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Dorsal depilated BALB-C mice were dosed topically for 14 days with 100mg topical IMI cream (Day 1-7: induction phase, Day 8-14: treatment phase). N=4 animals were assigned to each treatment group with each group receiving 100mg of allocated treatment on Day 8-14 once daily.

- Dose dependent response was observed over the VYN201 concentration range 0.001% to 0.1%
- There was a 94% reduction in composite score for VYN201 0.1% relative to vehicle control group at Day 7
- VYN201 0.1% had comparable efficacy to clobetasol propionate 0.05% cream

- Animals treated with VYN201 0.1% continued to gain body weight in a similar manner to healthy control group treated with vehicle
- Clobetasol cream 0.05% group had a 17% reduction in body weight compared to the VYN201 0.1% group at treatment day 7
Dorsal depilated BALB-C mice were dosed topically for 14 days with 100mg topical IMI cream (Day 1-7: induction phase, Day 8-14: treatment phase). N=4 animals were assigned to each treatment group with each group receiving 100mg of allocated treatment on Day 8-14 once daily.

- Strong correlation between improvement in clinical severity scores and reduction in many pro-inflammatory biomarkers relevant to Th17-mediated autoimmune diseases.
- Dose-dependent reduction in biomarker expression was observed with VYN201 0.1% as having the greatest effect.
- IL1β, IL-6 and IL-23 precipitate the differentiation of naïve Th0 immune cells to Th17 cells.
- Th17 cells produce a range of cytokines that drive inflammation in autoimmune diseases. These include IL17, IL36 and TNFα.
VYN201 Vehicle

- No appreciable improvement in clinical signs

VYN201 0.1%

- Substantial resolution of clinical signs
- Skin presents with normal physiology with no evidence of striae rubrae or atrophy
- No evidence suggestive of intolerance

Clobetasol Cream 0.05%

- Substantial resolution of clinical signs
- Significant evidence of dermal atrophy (clear presence of both rhytides/fine wrinkles and deep wrinkles)
- Marked dermal translucency and elastolysis

VYN201: Normal Skin Physiology in TH17-Mediated Murine Inflammation Model Suggests VYN201 Well Tolerated (Day 7)
VYN201 Significantly Reduced Expression of Several Key Pro-Inflammatory Proteins Relevant to Th17-mediated Autoimmune Diseases in Human Tissue$^1$

>95% Inhibition seen with assays for IL-36γ & LP-10

**Interleukin 36-gamma**

IL36γ is implicated in upregulating IL-17A signaling-related genes and so able to amplify keratinocyte inflammatory responses by promoting not only their own expression but also that of other cytokines related to Th17 signaling.

**CXC motif chemokine ligand 10 (LP-10)**

An inflammatory cell chemoattractant secreted in response to interferon gamma. LP-10 is significantly overexpressed in many autoimmune diseases (>25-fold) vs. healthy skin$^1$

**Interleukin 17-alpha**

T-cells are polarized to Th1 and Th17 cells, the latter of which drives the production of IL17a which further upregulates the migratory action of pro-inflammatory cells and further inflammatory cell activation.

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Female hairless mice (n=4/group) had two identical 10mm incisions made either side of the flank. Animals were topically dosed 1X daily with 100mg VYN201 vehicle, VYN201 1% or a hydroalcoholic gel* until each wound had completely healed.

- Statistically significant difference in composite global external healing score for VYN201 vehicle and 1% compared to Hydroalcoholic gel
- Complete healing occurred for VYN201 1% and VYN201 vehicle approximately 5 days earlier compared to Hydroalcoholic gel  
  (Mean day to heal: 15.5 vs. 21 days)

* A negative control known to delay wound healing

Global External Lesion Score is a composite severity score of lesion length, width, swelling and visibility.
Fibrotic tissue mass is scored on a 4-point severity scale: 0=No tissue mass; 1=small tissue mass; 2=moderate tissue mass; 3=large tissue mass

- Animals treated with VYN201 1% had statistically significant less tissue mass/fibrosis compared to VYN201 vehicle or Hydroalcoholic gel, indicative of the known anti-fibrotic mechanism for BET inhibition
VYN201: Little Evidence of Residual Swelling and Macular Wound Appearance in Murine Skin Healing Model

VYN201 Vehicle
• Still evidence of minor swelling around incision sites

VYN201 1%
• Little evidence of residual swelling
• Wound appears more macular in nature compared to VYN201 vehicle or the hydroalcoholic gel
• Incision sites appear less distinct and leave a more aesthetic outcome compared to other treatments

Hydroalcoholic gel
• Moderate swelling clearly evident at end of treatment
• Although healed, residual scabbing still remains
• Incision sites clearly visible
Summary of Preclinical Studies

- VYN201 significantly reduced the expression of several key pro-inflammatory cytokines relevant to Th17-mediated autoimmune diseases.
- VYN201 demonstrated improvement in reducing fibrotic tissue mass and overall skin repair outcomes.
- Key highlights from the preclinical studies:
  - VYN201 exhibited anti-inflammatory effect similar to super-potent glucocorticosteroids.
  - VYN201 appeared well-tolerated in mice, as seen through animal body weight and skin condition.
  - VYN201 also demonstrated stronger inhibition of key Th17 cytokines in ex vivo data with human skin tissue when directly compared to JAK1/2 inhibitor, ruxolitinib.
  - VYN201, demonstrated improvements in reducing fibrotic tissue mass and overall skin repair outcomes with no negative impact on healing time. The results support the continued progression of VYN201 development program.