Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04755) as a Potential Topical Treatment for Tendinopathy

Vishal Deshmukh, PhD, Timothy Seo, MS, Maureen Ibanez, MS, Luis Dellamore, BS, Josh Stewart, BS, Brian Hofilen, BA, and Yusuf Yazici, MD
Samumed, LLC, San Diego, CA

P1077

Background

- Tendinopathy is an inflammatory, degenerative, fibrotic condition affecting tendons, caused by injuries or overuse. It is characterized clinically by pain, swelling, and impaired performance. 1,2 Depending on the affected tendon, it can commonly present in man termed as Achilles’ heel, tennis elbow, and jumper’s knee.
- Current therapeutic options alleviate symptoms only, rather than treating underlying pathology, therefore presenting an unmet medical need. 3
- The Wnt pathway plays an important role in tenocyte differentiation and is upregulated in tendinopathy. Altered Wnt signaling may contribute to tissue malaplasia and failed healing in some cases of tendinopathy. 5
- Samumed is developing SM04755, a potent small molecule Wnt signaling pathway inhibitor, as a potential topical therapeutic for the treatment of tendinopathy.

Methods

- Wnt pathway inhibition was measured by a cellular Wnt pathway-based reporter assay in SW480 colon cancer cells and was further confirmed by qRT-PCR for Wnt target genes.
- Effects on fibrosis were assessed in TGF-β-stimulated human dermal fibroblasts (HDFs) by measuring smooth muscle actin (αSMA), plasminogen activator inhibitor (PAI-1), connective tissue growth factor (CTGF), and collagen expression by qRT-PCR.
- In vivo and in vitro tendon regeneration were evaluated by differentiation of human mesenchymal stem cells (hMSCs) into tenocytes and assessment of scleraxis (SCX), tenomodulin, and tenascin C expression by high-content imaging and qRT-PCR in rat tendons.
- Pharmacokinetics were evaluated by topical application on rats, followed by analysis of compound concentrations in tendon and plasma by LC-MS.
- In vivo efficacy of topical SM04755 was evaluated in single or repeat intra-tendon collagenase injection-induced rotator tendinopathy models by scoring (range 5-20) histological indicators of tendon health.
- In vivo inflammation was measured by chemokine ligand 1 (CXCL1) levels in plasma by ELISA and other inflammatory markers (IL-1β, TNF-α, IFN-γ, IL-6 and IL-8) in the tendon by qRT-PCR.

Results

SM04755 demonstrated specific and potent inhibition of Wnt signaling

- SM04755 prevented and reversed fibrosis in vitro
- SM04755 induced tenocyte differentiation from hMSCs in vitro
- SM04755 demonstrated sustained local and minimal systemic exposure

Conclusions

- In preclinical tendinopathy models, topical SM04755 reduced inflammation, differentiated progenitor cells into tenocytes, inhibited fibrotic markers, increased tendon regeneration markers, and improved tendon structure micro- and macroscopically.
- SM04755 demonstrated sustained tendon exposure, with minimal systemic exposure, in multiple species.
- A Phase 1 trial with healthy volunteers is on-going.

References

1. Khan KM, et al. BMJ. 2002;324: