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

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Objective: Wnt signaling affects pathogenesis of osteoarthritis (OA) by regulating chondrogenic stem cell differentiation and cartilage catabolism¹. Both excessive Wnt pathway activation and repression are implicated in OA^{2,3}. The aim of this animal study was to determine an optimal dose for SM04690, a small-molecule Wnt pathway inhibitor, to protect and regenerate cartilage in a preclinical OA model.

Material and methods: SM04690 joint and plasma levels were measured on Days 30, 90, 180 after single intra-articular (IA) injection in rats (0.3, 1, 3, 9 µg) and dogs (3, 30 µg). Surgical knee OA was induced in rats (8-12/group), and a single IA injection of SM04690 (0.1 µg, 0.3 µg, 1 µg) given. Chondrogenic matrix production (Col2a1, Aggrecan, Sox9, Col10a1) and cartilage catabolism (MMP1, 3, 13, ADAMTS5) markers were measured by qPCR at Day 35. Serum OA biomarkers (COMP, PIIANP) were also measured. Histologic severity of OA was assessed by OARSI scoring at Day 90. Safety was assessed in rats (8-12/group) and dogs (6-8/group). All comparisons were to vehicle.

Results: SM04690 showed dose-linear IA concentrations (>180 days), with no detected systemic exposure. In the rat OA model, changes with 0.1 µg dose were not significant, but 0.3 µg increased ($p < 0.05$) chondrocyte differentiation and decreased ($p < 0.05$) cartilage catabolism markers. SM04690 1 µg had no effects on cartilage differentiation markers but decreased ($P < 0.05$) MMP1, 13 and ADAMTS5 expression (not MMP3). Serum COMP decreased and PIIANP increased at 0.3 µg ($P < 0.05$), but showed no changes at 1 µg. SM04690 0.3 µg decreased OARSI scores ($P < 0.05$), while 0.1 µg and 1 µg doses did not. Doses were well-tolerated in rats and no-observed-adverse-effect-level in dogs was 1750 µg (58 µg rat dose equivalent; 194-fold over pharmacologically active dose).

Conclusions: In a rat knee OA model, 0.3 µg SM04690 maintained cartilage homeostasis, and inhibited protease production, compared to vehicle. Lower and higher doses were not effective. SM04690 was well-tolerated in animals at doses 58-fold higher than those tested for efficacy. These data suggested SM04690 caused dose-dependent Wnt signaling modulation within a homeostatic range.

References: ¹Lane NL. *Nat Rev Rheumatol* 2013; ²Monteagudo S et al. *Nat Commun* 2017; ³Nalesso G et al. *Ann Rheum Dis* 2016.