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## **Assessment of Health-Related Quality of Life in a 52-Week, Phase 2, Randomized, Controlled Trial of a Novel, Intra-Articular, Wnt Pathway Inhibitor (SM04690) for Treatment of Knee Osteoarthritis**

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**Background/Purpose:** SM04690, a small molecule, intra-articular (IA) Wnt pathway inhibitor, is in development for knee OA treatment. A phase 2, 52-week, trial evaluated changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain & Function and medial joint space width (mJSW) by x-ray. Health-related quality of life (HRQoL) was measured by Short Form Survey SF-36. The objective of this study was to assess the effect of SM04690 treatment on HRQoL.

**Methods:** Subjects with ACR-defined knee OA, Kellgren-Lawrence grades 2-3, received 2 mL IA SM04690 (0.03, 0.07, 0.23 mg) or placebo (PBO) in the target (most painful) knee. SF-36 was assessed (Weeks 0, 4, 13, 26, 39, 52). Baseline-adjusted analysis of covariance (with multiple imputation for missing data) was conducted in the intent-to-treat (ITT) population, with improvements  $\geq$  minimum clinically important differences (MCID) noted. Two subgroups were explored: 1) unilateral symptomatic knee OA (pre-specified: UNI) and 2) unilateral symptomatic knee OA without widespread pain or comorbid symptoms (Widespread Pain Index  $\leq 4$  and Symptom Severity  $\leq 2$ , post-hoc: UNI-WP).

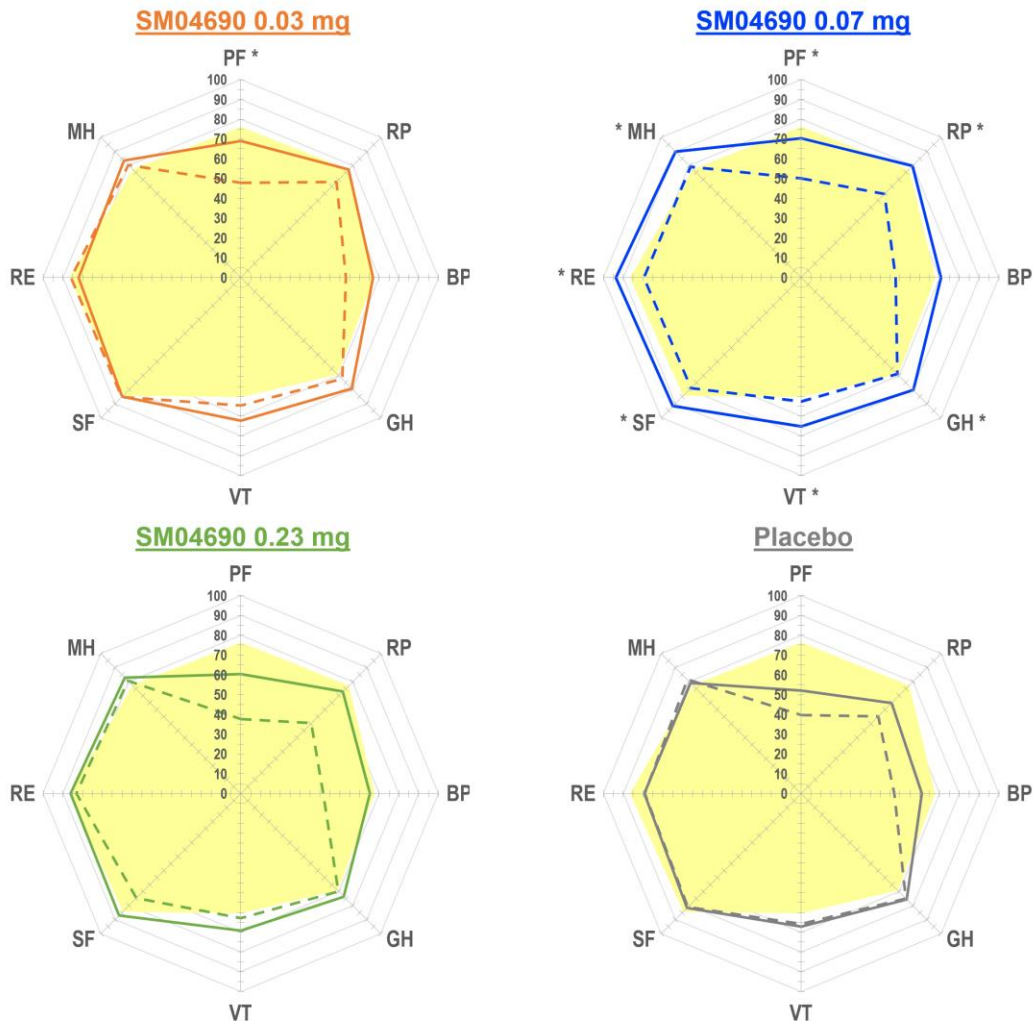
**Results:** 455 subjects (mean age 60.3 [ $\pm 8.7$ ] years, BMI 29.9 [ $\pm 4.6$ ] kg/m<sup>2</sup>, female 58.9%, KL 3 [64.4%], with UNI OA [36.0%]) were enrolled (n=402 [88.4%] completers).

In ITT, improvements from baseline were reported in 0.03 mg (n=112), 0.07 mg (n=117), 0.23 mg (n=110) and PBO (n=116) groups, with scores  $\geq$  MCID in Physical Component Summary (PCS), Physical Functioning (PF), Role-Physical (RP), and Bodily Pain (BP) domains at Weeks 13 to 52. Improvements vs PBO reported in 0.07 mg at Week 13 were significant in Mental Component Summary (MCS [P=0.024]) and Role-Emotional (RE [P=0.036]) domains.

In UNI subgroup, at Week 52, all groups reported improvements  $\geq$  MCID as in the ITT across all domains with 0.07 mg (n=35) significant vs PBO (n=39) in MCS (P=0.015), General Health (GH [P=0.028]), RE (P=0.009), and Mental Health (MH [P=0.011]) domains.

In UNI-WP subgroup at Week 52, all groups reported changes  $\geq$  MCID in PCS, PF, RP, and BP domains, and across all domains with 0.07 mg. Improvements vs PBO (n=32) with 0.03 mg (n=34) were significant in PF (P=0.025), and with 0.07 mg (n=29) in MCS (P=0.002) and all domains excluding BP (PF [P=0.025], RP [P=0.027], GH [P=0.035], Vitality (VT [P=0.014]), Social Functioning (SF [P=0.028]), RE [P=0.003], MH [P=0.003]), which met or exceeded normative scores across all domains, except PF (Figure).

**Conclusion:** In this phase 2 trial, subjects receiving 0.07 mg SM04690 reported statistically significant and clinically meaningful HRQoL improvements in the ITT and subgroup analyses compared with PBO. In the UNI and UNI-WP subgroups at Week 52, HRQoL improvements mirrored changes observed from analyses in WOMAC Pain and Function and mJSW (Yazici et al., *Arthritis Rheumatol* 2017) and support further investigation of SM04690 for treatment of knee OA.



**Figure.** Spidergrams of baseline (dash line) and Week 52 (solid line) in each SF-36 domain score over age- and gender-matched normative scores (yellow) within the Unilateral Symptomatic without Widespread Pain subgroup analysis.

\* Baseline-adjusted ANCOVA reported analysis compared to PBO with P < 0.05

PF: Physical Functioning; RP: Role-Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role-Emotional; MH: Mental Health