**A 52-Week, Randomized, Double-Blind, Phase 2 Study of an Intra-articular Wnt Pathway Inhibitor (SM04690) for Osteoarthritis**

Jeyanesh R. S. Tambiah¹, Sarah Kennedy¹, Christopher Swearingen¹, Ismail Simsek¹, Andreas Gomoll², Deryk G. Jones³, Morgan Jones⁴, and John Bergfeld⁴

¹Samumed, LLC, San Diego, CA  
²Hospital for Special Surgery, New York, NY  
³Ochsner Health System, Jefferson LA  
⁴Cleveland Clinic, Cleveland, OH

**Introduction:** SM04690 is a Wnt pathway inhibitor in development as a potential disease-modifying osteoarthritis drug for knee OA. A phase 2a study was conducted to identify target population and dose. The primary endpoint was change from baseline in WOMAC Pain at Week 13. Secondary endpoints included change in WOMAC Pain, Function, and radiographic medial joint space width (mJSW) at Week 52.

**Methods:** Knee OA subjects with Kellgren-Lawrence (KL) grades 2-3 received a single 2 mL injection of SM04690 (0.03 mg, 0.07 mg, 0.23 mg) or saline (PBO) in the most painful knee. WOMAC Pain and Function subscores were measured (Weeks 0, 4, 13, 26, 52). Knee radiographs (PA, weight-bearing, positioned) were taken (Weeks 0, 26, 52). Analysis of covariance adjusted for baseline with multiple imputation in the intent-to-treat (ITT) population was performed. An additional pre-specified subgroup analysis of subjects with unilateral symptoms (UNI) was studied to limit bias from the contralateral knee.

**Results:** 455 subjects (mean age 60.3 [±8.7] years, BMI 29.9 [±4.6] kg/m², KL 3 [64.4%], UNI [36.0%]) were enrolled. In ITT, minimal clinically important differences from baseline were seen in all WOMAC subscores at all timepoints but were not significant compared to PBO. In the UNI subgroup (n=164), 0.07 mg SM04690 showed statistically significant improvements in WOMAC Pain (-4.4, *P*=0.049), Function (-17.5, *P*=0.035), and mJSW (0.39 mm, *P*=0.021) at Week 52 compared to PBO (Figure).

**Conclusion:** A target population of unilateral symptomatic subjects was identified, in which a dose of 0.07 mg of SM04690 demonstrated significant improvements in WOMAC Pain and Function and mJSW at Week 52 compared to PBO. Clinical studies are ongoing.