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## **SM04690, A Wnt Pathway Inhibitor: Anti-Inflammatory and Cartilage Protective Effects in Preclinical OA Models**

Vishal Deshmukh, Tim Seo, Christopher Swearingen, Yusuf Yazici

Samumed, LLC, San Diego, CA

**Problem statement:** Osteoarthritis (OA) is characterized by pain, swelling, and reduced function in the knee joint. Upregulated Wnt signaling drives OA through synovial inflammation, increased subchondral bone, and thinning cartilage. SM04690, a small molecule Wnt pathway inhibitor that demonstrated chondrogenic and anti-inflammatory properties preclinically, was further evaluated to determine its potential to reduce inflammation, protect cartilage, improve joint health, and modify pain in OA.

**Methods:** Cytokine secretion (IL-6 and TNF- $\alpha$ ) from IL-1 $\beta$ -stimulated and SM04690-treated synovial fibroblasts was measured by ELISA. A single intra-articular injection of SM04690 or vehicle was evaluated in an *in vivo* rat knee monosodium iodoacetate (MIA) OA model. Joint inflammation was evaluated by H&E staining, inflammatory cytokines (IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, TNF- $\alpha$  and IFN- $\gamma$ ) by qPCR, and cartilage protection by qPCR for matrix metalloproteinases (MMPs). Histological evaluation of cartilage health was performed using OARSI score and thickness by Safranin-O staining. Pain was measured as paw withdrawal threshold using Von Frey apparatus and weight distribution using incapacitance meter and analyzed using generalized estimating equation regression.

**Results:** SM04690 dose-dependently inhibited IL-1 $\beta$ -induced cytokine secretion in synovial fibroblasts (EC<sub>50</sub> ~ 30 nM; Fig. 1). In the rat MIA OA model, compared with vehicle, SM04690 injection reduced visible knee swelling, inflammatory cells, and proinflammatory cytokine and MMP production ( $p < 0.05$ ). SM04690 increased ( $p < 0.01$ ) paw withdrawal threshold from Day 6 and improved weight distribution to the affected limb in treated rats, at multiple timepoints, compared with vehicle (Fig. 2). SM04690 increased Safranin-O stained cartilage thickness and decreased OARSI score ( $p < 0.05$ ) compared with vehicle.

**Conclusions:** In a rat MIA OA model, SM04690 injection reduced inflammation, protease production, and pain, with improved cartilage and joint health, compared with vehicle. Previously demonstrated regenerative effects in nonclinical studies, along with anti-inflammatory properties, show SM04690 may improve symptoms and potentially provide disease modification in OA. Clinical studies are ongoing.

**Disclosures of interest:** V. Deshmukh, T. Seo, C. Swearingen, and Y. Yazici are shareholders and employees of Samumed, LLC.

Figure 1. SM04690 inhibited inflammatory cytokine production in synovial fibroblasts *in vitro*

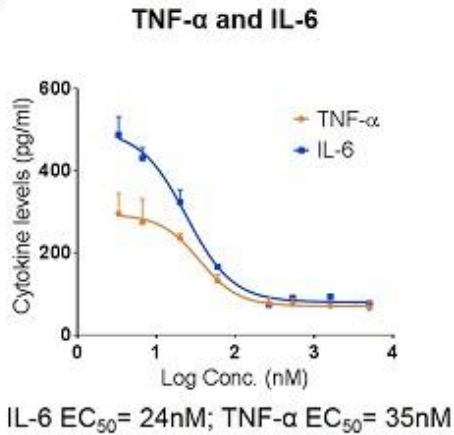


Figure 2. SM04690 inhibited inflammatory cytokine production and decreased inflammation and pain in the MIA model of OA

