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Safety, Clinical, and Imaging Outcomes of a Novel, Intra-articular, Injectable, Wnt Inhibitor (SM04690) in the Treatment of Osteoarthritis of the Knee: Exploratory Analysis of Results from a 24 Week, Randomized, Double-Blind, Placebo-Controlled Phase 1 Study

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Background: Wnt signaling pathway plays a central role in joint tissue formation and altered Wnt signaling has been associated with cartilage loss in preclinical/clinical studies.[1] SM04690 is an IA small-molecule inhibitor of the Wnt pathway.

Objectives: To report safety, clinical and imaging efficacy results from a 24-week Phase 1 randomized, double-blind, placebo-controlled, dose-escalation clinical trial of a small-molecule Wnt pathway inhibitor, SM04690, in knee OA.

Methods: Subjects with symptomatic, radiographic knee OA were randomized to receive a single IA injection in the target knee with either 0.03, 0.07, 0.23 mg SM04690 or vehicle (volume 2mLs) in a 4:1 SM04690 (N=16): vehicle (N=4) ratio. Safety, pharmacokinetics, WOMAC Total, Function, Pain subscales and strict OARSI responses[2], and radiographs were collected at baseline and during the 24-week trial. Analyses of efficacy outcomes were conducted using a modified Intention-To-Treat (mITT) baseline-adjusted analysis of covariance (ANCOVA).

Results: A total of 61 subjects (female N=41, mean age 62.6 yrs, BMI 30.4 kg/m^2) were enrolled. Serum levels of SM04690 in all subjects were below limits of detection at all time points. Two dose-limiting toxicities (DLTs), paroxysmal tachycardia, (also an SAE), and increased pain were reported in 0.07 mg cohort. A total of 72 AEs were reported in 28 (46%) subjects; 16 AEs in 8 subjects were considered possibly or probably related to study drug. At Week 24, improved WOMAC Total score was seen for both 0.03 mg and 0.07 mg cohorts (change from baseline, -27.4 and -26.6, respectively) compared to placebo (-21.7). (Figure 1). Odds of having an OMERACT-OARSI strict response in 0.07 mg cohort were higher than in the placebo cohort at

Week 12 (odds ratio=5.7, 95% CI: 1.1, 30.0, *P*=0.04); odds of an OMERACT-OARSI strict response in 0.03 mg cohort were higher than in the placebo cohort at Week 24 (odds ratio=4.8, 95% CI: 0.9, 25.8, *P*=0.07) (Figure 2). Joint space width by radiographs showed no change from baseline to Week 24 in the 0.03 mg cohort (0.00 mm), an increase in the 0.07 mg cohort (0.49 mm), and a decrease in the 0.23 mg cohort (-0.15 mm), with the placebo cohort exhibiting a larger decrease (-0.33 mm). Compared to placebo, the change in joint space width seen in 0.07 mg cohort was statistically significant (*P*=0.02).

Conclusion: These Phase 1 data suggested that an intra-articular injection with a novel Wnt inhibitor SM04690 into the knee of OA patients was safe and well tolerated. SM04690 appeared to potentially improve function, pain and knee joint space width. Additional studies are underway to further evaluate safety, tolerability, efficacy and potential DMOAD properties.

References:

1. Gelse K. *Osteoarthr Cartil* 2002; 20(2): 162-71.
2. Pham T, et al. *J Rheumatol.* 2003;30(7):1648-1654

Figure 1. Change from Baseline in WOMAC Total over time by Cohort

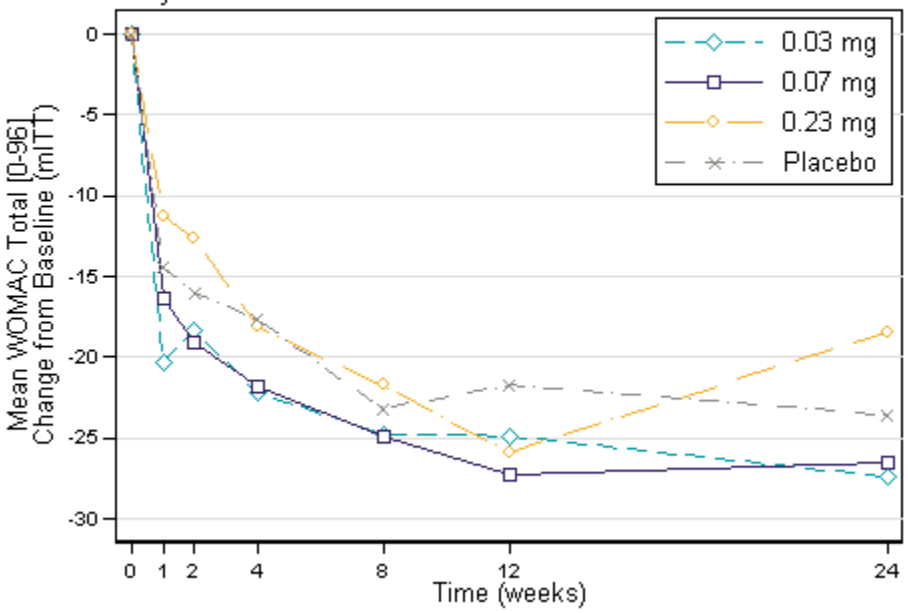

Figure 2. Strict OARSI Response by Cohort as Weeks 12 and 24