Accepted as poster# 1 at the Pan American League of Rheumatology Associations (PANLAR) Congress, April 7-10, 2018, Buenos Aires, Argentina

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

V. Deshmukh, T. Seo, M. Grifman, C. Swearingen, Y. Yazici
Samumed, LLC, San Diego, CA, USA

Objectives: 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\(^1\), 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-1β-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-1α, IL-1β, 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 incapacitance meter and analyzed using generalized estimating equation regression.

Results: SM04690 dose-dependently inhibited IL-1β-induced cytokine secretion in synovial fibroblasts (EC\(_{50}\) ~ 30nM; 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 from day 6 and improved weight distribution to the affected limb in treated rats, at multiple timepoints, compared to vehicle (Fig.2). SM04690 increased Safranin-O stained cartilage thickness and decreased OARSI score (p<0.05) compared to vehicle.

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\(^1\), along with anti-inflammatory properties, show SM04690 may improve symptoms and potentially provide disease modification in OA. Clinical studies are ongoing.

\(^1\)Deshmukh et al. OAC 2017
Figure 1. SM04690 inhibited inflammatory cytokine production in synovial fibroblasts \textit{in vitro}

![Graph showing cytokine levels](image)

**IL-6 EC\textsubscript{50} = 24nM; TNF-\alpha EC\textsubscript{50} = 35nM**

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

![Images and graphs depicting experiment results](image)