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Treatment of Knee Osteoarthritis with SM04690 Improved WOMAC A1 “Pain on Walking” – Results from a 52-Week, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Intra-Articular, Wnt Pathway Inhibitor

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Background: Knee osteoarthritis (OA) is characterized by pain, functional limitation, and physical disability due to articular cartilage degradation and bone remodeling. Wnt signaling is involved in these cellular processes. SM04690, a small molecule, intra-articular (IA), Wnt pathway inhibitor, is in development for treatment of knee OA as a potential disease-modifying OA drug (DMOAD). A phase 2, multicenter, 52-week, randomized, double-blind, placebo (PBO)-controlled trial of SM04690 was conducted. Safety and efficacy outcomes including the Western Ontario and McMaster Universities Arthritis Index (WOMAC) were evaluated.

Methods: Subjects with ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, received a single 2 mL IA injection of SM04690 (0.03, 0.07 or 0.23 mg) or PBO in the target (most painful) knee. WOMAC was assessed at baseline and 4, 13, 26, 39 and 52 weeks post-injection. WOMAC question A1, (“how much pain have you had when walking on a flat surface?”), was analyzed as a post-hoc exploratory outcome. Analysis of covariance adjusted for baseline WOMAC A1 score in the intent-to-treat (ITT) population was conducted. Two subgroups identified in the primary analysis (Yazici Y et al., *Arthritis Rheumatol* 2017) were also explored: 1) subjects with unilateral symptomatic knee OA (pre-specified) and 2) subjects with unilateral symptomatic knee OA without widespread pain or comorbid symptoms (Widespread Pain Index ≤ 4 and Symptom Severity ≤ 2 [WP-], post-hoc).

Results: 455 subjects (mean age 60.3 [± 8.7] years, BMI 29.9 [± 4.6] kg/m², female 58.9%, KL 3 [64.1%], unilateral symptomatic OA [36.0%]) were enrolled; 402 [88.4%] completed the study. No safety signals were observed.

For WOMAC A1, in the ITT population, no statistically significant differences between treatment groups and PBO were seen, although the 0.07 mg dose demonstrated improvements compared with PBO at all timepoints (Figure). In unilateral symptomatic subjects, 0.07 mg showed significant improvements in WOMAC A1 compared with PBO at Weeks 39 (-1.2, 95% CI [-2.3, -0.0], P=0.043) and 52 (-1.1, 95% CI [-2.0, -0.1], P=0.027).

In unilateral symptomatic WP- subjects, the 0.07 mg dose showed significant improvements in WOMAC A1 compared with PBO at Weeks 26 (-1.2, 95% CI [-2.1, -0.2], P=0.015), 39 (-1.8, 95% CI [-3.0, -0.6], P=0.004) and 52 (-1.4, 95% CI [-2.5, -0.4], P=0.010).

Conclusion: In this phase 2 study, improvements compared with PBO in WOMAC A1 were seen in clinically relevant unilateral symptomatic and unilateral symptomatic WP- subgroups. The

improvements seen in this combined, multi-dimensional outcome of pain and function suggested SM04690 has a potential role in the treatment of signs and symptoms of knee OA.

Improvement of SM04690 over Placebo

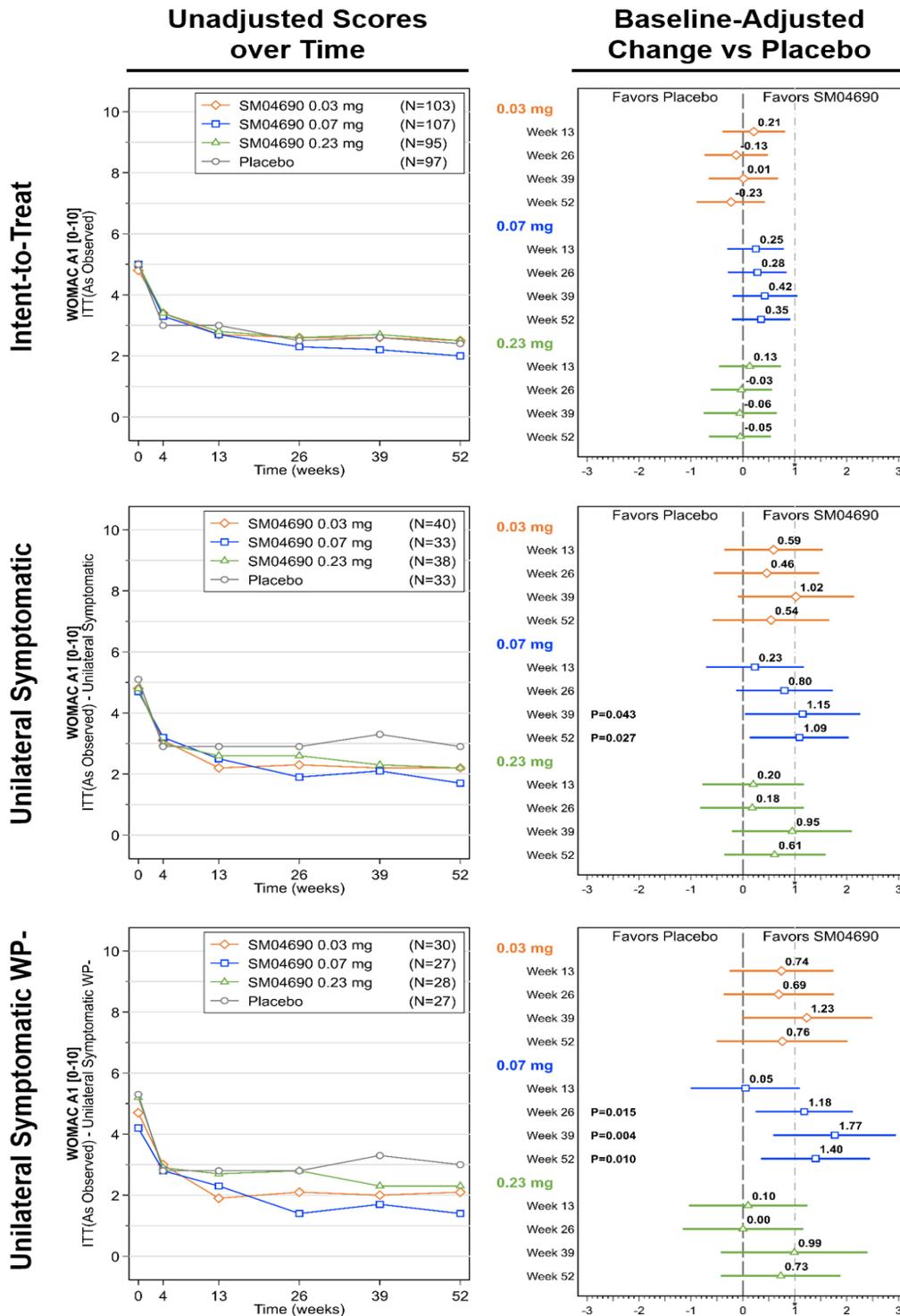


Figure. Change and Ladder plots depicting average WOMAC A1 improvement in SM04690 over placebo adjusted for baseline WOMAC A1.

*Minimal clinically important difference (MCID) defined as 10% of WOMAC A1, or 1 point.