A small-molecule Wnt pathway modulator (SM04554) as a potential topical treatment for androgenetic alopecia

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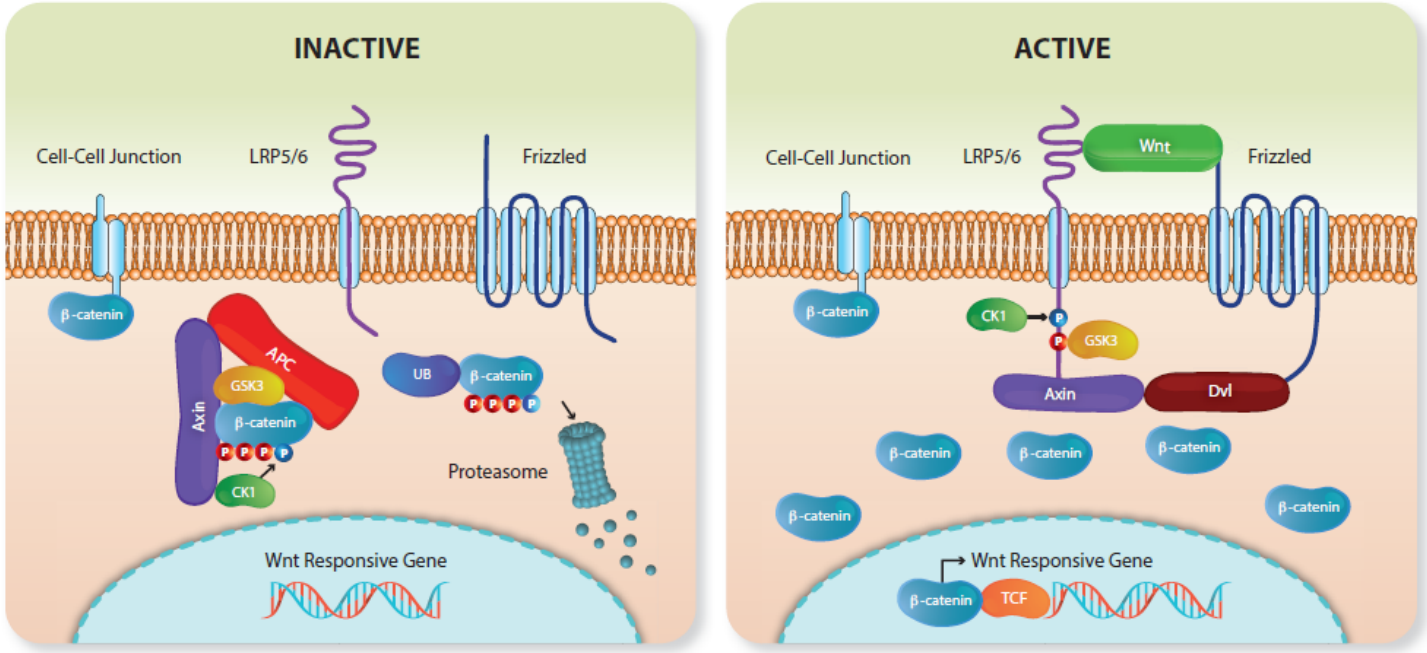
Disclosures and disclaimer

- Ismail Simsek, Anita DiFrancesco, Christopher J. Swearingen, David Herman, and Yusuf Yazici are employees and shareholders of Samumed LLC
- This presentation is not intended to provide a comprehensive overview of all studies using SM04554
- SM04554 is an investigational compound; SM04554 has not been approved by the U.S. Food and Drug Administration (FDA) or any other pharmaceutical regulatory authority, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidate
- While the complete mechanism of action (MOA) for SM04554 is unknown, further investigation is being conducted. All of the MOA information is based on non-clinical data and the relationship to clinical benefit is unknown
- This presentation is intended as a scientific exchange of medical information, is provided for educational purposes only, and is not intended for any promotional purpose or to offer medical advice

Wnt signaling pathway

- Highly conserved across all animals
- Involved in the development of multiple tissues
- Plays a critical role in self-renewal and fate determination of mesenchymal stem cells



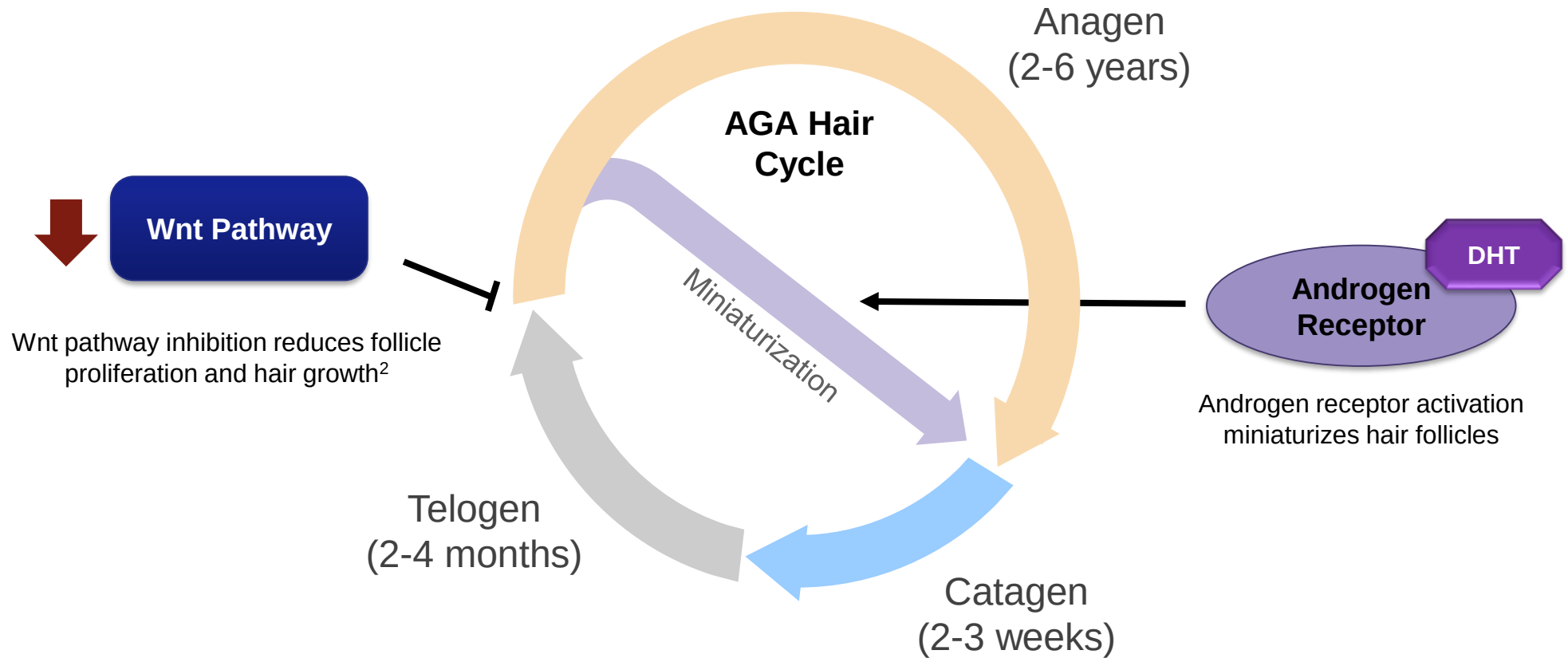
Wnt pathway plays a key role in tissue repair and regeneration

Image adapted from Lim, et al. *Science*. 2013

1. Nusse, et al. *Cold Spring Harbor Lab Press*. 2013
2. Clevers, et al. *Science*. 2014

Androgenetic alopecia and hair growth cycle

- Male AGA characterized by progressive hair follicle miniaturization and decreased hair growth
- Wnt pathway activity is decreased in AGA[1]



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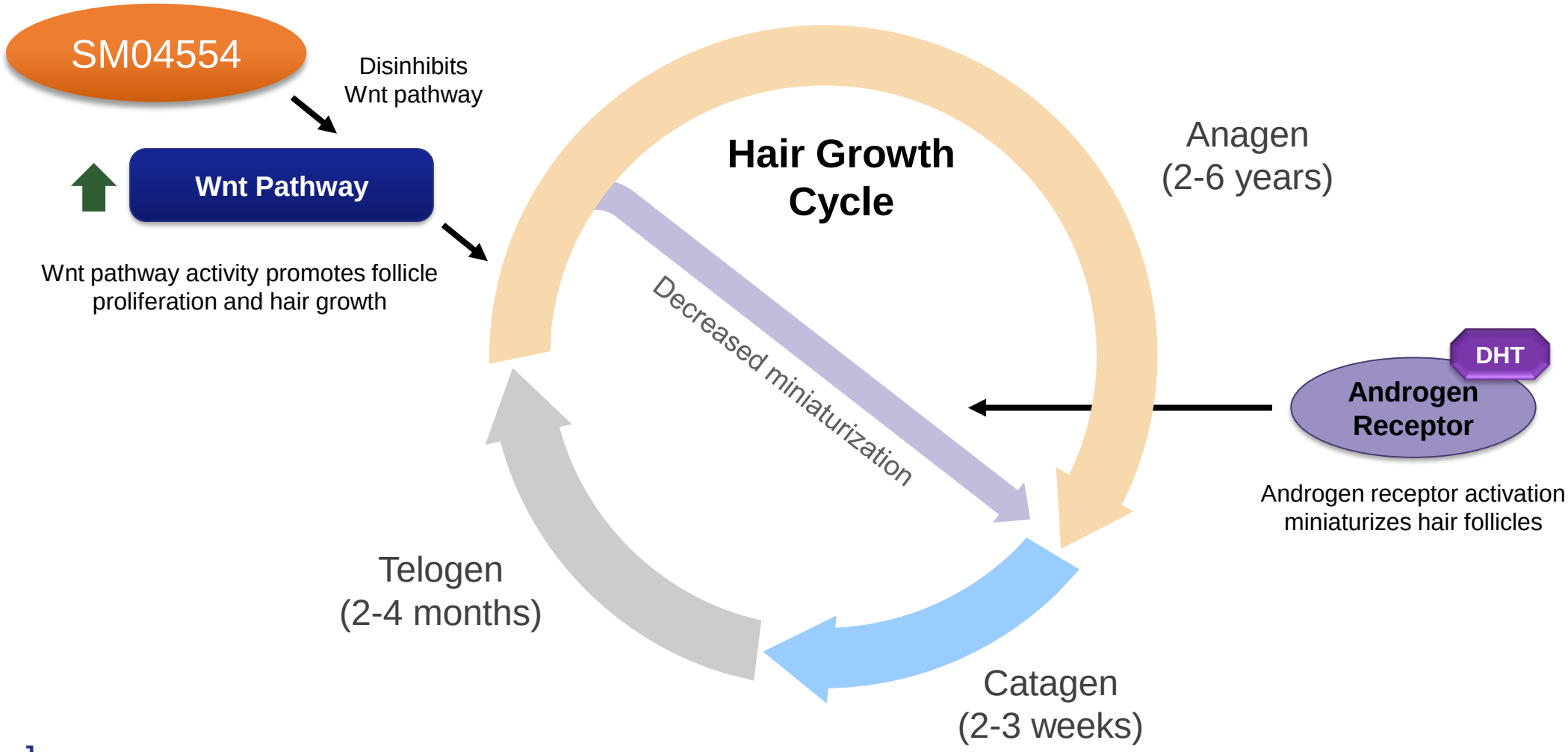
1. Leirõs, GJ, et al. *Br. J. Dermatol.* 2012
2. Beaudoin GM, 3rd, et al. *PNAS*. 2005

Hypothesis: SM04554 disinhibition of the Wnt signaling pathway leads to hair growth



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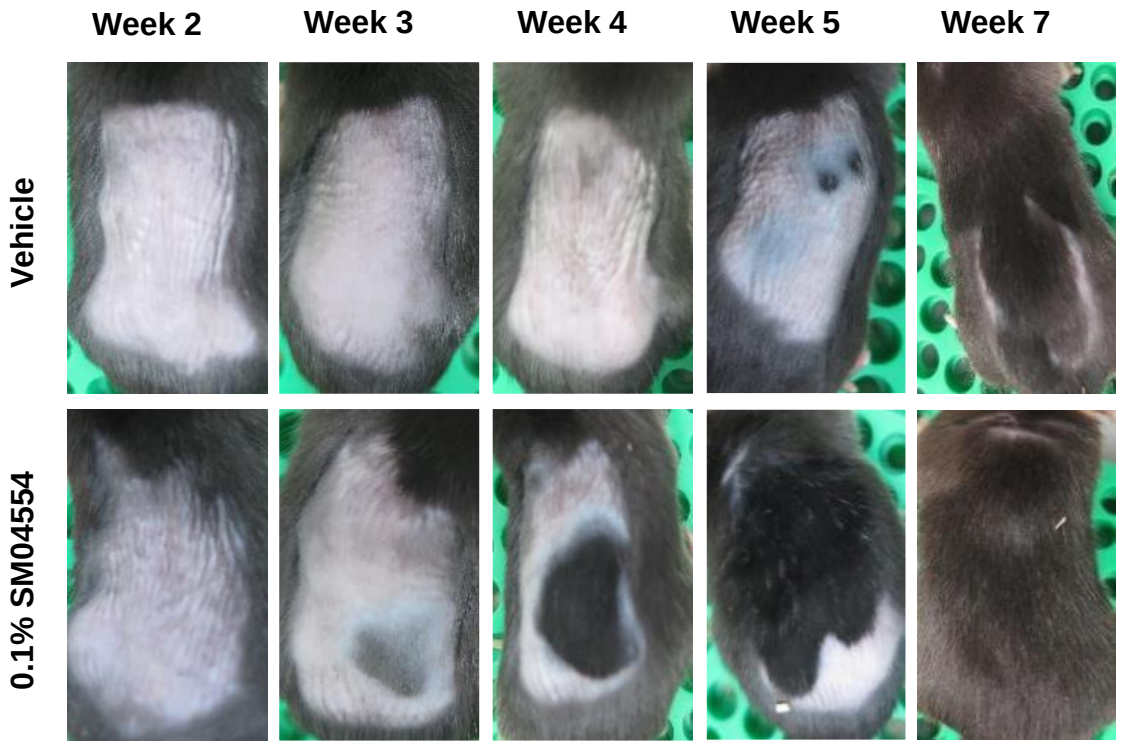
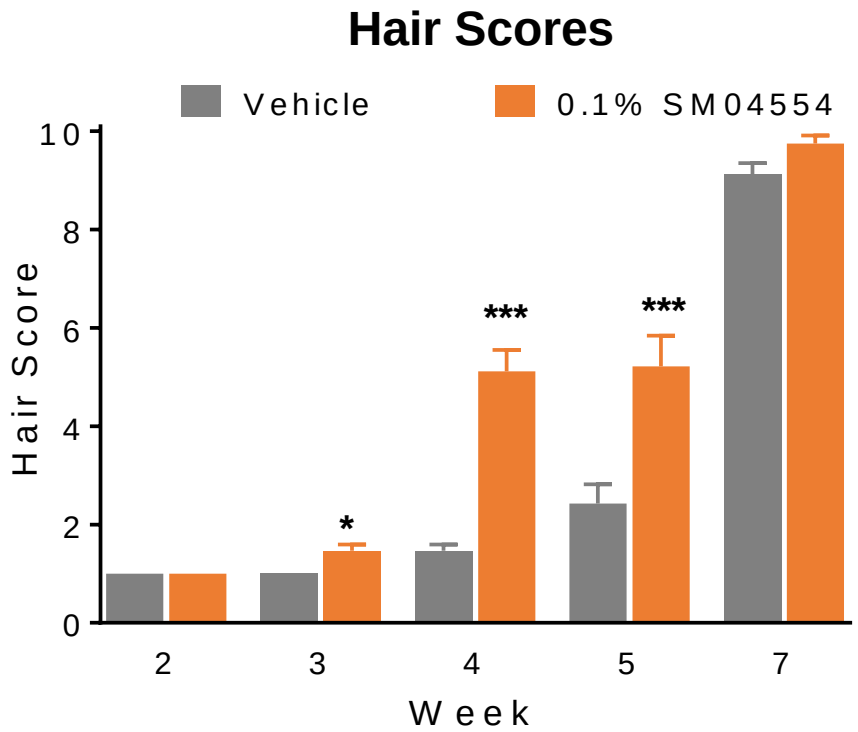
SM04554 accelerated hair growth in mice





Hair Score = Semi-quantitative visual score (1-10)

*p<0.05, ***p<0.001 vs. vehicle
n=23/group at baseline
12 sections/mouse

C57Bl/6 mice daily topical treatment starting Day 50

Mice begin telogen ~ post-natal Day 49 and enter anagen 4-5 weeks later[1]

1. Müller-Röver S. *JID.* 2001

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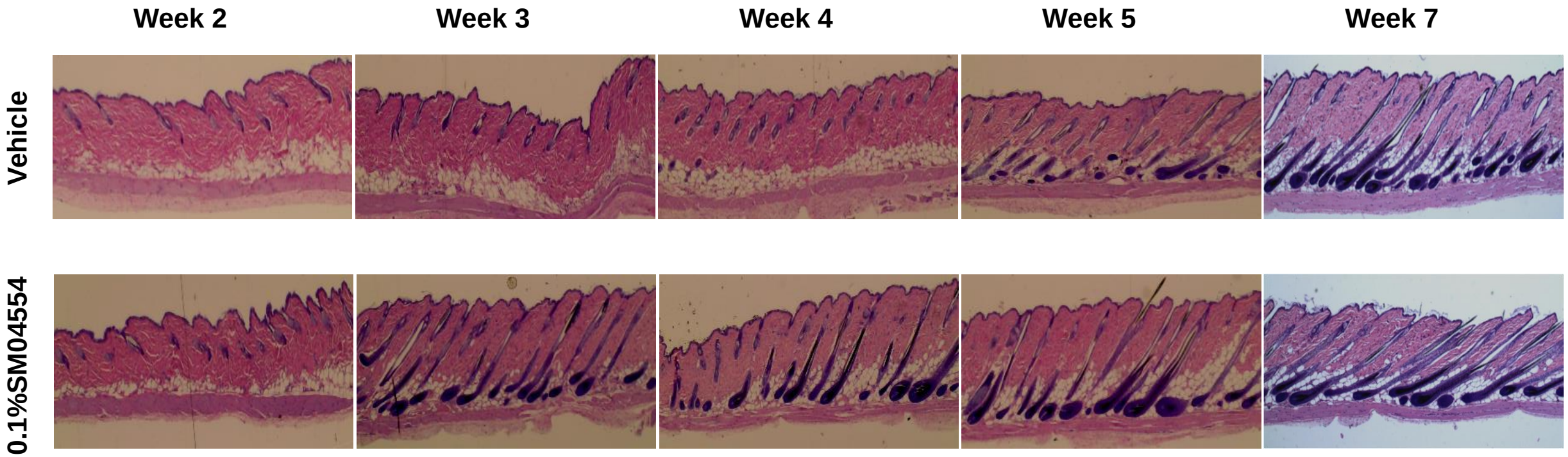
SM04554 shortened telogen and accelerated anagen in mice



n=23/group at baseline
12 sections/mouse

C57Bl/6 mice daily topical treatment starting Day 50

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SM04554 preclinical summary

Safety

- Topical SM04554 led to biologically active compound levels in the skin with minimal systemic exposure
- SM04554 appeared to be safe and well tolerated compared to vehicle
  - Genotoxicity studies showed no mutagenic signal
  - No dermal safety signals were observed up to the highest formulable dose in dermal toxicity studies

Efficacy (compared to vehicle)

- SM04554 increased Wnt signaling
- Topical SM04554 increased hair growth

Clinical Development

SM04554 phase 1 studies summary

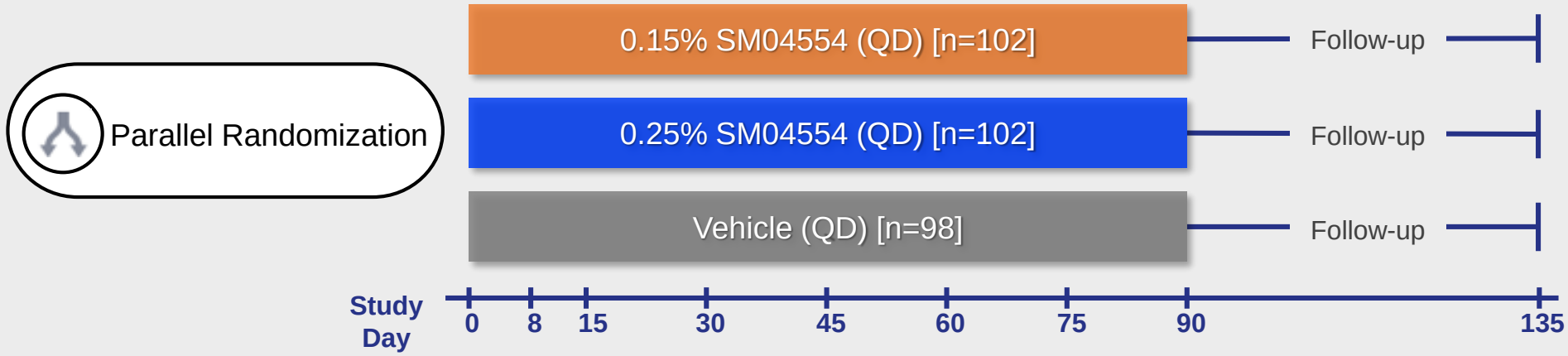
- SM04554 appeared safe and well tolerated when dosed daily (14 days)
- No SAEs/DLTs reported
- Most adverse events considered unrelated to study medication by investigator
- Laboratory parameters, ECGs, and vital signs unremarkable during study. No clinically significant changes reported in any subjects
- Low systemic exposure
  - Low concentrations in plasma (≤1.21 ng/mL), but not detected in all subjects at all time points

SM04554: AGA – 02

Phase 2, Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study of the Safety and Efficacy of Topical SM04554

Subjects with AGA | N= 302 | Aged 18-55 | Diagnosed AGA | NH Classification: 4, 5, 5A, 5V, or 6

Androgenetic Alopecia



Primary outcomes	• Quantification by macrophotography of non-vellus hair count – Pre-treatment (Day 0) compared to Day 45, 90, and 135 • Hair growth and quality by subject completed Men's Hair Growth Questionnaire (MHGQ)
Secondary outcomes	• Safety and tolerability • Hair growth by investigator scale • Quality of life by Kingsley Alopecia Profile (KAP) • Hair density by macrophotography

SM04554-AGA-02 phase 2 study

Baseline demographics and characteristics

		Vehicle	0.15% SM04554	0.25% SM04554
N (Safety Population)		98	102	102
Age at Consent (Years) [Mean (SD)]		45.0 (8.6)	44.2 (8.2)	44.7 (8.8)
Race [N(%)]				
	White	90 (92%)	89 (87%)	88 (86%)
	Black	6 (6%)	10 (10%)	10 (10%)
Norwood-Hamilton [N(%)]				
	4	35 (36%)	29 (28%)	36 (35%)
	5	17 (17%)	9 (9%)	14 (14%)
	5A	22 (22%)	18 (18%)	11 (11%)
	5V	14 (14%)	26 (26%)	22 (22%)
	6	10 (10%)	20 (20%)	19 (19%)

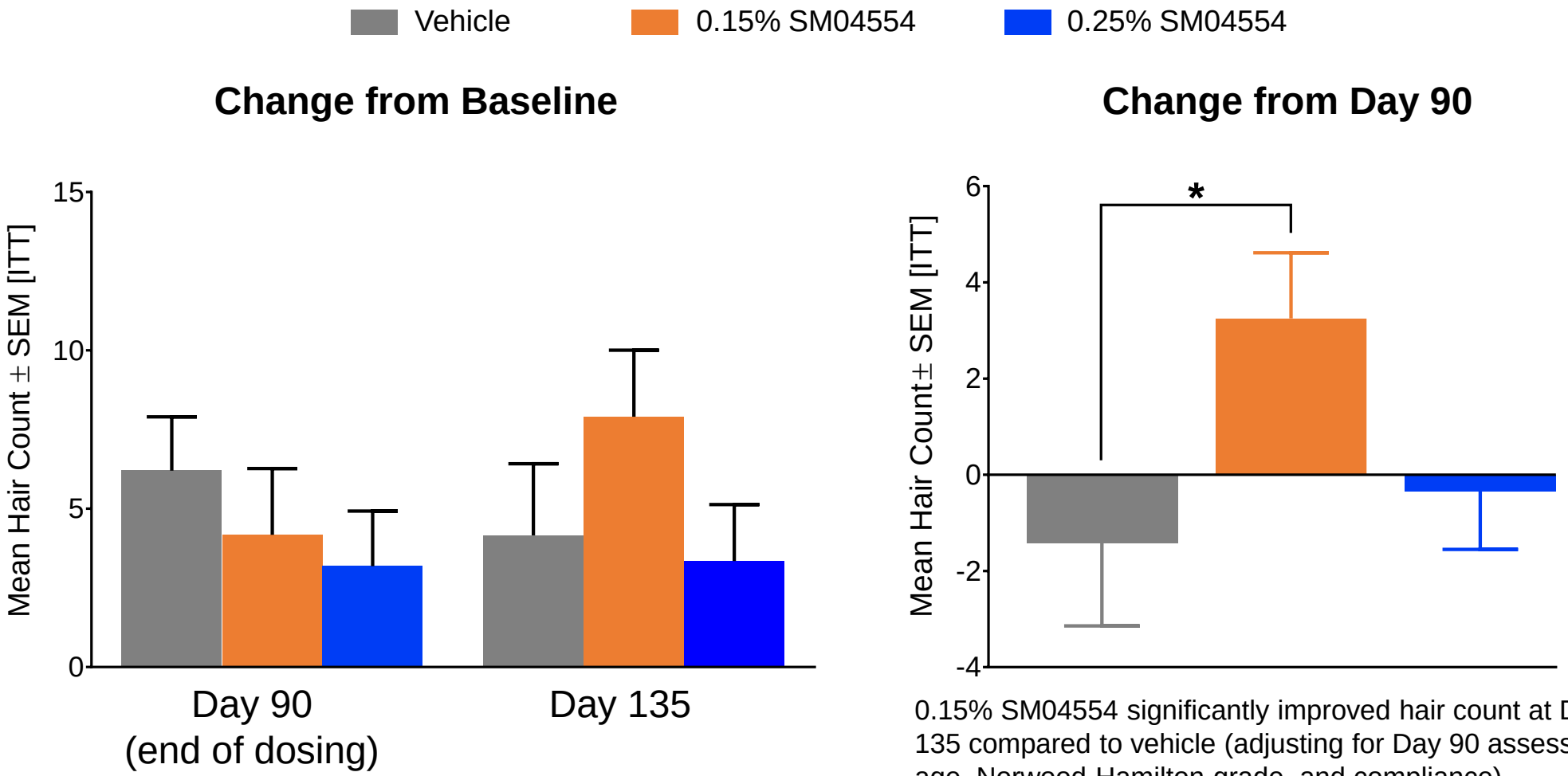
SM04554-AGA-02 phase 2 study

Adverse event summary

SM04554 appeared safe and well tolerated

- Adverse event frequency was similar across all treatment groups and placebo
- Most Common Related AEs:
  - Application site erythema, pruritus, and paresthesia (burning/stinging and tingling)
- Laboratory parameters, ECGs, and vital signs were unremarkable during the study. No clinically significant values or changes from baseline reported in any subjects

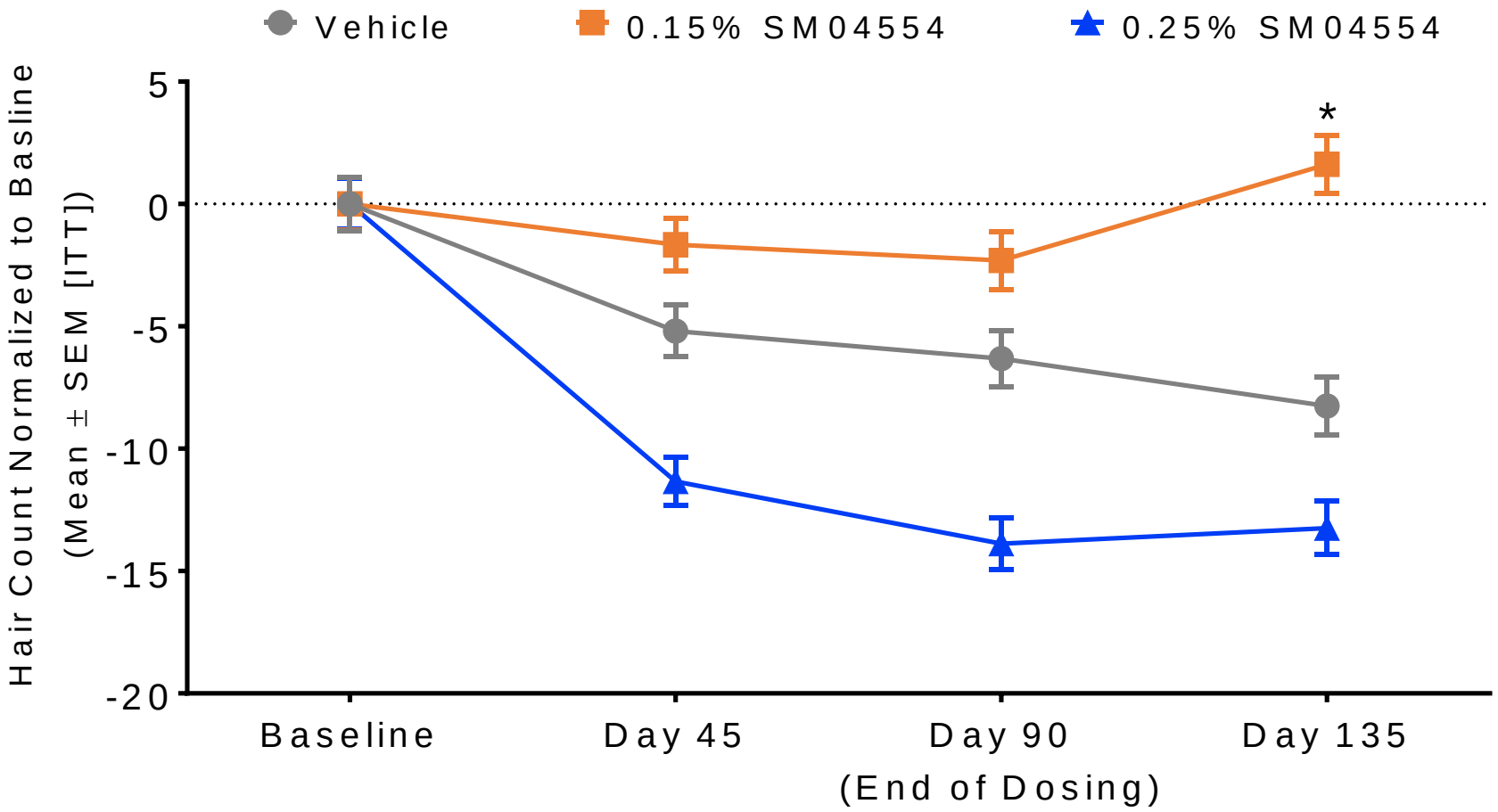
SM04554 increased non-vellus hair counts from baseline



0.15% SM04554 significantly improved hair count at Day 135 compared to vehicle (adjusting for Day 90 assessment, age, Norwood-Hamilton grade, and compliance)

*p<0.025 vs. vehicle
Differences in change evaluated by ANCOVA

SM04554 increased absolute non-vellus hair count ITT



*p<0.001 vs. vehicle
Differences in absolute hair count estimated using Poisson regression; adjusted means presented
Post-hoc analysis

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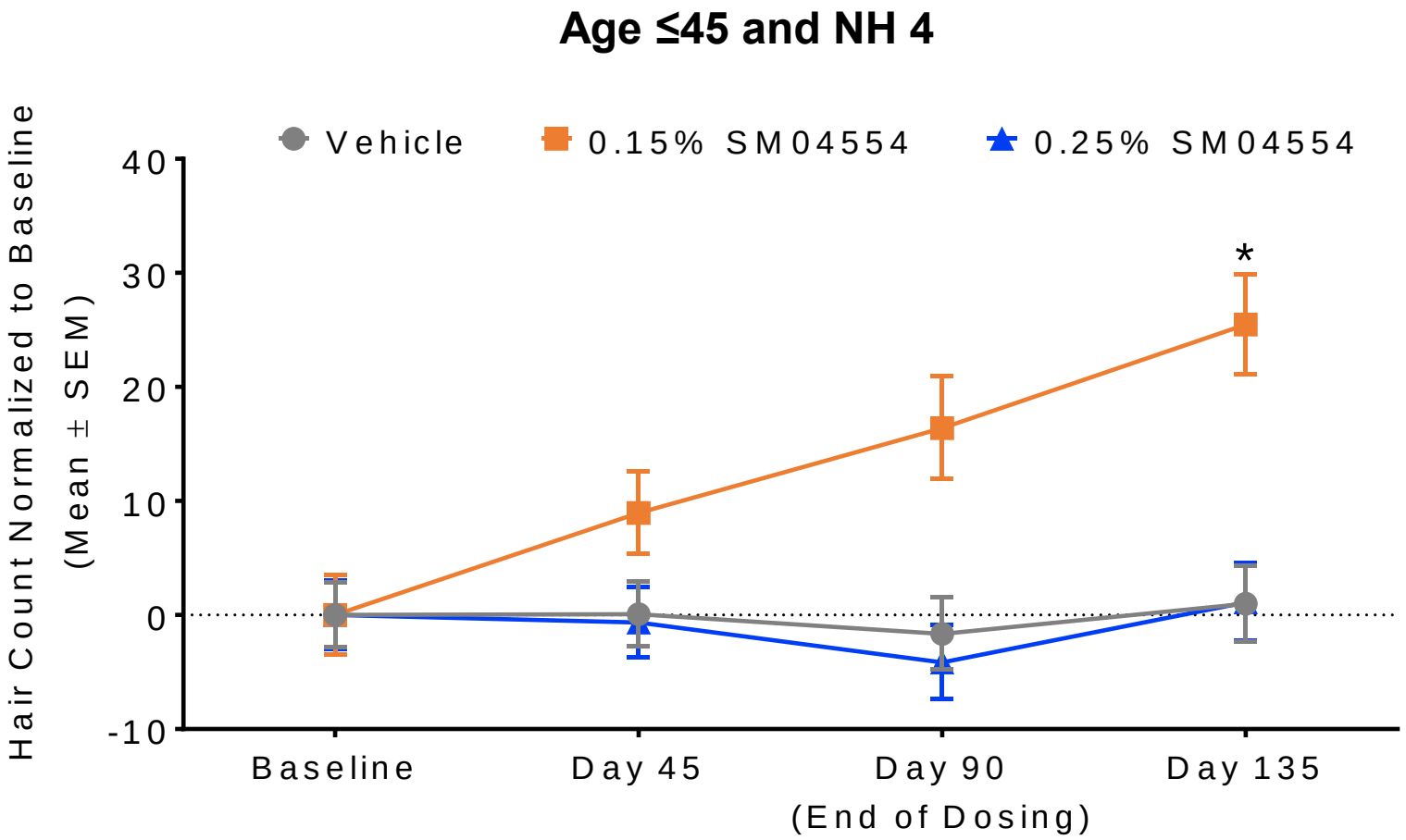
SM04554 increased absolute non-vellus hair count in “optimal” population



*p=0.005 vs. vehicle
Differences in absolute hair count estimated using Poisson regression; adjusted means presented
Post-hoc analysis

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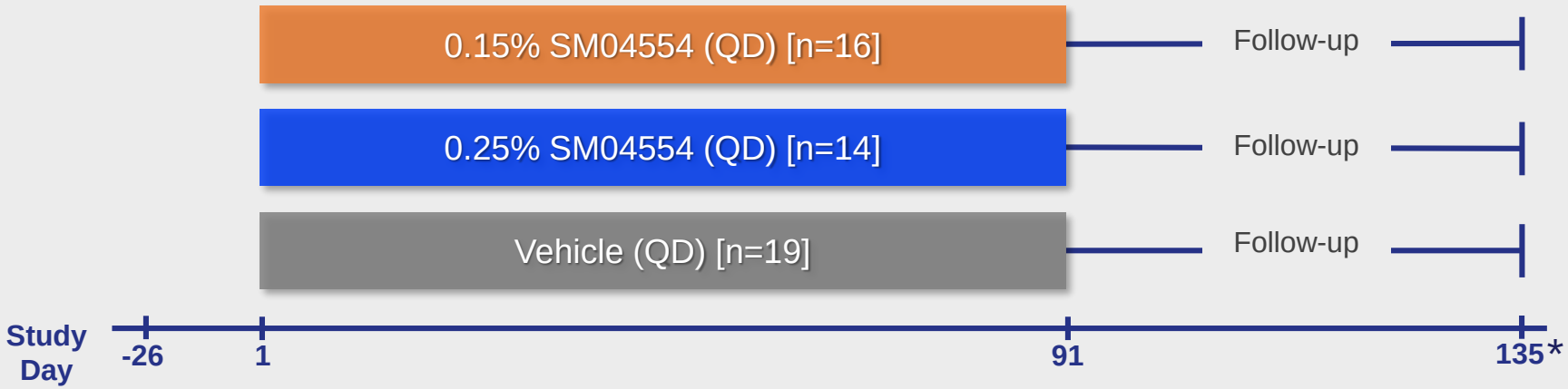
SM04554: AGA – 04

Phase 2, Multicenter, Randomized, Double-Blind Study of SM04554 Analyzed by Scalp Biopsy

Subjects with AGA

N= 49 | Aged 18-65 | Diagnosed AGA | NH Classification score of 4, 5, 5A, 5V, or 6

Androgenetic Alopecia



* 28 subjects consented for optional Day 135 sample

Primary outcomes	• Histological quantification of follicle size and phase – Pre-treatment (Day -26) compared to Day 91
Secondary outcomes	• Safety and tolerability • Histological quantification of follicle size and phase – Pre-treatment (Day -26) compared to Day 135 • Histological quantification of follicle density by size and phase • Immunohistochemical analysis of proliferative and Wnt pathway signals

SM04554-AGA-04 phase 2 biopsy study

Baseline demographics and characteristics

		Vehicle	0.15% SM04554	0.25% SM04554
Intention-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(%)]				
	White	12 (63%)	12 (75%)	10 (71%)
	Black	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

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SM04554-AGA-04 phase 2 study

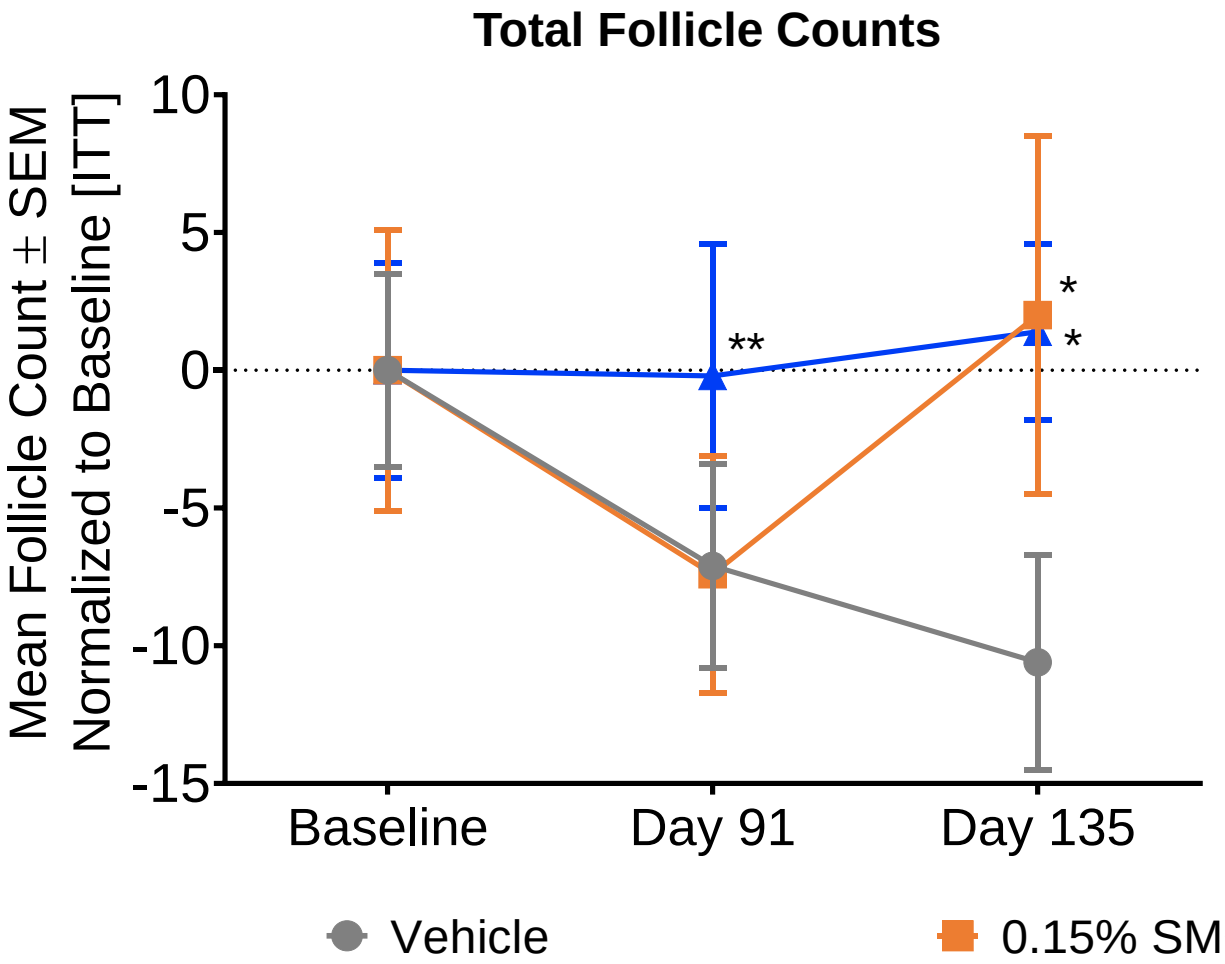
Adverse event summary

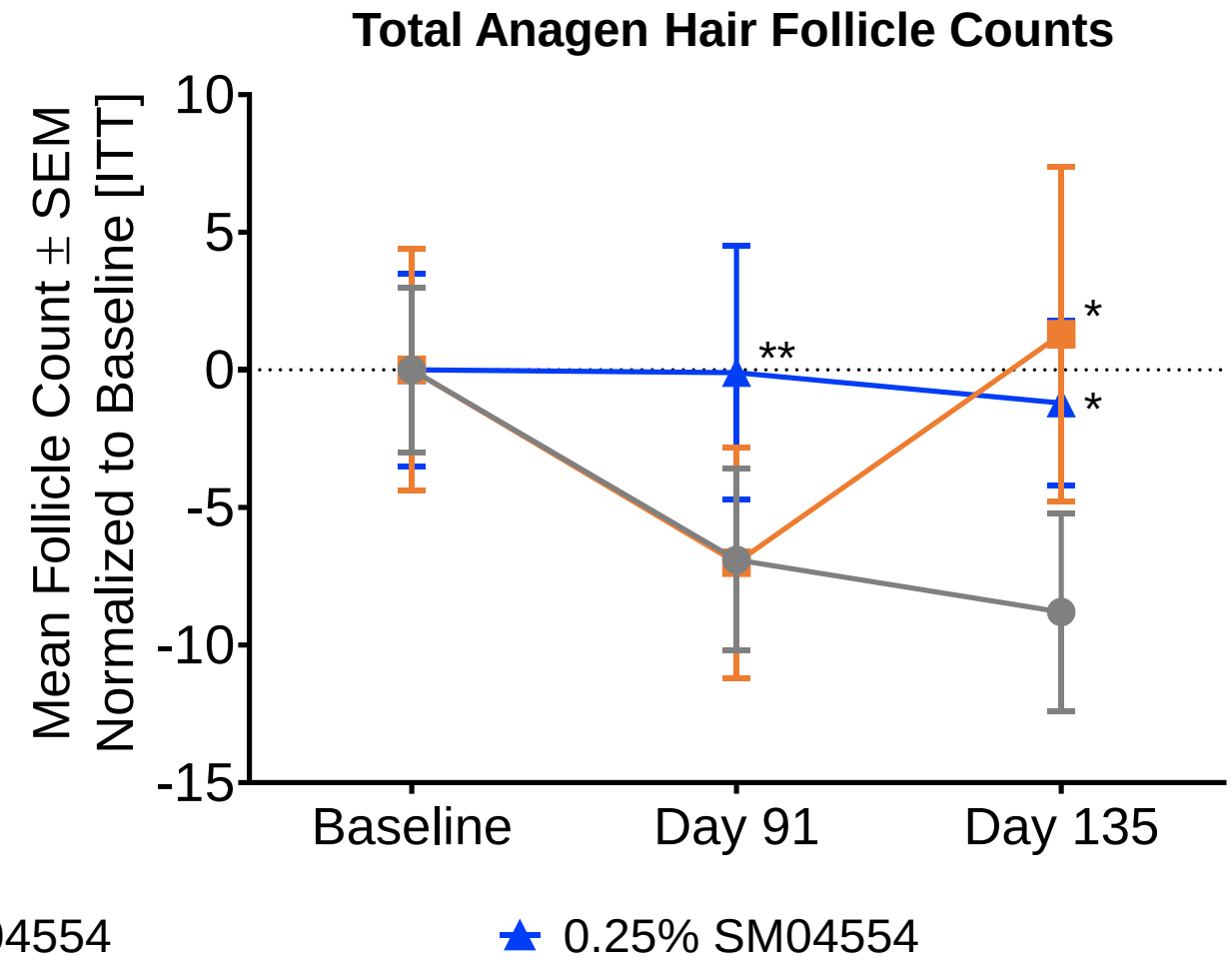
SM04554 appeared safe and well tolerated

- Adverse event frequency was similar across all treatment groups and placebo
- Most Common Related AEs*:
  - Application site pruritus, scaling, and paresthesia (burning/stinging and tingling)
- Laboratory parameters and vital signs were unremarkable during the study. No clinically significant values or changes from baseline were reported in any subjects

*AEs Identified by Investigator Scalp Assessment

SM04554 increased total and anagen follicle counts





*p<0.05, **p<0.01 vs. vehicle

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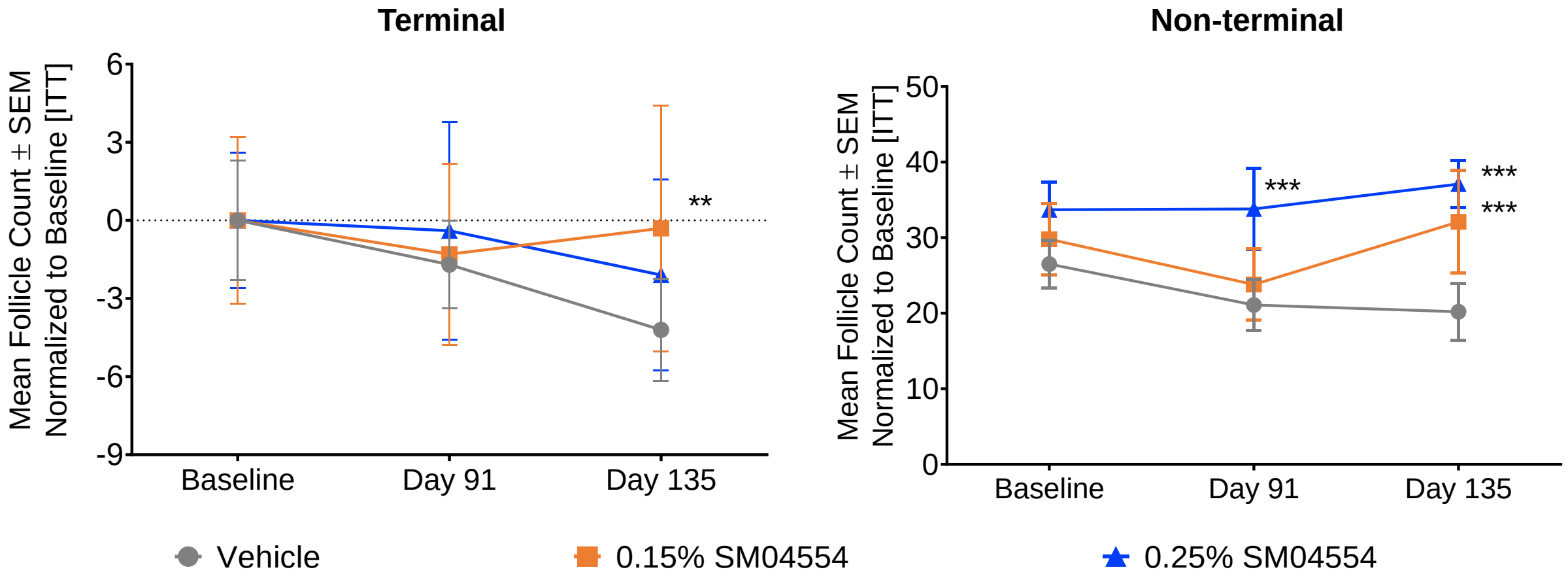
SM04554 increased terminal (>60 µm) and non-terminal (≤60 µm) hair follicle counts



**p=0.01, ***p<0.001 vs. vehicle

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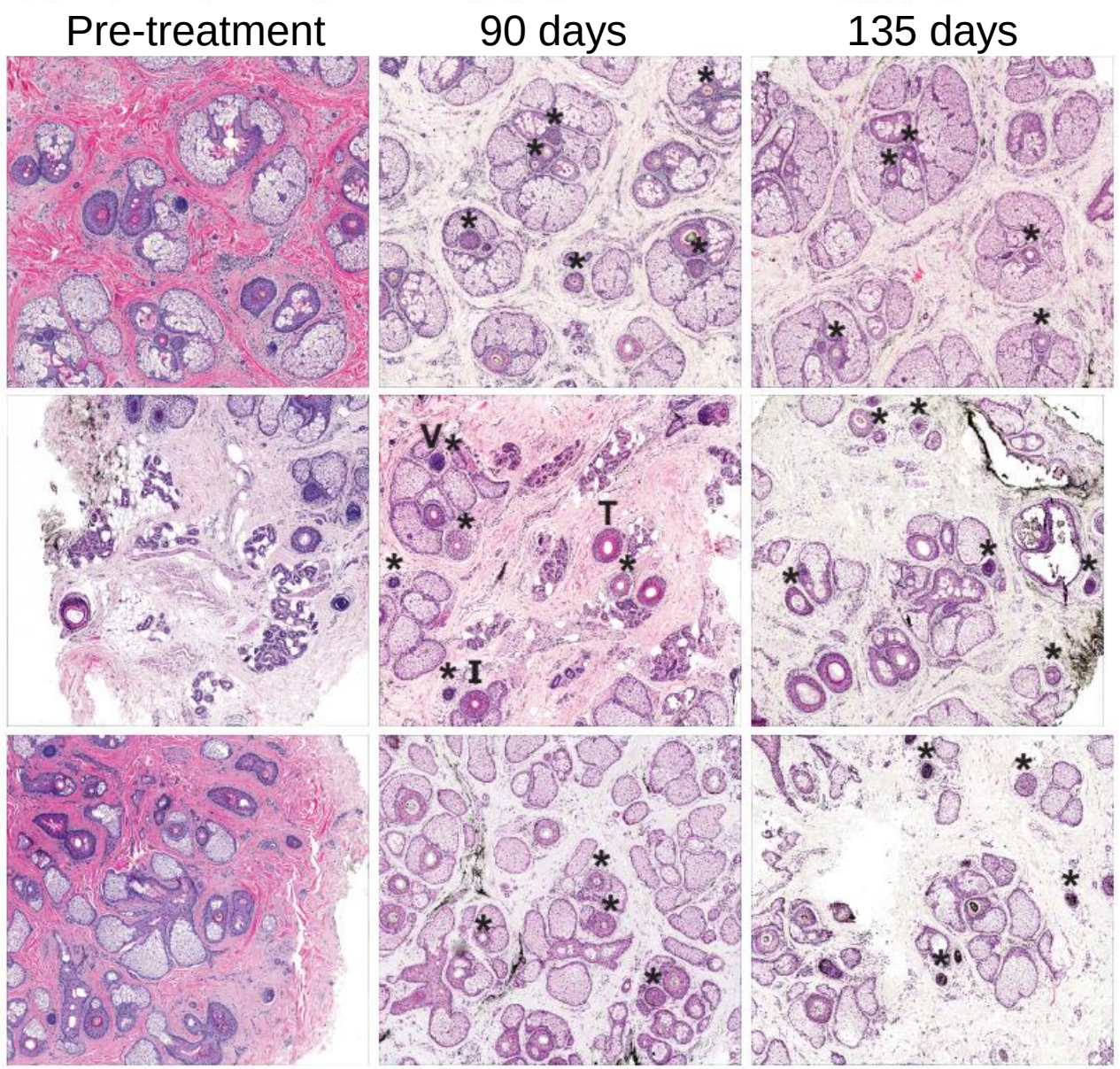
SM04554 increased non-vellus hair follicles

T-terminal anagen (>60 µm)
I-indeterminate anagen (30-60 µm)
V-vellus anagen (<30 µm)

* - highlighting non-terminal follicles in tissue profile



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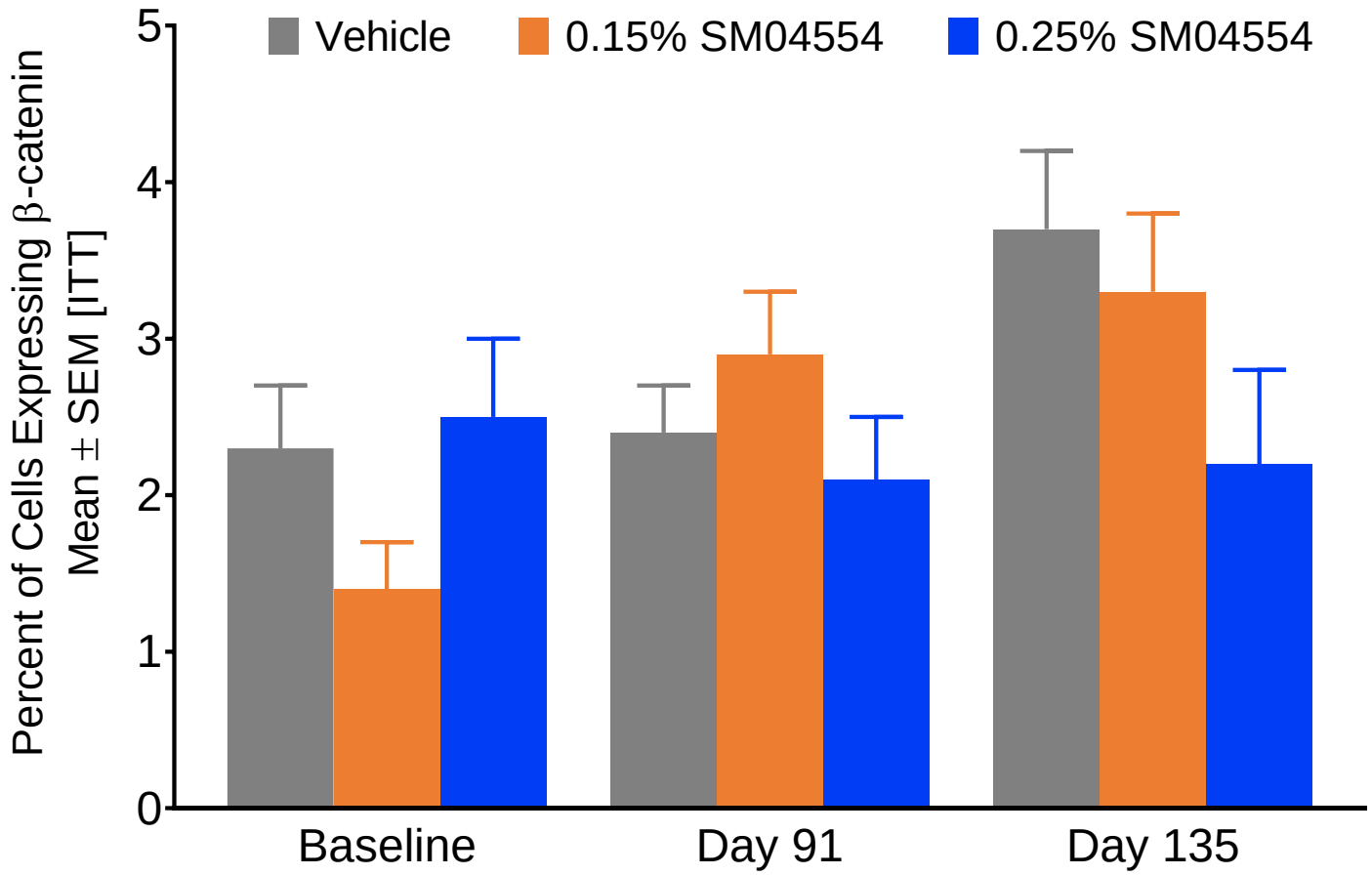
β-catenin expression was not increased in epidermis and infundibulum



β-catenin was found to be membrane bound in the skin (i.e. not nuclear/active)

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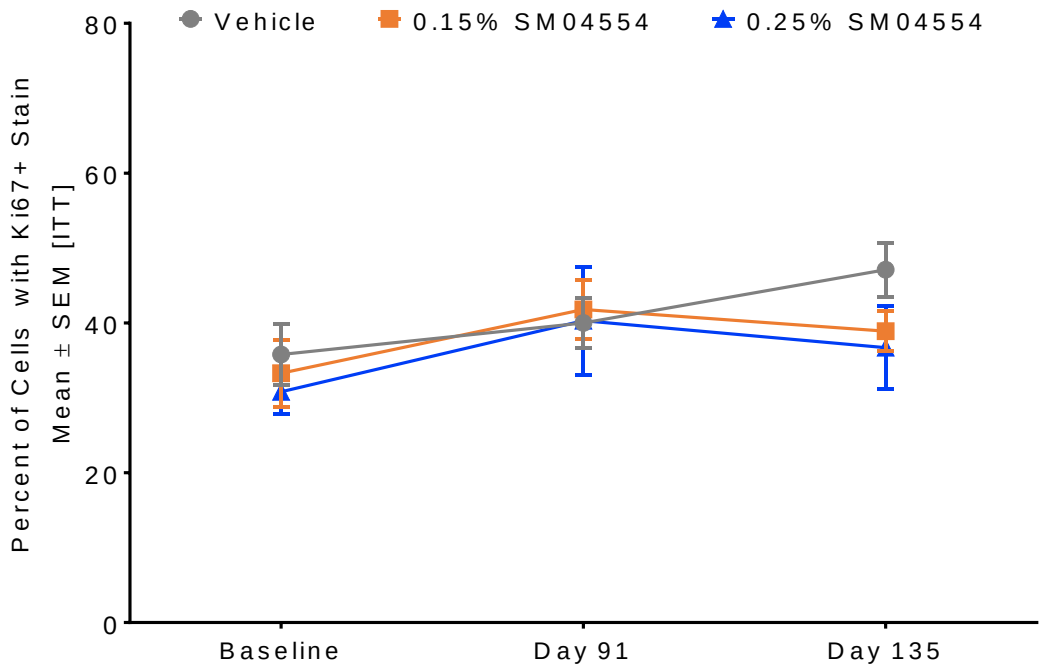
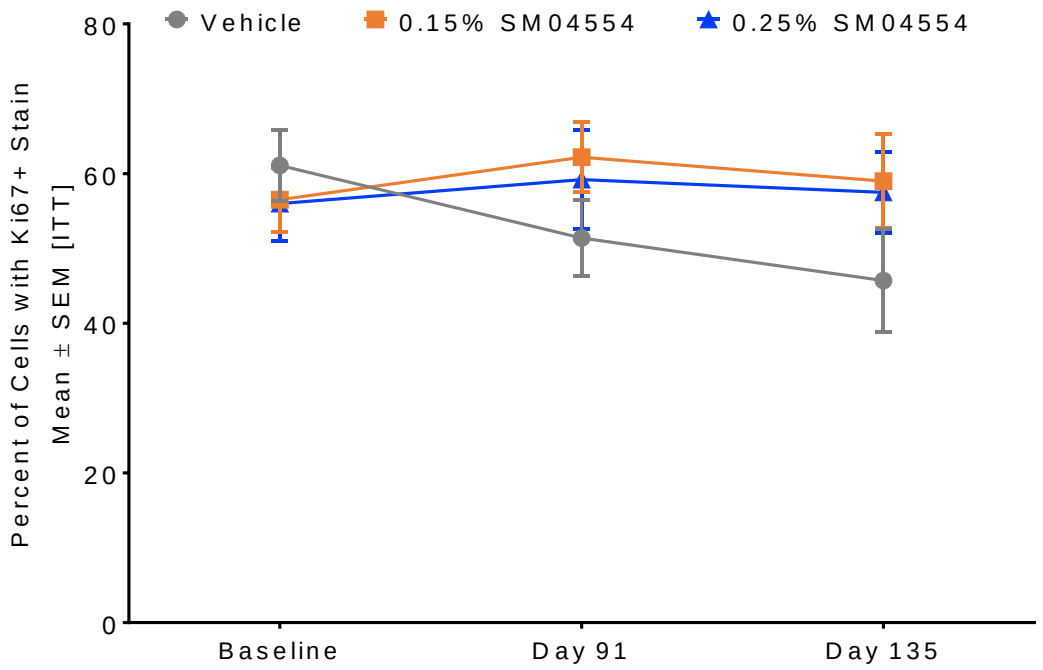
SM04554 effects on Ki67 in epidermis, infundibulum, and hair bulb

Ki-67 in Epidermis and Infundibulum



Ki-67 in Hair Bulb



- Ki-67 protein is a marker of cell proliferation
- No significant difference seen in **epidermal** Ki-67 between 0.15% or 0.25% and vehicle, indicated no difference in proliferative signal
- Ki-67 increased in the **hair bulb**, possibly suggesting hair growth and/or new follicle formation

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Summary of all clinical study findings

- Clinical safety, pharmacokinetic, and immunochemistry assessments supported that SM04554 appeared safe and well tolerated with little systemic exposure

- Positive hair bioactivity documented at macro and micro levels with 0.15% and 0.25% SM04554 doses

SM04554: AGA – 05

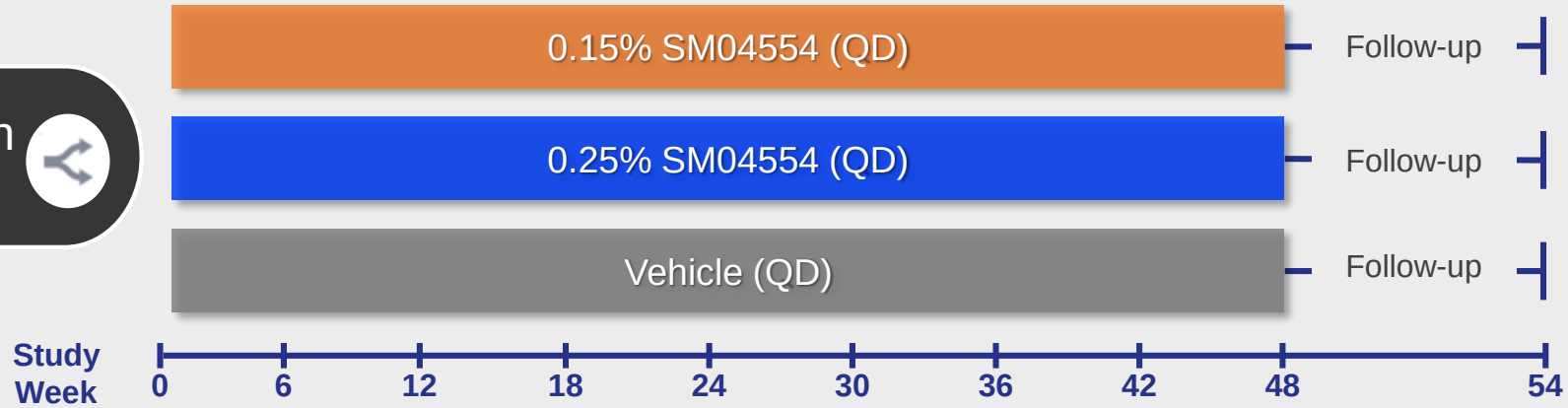
FPFV: Nov 2018; LPLV: June 2020

Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Efficacy and Safety in Male Subjects

11 centers in Turkey | N= 625 | Aged 18-45 | Diagnosed AGA | NH Classification score of 3V or 4

Androgenetic Alopecia

Randomization 2:2:1



Primary outcome	• Absolute non-vellus hair count in target area by phototrichogram analysis at Week 48
Secondary outcome	• Safety and tolerability • Hair counts (non-vellus, vellus) at Weeks 12, 24, and 36 • Hair density at Weeks 12, 24, 36, and 48 • Subject assessment of hair growth every 6 weeks
Exploratory outcome	• Change in hair composition using hair to hair match

Questions

Ismail Simsek – ismail@samumed.com

For AGA-05: Samumed Clinical Trials 1-855-222-0515 clinicaltrials@samumed.com

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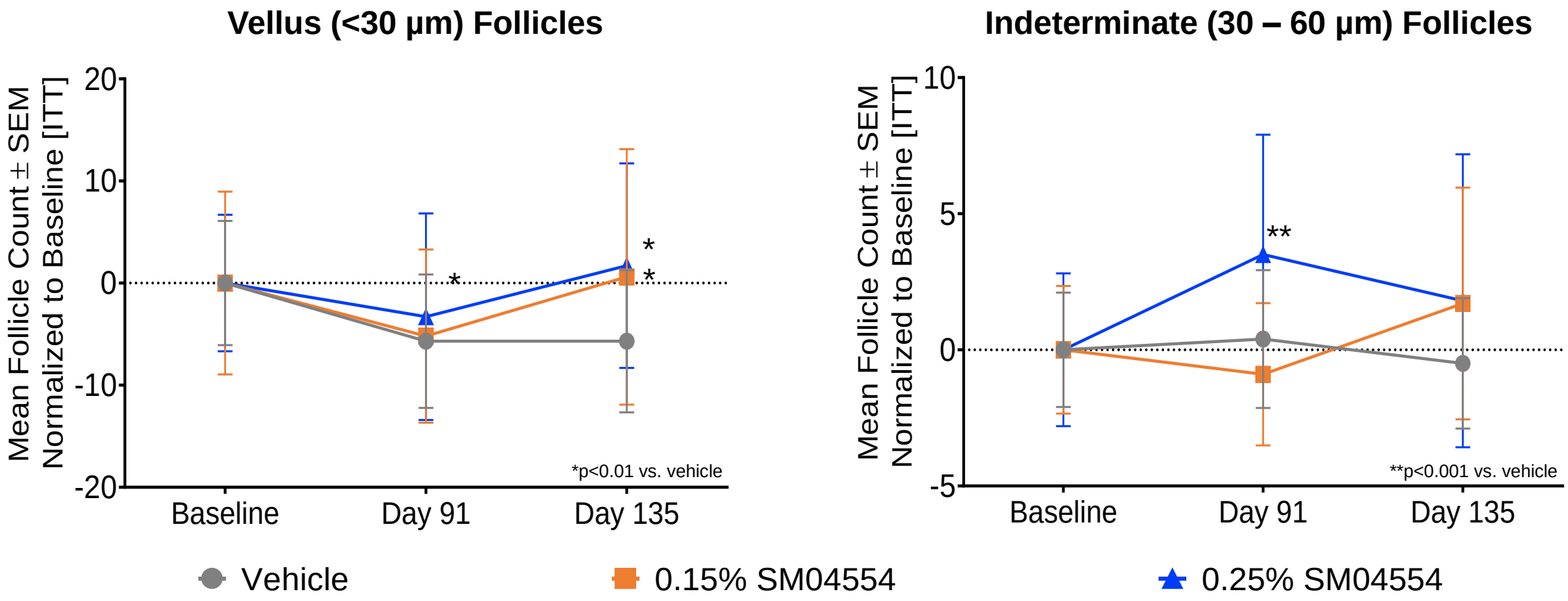
Thank you

SM04554-AGA-04 Phase 2 study

Non-terminal hair follicle counts



SM04554 significantly increased vellus and indeterminate hair follicle counts compared to vehicle