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

Vishal Deshmukh, Timothy Seo, Brian Hofilena, Luis Dellamary, and Yusuf Yazici

Samumed, LLC San Diego, CA, USA

Purpose: Tendinopathy is an inflammatory and degenerative disorder caused by injuries and/or overuse. Untreated, affected tendons become fibrotic, with micro tears that can lead to pain and rupture. Current therapeutic options treat symptoms and not underlying causes. Stem cell- and growth factor-based treatments are under investigation, but have not established safety or efficacy. 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 in nonclinical models (Deshmukh et al. Arth Rheum 2016). Two further experiments are presented: 1. Dose responses of SM04755 in an acute tendinopathy model; 2. A delayed SM04755 treatment model was studied to examine its effects in established tendon injury.

Methods: SM04755 was assessed in intra-tendon collagenase-induced rodent Achilles tendinopathy models. Tendinopathy was induced by collagenase injection (500 µg). In the acute dose response model, a single injection of collagenase or sham per animal on Day -4, followed on Day 0 by daily topical delivery of vehicle, 0.3 mg/cm², or 0.9 mg/cm² SM04755. 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/cm² SM04755. Achilles tendons were harvested on Days 7, 14, 21 and 28. Histological analyses were performed by blinded observers and tendons scored based on linearity, tendon cell shape, tendon cell density, inflammation, and hemorrhage (range 5-20). Animal studies were approved by the Samumed, LLC Animal Committee and performed in accordance with the U.S. Department of Agriculture’s Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals. Statistical analyses used one-way ANOVA for multiple group comparisons and t-tests for comparison between two groups.

Results: In the acute dose response model, SM04755 improved tendon health from baseline compared to vehicle as assessed by tendon histology scores. Tendon health scores for vehicle were 10.77 [±1.46], 10.44 [±1.48], and 12.70 [±1.02] at Days 7, 14, and 21, respectively. In the 0.3 mg/cm² SM04755 dose group, tendon health scores were 12.30 [±0.48] at Day 7 (NS), 10.45 [±1.29] at Day 14 (NS), and 14.37 [±0.82] at Day 21 (P<0.05). In the 0.9 mg/cm² SM04755 dose group, tendon health 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 delayed treatment model, scores for vehicle were 12.35 [±0.30], 10.09 [±0.76], 11.92 [±0.77] and 13.72 [±0.35] at Days 7, 14, 21, and 28, respectively. The 0.3 mg/cm² dose group 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, the 0.9 mg/cm² SM04755 dose resulted in improved tendon health from baseline compared to vehicle at both Day 14 and 21. The 0.9 mg/cm² dose showed statistically meaningful improvement at Day 14 while the 0.3 mg/cm² dose did not, indicating a faster
response at the higher dose. Additionally, 0.3 mg/cm² 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. Chronic tendinopathy currently has limited therapeutic options, which alleviate symptoms, mainly pain. SM04755 demonstrated accelerated improvement of tendon histology compared to vehicle in acute and established injury models, suggesting that topically applied SM04755 has potential as a therapeutic intervention for tendinopathy. Clinical studies are planned.
Figure 1. Progression of tendon health scores after SM04755 treatment in the collagenase model

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