SM04690 caused dose-dependent Wnt pathway modulation within a homeostatic range in a rat model of knee osteoarthritis

Vishal Deshmukh1, Charlene Barroga1, Sunil KC1, Rik Lories2, and Nancy E. Lane3
1Samumed, LLC, San Diego, CA 2Skeletal Biology and Engineering Research Center, Leuven, Belgium 3UC Davis Medical Center, Davis, CA

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Background

- Knee osteoarthritis (OA) is characterized by degradation of articular cartilage, subchondral bone remodeling, and osteophyte formation.1
- Wnt signaling affects OA pathogenesis by regulating chondrogenic stem cell differentiation in vitro and cartilage catabolism in vivo, thereby suggesting a potential role in OA.2 Absence as well as excessive Wnt pathway activation disturbs homeostasis and triggers OA in in vivo models.3 5 Therefore, potential pharmacological Wnt pathway inhibition cannot be excessive in order to achieve optimal restoration of joint homeostasis and stem cell activity.6
- SM04690, a small-molecule Wnt pathway inhibitor, has been shown to prevent or slow cartilage loss in preclinical OA models. Evidence of non-linear SM04690 dose response effects in these models is presented.

Methods

- Pharmacokinetics: Single intra-articular (IA) SM04690 injection into rats (0.3 µg, 1 µg, 3 µg, 9 µg) was performed. Bone and cartilage samples were isolated, and SM04690 levels were measured by HPLC-mass spectrometry.
- Rat OA model: SM04690 efficacy was evaluated in a rat instability OA model (anterior cruciate ligament transection + partial medial meniscectomy [ACLT + pMMx]) with IA injection of vehicle or SM04690 (0.1 µg, 0.3 µg, 1 µg) at Week 1. Chondrocyte differentiation markers (collagen type II alpha 1 chain [Col2a1]; cartilage oligomeric matrix protein [COMP]; Aggrecan; collagen type X alpha 1 chain [Col10a]; sex-determining region-Y-box 9 [Sox9]) and protease enzymes (matrix metalloproteinases [MMP1, 3, 13], Aggrecanase [ADAMTS5]) were evaluated in cartilage using qPCR, OA serum biomarkers (COMP; procollagen type IIIA N-propeptide [PIIANP]) by ELISA (Week 5), and cartilage pathology using Safranin O-stained sections (Week 13).
- Statistics: Data are shown as mean ± SEM. One-way ANOVA was used to evaluate differences between vehicle and treatment groups.

Results

Dose-dependent SM04690 exposure in rat and dog cartilage following single IA injection

Figure 1. SM04690 showed dose-dependent exposure in cartilage in a) naive rats and b) beagle dogs following single IA injection.

Non-linear dose effects of SM04690 on cartilage degradation in the ACLT + pMMx model of OA

Figure 2. SM04690 dose-dependently decreased expression of MMP13 and ADAMTS5, but not MMP1 or MMP3, compared with vehicle (n=7 for vehicle; n=8 for treatment; *p<0.05; **p<0.01; ***p<0.001).

Effects of SM04690 on chondrocyte markers in the ACLT + pMMx model of OA

Figure 3. SM04690 (0.3 µg but not 1 µg) increased expression of Col2a1, COMP, and Aggrecan with no effects on Col10a (hypertrophy marker) or Sox9 compared with vehicle (n=7 vehicle; n=8 treatment; *p<0.05; **p<0.001).

Effects of SM04690 on OA serum biomarkers in the ACLT + pMMx model of OA

Figure 4. SM04690 (0.3 µg but not 1 µg) decreased COMP and increased PIIANP compared with vehicle (n=12; *p<0.05; **p<0.01).

Effects of SM04690 on knee joint pathology

Figure 5. (a) SM04690 increased cartilage thickness compared with vehicle. (b) SM04690 (0.3 µg but not 0.1 µg or 1 µg) decreased OARSI scores compared with vehicle in two independent experiments (n=9-12/group; *p<0.05).

Discussion and Conclusions

- Linear pharmacokinetics with dose-dependent exposures were observed for SM04690 in rat and dog cartilage following single IA injection.
- SM04690 was well-tolerated in naïve animals at doses up to 58-fold higher than those tested for efficacy in the ACLT + pMMx model (Poster# P728).
- In this rat knee OA model, data suggested that SM04690 demonstrated generally non-linear dose-responses.

References