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). 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/m², 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.

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