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SM04690, a small molecule Wnt pathway inhibitor, appeared to have no deleterious effects on bone, joint, and tissue health in knee OA models

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Objective: Wnt signaling modulates bone and cartilage turnover. Animal and human data from SM04690 (a Wnt pathway inhibitor with cartilage protective and regenerative effects), were reviewed to determine effects on bone, joint, and tissue health.

Material and methods: SM04690 was administered by intra-articular (IA) injection in a rat surgical knee OA model (0.3 µg, 1 µg); in normal dogs (50 µg, 1750 µg, 35,000 µg single injection, or 12 µg, 36 µg, 116 µg, up to 9 repeat injections) and in knee OA subjects (30 µg, 70 µg, 230 µg). In the rat model, subchondral bone volume/total volume (BV/TV) ratios were evaluated at week 13 with Image J software. Osteoblast markers were measured by qPCR at week 5. In dogs, joint histology was semi-quantitatively evaluated (cartilage, meniscus, subchondral bone, synovium), at Day 111 post single IA injection, or Day 94 or 273, after 3 or 9 repeat injections. In a human phase 1 trial, bone health serum biomarkers were collected (Weeks 0, 4, 12, 24); bone mineral density (BMD) in knee and hip joints was measured by qCT (Weeks 0,12, 24) and DEXA scans, respectively (Weeks 0, 24), and bone marrow edema (BME) assessed with knee MRI (Weeks 0, 12, 24).

Results: In the rat OA model, SM04690 (0.3 µg, 1 µg) had no effects on week 13 BV/TVs, or osteoblast marker expression compared to vehicle. In dogs, joint histology was normal with single IA 50 µg, 1750 µg and all repeat IA doses. Synovial inflammation was observed with the 35,000 µg dose at day 2 which resolved by Day 111. There was no evidence of non-target tissue reactions in any treatment group. The no-observed-adverse-effect-levels in dogs for single and repeat injections were 1750 µg and 116 µg, respectively, an equivalent 8-fold safety margin to highest human IA dose. In humans, there were no concerning shifts of serum biomarkers between groups and no appreciable BMD or BME effects seen in knee and hip joints.

Conclusions: SM04690 had no appreciable bone, joint, or tissue health effects at pharmacologically active or higher dose equivalents, and appeared safe and well-tolerated in rats, dogs and humans.