

Experimental tendinopathy treatment with SM04755, a topical small molecule inhibitor of the Wnt pathway

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Introduction: 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. 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 vehicle, 10 mg/mL, or 30 mg/mL 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 10 mg/mL 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 compared to vehicle as assessed by tendon histology scores. Tendon health scores for vehicle were 10.77 [±1.46], 10.44 [±1.48], and 12.7 [±1.02] at Days 7, 14, and 21, respectively. In the 10 mg/mL 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 30 mg/mL 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 10 mg/mL 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).

Discussion: The 30 mg/mL SM04755 dose resulted in improved tendon health compared to vehicle at both Day 14 and 21. The 10 mg/mL dose showed improvement at Day 21, indicating a faster response at the higher dose. Additionally, 10mg/mL 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, reducing effect size.

Significance: Chronic tendinopathy currently has limited therapeutic options, which alleviate symptoms, mainly pain. SM04755 demonstrated accelerated improvement of tendon histology in acute and established injury models, suggesting that topically applied SM04755 has potential as a therapeutic intervention for tendinopathy. Clinical studies are planned.

References: 1. Deshmukh V, Pedraza M, Ibanez M, Dellamary L, Stewart J, Seo T, Melchior B, Hood J, Yazici Y. Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04755) As a Potential Topical Treatment for Psoriasis [abstract]. *Arthritis Rheumatol* 2016;68(suppl 10).

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Figure 1. Kinetics of tendon healing in the collagenase model after SM04755 treatment

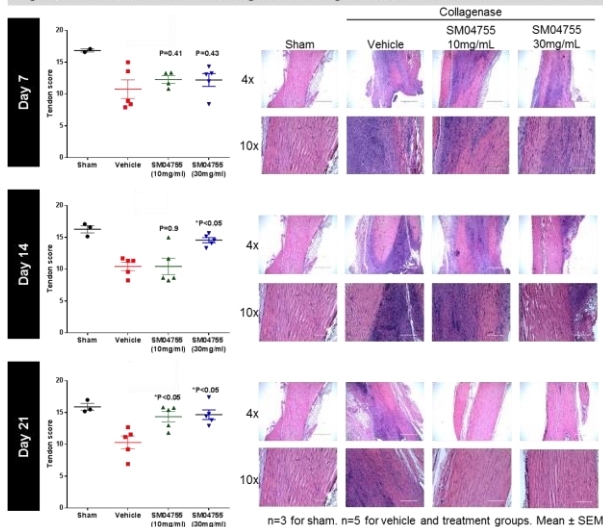


Figure 2. Delayed treatment with SM04755 in the collagenase model

