Abstract:

**Purpose:** The Wnt signaling pathway plays a central role in formation of joint tissues. Altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies[2] in osteoarthritic (OA) joints, increased Wnt signaling stimulates cartilage destroying metalloprotease production and drives resident stem cells to become osteoblasts instead of chondrocytes.[2] In an animal model, inhibition of the Wnt pathway reversed both these processes leading to increased cartilage stability and formation.[3] Therefore, a drug which inhibits the Wnt pathway in knee OA can be potentially disease modifying, compared to current treatments which only relieve the signs and symptoms of OA.

**Methods:** In the completed Phase 1 study, escalation cohorts were dosed as 0.03 mg, 0.07 mg, and 0.23 mg SM04690 per 2 mL injection. A sample size of 20 subjects (randomized, 16 active: 4 placebo) per dosing cohort were selected. Subjects were administered a single IA injection in the target knee on Treatment Day 1 and participated in a follow-up period of 24 weeks. Safety, pharmacokinetics (PK), biomarker, and preliminary efficacy data, including the Western Ontario and McMaster Universities Arthritis Index (WOMAC Likert v3.1), were collected.

**Results:** 61 subjects (average age 62.6 [±5.7] years, female N=41 [67%], average BMI 30.4 [±4.7] kg/m2) were enrolled. Average change in WOMAC Function [score range 0­68] at 12 weeks was -18.4 points for 0.03 mg, -19.2 for 0.07 mg, -17.6 for 0.23 mg and -15.8 for placebo; 24 week change in WOMAC Function was -20.1 points for 0.03 mg, -19.2 for 0.07 mg, -12.0 for 0.23 mg and -15.9 for placebo. Average change in WOMAC Pain [score range 0­20] at 12 weeks was -5.6 points for 0.03 mg, -5.7 for 0.07 mg, -5.7 for 0.23 mg and -4.6 for placebo; 24 week change in WOMAC Pain was -5.0 points for 0.03 mg, -5.3 for 0.07 mg, -4.3 for 0.23 mg and -4.0 for placebo. OMERACT­OARSI strict response was seen as early as Week 1 in 0.03 and 0.07 mg dose groups compared to placebo (41% and 38%, respectively compared to 17%) (Figure); 0.23 mg response was 13%. Greater OMERACT­OARSI strict response was demonstrated in both 0.03 mg and 0.07 mg cohorts compared to Placebo at 12 weeks (56% and 75%, respectively compared to 42%) as well as 24 weeks (73% and 53%, respectively compared to 53%); 0.23 mg response was 44% at week 12 and 25% at week 24.

**Conclusions:** The OMERACT-OARSI strict response data derived from this Phase 1 analysis provided evidence of a potential treatment effect for the novel Wnt inhibitor SM04690 compared to placebo. This data along with safety and other preliminary efficacy support continued development of the molecule into phase 2 studies.

References:

Category (Complete): Clinical Trials
Keyword (Complete): WOMAC ; OMERACT-OARSI Criteria ; Intra-Articular Injection ; Knee Osteoarthritis

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