Accepted as an oral presentation at the 4th International Dermatology and Cosmetology Congress (INDERCOS) 2019, Istanbul, Turkey, March 27-30, 2019

A Small-Molecule Wnt Pathway Modulator (SM04554) as a Potential Topical Treatment for Androgenetic Alopecia

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Background: Androgenetic alopecia (AGA) is the most common form of hair loss in men. Wnt signaling, reduced in AGA, is critical to growth and maintenance of follicles and hair. SM04554, a novel, small-molecule, topical Wnt pathway modulator, was evaluated as an AGA treatment. Safety, tolerability, and efficacy were characterized in two double-blind, vehicle-controlled clinical trials.

Methods: Male subjects with AGA (Norwood-Hamilton [NH] 4-6), 18-65 years, were treated daily for 90 days with topical 0.15% SM04554, 0.25% SM04554, or vehicle. Adverse events (AEs) were collected. Study 1: Hair counts were assessed with scalp macrophotography (Baseline [BL], Days 90, 135). Study 2: Hair follicles (vellus [<30µm diameter], indeterminate [30-60µm], terminal [>60µm]) were counted and categorized by hair cycle phase from horizontally sectioned scalp biopsies (BL, Days 91, 135). Nuclear expression of β-catenin and Ki-67 were measured in epidermis and follicular infundibula and Ki-67 was assessed in hair bulbs.

Results: Common AEs included local erythema, pruritis, and exfoliation. These were mild and were not significantly different between treatment and vehicle groups. Study 1 enrolled 302 subjects (0.15% n=102, 0.25% n=102, vehicle n=98). The 0.15% group exhibited significant improvements in hair count (P=0.025) and density (P=0.011) at Day 135 vs. vehicle adjusting for age, NH grade, compliance, and Day 90 assessment. Study 2 enrolled 49 subjects (0.15% n=16, 0.25% n=14, vehicle n=19). All comparisons were between SM04554 and vehicle. Significantly higher total follicle counts were seen at Days 91 (P<0.001) and 135 (P<0.001) in the 0.25% group and at Day 135 (P<0.001) in the 0.15% group. The 0.25% group exhibited significantly higher numbers of vellus (P<0.01), indeterminate (P<0.001), total anagen (P<0.001), and terminal anagen (P=0.01) follicles at Day 91. At Day 135, the 0.25% group had significantly higher numbers of vellus (P<0.01), total anagen (P<0.01), and terminal catagen/telogen (P<0.01) follicles. The 0.15% group exhibited significantly higher numbers of vellus (P<0.01), terminal (P=0.01), total anagen (P<0.01), and terminal catagen/telogen (P=0.03) follicles at Day 135. No significant differences were seen in epidermal β-catenin and Ki-67 between treatment and vehicle groups. Ki-67 was increased in the hair bulb for both SM04554 groups vs. vehicle at Day 91 (0.15% [P=0.07], 0.25% [P=0.25]).

Conclusion: SM04554 appeared safe and well tolerated. Increased hair and follicle counts suggested that SM04554 may promote hair regrowth, new follicle formation, and/or reactivation of miniaturized follicles. Epidermal β-catenin and Ki-67 indicated no significant proliferative

signal, while Ki-67 in the hair bulb may suggest hair growth and/or follicle formation. These studies indicated that topical SM04554 is a potentially efficacious treatment for AGA in men. A Phase 3 trial is underway in Turkey.