Cartilage regeneration in a rat model of knee OA by SM04690, a potential disease modifying Wnt pathway inhibitor

Vishal Deshmukh1, Charlene Barroga1, Sunil KC1, Maureen Ibanez1, Luis Dellamary1, Josh Stewart1, Haide Hu2, Betty Tam1, John Hood2, Yusuf Yazici1

1Samumed, LLC, San Diego, CA, USA, 2Formerly Samumed, LLC

Introduction: Increased Wnt signaling in osteoarthritis (OA) leads to cartilage thinning and bone remodeling. SM04690, a small-molecule Wnt pathway inhibitor, was evaluated for its potential to induce chondrogenesis, protect cartilage, limit inflammation, and improve joint health.

Methods: SM04690-induced chondrogenesis from human mesenchymal stem cells (hMSCs) was evaluated by qPCR and histology. In vivo efficacy was measured in a rat knee surgical OA model by histology (OARSI score) and biomarkers, and in the rat monosodium iodoacetate (MIA) injection-induced OA model by histology. Pro-inflammatory cytokines were measured by ELISA, and pain was assessed by paw withdrawal thresholds using Von Frey apparatus. Animal studies were approved by the Samumed, LLC Animal Committee and performed in accordance with the U.S. Department of Agriculture’s (USDA) Animal Welfare Act (9 CFR Parts 1, 2, and 3), the Guide for the Care and Use of Laboratory Animals, and Samumed, LLC protocols. For parametric data, t-tests were used to compare 2 groups and one-way ANOVA for >2 groups. Mann-Whitney U test was used to analyze non-parametric data.

Results: In vitro, SM04690 induced differentiation of hMSCs into mature, functional chondrocytes. In rats, a single SM04690 intra-articular injection resulted in therapeutic concentrations >180 days, without detectable systemic exposure or toxicity. In rat OA models, compared to vehicle, SM04690 regenerated cartilage, decreased OARSI score (p<0.05), inhibited proteases (p<0.05), and improved OA biomarkers (p<0.05). In the MIA model, compared to vehicle, SM04690 inhibited inflammatory cytokine production (p<0.05) and increased paw withdrawal threshold (p<0.05).

Conclusions: Preclinically, SM04690 induced chondrogenesis, regenerated cartilage, inhibited protease release, improved cartilage health, and reduced inflammation and pain compared to vehicle. SM04690 has potential as a disease modifying therapy for OA.

Significance: OA therapeutic options are currently limited to symptom relief and not disease modification. Disease modifying treatments are not currently approved for use in humans. A single IA injection of a small molecule Wnt pathway inhibitor, SM04690, demonstrated reduced inflammation, increased cartilage protection, and cartilage regeneration in a rodent model of OA. Additionally, toxicity studies in rats demonstrated no observed systemic toxicity. These data suggested SM04690 may be an effective disease modifying treatment for OA. Clinical studies are ongoing.