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

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Background: SM04690, a small molecule intra-articular (IA) Wnt pathway inhibitor, is in development as a potential disease-modifying knee osteoarthritis drug. 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 increases led to WOMAC subscore responder improvements. To address this question, a concordance analysis was performed.

Objective: To evaluate concordance, or level of agreement, between mJSW and WOMAC Pain and Function "responders."

Methods: Subjects with ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, received 2 mL IA SM04690 (0.03, 0.07, 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 who achieved both WOMAC Pain and Function improvements of ≥50% and ≥20 [scaled to 100] points. Receiver-operator characteristic (ROC) curves were generated with area under curve (AUC) to estimate concordance (AUC > 0.7 = 'acceptable' and > 0.8 = 'excellent' concordance[1]). 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).

Results: 455 subjects were enrolled (mean age 60.3 [±8.7] years, BMI 29.9 [±4.6] kg/m^2, 268 [58.9%] female, 292 [64.2%] KL Grade 3, 164 [36.0%] UNI knee OA). In the 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, NS; UNI-WP, P=0.047) and 0.07 mg (UNI, P=0.009; UNI-WP, P=0.013) doses also demonstrated increased mJSW compared to PBO at Week 52. In ITT, no treatment group achieved AUC > 0.7 (Figure). In UNI, the 0.07 mg dose demonstrated acceptable concordance between response and mJSW (AUC=0.783). In UNI-WP, the 0.07 mg dose showed 'excellent' concordance (AUC = 0.825).

Conclusions: In this post-hoc analysis, treatment with SM04690 maintained or increased mJSW in the 0.03 and 0.07 mg doses compared to PBO over 52 weeks. In UNI and UNI-WP 0.07 mg cohorts, changes in mJSW were concordant with WOMAC Pain and Function response.

Reference: [1]Hosmer DW & Lemeshow S. (2000). Applied Logistic Regression. New York: John-Wiley & Sons, Inc.

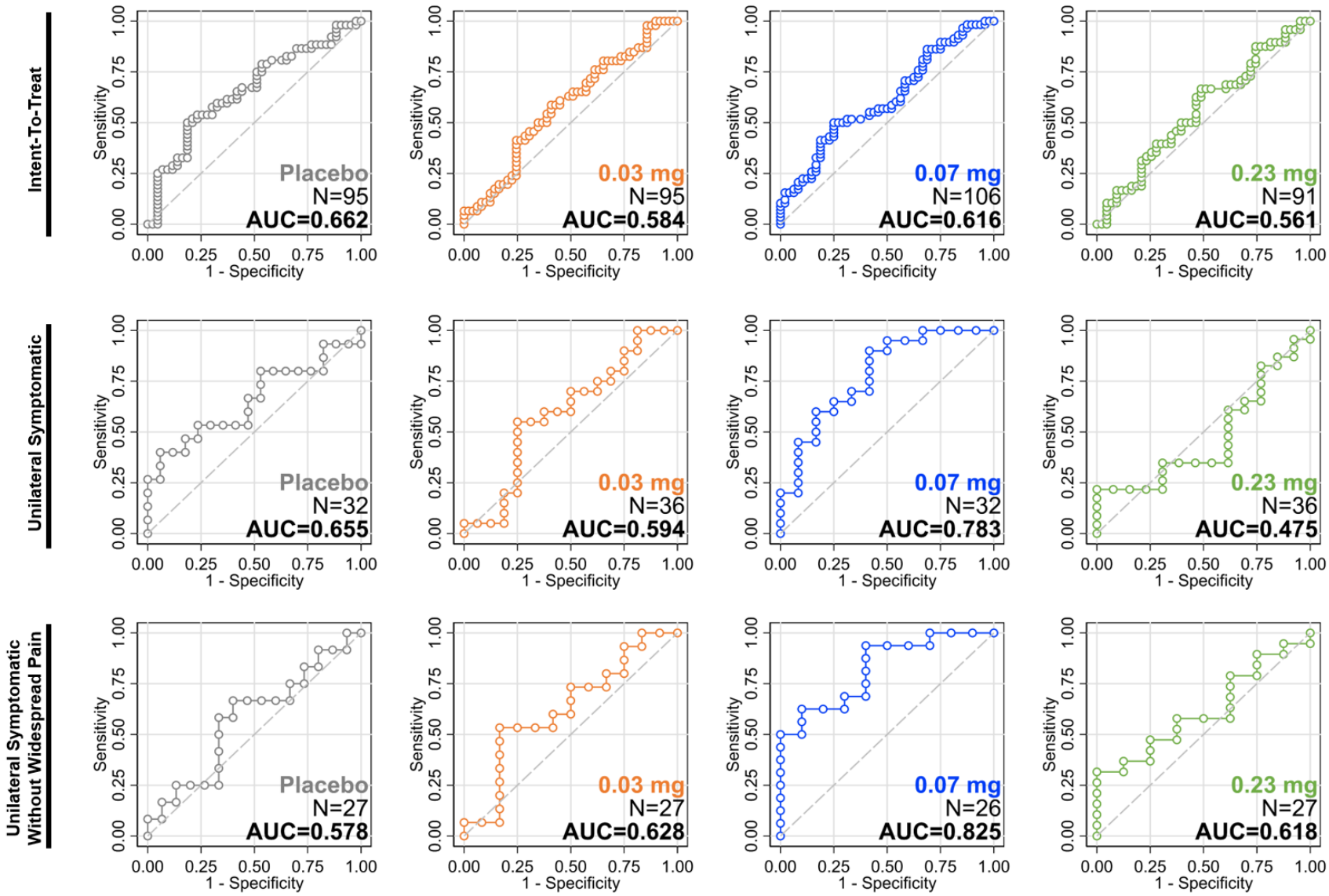

Figure. ROC Curves Illustrating Concordance between WOMAC Pain and Function Response and mJSW Change by Treatment Group and Analysis Group