Accepted as poster #SAT0586 at Annual European Congress of Rheumatology (EULAR) 2018, Amsterdam, Netherlands, June 13-16, 2018

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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Background: Knee osteoarthritis (OA) is characterized by pain, disability and joint deformity due to articular cartilage degradation and bone remodeling. Wnt signaling is involved in these cellular processes. SM04690, a small molecule Wnt pathway inhibitor, is in development as a potential disease-modifying OA drug (DMOAD) for knee OA.

Objective: A phase 2, multicenter, 52-week, placebo-controlled (PBO) 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 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 was conducted using multiple imputation for missing data. Exploratory subgroups included: 1) unilateral symptomatic subjects (pre-specified; determined by history and examination) and 2) unilateral symptomatic subjects without comorbid pain (post-hoc; Widespread Pain Index≤4, Symptom Severity≤2 [WP-]).

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, 91% with radiographic bilateral OA. Seventeen serious adverse events, all unrelated to SM04690, were reported. The primary endpoint of Week 13 change from baseline in WOMAC Pain was not met. In ITT, at all timepoints, minimum clinically important differences (>10% full range) in WOMAC Pain and Function compared to baseline were seen in all groups. In 0.07 mg unilateral symptomatic subjects, at 52 weeks, WOMAC Pain (4.4; *P*=0.049), and Function (17.5, *P*=0.035) were significantly improved compared to PBO. In 0.07 mg unilateral symptomatic WP- subjects 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 to PBO (**Figure 1**). At 26 and 52 weeks, 0.07 mg unilateral symptomatic (0.5 mm, *P*=0.006 and 0.4 mm, *P*=0.021, respectively) and 0.07 mg unilateral symptomatic WP- (0.5 mm,

P=0.016 and 0.4 mm, *P*=0.032, respectively) subgroups demonstrated significant increases from baseline in mJSW compared to PBO (**Figure 1**).

Conclusion: A target subgroup of unilateral symptomatic knee OA subjects and potential optimal dose (0.07 mg) of SM04690 were identified. Clinical and radiographic outcomes suggested that SM04690 has potential as a DMOAD, especially in subjects with unilateral symptomatic WP-knee OA. Further studies are ongoing.

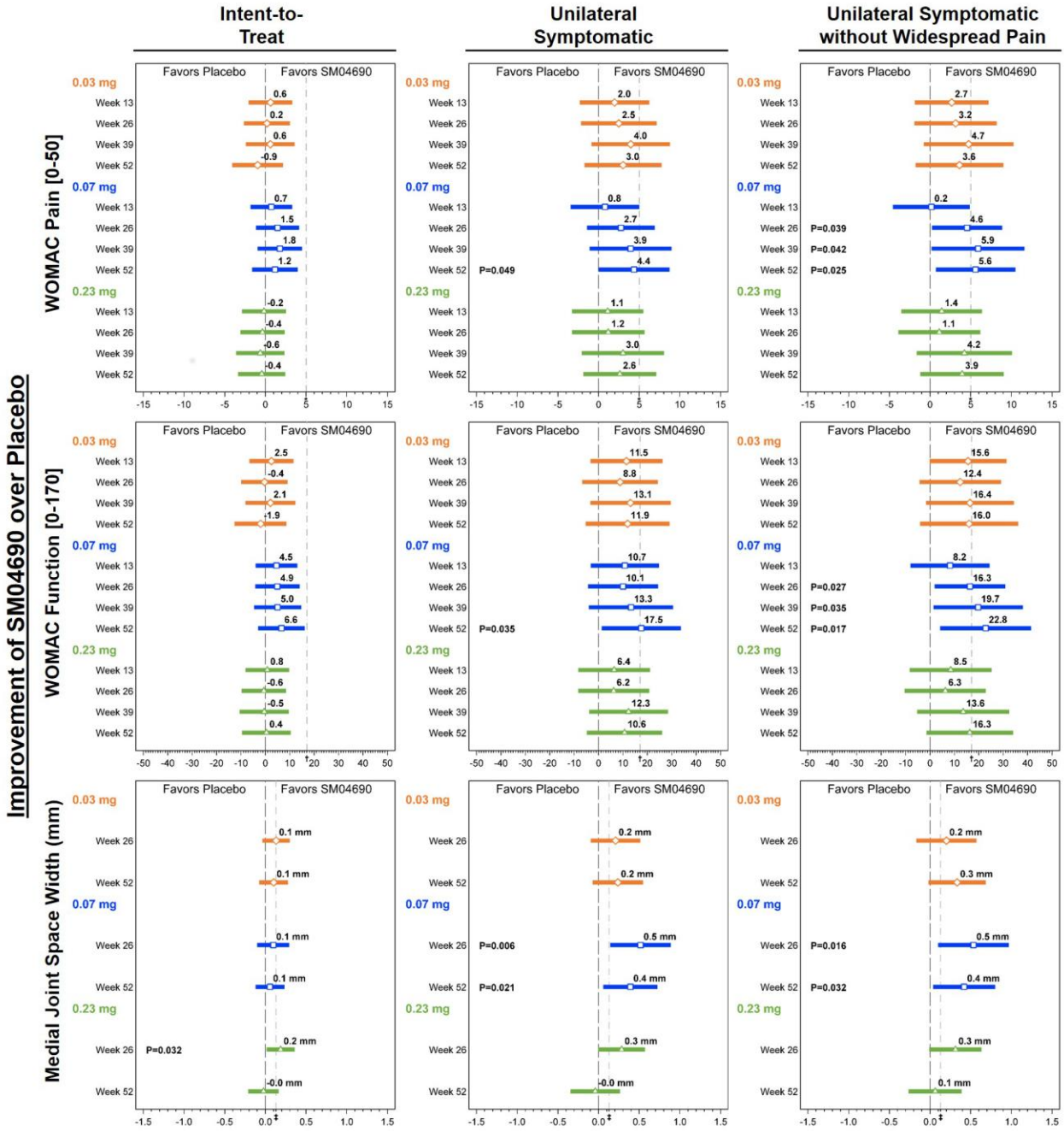

Figure 1. Ladder plots depicting mean improvement (and 95% confidence intervals) of SM04690 over placebo adjusted for baseline.
*Minimal clinically important difference (MCID) defined as 10% of WOMAC Pain scale, or 5 points. †MCID defined as 10% of WOMAC Function scale, or 17 points.
‡Minimum detectable difference (MDD) defined as 0.13 mm of mJSW.