Reduction of telogen rate and increase of hair density in androgenetic alopecia by a cosmetic product: results of a randomized, prospective, vehicle controlled double blind study in men

Julia Welzel, Helmut H. Wolff, Wolfgang Gehring

ORIGINAL CONTRIBUTION

JCD
Journal of
Cosmetic Dermatology

WILEY

Reduction of telogen rate and increase of hair density in androgenetic alopecia by a cosmetic product: Results of a randomized, prospective, vehicle-controlled double-blind study in men

Julia Welzel M.D[1] | Helmut H. Wolff M.D[2] | Wolfgang Gehring M.D[3]

[1]Department of Dermatology and Allergology, University Hospital Augsburg, Augsburg, Germany

[2]Department of Dermatology and Venerology, University of Lübeck, Lübeck, Germany

[3]Department of Dermatology, Municipal Clinics Karlsruhe, Karlsruhe, Germany

Correspondence
Julia Welzel, Department of Dermatology, University Hospital Augsburg, Sauerbruchstraße 6, Augsburg 86179, Germany.
EMail: julia.welzel@uk-augsburg.de

Abstract

Background: Considerable parts of the global population are affected by androgenetic alopecia (AGA).

Aims: The efficacy of a foam containing nicotinic acid hexyl ester, polyphenols, zinc, glycine, and caffeine in comparison with a vehicle control foam was assessed in a double-blind vehicle-controlled study in men with AGA over 6 months.

Patients/Methods: Sixty-two men with AGA were assigned either to the active ingredients (verum) or the vehicle group. They applied the products twice daily on affected scalp areas over 6 months. Automated phototrichograms were obtained at baseline, after 3 and 6 months. In addition, a clinical rating by a dermatologist and by the subjects themselves was documented using standardized questionnaires.

Results: The reduction of the telogen rate from T0 to T6 was significantly stronger in the verum group compared to the vehicle group. The reduction was significant from T0 to T3 and T6 in the verum group, but in the vehicle group only from T0 to T3, not to T6. Significantly increased hair density was noticed in both groups at all time points, but the change from T0 to T6 did not differ significantly between the groups. Cosmetic acceptance of the foam and its application regimen was generally good in both groups. Slight reddening and burning after application of verum in six cases was probably due to the presence of hexyl nicotinate.

Conclusion: The study demonstrated a reduction of the telogen rate by a cosmetic foam in men affected by AGA, indicating a benefit for cosmetic intervention against male pattern hair loss.

KEYWORDS
androgenetic alopecia, claim substantiation, hair growth, hair treatment, telogen rate

1 | INTRODUCTION

Androgenetic alopecia (AGA) is a common form of hair loss affecting men and women worldwide with a higher frequency in Caucasian than in Asian and African populations.[1] It is associated with psychological stress including loss of self-esteem, loss of attractiveness, fear of becoming bald, negative effects on social life, and feelings of depression as well as concerns about getting older.[2] It is thought that 5α-Dihydrotestosterone (DHT) is responsible for the gradual miniaturization of genetically susceptible hair follicles resulting in a reduction of the cellular hair matrix volume and a decrease of the duration of the anagen growth phase.[3–5] Oral finasteride, topical minoxidil, low-level laser therapy (LLLT), hair transplantation, and platelet-rich plasma therapy (PRP) are therapeutic options[6] among that only oral finasteride (for men) and topical minoxidil (for both men and women) have been approved by the FDA.[7,8] They may show adverse effects, which force patients to stop the treatment, for example, rarely gynecomastia in the case of finasteride[9] and frequently generalized hypertrichosis in the case of minoxidil.[10] New topical treatment regimen with finasteride has been developed to reduce side effects[11,12] but consequences of the observed decrease in plasma dihydrotestosterone levels observed both in men and women as well as environmental effects from rinsed of finasteride remain to be investigated. In addition to pharmacological options, a wide range of cosmetics, natural products and interventions claim to improve hair growth in AGA sufferers. However, no evidence-based recommendations for these treatment options are available. Controlled studies are required to evidence the relevance of these treatment options[6] using validated methods for the quantification of hair loss and growth.[6,13,14]

Among the ingredients with a potential for cosmetic use against AGA are Hexyl nicotinate (NHE), which enhances cutaneous blood flow[15–17] and caffeine for its inhibitory effect on phosphodiesterase resulting in increased cAMP levels in cells[18] as a proposed mechanism of the stimulation of the proliferation of hair follicles.[19] The non-inferiority of a caffeine-based 0.2% topical liquid to minoxidil 5% in the treatment of men with AGA has been demonstrated.[20] Polyphenols (Dihydroquercetin-glycoside [DHQG] and Epigallocatechingallate-glucoside [EGCG2]) induced a stimulation of the metabolism of human fibroblast dermal papilla cells, proliferation and anti-apoptotic effect of the outer root sheath cells, and activation of the Wnt/β-catenin pathway.[21–23] Combined with glycine as a constituent of the hair's keratin-associated protein composition[24] and zinc, which is crucial for the incorporation of cysteine into the keratin,[25] DHQG and EGCG2 stimulated the hair growth both in vitro and in vivo, where a 3 months treatment with a hair lotion containing 3% of polyphenols, zinc salt and glycine-complex increased the anagen rate, reduced the telogen, and lead to improved hair density as compared to placebo lotion in an open comparison.[23]

The efficacy and safety of a combination of a shampoo and a lotion with the nano-encapsulated combination of the aforementioned ingredients was evaluated in a prospective, single-arm, open-label study with 35 women and 10 men with androgenic alopecia and telogenic effluvium, demonstrating, besides good tolerance, an increase in anagen rate, numbers of total follicular units, a total of hairs, and median hair number per follicle unit with corresponding decrease in hair shedding after 90 days.[26]

Based on these results, a leave-on cosmetic foam product containing the active ingredients NHE, the polyphenols DHQC and EGCG2, zinc salt, glycine, and caffeine adapted to the concentration of the lotion as described by Chajra et al.[23] was developed. The hypothesis of a positive effect on hair growth parameters in men suffering from AGA was tested in a randomized, double-blind, vehicle-controlled 6 months study. The primary hypothesis was that telogen rate decreases more with verum than with vehicle foam after 6 months of twice-daily application. The secondary endpoint was the increase in hair density for the verum group as compared to the vehicle group. Finally, a safety profile for the verum group was to be explored.

2 | MATERIALS AND METHODS

2.1 | Study subjects

Sixty-two men (aged from 19 to 67 years, mean 42 years) with AGA (stage 2–7, Hamilton-Norwood Scale,[27] mean 4) and a telogen rate above 20% were included in the study. The men were randomly assigned either to verum or placebo (see below, 1:1 randomization according to a randomization list). The mean duration of hair loss was 13.6 years. Exclusion criteria included skin problems of the scalp and other diseases, which required dermatological treatments. Also, subjects with known intolerance against components of the test products were excluded. Furthermore, former surgical corrections of scalp hair loss and therapeutic measures were considered as exclusion criteria. All subjects had not received any treatment for hair loss for at least 3 months before the onset of the study. 66% of the subjects reported no previous treatment, while 34% had previously attempted treatment: five with minoxidil, four with finasteride, 12 with caffeine shampoo, and four with other therapies. All subjects were enrolled after signing the written informed consent. They were informed in advance by means of an information sheet and a detailed personal consultation. The study had a positive approval from the local internal review board (No. BKF2017-13).

2.2 | Test products

A cosmetic foam product containing polyphenols (DHQG and EGCG2), NHE, zinc salt, glycine, and caffeine was used as verum. The vehicle consisted of a foam without these active ingredients (Table 1). The subjects applied the respective foam on affected scalp areas for a period of 6 months according to a defined application mode and frequency: 1 g, corresponding to one pump stroke of the container, was distributed twice daily on dry hair and scalp under gentle massage. The subjects were advised not to wash their hair for at least 4 h after applying the foam.

TABLE 1 Composition of the verum foam and the vehicle foam

Verum	Vehicle
Alcohol denat.	Alcohol denat.
Aqua	Aqua
Propane	Propane
Butane	Butane
Glycerin	
Sodium Metabisulfite	
Glycine	
Laryx europaea wood extract	
Zinc Chloride	
Camellia chinensis leaf extract	
Hexyl Nicotinate	
Panthenol	Panthenol
Caffeine	
Piroctone Olamine	
Zinc PCA	
Menthol	Menthol
Cetyl Alcohol	Cetyl Alcohol
Stearyl Alcohol	Stearyl Alcohol
Sodium Cetearyl Sulfate	Sodium Cetearyl Sulfate
Isobutane	Isobutane
Citric Acid	Citric Acid
Sodium Hydroxide	Sodium Hydroxide
Parfum	Parfum
Denatonium Benzoate	Denatonium Benzoate
t-Butyl Alcohol	t-Butyl Alcohol

Note: INCI declaration: list of ingredients in the order of their concentrations.

2.3 | Double-blind, vehicle-controlled test design

Each subject received one coded foam spray container monthly containing 60 g of either the verum or the vehicle. Neither the study center nor the study participants were informed about the assignment throughout the observation period and data processing.

2.4 | Evaluation and measurements

Clinical examinations and measurements were performed at baseline (T0), after 3 months (T3), and after 6 months (T6). Skin tolerance, effects on hair density, hair structure, hair loss, hair volume, and scalp condition were clinically evaluated by a dermatologist and rated on a scale from 1 = very poor to 10 = very good. The

participants subjectively assessed skin tolerance, efficacy against hair loss, effects on hair density, hair volume, hair structure, scalp condition, and also cosmetic properties (effect on combing, styling, sheen, and greasiness of the hair, scalp feeling, handling, consistency of the foam, distribution on the hair, penetration on hair and scalp, economicalness of use, and smell) using the same scale as the dermatologist.

TrichoScan (DermoScan GmbH) examinations were performed at each visit on an area of 1 cm^2 at the left temporal region 5 cm above the ear. This area was shaved by trained personal with a hair clipper (Moser), cutting the hair to a maximal length of about 0.3 mm above the skin surface. A template was used to allow measuring the hair parameters before, during, and after treatment at the same scalp area without tattooing. The hair was then dyed with black hair color (Goldwell Topchic 2 N Black, Kao Germany GmbH). The hair trimmer and the black color were provided as a kit. After 10 min, the color was carefully removed and digital images were taken by means of a digital epiluminescence microscopy system (Dermogenius ultra, DermoScan GmbH). Standardized and reproducible conditions of photography for distance, light, and zoom were taken with the same device after 3 days, again after dying, at each visit. The TrichoScan software analyses hair density (n/cm^2) and the anagen/telogen ratio. Assuming a hair growth rate of 0.3 mm per day, all hairs in the anagen phase would have grown to a length of about 1.2 mm within these 3 days. The percentage of short hairs (≤0.6 mm) 3 days after shaving corresponds, therefore, to the telogen rate. Hair density was calculated by image analysis.

2.5 | Statistics

The analyses were performed by the Software R version 3.5.2 program version. Parameters between the two groups were compared using the Wilcoxon Rank-Sum test. Difference in the parameters within the group at different time points was compared using Wilcoxon's Signed-Rank test. The significance level was set to $p ≤ 0.05$. The telogen rate and the hair density at baseline (T0) were set to 100% for clearer graphical representations. Clinical evaluations by the dermatologist and subjective evaluations by the participants for verum and vehicle were compared by Wilcoxon's Signed-Rank test, with a significance level set at 0.05.

3 | RESULTS

3.1 | Study population

Sixty-two male subjects were included. Two participants in the verum group and one participant in the vehicle group dropped out due to personal reasons. Both groups were comparable in terms of age, duration (Table 2a), and severity of AGA according to the Hamilton-Norwood scale[27] (Table 2b).

TABLE 2 Comparison of age and AGA characteristics in the verum and vehicle groups. (a) Age and Duration of AGA. The study groups were comparable with regard to the subjects' age and the duration of AGA. (b) Severity of AGA. The study groups were comparable with regard to the severity of AGS according to the Hamilton-Norwood Scale[25]

(a)		
	Study subjects' age mean (standard deviation)	Duration of AGA mean (standard deviation)
Verum group	43.5 (16.10)	13.7 (10.29)
Vehicle group	41.2 (13.30)	13.4 (8.79)
(b)		
Hamilton-Norwood Scale[25]	**Frequency (verum/vehicle)**	**[%] of the study subjects (verum/vehicle)**
1	0 (0/0)	0 (0/0)
2	9 (4/5)	15 (13/16)
3	11 (9/2)	18 (29/06)
4	6 (3/3)	10 (10/10)
5	19 (8/11)	31 (26/35)
6	16 (7/9)	26 (23/29)
7	1 (0/1)	2 (0/3)

3.2 | Telogen rate

The Wilcoxon Rank-Sum Test revealed a significantly stronger decrease in the telogen rate in the verum group as compared to the vehicle group from T0 to T6 ($p = 0.02$). The data of the telogen rates within the observation time of 6 months are illustrated in a graph (Figure 1). In the verum group, using the Wilcoxon's Signed-Rank test, a statistically significant decrease of the telogen rate from T0 (50.0%) to T6 (41.0%) ($p = 0.003$) was detectable. The telogen rate at T3 (41.5%) was significantly decreased compared to T0 ($p = 0.0003$), too. The vehicle group also showed a significant reduction of the telogen rate from T0 (45.8%) to T3 (39.2%) ($p = 0.03$) but no difference from T0 to T6 (45.7%) ($p = 0.8$) (Figure 2).

3.3 | Hair density

The improvement in hair density within the observation time of 6 months is illustrated in exemplary TrichoScan images from 2 subjects from the verum group at T0 and T6 (Figure 3). In the verum group, a significant increase in hair density was observed from T0 (171.3/cm^2) to T3 (217.0/cm^2) ($p < 0.001$) and from T0 (171.3/cm^2) to T6 (200.6/cm^2) ($p = 0.001$). The vehicle group also experienced a significant increase in hair density from T0 (179.7/cm^2) to T3 (217.4/cm^2) ($p < 0.001$) and from T0 (179.7/cm^2) to T6 (202.1/cm^2) ($p = 0.04$) (Figure 4). No statistically significant difference existed between verum and vehicle with regard to the change in hair density from T0 to T6.

3.4 | Dermatologist's clinical assessment and subject's assessment

The subjects and the dermatologist evaluated the effects of the vehicle and the verum foam on a scale from 1 = very poor to 10 = very
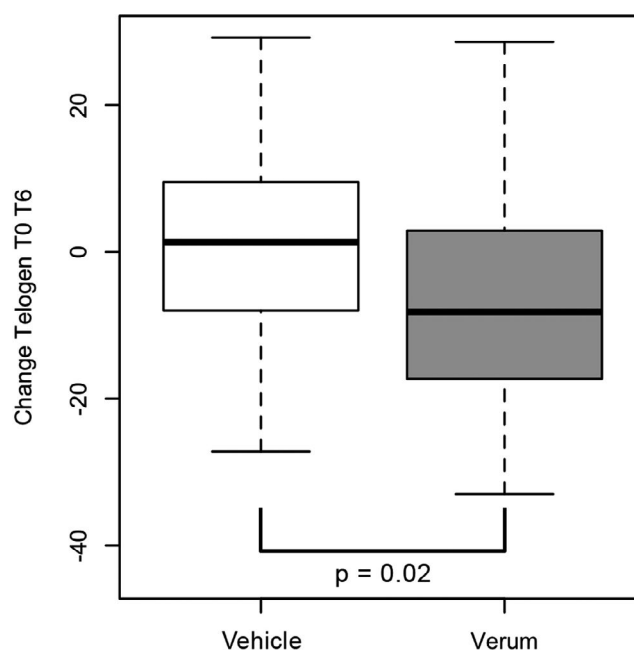

FIGURE 1 Difference in telogen rate between verum and vehicle. The change in telogen rate determined by digital image analysis of epiluminescence microscopical photograph (TrichoScan) from initial (T0) to final examination after 6 months (T6) was compared for vehicle and verum by Wilcoxon Rank-Sum test. In the graph, the change telogen rates (%) is represented. Absolute data and p-values are represented in the tables below)

good (Tables 3 and 4). No significant differences were found between the verum and vehicle groups for any parameter in the dermatologists and the subjective assessment. Trends to superiority of the verum were found for the subjects' ratings of skin tolerance as well as the effects on hair loss and hair volume. The dermatologist

FIGURE 2 Time course of telogen rate. Telogen rates determined by digital image analysis of epiluminescence microscopical photograph (TrichoScan) initially (T0), after 3 months (T3), and after 6 months (T6) were compared for vehicle and verum, respectively by Wilcoxon's Signed-Rank test. In the graph, the initial telogen rate in each group at T3 and T6 are given as % of the respective initial value. Absolute data are represented in Figure 1
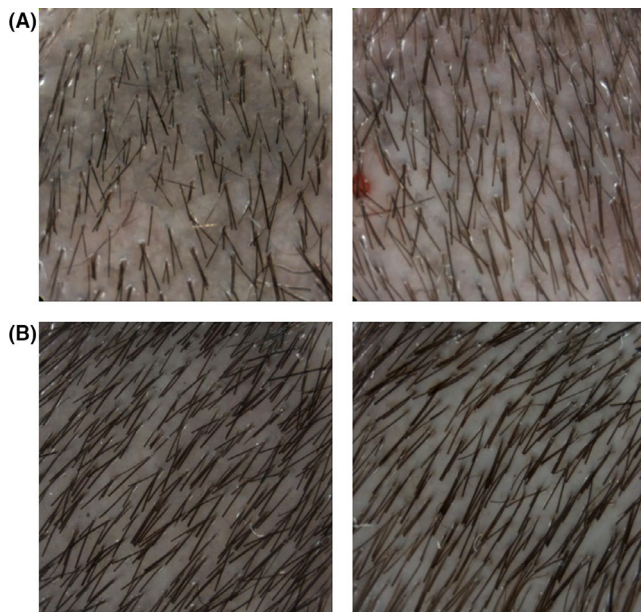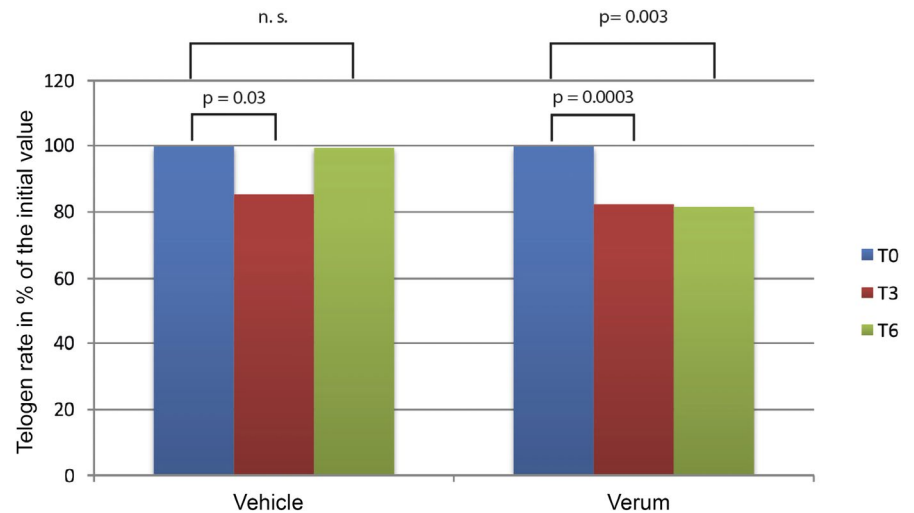

FIGURE 3 TrichoScan images. Epiluminscence microscopy images. (A) Subject No. 28 verum group - left at T0 and right at T6. (B) Subject No. 40 verum group - left at T0 and right at T6

generally assessed the effects of the verum and vehicle foam more positively than the subjects.

3.5 | Cosmetic acceptance and safety profile

The cosmetic acceptance of (verum and vehicle) foam was rated comparably by the subjects.

Dermatological discomfort was reported after 3 months of treatment: itching (vehicle n = 2), redness (verum n = 4, vehicle n = 1), dandruff (verum n = 2, vehicle n = 1), burning sensations (verum n = 2), eczema (vehicle n = 1), and pustules (vehicle n = 2). In seven cases (verum n = 4, vehicle n = 3), the adverse effects

were classified by the dermatologist as having a causal relationship to the test product; in three cases, a relationship was considered probable (verum n = 2, vehicle n = 1); and in three cases, not probable (verum n = 1, vehicle n = 2). After 6 months, one subject from the vehicle group reported an oily scalp and two subjects from the verum group described redness, probably caused by the foam.

To summarize redness and burning sensations, one participant of the vehicle group and six participants of the verum group informed about a slight transient reddening and/or burning immediately after application of the foam at the visit after 3 months and/or after 6 months. None of the test persons complained about the application frequency of the foam. Overall, 25 participants in the verum group and 19 in the vehicle group were willing to continue using the foam.

4 | DISCUSSION

Both verum and vehicle foam induced a decrease in telogen rate in men affected by AGA. This implies an increase in the anagen rate and hence improved hair growth. However, the effect was demonstrated for vehicle only after 3 months. Verum could improve the telogen rate in the study panel within 6 months significantly more than vehicle, as initially hypothesized. Therefore, it can be deduced that the anagen rate and as a result the hair growth increased markedly. This conclusion is confirmed by the increase in hair density which was evaluated as a secondary endpoint of the study. This parameter improved significantly in both groups (Figure 2) from T0 to T3 as well as from T0 to T6 without significant difference between verum and vehicle. Interestingly no significant change between T3 and T6 was detectable in both groups, indicating that the efficacy starts early and lasts during the treatment period. The slight decrease of the telogen rate and increase in hair density in the vehicle group might be due to the mechanical activation and subsequent increase of microcirculation due to the massage applied to the scalp, which leads to a better blood perfusion of the hair bulb. The more
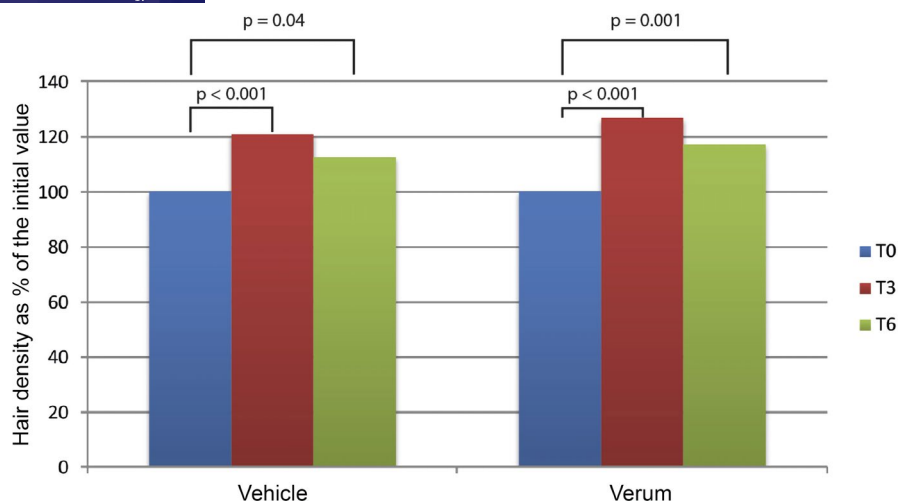
FIGURE 4 Time course of hair density. Hair densities determined by digital image analysis of epiluminescence microscopical photograph (TrichoScan) initially (T0), after 3 months (T3), and after 6 months (T6) were compared for vehicle and verum, respectively by Wilcoxon's Signed-Rank test. In the graph, the initial hair density in each group at T3 and T6 are given as % of the respective initial value. Group comparison by Wilcoxon Rank-Sum test showed no difference between verum and vehicle. Absolute data are represented in the table below

TABLE 3 Dermatologist's clinical assessment

	Verum – mean (std)	Vehicle – mean (std)	Group difference p-value
Skin tolerance	8.2 (1.68)	8.8 (1.02)	0.219
Effect on hair density	6.3 (1.44)	6.3 (1.64)	0.975
Effect on hair structure	5.9 (1.09)	5.8 (1.45)	0.546
Effect on hair loss	6.3 (1.34)	5.9 (1.16)	0.314
Effect on hair volume	6.3 (1.41)	6.0 (1.53)	0.649
Effect on scalp	5.3 (0.99)	5.3 (1.74)	0.454

Note: At the final examination, skin tolerance and effects on hair loss were clinically evaluated by the dermatologist, using a 10-grade score (10 = excellent to 0 = very bad). Mean score values and standard deviations (std) are shown as well as p-values for group comparison by Wilcoxon's Signed-Rank test which reached no significance for any parameter.

pronounced improvement of telogen rate and hair density within the first 3 months as compared to the last 3 months of the observation period both with verum and vehicle could be due to seasonal variations. The study started in autumn and winter and terminated in springtime. Even if hair loss occurs often in the summer and fall[28] and telogen hairs occur most frequently in the summer or the transition between summer and fall,[29,30] this factor should not be ignored. Further studies are needed to explore the relation between hair loss and seasonality.[28]

While the increase in anagen rate and hair density indicate a general improvement of hair growth, they do not allow conclusions

on the effect on vellus hair and areas of hair rarefaction which are important markers of AGA. With an observation period of more than 6 months, changes in the duration of the kenogen and the process of hair miniaturization could probably be evaluated to provide a better insight in the effects on this disorder.[31]

A trend to better skin tolerance was noted in the vehicle group. The dermatologist's clinical assessment of efficacy against hair loss was similarly positive for vehicle and verum. The increase of dermal blood circulation induced by NHE in the verum formulation may account for the poorer tolerance ratings and the reports of transient reddening and burning sensations of the scalp. For the other ingredients present in verum, but not in vehicle (Table 1) no irritation potential is to be expected at their respective concentration in the formulations. For polyphenols and caffeine anti-inflammatory effects have been described.[21,22,26]

Besides topical minoxidil and oral finasteride drug therapy of AGA[6] autologous biotechnologies represented by PRP and Human Follicle Stem Cells (HFSCs) as well as Low-Level Light therapy (LLLT) and microneedling have recently been in the focus of investigation for their potential to maintain improved hair growth instead of requiring permanent therapy. Their modes of action have been investigated,[32,33] revealing similarities between wound healing and hair growth stimulation. The involvement of Wnt-signaling in dermal papilla cells, mesenchymal stem cell-derived signal molecules, and growth factors obtained from platelets[34] as well as production of reactive oxygen species and transcription factors induced by nitric oxide formation upon red or infrared light absorption from LLLT by cytochrome C oxidase in follicle cells[35] explain sustainable improvement of hair growth observed in the clinical studies.[36] While the mode of action of the polyphenols present in the cosmetic foam studied here fits in well with the mechanisms observed with

TABLE 4 Subjects' assessment

	Verum – mean (std)	Vehicle – mean (std)	Group difference p-value
Skin tolerance	8.4 (2.01)	9.2 (1.74)	**0.088**
Effect on hair loss	5.1 (2.88)	3.6 (2.63)	**0.061**
Effect on hair volume	5.0 (2.73)	3.9 (2.76)	**0.091**
Effect on scalp	6.2 (2.70)	5.1 (2.53)	0.179
Effect on hair density	5.0 (2.43)	4.0 (2.75)	0.106
Effect on hair structure	5.3 (2.48)	4.3 (2.78)	0.157
Effect on combing	8.1 (1.90)	8.3 (2.35)	0.495
Effect on greasiness	7.2 (1.54)	7.5 (2.47)	0.152
Scalp feeling	7.6 (2.37)	8.1 (1.94)	0.478
Foam consistency	7.3 (2.60)	7.9 (2.18)	0.465
Penetration on hair and scalp	8.1 (1.90)	7.8 (2.00)	0.564
Smell	7.7 (2.42)	8.4 (1.79)	0.243
Effect on sheen	6.5 (2.05)	5.8 (2.35)	0.364
Effect on styling	7.6 (1.95)	7.1 (2.56)	0.657
Handling of the spray flacon	8.2 (2.02)	7.5 (2.44)	0.305
Distribution on the hair	8.0 (1.58)	7.9 (2.05)	0.804
Economicalness	6.1 (2.66)	6.8 (2.06)	0.384

Note: At the final examination, skin tolerance, effects on hair, and scalp as well as cosmetic properties were subjectively evaluated by the participants, using a 10-grade score (10 = excellent to 0 = very bad). Mean score values and standard deviations (std) are shown as well as *p*-values for group comparison by Wilcoxon's Signed-Rank test which reached no significance for any parameter, but trends to inferior tolerance and superior effects on hair loss and hair volume in the verum group (*p*-value marked bold).

the above therapies, the contribution of NHE and caffeine is less well understood. The effects are likely to be transient and less pronounced. Potential benefits of the combined use of the various approaches require future investigation.

Additional data on seasonal variations of the effects of the foam would be helpful to overcome the limitations set by the test schedule. Additionally, the role of massage of both vehicle and verum on scalp circulation as a stimulating effect on hair growth requires further attention. No global pictures were taken as the main aim of the study was the analysis of the effects on hair growth and the dermatologist's and subjects' evaluation of the effects on hair loss, volume, and density provide some information on the overall effect. The reports of scalp redness and burning sensations in the verum group interfered with the double-blind design and might have induced a bias in the dermatologist's and subjects' assessment, but not in the objective evaluation of the anagen rate and hair density as primary and secondary end-points.

5 | CONCLUSION

The double-blind vehicle-controlled study demonstrated the efficacy of the active ingredients of a foam formulation: the study hypothesis that the verum foam significantly reduces the telogen rate in men with AGA compared to the vehicle foam after 6 months of twice-daily use was confirmed. Hair density increased significantly, too, although differences between verum and vehicle after 6 months were not significant. The foam with the active ingredients can, therefore, be considered as suitable to counteract increased telogen rates and decreases in hair density in AGA. The mechanisms of action of NHE, polyphenols (DHQG and EGCG2), caffeine, zinc salt, and glycine as far as they are known are independent of gender so that it is likely to work also in women. Like with Minoxidil and Finasteride a permanent application is required to maintain the improved hair growth status. Further studies with larger sample size, longer follow-up period and with other forms of hair loss are still necessary. More research is also required in order to confirm the efficacy in women and evaluate seasonal trends, with global pictures complementing the trichoscan analysis.

DISCLOSURE
Julia Welzel gave lectures for Sebapharma GmbH & Co. KG and designed and performed studies for Sebapharma GmbH & Co. KG together with Helmut H Wolff. Wolfgang Gehring is a member of the scientific advisory board of Sebapharma GmbH & Co. KG.

AUTHOR CONTRIBUTIONS
This study was planned by Julia Welzel, Helmut H. Wolf and Michaela Arens-Corell from Sebapharma. Wolfgang Gehring established the efficacy of NHE for cosmetic hair growth supporting products and contributed to the study design. Julia Welzel acquired the data set and analyzed the data. Julia Welzel drafted this paper. All authors critically revised this paper and approved the final version to be published. All authors agreed to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work were appropriately investigated and resolved.

ETHICAL APPROVAL
The human volunteers provided written informed consent. The study was approved by the local internal ethics review board (No. BKF2017-13).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Julia Welzel https://orcid.org/0000-0002-6099-7418

REFERENCES

1. Blume-Peytavi U, Blumeyer A, Tosti A, et al. S1 guideline for diagnostic evaluation in androgenetic alopecia in men, women and adolescents. *Br J Dermatol.* 2011;164(1):5-15.
2. Alfonso M, Richter-Appelt H, Tosti A, Viera M, García M. The psychosocial impact of hair loss among men: a multinational European study. *Curr Med Res Opin.* 2005;121(11):1829-1836.
3. Whiting DA. Possible mechanisms of miniaturization during androgenetic alopecia or pattern hair loss. *J Am Acad Dermatol.* 2001;45(3):S81-S86.
4. Messenger AG. The control of hair growth and pigmentation. *J Invest Dermatol.* 1993;101(1 Suppl):4S-9S.
5. Sawaya ME, Price VH. Different levels of 5α-reductase type I and II, aromatase, and androgen receptor in hair follicles of women and men with androgenetic alopecia. *J Invest Dermatol.* 1997;109(3):296-300.
6. Kanti V, Messenger A, Dobos G, et al. Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men – short version. *J Eur Acad Dermatol Venereol.* 2018;32(1):11-22.
7. Fischer TW. Behandlung der Alopecia androgenetica. *Ästh Dermatol Kosmetol.* 2019;11(4):34-42.
8. Suchonwanit P, Thammarucha S, Leerunyakul K. Minoxidil and its use in hair disorders: a review. *Drug Des Devel Ther.* 2019;13:2777-2778.
9. Ramot Y, Ramot Y, Czarnowicki T. Finasteride induced gynecomastia: case report and review of the literature. *Int J Trichol.* 2009;1(1):27-29.
10. Dawber RPR, Rundegren J. Hypertrichosis in females applying minoxidil topical solution and in normal controls. *J Eur Acad Dermatol Venereol.* 2003;17(3):271-275.
11. Suchonwanit P, Srisuwanwattana P, Chalermroj N, Khunkhet S. A randomized, double-blind controlled study of the efficacy and safety of topical solution of 0.25% finasteride admixed with 3% minoxidil vs. 3% minoxidil solution in the treatment of male androgenetic alopecia. *J Eur Acad Dermatol Venereol.* 2018;32:2257-2263.
12. Suchonwanit P, Iamsumang W, Rojhirunsakool S. Efficacy of topical combination of 0.25% Finasteride and 3% Minoxidil versus 3% Minoxidil solution in female pattern hair loss: a randomized, double-blind, controlled study. *Am J Clin Dermatol.* 2019;20:147-153.
13. Hoffmann R. TrichoScan: combining epiluminescence microscopy with digital image analysis for the measurement of hair growth in vivo. *Eur J Dermatol.* 2001;11(4):362-368.
14. Hoffmann R. Trichoscan: what is new? *Dermatology.* 2005;211(1):54-62.
15. Müller B, Kasper M, Surber C, Imanidis G. Permeation, metabolism and site of action concentration of nicotinic acid derivatives in human skin: correlation with topical pharmacological effect. *Eur J Pharm Sci.* 2003;20(2):181-195.
16. Oestmann E, Lavrijsen A, Hermans J, Ponec M. Skin barrier function in healthy volunteers as assessed by transepidermal water loss and vascular response to hexyl nicotinate: Intra- and inter-individual variability. *Br J Dermatol.* 1993;128(2):30-36.
17. Dowd PM, Whitefield M, Greaves MW. Hexyl-nicotinate-induced vasodilation in normal human skin. *Dermatologica.* 1987;174(5):239-243.
18. Bansal M, Pandey S, Manchanda K. Role of caffeine in the management of androgenetic alopecia. *Int J Trichol.* 2012;4(3):185-186.
19. Fischer TW, Hipler UC, Elsner P. Effect of caffeine and testosterone on the proliferation of human hair follicles in vitro. *Int J Dermatol.* 2007;46(1):27-25.
20. Dhurat R, Chitallia J, May TW, et al. An open-label randomized multicenter study assessing the noninferiority of a caffeine-based topical liquid 0.2% versus minoxidil 5% solution in male androgenetic alopecia. *Skin Pharmacol Physiol.* 2018;30(6):298-305.
21. Shubina VS, Shatalin YV. The effect of the liposomal form of flavonoid-metal complexes on skin regeneration after chemical burn. *Cell Tissue Biol.* 2012;6(4):396-406.
22. Kwon OS, Han JH, Yoo HG, et al. Human hair growth enhancement in vitro by green tea epigallocatechin-3-gallate (EGCG). *Phytomedicine.* 2007;14(7–8):551-555.
23. Chajra H, Lefevre F, Auriol D. Native polyphenols to kick-start hair regrowth. *Cosmet Toiletries.* 2017;132(6):24-35.
24. Rogers GE. Hair follicle differentiation and regulation. *Int J Dev Biol.* 2004;48(2-3):163-170.
25. Hsu JM, Anthony WL. Impairment of cystine-35S incorporation into skin protein by zinc-deficient rats. *J Nutr.* 1971;101(4):445-452.
26. Anzai A, Pereira AF, Malaquias KR, Guerra LO, Mercuri M. Efficacy and safety of a new formulation kit (shampoo + lotion) containing anti-inflammatory and antioxidant agents to treat hair loss. *Dermatol Ther.* 2020;33(3):e13293.
27. Norwood OT. Male pattern baldness: classification and incidence. *South Med J.* 1975;68(11):1359-1365.
28. Hsiang E, Semenov Y, Aguh C, Kwatra SG. Seasonality of hair loss: a digital epidemiology analysis from 2004 to 2016. *J Invest Dermatol.* 2017;137(10):S240.
29. Kunz M, Seifert B, Trüeb RM. Seasonality of hair shedding in healthy women complaining of hair loss. *Dermatology.* 2009;219(2):105-110.
30. Courtois M, Loussouarn G, Hourseau S, Grollier JF. Periodicity in the growth and shedding of hair. *Br J Dermatol.* 1996;134(1):47-54.
31. Guarrera M, Rebora A. The higher number and longer duration of Kenogen hairs are the main cause of the hair rarefaction in androgenetic alopecia. *Skin Appendage Disord.* 2019;5:152-154.
32. Gentile P, Garcovich S. Systematic review of platelet-rich plasma use in androgenetic alopecia compared with Minoxidil®, Finasteride®, and adult stem cell-based therapy. *Int J Mol Sci.* 2020;21:2702-2728.
33. Gentile P, Garcovich S. Autologous activated platelet-rich plasma (AA-PRP) and non-activated (A-PRP) in hair growth: a retrospective, blinded, randomized evaluation in androgenetic alopecia. *Expert Opin Biol Ther.* 2020;20:327-337.
34. Gentile P, Garcovich S. Advances in regenerative stem cell therapy in androgenic alopecia and hair loss: Wnt pathway, growth-factor, and mesenchymal stem cell signaling impact analysis on cell growth and hair follicle development. *Cells.* 2019;8:466-487.
35. Yoon JS, Ku WY, Lee JH, Ahn HC. Low-level light therapy using a helmet-type device for the treatment of androgenetic alopecia. A 16-week, multicenter, randomized, double-blind, sham device-controlled trial. *Medicine.* 2020;99(29):e21181.
36. Gentile P, Dionisi L, Pizzicannella J, de Angelis B, de Fazio D, Garcovich S. A randomized blinded retrospective study: the combined use of micro-needling technique, low level laser therapy and autologous non-activated platelet-rich plasma improves hair regrowth in patients with androgenic alopecia. *Expert Opin Biol Ther.* 2020;20(9):1099-1109.