Small Molecule Wnt Pathway (SM04755) Inhibitor as a Potential Topical Treatment for Psoriasis

Vishal Deshmukh, Melinda Pedraza, Lisa Lamangan, and Yusuf Yazici

Samumed, LLC, San Diego, CA

SM04755, a novel, topical small-molecule Wnt pathway inhibitor previously demonstrated inhibition of inflammation and keratinocyte proliferation in vitro and in an Imiquimod (IMQ)-induced mouse psoriasis (PSO) model. Further inflammation and skin effects were evaluated in an ICR scid mouse reconstitution model with minor histocompatibility mismatched naïve CD4+ T lymphocytes, more closely resembling human PSO pathophysiology.

H-2Dd haplotype donor mice were identified from F2 (BALB/c x 129/SvJ) by flow cytometry. CD4+/CD45RBHi cells from donor mice spleens were purified and injected intravenously into CB17/ICR-Tac Prkdcscid (ICR scid) mice (5 x 10^5 cells/mouse). Skin appearance and ear thickness were evaluated weekly for PSO-like signs (lesions, increased thickness). PSO mice were randomized and treated with SM04755 (400 µg/cm^2) or vehicle. After 14 weeks, body and spleen weights were measured, and inflammatory cytokines evaluated (IL-1β, TNF-α, IL-6) in tissues from skin, ears, spleen and plasma using ELISA. Epidermal thickness and infiltrating cells in skin were histologically evaluated.

Immune reconstitution of ICR scid mice resulted in PSO-like signs, with lesions and increased thickness of the skin and ears. Compared to vehicle, topical SM04755 (400 µg/cm^2) significantly (p<0.01) decreased skin and ear thicknesses and improved skin appearance. Body weights were also significantly (p<0.05) higher in treated mice. SM04755 significantly reduced microscopic epidermal thickness (p<0.05) and immune infiltration in the skin compared to vehicle. Inflammatory cytokine levels in the skin, ears, spleen and plasma, as well as spleen weight, were significantly (p<0.05) reduced in SM04755-treated animals compared with vehicle.

In a mouse model of minor histocompatibility mismatched T lymphocyte reconstitution-induced PSO, topical SM04755 inhibited inflammation and decreased skin and ear thicknesses compared to vehicle. SM04755 has potential as a topical therapy for PSO. Clinical trials are ongoing.