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## **Experimental Tendinopathy Treatment with SM04755, a Topical Small Molecule Wnt Pathway Inhibitor**

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**Introduction:** Tendinopathy is an inflammatory and degenerative disorder. The Wnt pathway is upregulated in chronic tendinopathy and involved in inflammation, tenocyte differentiation and fibrosis. SM04755, a topical small molecule Wnt pathway inhibitor, has been shown to inhibit inflammation, reduce fibrosis and increase tenocyte differentiation in nonclinical models. Results from SM04755 treatment in acute and delayed treatment Achilles collagenase tendinopathy models in rodents are presented.

**Methods:** In the acute treatment model, a single injection of collagenase (500 µg) or sham into rodent Achilles tendons on Day -4 was followed on Day 0 by daily vehicle, 0.3 mg/cm<sup>2</sup>, or 0.9 mg/cm<sup>2</sup> SM04755 treatment. Achilles tendons were harvested on Days 7, 14, and 21. In the delayed treatment model, collagenase injections were given at Days -28 and -14, followed on Day 0 with daily vehicle or 0.3 mg/cm<sup>2</sup> SM04755. Achilles tendons were harvested on Days 7, 14, 21 and 28. Blinded histology analyses scored tendon health. Statistical analyses used one-way ANOVA for multiple group comparisons.

**Results:** In the acute treatment model, SM04755 significantly improved tendon health at Day 14 for 0.9 mg/cm<sup>2</sup> dose compared to vehicle and 0.3 mg/cm<sup>2</sup> and at Day 21 for 0.3 and 0.9 mg/cm<sup>2</sup> doses (p<0.05) compared to vehicle (Figure 1). In the delayed treatment model, 0.3 mg/cm<sup>2</sup> significantly improved tendon health on Day 21 (p<0.05) compared to vehicle, although not at other timepoints (Figure 2).

**Discussion:** In the acute treatment model, faster healing after the higher dose of SM04755 was observed compared to vehicle and lower dose SM04755. Additionally, 0.3 mg/cm<sup>2</sup> SM04755 promoted tendon healing in an established, repeat collagenase tendon injury model with delayed intervention. Limitations of the collagenase model were absent fibrotic changes, allowing spontaneous healing in the vehicle group by Day 28, possibly reducing effect size. Topical SM04755 has potential as a treatment for tendinopathy. Clinical studies are planned.

Figure 1. Progression of tendon health scores after SM04755 treatment in the acute treatment collagenase model

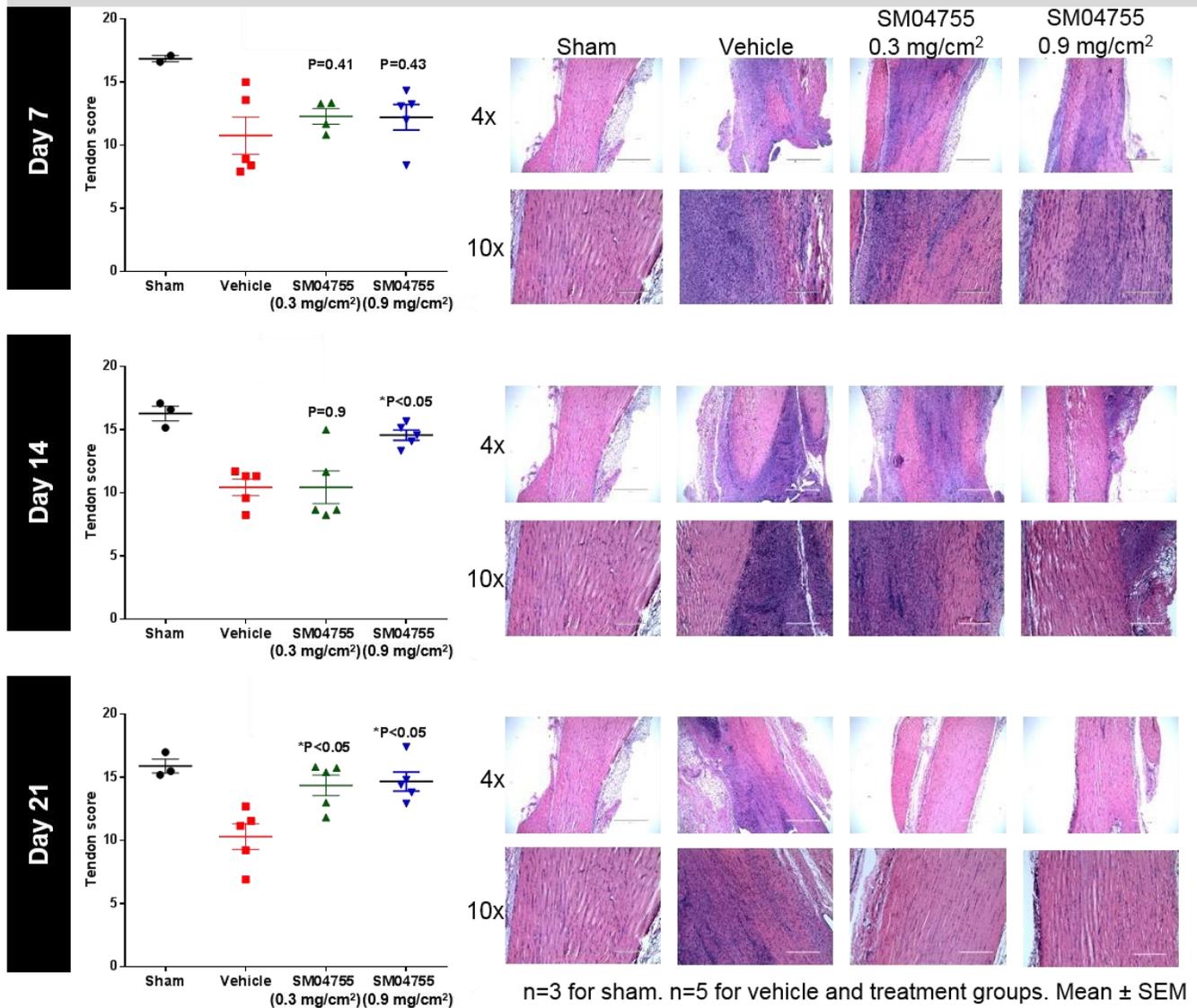


Figure 2. Treatment with SM04755 in the delayed treatment collagenase model

