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

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• Chronic tendinopathy is an inflammatory, degenerative, and fibrotic condition caused by injuries or overuse. It is characterized clinically by pain, swelling, and impaired performance.1

• Current therapeutic options focus on alleviating the symptoms and pain rather than treatment of the underlying pathology, therefore presenting an unmet medical need.2

• The Wnt pathway plays an important role in tenocyte differentiation. It is upregulated in chronic tendinopathy, in osseous deposits in animal tendons, as well as in clinical tendinopathy samples. Altered Wnt signaling may contribute to tissue metaplasia and failed healing in some cases of tendinopathy.4

• Samumed is developing SM04755, a potent small molecule Wnt signaling inhibitor, as a potential topical treatment for the treatment of tendinopathy.4

Methods

• To identify Wnt signaling inhibitors, a small molecule chemical library was screened in a cellular Wnt pathway-based assay using a β-catenin/TGF-responsive reporter in SW480 colorectal cancer cells. Wnt pathway inhibition was further confirmed by qRT-PCR for Wnt target genes in SW480 colorectal cancer cells.

• Effects on fibrosis were assessed in TGF-β-stimulated human dermal fibroblasts (HDFs) by measuring smooth muscle actin (αSMA), tenomodulin, and tenascin C as measured by high-content imaging (range 5-20) histological indicators of tendon health.

• Pharmacokinetics of SM04755 in rat tendon and plasma following a single topical application of SM04755 at 0.3, 0.1, and 0.03 mg/cm² was evaluated by measuring compound concentrations in tendon and plasma by LC-MS. Plasma by ELISA and other inflammatory markers (IL-1β, IFN-α, IFN-γ, IL-6, TNF-α) by measuring smooth muscle actin (αSMA) by measuring smooth muscle actin (αSMA).

• A Phase 1 trial with healthy volunteers is planned to start in 2016.

Results

• Topical SM04755 reduced markers of tendon inflammation and an inflammatory marker (CXCL1) in plasma, showed evidence of tendon regeneration, and increased tendon health scores compared to a vehicle rodent tendinopathy model.

• Plasma and systemic exposure were minimal in rats.

• SM04755 demonstrates potential to promote tendon healing in chronic tendinopathy.

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Discussion

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