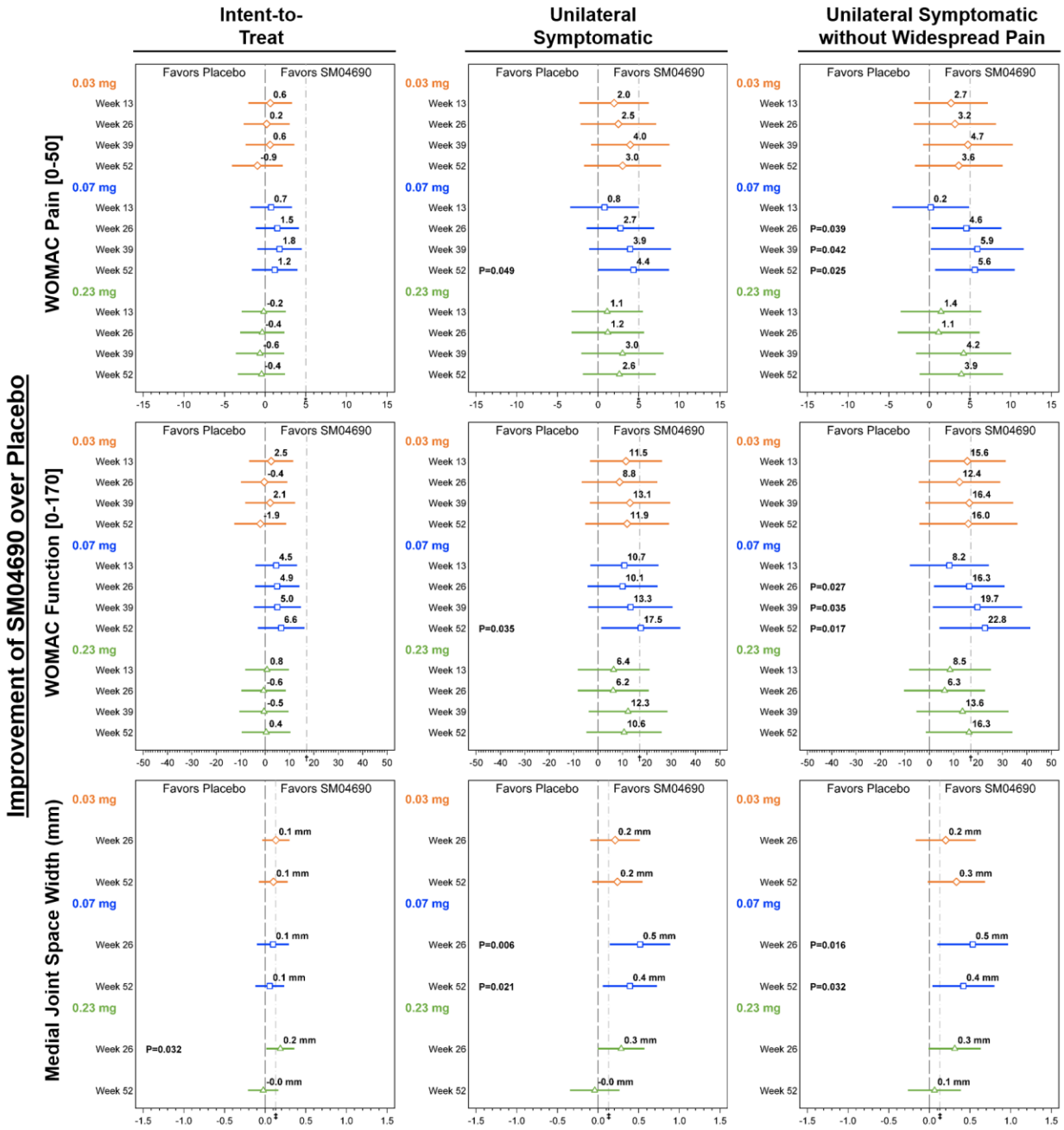

Figure. Ladder plots depicting mean improvement (and 95% confidence intervals) of SM04690 over placebo adjusted for baseline.
*Minimal clinically important difference (MCID) defined as 10% of WOMAC Pain scale, or 5 points. †MCID defined as 10% of WOMAC Function scale, or 17 points.
‡Minimum detectable difference (MDD) defined as 0.13 mm of medial joint space width.