Experimental Tendinopathy Treatment with SM04755, a Topical Small Molecule Inhibitor of the Wnt Pathway

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Background: Tendinopathy is an inflammatory and degenerative disorder caused by injuries and overuse. The Wnt pathway is upregulated in chronic tendinopathy and involved in inflammation, tenocyte differentiation, and fibrosis. SM04755, a novel, topical, small molecule Wnt pathway inhibitor, has previously been shown to inhibit inflammation, reduce fibrosis, and increase tenocyte differentiation (Deshmukh et al., *Arthritis Rheumatol*, 2016). Two further experiments are presented: 1. SM04755 treatment in an acute dose-response tendinopathy model and 2. SM04755 treatment in a repeat injury/delayed treatment (RIDT) tendinopathy model. These models simulate acute and acute-on-chronic clinical tendinopathy, respectively.

Methods: SM04755 was assessed in rodent Achilles tendinopathy models, induced by intratendon collagenase injection (500 µg). In the acute dose response model, a single injection of collagenase or sham per animal on Day -4 was followed on Day 0 by daily topical vehicle, or 0.3 mg/cm² or 0.9 mg/cm² SM04755. Achilles tendons were harvested on Days 7, 14, and 21. In the RIDT model, collagenase injections were given at Days -28 and -14, followed on Day 0 with daily topical vehicle or 0.3 mg/cm² SM04755. Achilles tendons were harvested on Days 7, 14, 21, and 28. Blinded histology analyses scored tendon health based on linearity, tendon cell shape, tendon cell density, inflammation, and hemorrhage (range 5-20). Statistical analyses: one-way ANOVA for multiple group comparisons, t-tests for two group comparisons.

Results: In the acute dose-response model, SM04755 improved tendon health from baseline compared to vehicle as assessed by tendon histology scores. Vehicle scores were 10.77 [±1.46] at Day 7, 10.44 [±0.66] at Day 14, and 10.31 [±1.02] at Day 21. SM04755 (0.3 mg/cm²) scores were 12.30 [±0.62] at Day 7 (NS), 10.45 [±1.29] at Day 14 (NS), and 14.37 [±0.82] at Day 21 (P<0.05). SM04755 (0.9 mg/cm²) scores were 12.22 [±1.02] at Day 7 (NS), 14.57 [±0.41] at Day 14 (P<0.05), and 14.67 [±0.76] at Day 21 (P<0.05) (Fig. 1). In the RIDT model, vehicle scores were 12.35 [±0.30] at Day 7, 10.09 [±0.76] at Day 14, 11.92 [±0.77] at Day 21, and 13.72 [±0.35] at Day 28. SM04755 (0.3 mg/cm²) scores were 11.86 [±2.13] at Day 7 (NS), 9.44 [±0.48] at Day 14 (NS), 14.61 [±0.77] at Day 21 (P<0.05), and 14.93 [±0.46] at Day 28 (NS) (Fig. 2).

Conclusion: In the acute dose-response model, SM04755 (0.3 mg/cm²) showed statistically significant improvements in tendon scores compared to vehicle at Day 21. The 0.9 mg/cm² dose achieved significance at Days 14 and 21, indicating faster response at higher SM04755 dose. In the RIDT model, SM04755 0.3 mg/cm² dose promoted accelerated tendon healing compared to vehicle. Therefore, SM04755 demonstrated accelerated improvement of tendon histology in acute and RIDT models compared to vehicle and has potential as a tendinopathy therapy. Clinical studies are planned.
Figure 1. Progression of tendon health scores after SM04755 treatment in the collagenase model

Day 7

Day 14

Day 21

n=3 for sham. n=5 for vehicle and treatment groups. Mean ± SEM

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

Day 21

n=3 for sham. n=5 for vehicle and treatment groups. Mean ± SEM