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

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**Background:** Psoriasis (PSO) is an autoimmune disease, causing patches of thick, inflamed, scaly skin due to excessive proliferation of skin cells. Wnt signaling plays an important role in PSO, regulating inflammation and keratinocyte proliferation. SM04755, a novel, topical small-molecule Wnt pathway inhibitor was previously shown to inhibit inflammation and keratinocyte proliferation in vitro and in an IMQ-induced mouse PSO model.

**Objective:** In this study, the effects of SM04755 on inflammation and skin health were evaluated in two models that closely resemble human PSO pathophysiology: reconstitution of ICR scid mice with minor histocompatibility mismatched naïve CD4⁺ T lymphocytes and an IL-23 intra-dermal injection model.

**Methods:** For (A) immune reconstitution model, peripheral blood mononuclear cells were isolated from F₂ (BALB/c x 129/SvJ) mice and analyzed by flow cytometry to identify H-2Dd haplotype donor mice. CD4⁺/CD45RB⁺ cells from donor mice spleens were purified and injected intravenously into CB17/ICR-Tac Prkdc/scid (ICR scid) mice (5x10⁵ cells/mouse). Skin appearance and ear thickness were evaluated weekly. At the first visible PSO-like signs, mice were randomized and treated with SM04755 (400 µg/cm²) or vehicle. After 14 weeks, body and spleen weights were measured, and inflammation was evaluated by measuring cytokines (IL-1β, TNF-α, IL-6) in tissues from skin, ears, spleen and plasma using ELISA. Epidermal thickness and skin immune cell infiltration were histologically evaluated. For (B) the IL-23 model, rIL-23 was injected intra-dermally into mouse ears, every other day for 35 days. Mice were randomized on Day 16 and treated with SM04755 (400 µg/cm²) or vehicle or Clobetasol daily for 20 days. Ear thickness was measured every 3 days. Skin immune cell infiltration was histologically evaluated.

**Results:** (A) Immune reconstitution of ICR scid mice resulted in PSO-like signs, with skin lesions and increased thickness of the skin and ears. Treatment with topical SM04755 (400 µg/cm²) significantly (p<0.01) decreased skin and ear thicknesses and improved skin appearance compared to vehicle. Body weights were significantly (p<0.05) higher in treated compared to vehicle mice. SM04755 significantly reduced histologically measured epidermal thickness (p<0.05) and immune cell infiltration in the skin compared to vehicle. Further, inflammatory cytokine levels in the skin, ears, spleen and plasma and spleen weight were significantly (p<0.05) reduced in SM04755 treated animals compared with vehicle. (B) Intradermal IL-23 injection into mouse ears resulted in inflammation and ear thickening by day 16 compared to sham. Treatment with topical SM04755 (400 µg/cm²) significantly (p<0.05) decreased ear thickness, immune cell infiltration, and improved appearance compared to vehicle.
Conclusion: In two mouse models of (A) minor histocompatibility mismatched T lymphocyte reconstitution-induced PSO and (B) IL-23 injection-induced PSO, topically applied SM04755 inhibited key pathophysiological features of PSO at macro- and microscopic levels, compared to vehicle. SM04755 has potential as a topical therapy for PSO. Clinical trials are ongoing.