

Interim Results from a 52 week Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Intra-Articular, Wnt Pathway Inhibitor (SM04690) for the Treatment of Knee Osteoarthritis

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Introduction: Knee osteoarthritis (OA) is characterized by pain, disability and joint deformity due to articular cartilage degradation and bone remodeling. Increased Wnt signaling amplifies these cellular processes and inflammation. SM04690, a small molecule Wnt pathway inhibitor, is in development as a potential disease modifying drug for knee OA. A phase 2, multicenter, 52-week, randomized, double-blind, placebo-controlled (PBO) trial was conducted to explore the safety and efficacy of SM04690 in knee OA subjects. Interim results from Week 39 are presented.

Methods: This study was approved by institutional review boards and informed consent from all subjects obtained. Subjects with knee OA, Kellgren-Lawrence (KL) grades 2-3, received a single 2 mL injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or PBO in their target (most painful) knee. Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain [0-50] and Function [0-170] subscores were assessed at Weeks 0, 4, 13, 26, 39, 52 and radiographs measuring target knee medial compartment joint space width (mJSW) were taken at Weeks 0, 26, 52. Statistical analysis utilized an ANCOVA adjusted for baseline in the intention-to-treat (ITT) population with multiple imputation. Two subgroups were explored: 1) unilateral symptomatic knee OA subjects (pre-specified and investigator determined) and 2) unilateral symptomatic knee OA subjects with Widespread Pain Index ≤ 4 and Symptom Severity ≤ 2 [WP-] (post-hoc).

Results: 455 subjects (mean age 60.3 [± 8.7], BMI 29.9 [± 4.6] kg/m², female 58.9%, KL 3 [64.4%], unilateral symptomatic OA [36.0%]) were enrolled. Eight serious adverse events, deemed unrelated to drug per investigator, were reported in seven subjects at interim analysis. In the ITT population, minimally important differences (MIDs) ($>10\%$ full range) were seen in all groups at all timepoints in WOMAC Pain and Function compared to baseline (**Fig. 1**). In unilateral symptomatic subjects, improvements in WOMAC Pain and Function for all SM04690 groups compared to PBO were observed, while 0.07 mg-treated unilateral symptomatic WP- subjects showed MID and statistically significant improvements in WOMAC Pain and Function compared to PBO at Weeks 26 and 39 (**Fig. 2**).

At Week 26 in ITT population, mean mJSW changes from baseline were -0.20 [± 0.59] mm in PBO, -0.07 [± 0.62] mm in 0.03 mg, -0.11 [± 0.87] mm in 0.07 mg, and -0.03 [± 0.58] mm in 0.23 mg. In unilateral symptomatic subjects, mean mJSW changes were -0.28 [± 0.63] mm in PBO, -0.05 [± 0.69] mm in 0.03 mg, 0.26 mm [± 0.92] mm in 0.07 mg, and -0.00 [± 0.63] mm in 0.23 mg. In unilateral symptomatic WP- subjects, mean mJSW changes were -0.28 [± 0.66] mm in PBO, -0.06 [± 0.77] mm in 0.03 mg, 0.28 mm [± 1.01] in 0.07 mg, and -0.05 [± 0.60] mm in 0.23 mg (**Fig. 2**). In comparison to PBO at 26 weeks, the 0.23 mg dose in the ITT population ($P=0.036$), the 0.07 mg unilateral symptomatic ($P=0.007$), and 0.07 mg unilateral symptomatic WP- ($P=0.017$) achieved statistical significance.

Discussion: In this phase 2 study, statistically significant improvements in WOMAC Pain and Function were seen, compared to PBO, in both unilateral symptomatic and unilateral symptomatic WP- subgroups for SM04690 0.07 mg dose at weeks 26 and 39. SM04690 0.07 mg dose also improved mJSW at 26 weeks compared to PBO in these subgroups. Radiographic and clinical outcomes suggested SM04690 has potential as a disease modifying osteoarthritis drug for knee OA treatment. Study limitations included this analysis being interim and the study was not formally powered.

Significance: OA therapeutic options are currently limited to symptom relief only. In this study, a single intra-articular injection of SM04690, a Wnt pathway inhibitor, demonstrated improved patient reported outcomes (at 26 and 39 weeks) with maintained or improved mJSW compared to PBO at 26 weeks in relevant knee OA subpopulations. These data suggested SM04690 has potential as a disease modifying OA treatment. Clinical studies are ongoing.

