**Background**

- Psoriasis is a chronic, relapsing autoimmune disease, characterized by thick patches of inflamed scaly skin resulting from excessive inflammation and proliferation of skin cells.
- Wnt signaling plays an important role in psoriasis by regulating inflammation, keratinocyte proliferation, and dermal fibrosis.1,2
- Treatment of mild to moderate psoriasis (<10% BSA) using a safe and effective topical agent remains an unmet medical need.
- SM04755, a novel, topical, small molecule Wnt pathway inhibitor was evaluated in a series of preclinical studies to determine its ability to inhibit inflammation, keratinocyte proliferation, and dermal fibrosis, thereby potentially improving skin health in psoriasis.

**Hypothesis**: Inhibition of Wnt signaling using SM04755 would result in decreased inflammation, keratinocyte proliferation, and fibrosis, thus providing benefit in psoriasis.

**Methods**

- Cytokine-induced keratinocyte proliferation was measured in primary human keratinocytes using an EdU incorporation assay.
- Effects on fibrosis were assessed in TGF-β1-stimulated human dermal fibroblasts (HDFα) by measuring smooth muscle actin (αSMA), plasminogen activator inhibitor (PAI-1), connective tissue growth factor (CTGF), and collagen expression by qPCR.
- In vivo efficacy was evaluated in an imiquimod (IMQ)-induced mouse psoriasis model with daily topical IMQ (0.3 mg/cm²) application on the back and ear for 20 days, followed by daily treatment with SM04755 starting on day 3 after first IMQ application. Efficacy was assessed by measurement of skin and ear thickness, spleen size, and inflammation using qPCR.

**Results**

**SM04755 inhibited inflammatory cytokine secretion in vitro**

![Figure 1](image1)

**SM04755 inhibited cytokine induced proliferation of primary human keratinocytes in vitro**

![Figure 2](image2)

**SM04755 prevented fibrosis in vitro**

![Figure 3](image3)

**SM04755 reduced inflammatory markers in a mouse IMQ-induced psoriasis model**

![Figure 4](image4)

**SM04755 reduced ear thickness and improved skin appearance in a mouse IMQ-induced psoriasis model**

![Figure 5](image5)

**SM04755 reduced thickness, inflammation, and proliferation, and improved skin appearance in a mouse IMQ-induced psoriasis model**

![Figure 6](image6)

**Conclusions**

- SM04755, a potent and specific inhibitor of Wnt signaling, inhibited inflammation, keratinocyte proliferation, and fibrosis in vitro.
- In an in vivo mouse model of IMQ-induced psoriasis, topically applied SM04755 inhibited inflammation and cell proliferation and decreased skin thickness, compared to vehicle.
- SM04755 has potential as a topical therapy for psoriasis.
- A Phase 1 trial with healthy volunteers is underway.

**References**