

## **A Small Molecule Modulator of the Wnt Pathway (SM04554) as a Potential Topical Treatment for Androgenetic Alopecia (AGA)**

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### **Aim**

SM04554, a novel, small molecule Wnt signaling modulator was evaluated in preclinical studies for hair follicle regeneration and hair growth as a potential treatment for AGA.

### **Methods**

Male CD1 and C57Bl/6 mice were depilated with Nair and treated with SM04554 or vehicle. Effects during telogen phase were measured using C57Bl/6 mice, shaved and treated starting on post-natal day (P) 49. Effects of various dosing regimens (treatment durations and on-off cycles) was evaluated in NIH-III nude mice and Hanford mini-pigs. Assessment of visual hair growth and histological follicle counts were performed at multiple timepoints in all studies, with classification of follicle types (vellus, indeterminate and terminal) in the mini-pig study. Activation of Wnt signaling, hair cycle and follicle proliferation were measured by immunostaining for  $\beta$ -catenin, versican and Ki-67.

### **Results**

In CD1 mice, SM04554 induced hair growth with 4-days treatment, with a 2-fold increase ( $p \leq 0.05$ ) in total hair-follicle counts, compared to vehicle. In depilated C57Bl/6 mice, SM04554 induced hair growth with 10 days of treatment. In C57Bl/6 mice shaved and treated from P49, hair growth was observed after 3 weeks of treatment with SM04554 compared to 5 weeks with vehicle. In NIH-III nude mice, an increase in the number of hair-follicles (2-fold,  $p \leq 0.05$ ) was observed in SM04554-treated animals on day 14, with appearance of hair on day 28 and further increase with 42 days of treatment compared to no hair growth with vehicle. In mini-pigs, 42 days of SM04554 treatment showed a significant ( $p \leq 0.05$ ) increase in vellus follicle numbers that was sustained until day 112, as compared to other treatment intervals and vehicle. SM04554 increased total and nuclear  $\beta$ -catenin, versican and Ki-67 specifically in hair follicles compared to vehicle, indicating localized follicular activation of Wnt signaling and proliferation, not generalized to the epidermis.

### **Conclusion**

In rodents and mini-pigs, SM04554 increased follicle number and hair growth compared to vehicle. SM04554 has potential as a topical therapy for AGA. Clinical studies are ongoing.