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Radiographic outcomes were associated with pain and function responses: post-hoc analysis from a phase 2 study of Wnt pathway inhibitor, SM04690, for knee osteoarthritis

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Introduction: SM04690, a small molecule intra-articular (IA) Wnt pathway inhibitor, is in development as a potential disease-modifying osteoarthritis drug (DMOAD). A phase 2, 52-week, randomized controlled trial evaluated changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain & Function and medial joint space width (mJSW). It was hypothesized that observed mJSW improvement was associated with increased probability of symptomatic response. To test this hypothesis, a post-hoc concordance analysis was performed between mJSW change and WOMAC Pain & Function responders.

Objective: To evaluate concordance between mJSW and WOMAC Pain and Function responders.

Methods: Subjects with knee OA, Kellgren-Lawrence (KL) grades 2-3, received 2 mL IA SM04690 (0.03, 0.07, or 0.23 mg) or placebo (PBO) in the target (most painful) knee. WOMAC Pain [0-50] and Function [0-170] were assessed at Weeks 0, 4, 13, 26, 39, and 52 and knee radiographs at Weeks 0, 26, and 52. Baseline-adjusted logistic regression group analyses estimated concordance between mJSW change and pain and function changes for responders (defined as achieving both WOMAC Pain and Function improvements of ≥50% and ≥20 [scaled to 100] points). Receiver-operator characteristic (ROC) curves were generated with area under the curve (AUC) to estimate concordance (AUC > 0.7 = 'acceptable' and > 0.8 = 'excellent' concordance). Intention-to-treat (ITT) and two subgroups were analyzed: 1) unilateral symptomatic knee OA (pre-specified; UNI) and 2) unilateral symptomatic knee OA without widespread pain or comorbid symptoms (Widespread Pain Index ≤4 and Symptom Severity ≤2; post-hoc; UNI-WP). 455 subjects were enrolled (mean age 60.3 [±8.7] years, body mass index 29.9 [±4.6] kg/m^2, 268 [58.9%] female, 292 [64.2%] KL grade 3, and 164 [36.0%] UNI).

Results: In ITT, approximately 53% were responders across all groups. In UNI, 20 (56%) 0.03 mg; 20 (63%) 0.07 mg; 23 (64%) 0.23 mg; and 15 (47%) PBO, and in UNI-WP, 15 (56%) 0.03 mg; 16 (62%) 0.07 mg; 19 (70%) 0.23 mg; and 12 (44%) PBO were responders. The 0.03 mg (UNI, P=0.104; UNI-WP, P=0.047) and 0.07 mg (UNI, P=0.009; UNI-WP, P=0.013) doses demonstrated increased mJSW compared with PBO at Week 52. In ITT, no treatment group achieved ROC AUC > 0.7 (Figure). In UNI, the 0.07 mg dose demonstrated 'acceptable' (AUC=0.783), and in UNI-WP, the 0.07 mg dose showed 'excellent' (AUC=0.825) concordance between mJSW change and response.

Conclusion: In a post-hoc analysis of UNI and UNI-WP 0.07 mg cohorts, changes in mJSW were concordant with WOMAC Pain and Function responses. Concordance analysis can potentially characterize the strength of relationship between radiographic change and clinical outcomes when investigating potential DMOAD treatments in knee OA.

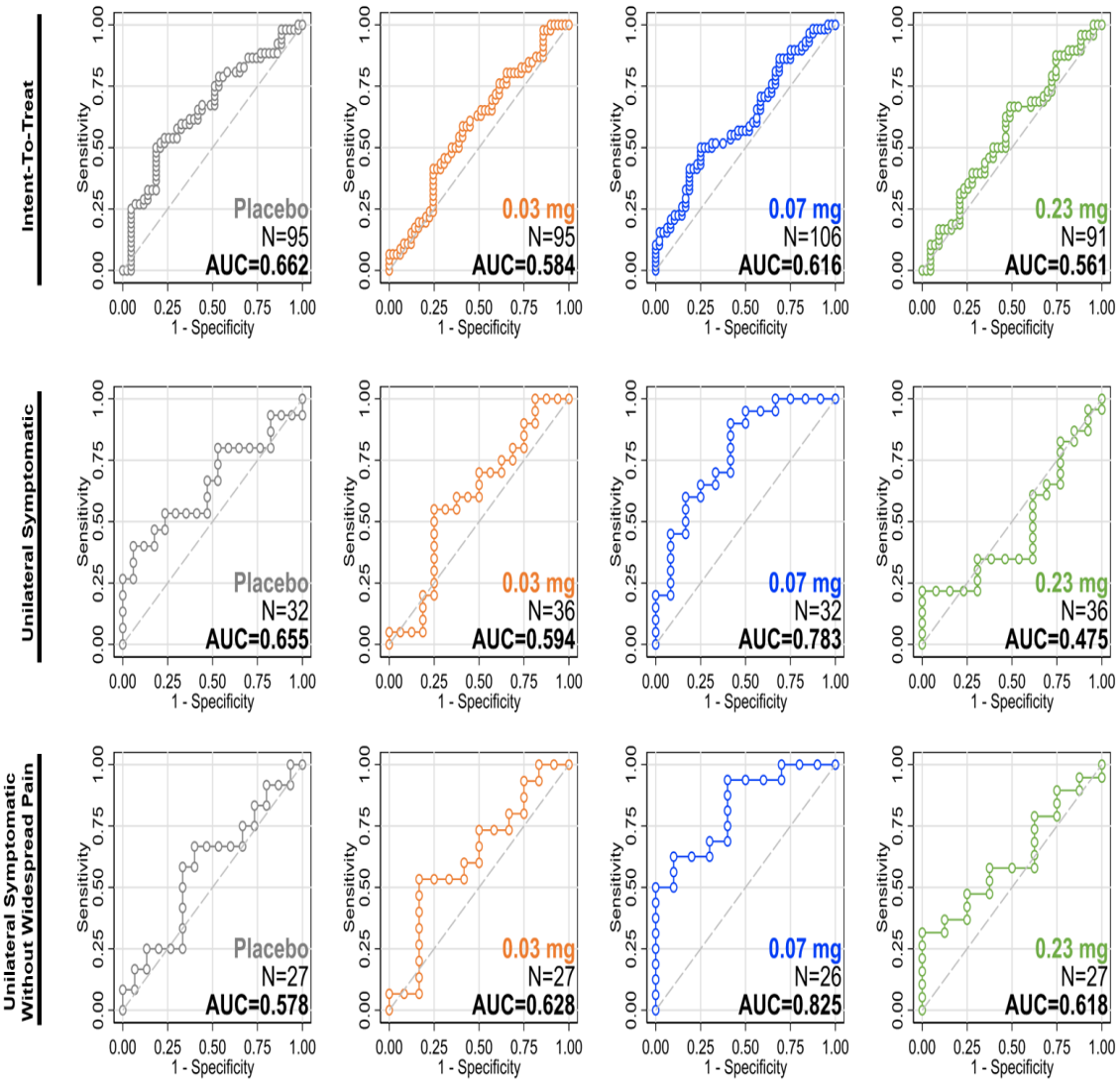

Figure. ROC Curves Illustrating Concordance between WOMAC Pain and Function Response and mJSW Change by Treatment Group and Analysis Group