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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Poster# P728

Background

- Wnt signaling plays a major role in maintaining articular cartilage and bone homeostasis and is involved in OA pathogenesis.[1]
- SM04690 is a small-molecule Wnt pathway inhibitor in development as a potential disease-modifying knee OA drug (DMOAD).[2,3]
- Systemic Wnt pathway inhibitors have shown deleterious effects on bone.[4]
- Animal and human data from SM04690 were reviewed to determine its effects on bone, joint, and tissue health.

Methods

- Vehicle or SM04690 (0.3, 1 µg) was intra-articularly (IA) injected in a rat surgical knee OA model (anterior cruciate ligament transection + partial medial meniscectomy [ACLT + pMMx]).
  - Osteoblast markers were evaluated by qPCR at Week 5.
  - Subchondral bone and total volume (BV/TV) ratios were evaluated at Week 13 (Image J software).
- In healthy dogs, inflammation was scored (0: normal; 1: minimal; 2: mild; 3: moderate; 4: marked) and joint histology (cartilage, meniscus, subchondral bone, synovium) semi-quantitatively evaluated (Mankin score):[5,6]
  - Acutely, 1 day and 110 days after single injection of vehicle or SM04690 (70, 1750, 35000 µg).
  - Subchronically, at 3 months after 3 repeat monthly injections of vehicle or SM04690 (12, 36, 116 µg) and after 28 days recovery.
  - Chronically, at 9 months after 9 repeat monthly injections of vehicle or SM04690 (12, 36, 116 µg) and after 28 days recovery.
- In a human phase 1 trial (n=61) of single IA knee injection of SM04690 or placebo (PBO):[3]
  - Bone mineral density (BMD) was measured by quantitative computed tomography (qCT) at baseline, Week 12, and Week 24 in ITT (all randomized subjects).
  - Bone marrow edema (BME) was assessed with magnetic resonance imaging (MRI) at baseline and Week 24 in the modified ITT population (all randomized subjects according to actual treatment received).
  - Bone health serum biomarkers were collected at baseline and Week 24 in the safety analysis set (all subjects exposed to study product).

Results

There were no significant differences in osteoblast markers between treatment with SM04690 and vehicle in a rat knee OA model

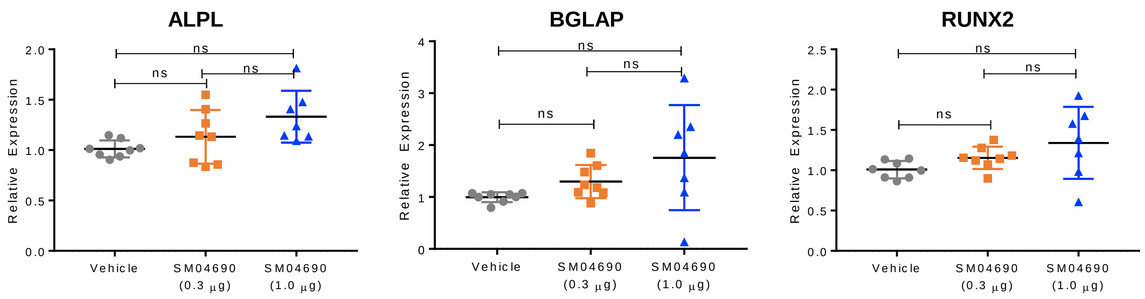

Figure 1. Osteoblast markers in subchondral bone in vehicle and treatment groups (ns = not significant).

SM04690 had no effects on subchondral bone in a rat knee OA model compared with vehicle

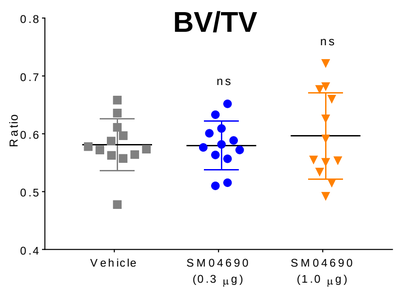

Figure 2. BV/TV from the ACLT + pMMx model in vehicle and treatment groups (ns = not significant).

SM04690 had no effects on bone mass compared with baseline or vehicle in healthy dog joint histology safety studies

- No histopathological changes in cartilage, meniscus, bone tissue density, or bone trabecular structure in SM04690- or vehicle-treated knees were noted.
- Minimal (grade 1) granulomatous periarticular inflammation was observed at 3 months after 3 repeat injections, resolving after 28 days recovery. Increased incidence and severity of granulomatous periarticular inflammation (minimal to moderate, grades 1-3) were observed at 9 months after 9 repeat injections and partially resolved to minimal (grade 1) and mild (grade 2) after 28 days recovery.
- No-observed-adverse-effect levels in dogs for single (1750 µg) and repeat (116 µg) injections were equivalent to a 61-fold and 36-fold safety margin, respectively, to highest human IA dose when scaled by body weight.

Results

There were no significant changes in BMD in SM04690-treated compared with untreated knees in a phase 1 trial

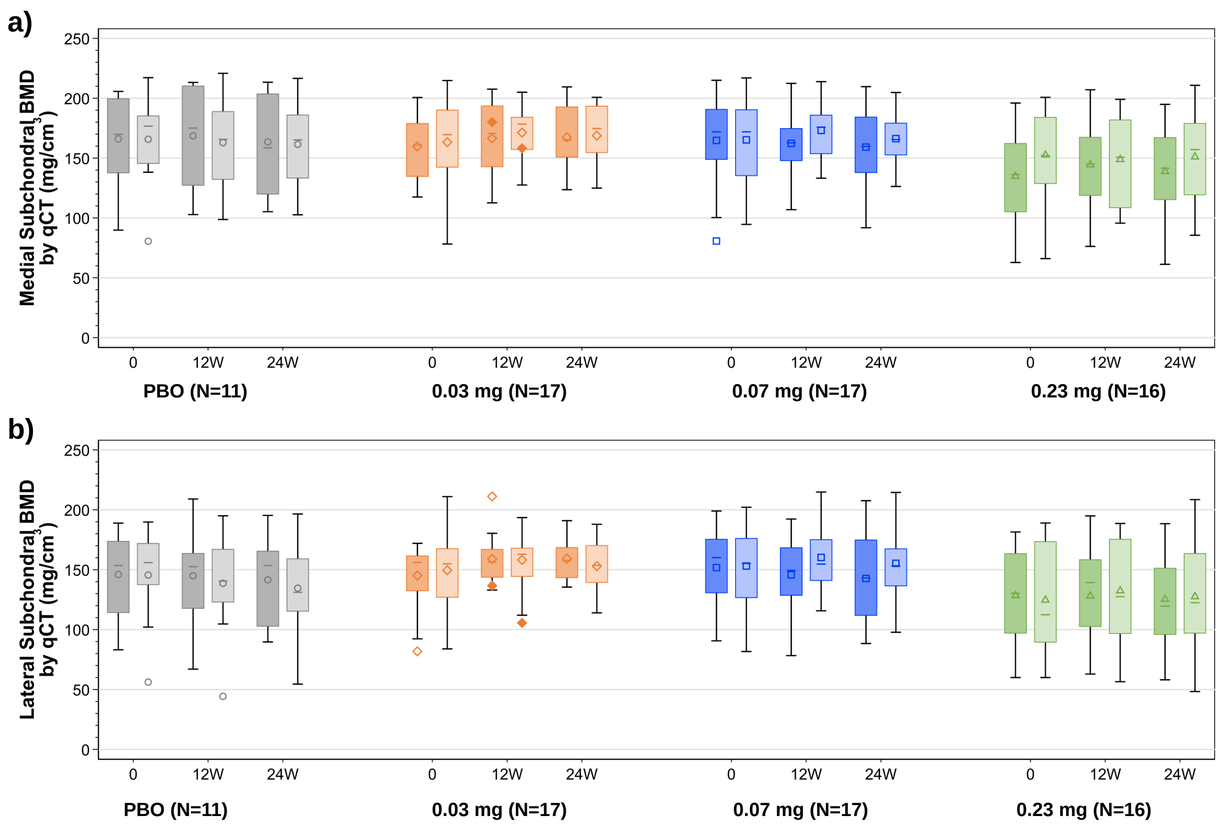

Figure 3. a) Medial and **b)** lateral subchondral qCT in the target vs. non-target knees.[3]
Interior bar: Median; **Box**: Interquartile [25th-75th] range; **Whisker**: 1.5x interquartile range; **Darker Shade**: Target knee; **Lighter Shade**: Non-target knee; **Interior Symbol**: Mean; **Exterior Symbol**: Outlier; **Filled Symbol**: Drop-out subject at 8W

SM04690 had no appreciable effects on BME compared with baseline in a phase 1 trial

Table 1. MRI safety findings: BME (n=58)

Edema Baseline	Edema Week 24	0.03 mg (N=15)	0.07 mg (N=16)	0.23 mg (N=16)	PBO (N=11)
None [N(%)]					
	None	10 (66.7%)	9 (56.3%)	4 (25.0%)	6 (54.5%)
	Focal	0	4 (25.0%)	1 (6.3%)	1 (9.1%)
	Diffuse	0	0	0	0
Focal [N(%)]					
	None	0	0	0	0
	Focal	3 (20.0%)	2 (12.5%)	9 (56.3%)	2 (18.2%)
	Diffuse	0	0	0	1 (9.1%)
Diffuse [N(%)]					
	None	0	0	0	0
	Focal	1 (6.7%)	1 (6.3%)	1 (6.3%)	0
	Diffuse	1 (6.7%)	0	1 (6.3%)	1 (9.1%)

OA serum biomarker changes from baseline at Week 24 comparing treatment with PBO were not statistically significant in a phase 1 trial

Table 2. Summary of OA serum biomarkers at baseline and Week 24 (n=60)

	0.03 mg (N=17)	0.07 mg (N=16)	0.23 mg (N=16)	PBO (N=11)
COMP [ng/ml]				
Baseline [Mean (SD)]	475.3 (167.6)	480.5 (475.1)	263.8 (92.6)	277.7 (79.3)
Week 24 [Mean (SD)]	369.6 (191.9)	316.4 (89.2)	212.2 (83.1)	257.7 (72.4)
P1NP [mcg/L]				
Baseline [Mean (SD)]	52.1 (18.2)	40.8 (13.2)	45.7 (15.4)	38.6 (9.4)
Week 24 [Mean (SD)]	53.8 (14.1)	43.5 (13.7)	47.1 (14.2)	40.4 (12.8)
β-CTX [pg/ml]				
Baseline [Mean (SD)]	333.6 (117.8)	236.4 (87.1)	300.1 (153.5)	345.5 (166.0)
Week 24 [Mean (SD)]	369.9 (165.8)	292.4 (146.8)	314.9 (181.5)	295.3 (119.2)

COMP: Cartilage oligomeric matrix protein, marker of collagen turnover; P1NP: Procollagen type 1 protein, marker of bone turnover; β-CTX: β-C-terminal telopeptide of type 1 collagen, marker of bone turnover

Conclusions

- SM04690 appeared generally safe and well-tolerated in preclinical and clinical studies.
- SM04690 had no appreciable bone, joint, or tissue health effects compared with baseline or vehicle at pharmacologically active or higher dose equivalents.

References

1. Lories RJ, et al. *Nat Rev Rheumatol.* 2013;9:328-39.
2. Deshmukh V, et al. *Osteoarthritis Cartilage.* 2018;26:18-27.
3. Yazici Y, et al. *Osteoarthritis Cartilage.* 2017;25:1598-1606.
4. Kahn M. *Nat Rev Drug Discov.* 2014;13:513-32.
5. Little CB, et al. *Osteoarthritis Cartilage*. 2010;18 Suppl 3:S80-92.
6. Roller BL, et al. *J Knee Surg.* 2015;28:175-82.

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