

Safety and Biopsy Outcomes of a Topical Treatment (SM04554) for Male Androgenetic Alopecia (AGA): Results from a Phase 2, Multicenter, Randomized, Double-blind, Vehicle-controlled Trial

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John Seykora, MD, PhD¹, Ismail Simsek, MD², Anita DiFrancesco², Christopher J. Swearingen, PhD², Yusuf Yazici, MD²
¹University of Pennsylvania, Philadelphia, PA, USA, ²Samumed LLC, San Diego, CA, USA

Poster #4555

Background

- In the U.S. approximately 35 million men are affected by Androgenetic Alopecia (AGA), which is a common form of hair loss in both men and women.^{1,2}
- Two products have been approved in the past 15 years: minoxidil (Rogaine®, Upjohn Co.), which is considered to have variable efficacy; and finasteride (Propecia®, Merck), which has label warnings for sexual adverse events.² Therefore, alternative treatment options with improved efficacy and safety profiles are needed.
- Wnt signaling supports hair growth: Wnt signaling initiates and maintains anagen phase³; Wnt pathway activation induces endogenous dermal progenitor cells to differentiate into a hair bulge, leading to new hair follicles³; Reduced Wnt signaling is associated with hair loss in AGA.⁴
- Samumed is developing SM04554, a novel topical small molecule, to treat AGA.
- SM04554 has been tested in Phase 1 and Phase 2 trials where it increased hair counts and appeared to be safe, well-tolerated, and potentially efficacious.^{5,6}
- Further safety and efficacy of SM04554, with scalp biopsy results, were examined in this Phase 2 study (SM04554-AGA-04).

Methods

- Male subjects [N=49], 18 – 65 years old with AGA (Norwood-Hamilton Classification score of 4, 5, 5A, 5V, or 6) were randomized to receive topical SM04554 solution 0.15%, 0.25%, or vehicle (applied to the scalp q.d. for 90 days) in a 1:1:1 ratio.
- After a 90-day treatment period, subjects were followed for 51 days.
- A 4 mm scalp biopsy (at leading edge of circumference of balding area within treatment area) was performed on Day -26 (baseline) and Day 91; an optional biopsy was performed on Day 135.
- Safety assessments included:
 - Investigator Scalp Assessment (scoring erythema, scaling, pruritus/itching, and burning/stinging, each on 0-4 scale)
 - Medical history, vital signs, clinical laboratory sampling
 - Collection of adverse events (AEs) and concomitant medications

SM04554-AGA-04 Subject Characteristics

	Vehicle	0.15% SM04554	0.25% SM04554
Intent to Treat (ITT) population [N]	19	16	14
Age at Consent (Years) [Mean (SD)]	50.5 (9.3)	49.5 (11.8)	48.2 (11.2)
Race [N(%)]			
<i>White</i>	12 (63%)	12 (75%)	10 (71%)
<i>Black</i>	7 (37%)	4 (25%)	4 (29%)
Norwood-Hamilton [N(%)]			
4	3 (16%)	2 (13%)	3 (21%)
5	8 (42%)	2 (13%)	4 (29%)
5A	1 (5%)	1 (6%)	3 (21%)
5V	3 (16%)	5 (31%)	2 (14%)
6	4 (21%)	6 (38%)	2 (14%)
Day 91 Biopsy [N]	18	13	12
Day 135 Optional Biopsy [N]	13	8	7

- Biopsies were horizontally-sectioned and hair follicles (vellus [$<30 \mu\text{m}$], indeterminate [$30-60 \mu\text{m}$], terminal [$>60 \mu\text{m}$]) were counted and categorized by hair-cycle phase.
 - Differences in absolute follicle count were estimated using Poisson regression.
 - Bonferroni correction alpha was 0.025 for the two treatment comparisons.
 - Each visit was analyzed separately in a model with treatment adjusted for baseline measure.
 - Comparisons were against vehicle follicle counts.
- Nuclear expression of β -catenin and Ki-67 were measured in epidermis and follicular infundibula and Ki-67 was assessed in hair bulbs. Baseline-adjusted Gamma regression estimated differences in nuclear expression outcomes between treatment groups and vehicle.
- Data presented are from the Intent-to-Treat (ITT) Analysis Set (i.e., all randomized subjects).

Results

Safety

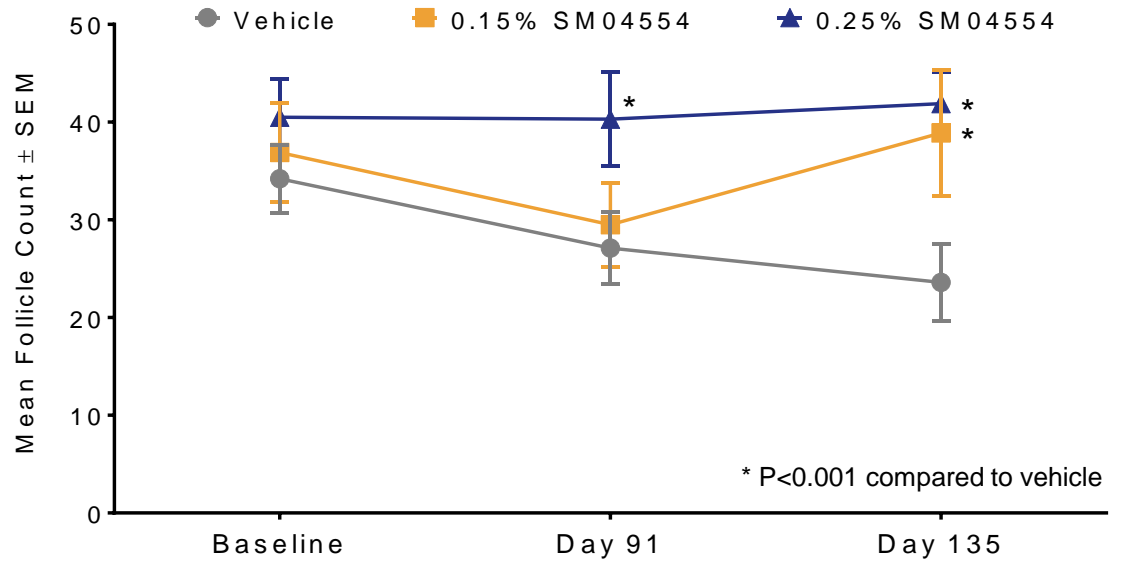
- No serious adverse events (SAEs) were reported.
- 48 adverse events (AEs) were experienced by 29 subjects:
 - 14 in the 0.15% SM04554 group
 - 16 in the 0.25% SM04554 group
 - 18 in the Vehicle group
- AEs considered related to study treatment were application site erythema (1), application site paraesthesia [burning and/or stinging] (1), application site pruritus (2), and skin exfoliation (2).
- Most AEs were mild (grade 1) or moderate (grade 2) in severity per Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (1-5 scale).
- No trends or imbalances were noted between all treatment and vehicle groups.
- Laboratory parameters and vital signs were unremarkable during the study.
- No clinically significant values or changes from baseline were reported in any of the subjects.

AEs in ≥2 Subjects by Prevalence

Preferred Term	Vehicle N=19	0.15% SM04554 N=16	0.25% SM04554 N=14	All N=49
Any AE [# of AEs / # of Subjects (%)]	18 / 11 (58)	14 / 9 (56)	16 / 9 (64)	48 / 29 (59)
Application site pruritus	2 / 2 (11)	2 / 2 (13)	1 / 1 (7)	5 / 5 (10)
Upper respiratory tract infection	2 / 2 (11)	1 / 1 (6)	1 / 1 (7)	4 / 4 (8)
Skin exfoliation	1 / 1 (5)	2 / 2 (13)	0 / 0 (0)	3 / 3 (6)
Application site paraesthesia	1 / 1 (5)	0 / 0 (0)	1 / 1 (7)	2 / 2 (4)
Contusion	0 / 0 (0)	2 / 2 (13)	0 / 0 (0)	2 / 2 (4)
Diarrhoea	1 / 1 (5)	0 / 0 (0)	1 / 1 (7)	2 / 2 (4)
Nasopharyngitis	0 / 0 (0)	1 / 1 (6)	1 / 1 (7)	2 / 2 (4)
Pain of skin	2 / 2 (11)	0 / 0 (0)	0 / 0 (0)	2 / 2 (4)

Total Follicle Count

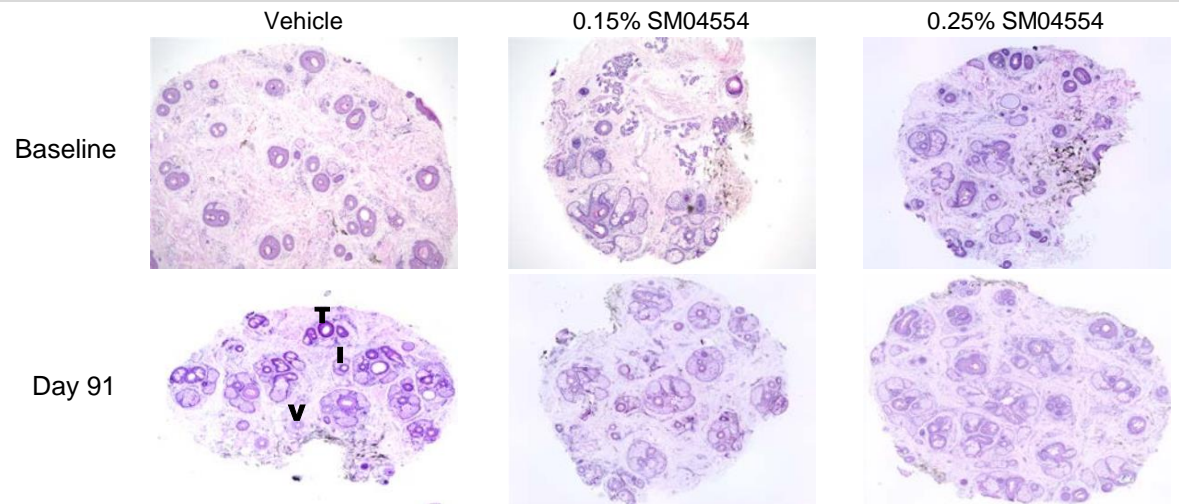
- The 0.25% group exhibited significantly higher total follicle counts at Days 91 (P<0.0001) and 135 (P=0.0002) compared to vehicle.
- The 0.15% group exhibited significantly higher total follicle counts at Day 135 (P=0.0002) compared to vehicle.



	Vehicle			0.15% SM04554			0.25% SM04554		
	Mean	SEM	N	Mean	SEM	N	Mean	SEM	N
Baseline	34.2	3.5	19	36.9	5.1	16	40.5	3.9	14
Day 91	27.1	3.7	18	29.5	4.3	13	40.3	4.8	12
Day 135	23.6	3.9	13	38.9	6.5	8	41.9	3.2	7

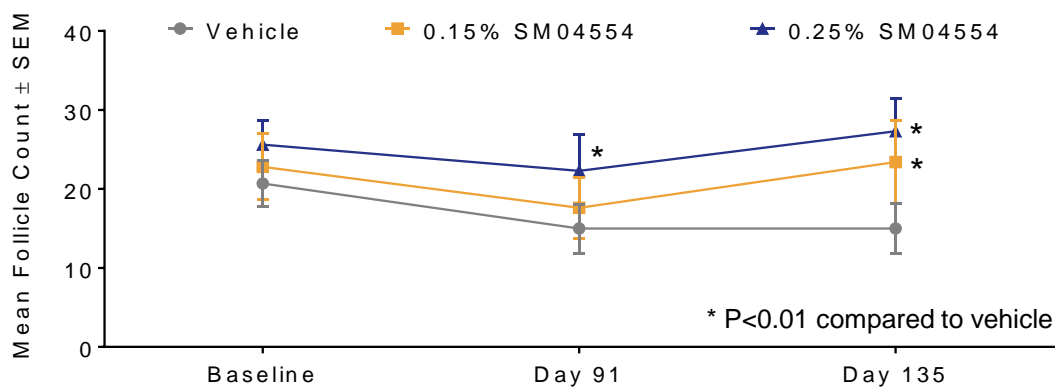
Results (continued)

Representative Biopsy Images



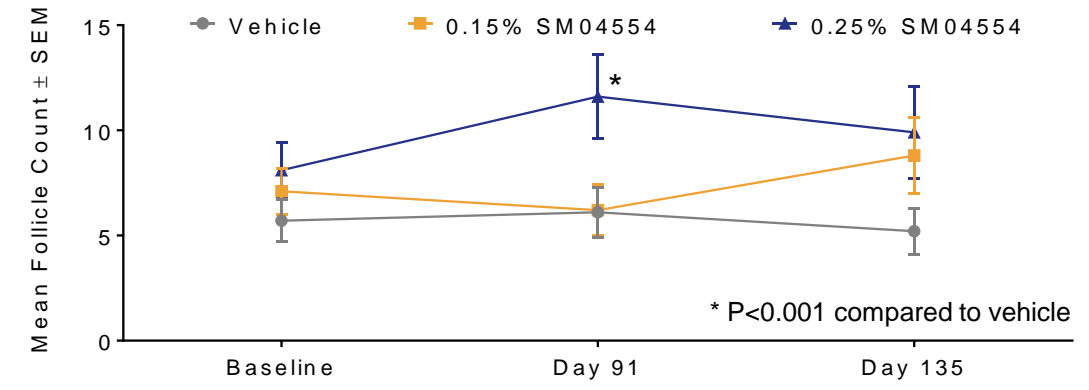
All images = 40x; T = Terminal; I = Indeterminate; V = Vellus

Vellus Follicle Count



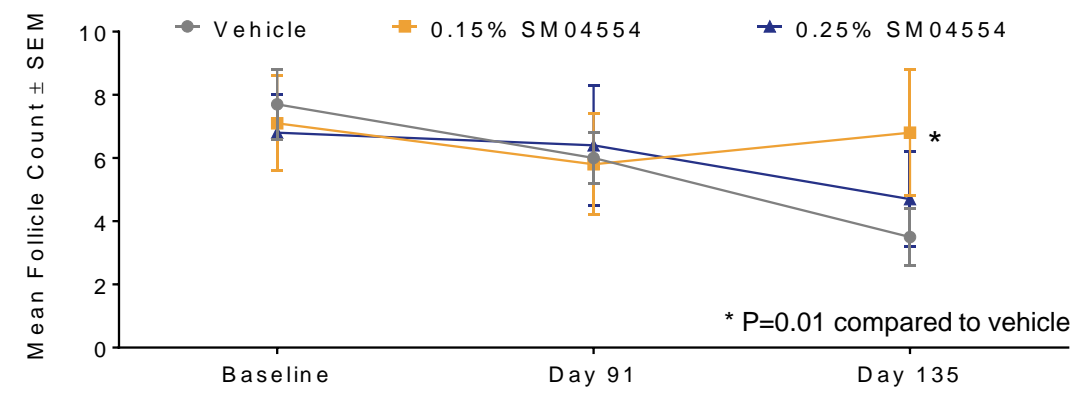
- The 0.25% group exhibited significantly higher numbers of vellus follicles at Day 91 (P=0.003) and Day 135 (P=0.002) compared to vehicle.
- The 0.15% group exhibited significantly higher numbers of vellus follicles at Day 135 (P=0.007) compared to vehicle.

Indeterminate Follicle Count



- The 0.25% group exhibited significantly higher numbers of indeterminate follicles at Day 91 (P=0.0004) compared to vehicle.

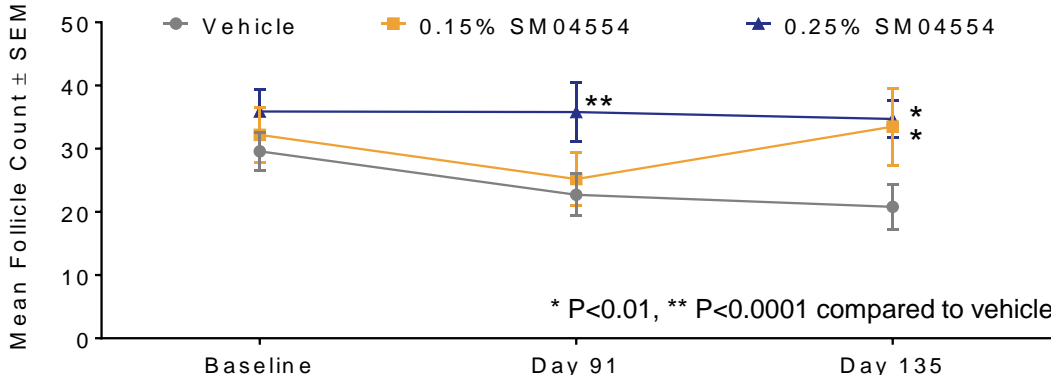
Terminal Follicle Count



- The 0.15% group exhibited significantly higher numbers of terminal follicles at Day 135 (P=0.01) compared to vehicle.

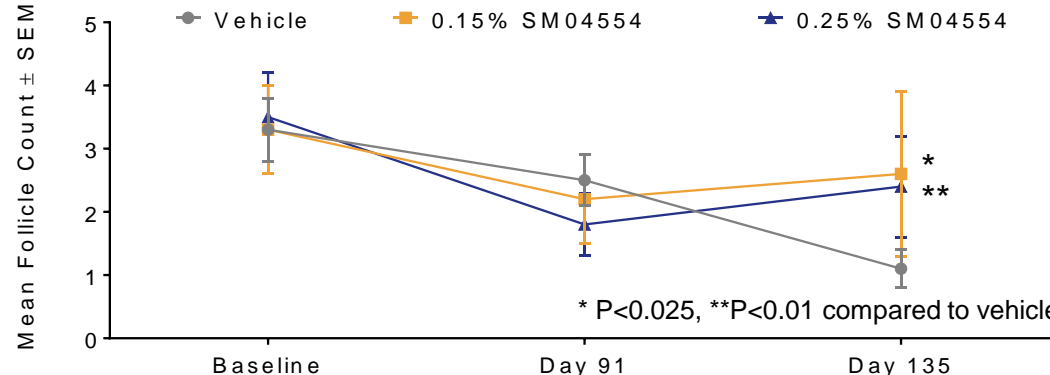
Results (continued)

Total Anagen Follicle Count



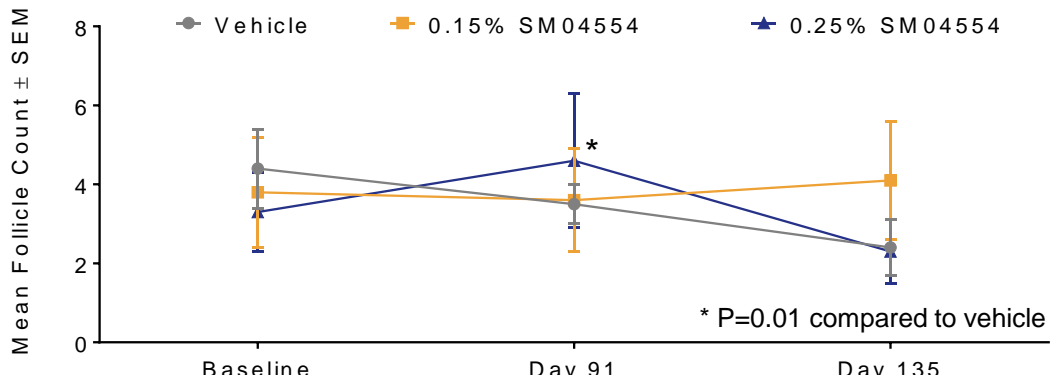
- The 0.25% group exhibited significantly higher numbers of total anagen follicles at Day 91 (P<0.0001) and Day 135 (P=0.004) compared to vehicle.
- The 0.15% group exhibited significantly higher numbers of total anagen follicles at Day 135 (P=0.004) compared to vehicle.

Terminal Catagen/Telogen Follicle Count



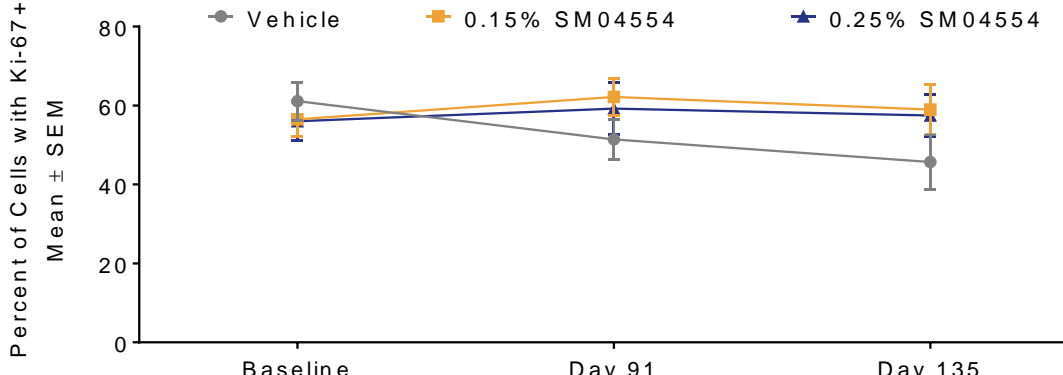
- The 0.25% group exhibited significantly higher numbers of terminal catagen/telogen follicles at Day 135 (P=0.006) compared to vehicle.
- The 0.15% group exhibited significantly higher numbers of terminal catagen/telogen follicles at Day 135 (P=0.0248) compared to vehicle.

Terminal Anagen Follicle Count



- The 0.25% group exhibited significantly higher numbers of terminal anagen follicles at Day 91 (P=0.01) compared to vehicle.

Ki-67 in Hair Bulb



- Ki-67 was increased in the hair bulb for both SM04554 groups at Day 91 (0.15% [P=0.07], 0.25% [P=0.25]) and for the 0.25% group at Day 135 (P=0.17) compared to vehicle.

Discussion

- SM04554 appeared safe and well-tolerated.
- No significant differences were seen between 0.15% or 0.25% SM04554 and vehicle in epidermal β -catenin and Ki-67, indicating no abnormal proliferative signal.
- Statistically significantly higher numbers of hair follicles estimated by Poisson Regression compared with the vehicle group in the ITT analysis set were observed as follows:
 - The 0.25% group exhibited significantly higher counts at Days 91 and 135 for total ($P<0.001$; $P<0.001$), vellus ($P=0.003$; $P=0.002$), and total anagen ($P<0.001$; $P=0.004$) follicles. Significantly higher counts were also seen at Day 91 for indeterminate ($P<0.001$) and terminal anagen ($P=0.01$) follicles, and at Day 135 for terminal catagen/telogen ($P=0.006$) follicles.
 - The 0.15% group exhibited significantly higher counts at Day 135 for total ($P<0.001$), vellus ($P=0.007$), terminal ($P=0.01$), total anagen ($P=0.004$), and terminal catagen/telogen ($P=0.0248$) follicles.
- A higher Ki-67 signal within the hair bulb was observed in both the 0.15% and 0.25% groups from Baseline to Day 91 and the 0.25% group from Baseline to Day 135 compared with the vehicle group, suggesting a more robust proliferation of hair bulb epithelial cells, which may have indicated hair growth and/or follicle formation.
- Increased follicle counts and hair bulb Ki-67 signals suggested treatment with SM04554 may have promoted follicular neogenesis and therefore may be a potential treatment for AGA. Assessment of follicle functionality, however, is needed.
- These results suggested that SM04554 may be the first treatment causing follicular neogenesis.
- This study supported further evaluation of SM04554 as a potential treatment of AGA.

References

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Disclosures

J. Seykora: Consultant; Samumed, LLC. **I. Simsek:** Salary, Contractual Services; Samumed, LLC. **A. DiFrancesco:** Salary, Contractual Services; Samumed, LLC. **C.J. Swearingen:** Salary, Contractual Services; Samumed, LLC. **Y. Yazici:** Salary, Contractual Services; Samumed, LLC.



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