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SM04690, a Wnt Pathway Inhibitor: Anti-Inflammatory and Cartilage Protective Effects in Preclinical Osteoarthritis Models

Vishal Deshmukh, Tim Seo, Christopher Swearingen, and Yusuf Yazici

Samumed, LLC, San Diego, CA, USA

Purpose: 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 chondrogenesis and anti-inflammatory properties preclinically (Deshmukh et al., *OAC* 2017; Deshmukh et al. *Arth Rheum* 2016), 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- α) from IL-1 β 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 α , IL-1 β , IL-6, TNF- α and IFN- γ) 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 incapitance meter and analyzed using generalized estimating equation regression accounting for repeated measurements.

Results: SM04690 dose-dependently inhibited IL-1 β -induced cytokine secretion in synovial fibroblasts (EC₅₀ ~30 nM; Fig. 1). In the rat MIA OA model, compared to vehicle, SM04690 injection reduced visible knee swelling, inflammatory cells, proinflammatory cytokine and MMP production ($P<0.05$). SM04690 increased ($P<0.01$) paw withdrawal threshold and improved ($P<0.05$) weight distribution to the affected limb in treated rats, at all post-treatment timepoints, compared to vehicle. SM04690 increased Safranin-O stained cartilage thickness and decreased OARSI score ($P<0.05$) compared to vehicle (Fig. 2).

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

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

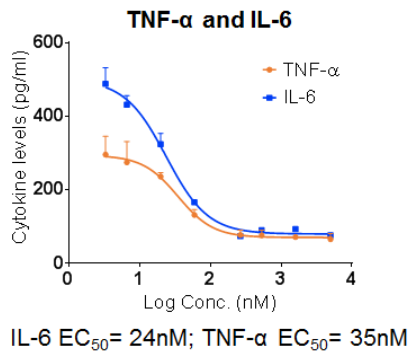


Figure 2. SM04690 inhibited inflammatory cytokine production and decreased inflammation and pain in the MIA model of OA

