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

Authors: Y. Yazici,[1] T.E. McAlindon,[2] A. Gibofsky,[3] N.E. Lane,[4] D. Clauw[5], N. Skrepnik,[6] E. Armas,[7] C.J. Swearingen,[1] A. DiFrancesco,[1] J.R.S. Tambiah,[1] M.C. Hochberg[8]

Affiliations: [1]Samumed, San Diego, CA; [2]Tufts Medical Center, Boston, MA; [3]Weill Cornell Medicine and Hospital for Special Surgery, New York, NY; [4]UC Davis Medical Center, Davis, CA; [5]University of Michigan, Ann Arbor, MI; [6]Tucson Orthopedic Institute, Tucson, AZ; [7]Well Pharma Medical Research, Miami, FL; [8]University of Maryland School of Medicine, Baltimore, MD

Background/Purpose: 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 and inflammation. SM04690, a small molecule Wnt pathway inhibitor, is in development as a potential disease modifying drug for knee OA. A phase 2, multicenter, 52-week, randomized, double-blind, placebo-controlled (PBO) trial was conducted to determine the safety and efficacy of SM04690.

Methods: Knee OA subjects with Kellgren-Lawrence (KL) grades 2-3, received a single 2 mL injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or PBO in target (most painful) knees. Western Ontario and McMaster Universities Arthritis Index Outcome (WOMAC) Pain [0-50] and Function [0-170] were assessed at Weeks 0, 4, 13, 26, 39 and 52 and radiographs taken at Weeks 0, 26 and 52 for medial joint space width (mJSW). Analysis of covariance adjusted for baseline in the intention-to-treat (ITT) population was conducted with multiple imputation. Two subgroups were explored: 1) unilateral symptomatic knee OA subjects as determined by investigator through history and examination (pre-specified) and 2) unilateral symptomatic knee OA subjects without widespread pain (Widespread Pain Index ≤4 and Symptom Severity ≤2 [WP], post-hoc).

Results: 455 subjects (mean age 60.3 [±8.7], BMI 29.9 [±4.6] kg/m^2, female 58.9%, KL 3 [64.4%], unilateral symptomatic OA [36.0%]) were enrolled. Serious adverse events, all deemed unrelated to SM04690, were reported in 17 (3.7%) subjects (4.5% [0.03 mg], 3.5% [0.07 mg], 3.8% [0.23 mg], 2.8% [PBO]).

In the ITT population, clinically meaningful outcomes improvements (>10% full range) compared to BL were seen in all groups at all timepoints. In unilateral symptomatic group, 0.07 mg had significant improvements in WOMAC Pain with clinically meaningful and significant improvements in WOMAC Function compared to PBO at Week 52. In unilateral symptomatic patients without WP, 0.07 mg had clinically meaningful and significant improvements in WOMAC Pain and Function compared to PBO at Weeks 26, 39 and 52 (**Figure**). At Week 52 in the ITT population, mean changes in mJSW were -0.14 mm in PBO, 0.10 mm in 0.03 mg *(NS*), 0.06 mm in 0.07 mg (*NS*), and -0.02 mm in 0.23 mg (*NS*).

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Conclusion: In this phase 2 study, improvements compared to PBO in WOMAC Pain and Function were seen in study subgroups of unilateral symptomatic and unilateral symptomatic without WP. SM04690 maintained or improved mJSW over 52 weeks. Radiographic and clinical outcomes suggested SM04690 has potential as a DMOAD for knee OA treatment.

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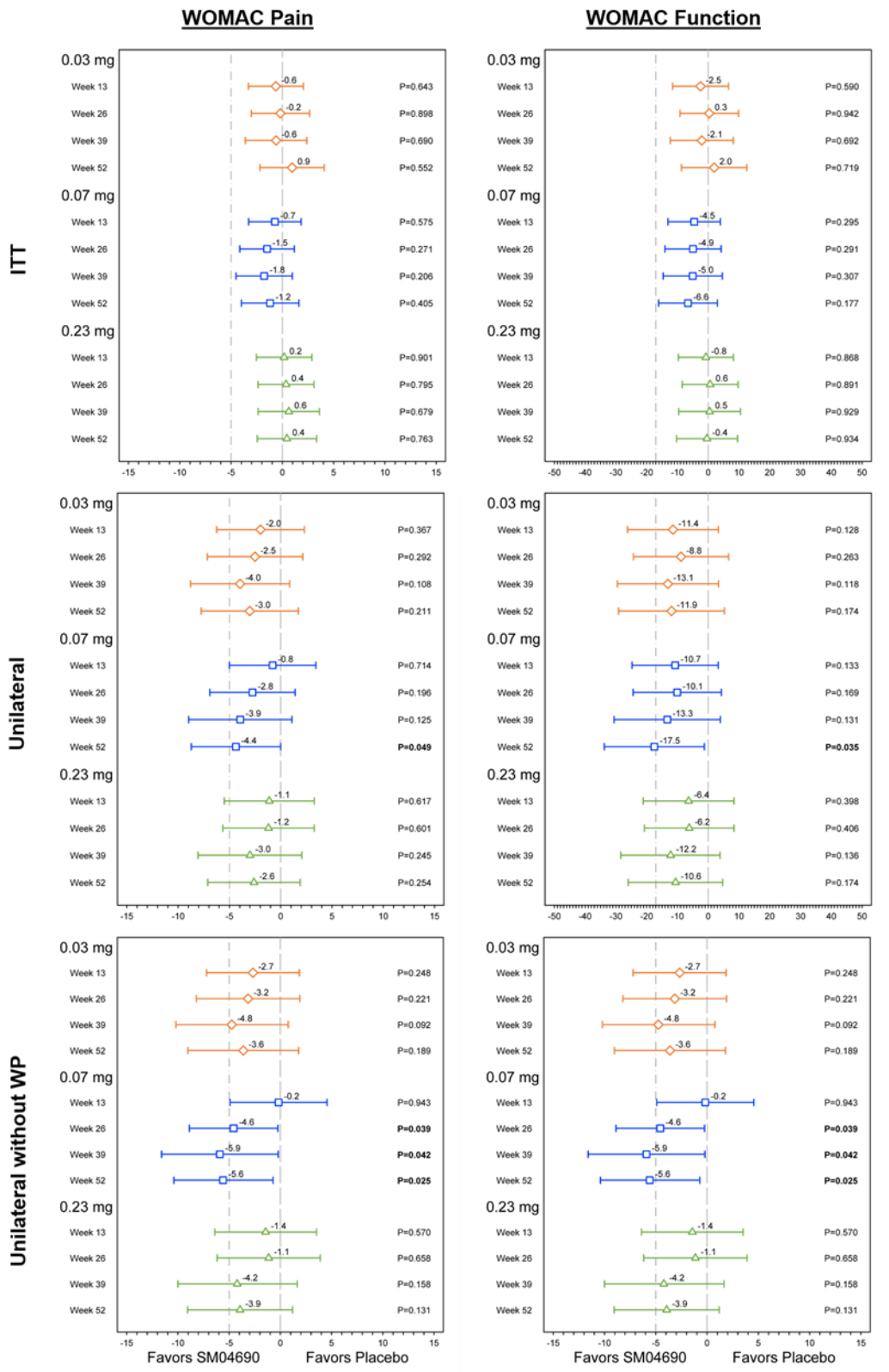

Figure. Ladder plots depicting mean imputed change from baseline in WOMAC Pain and Function between treatment groups and placebo adjusting for baseline. The x-axis represents change in WOMAC subscore of treatment group vs. placebo; 0 equals no effect (long dash) and 10% of outcome's minimal clinical important difference (short dash). Error bars represent 95% confidence interval.

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