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 ORIGINAL ARTICLE

A Long-Term Study of the Safety and Efficacy of a Nutraceutical Supplement for Promoting Hair Growth in Perimenopausal, Menopausal, and Postmenopausal Women

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ABSTRACT

The prevalence of female hair loss and hair thinning increases with advancing age and is most common among post-menopausal women. Recent statistics show that by age 60, an estimated 80% of women experience hair loss. A previous publication detailing the results of the 6-month randomized, double-blind, placebo-controlled phase of this study demonstrated the ability of a nutraceutical supplement to significantly improve hair growth and shedding compared to placebo. Here, we present results from a subsequent 6-month, open-label extension phase assessing the continued safety and efficacy of this nutraceutical for promoting and improving hair growth and evaluate potential long-term benefits on quality of life and menopausal symptoms. After a total of 12 months with the active nutraceutical, subjects had progressive improvements in hair growth, quality, and shedding. Quality of life measures and menopausal symptoms also improved over the duration of the study. When transitioned to daily intake of the supplement, subjects previously treated with placebo achieved significant increases in all hair counts, a significant decrease in shedding, and significant improvement in blinded investigator global hair growth and quality assessments. The results of this long-term study demonstrate that continued use of a novel nutraceutical provides significant incremental improvement over the beneficial effects achieved during the initial 6-month randomized, placebo-controlled phase. Continued use may provide ongoing improvements in hair growth and exert a positive effect on secondary symptoms of menopause, and quality of life in perimenopausal, menopausal, and postmenopausal women with self-perceived thinning hair (ClinicalTrials.gov Identifier: NCT04048031).

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INTRODUCTION

The prevalence of female hair loss and thinning increases with advancing age and is most common among post-menopausal women. Indeed, significant androgenetic hair loss occurs in perimenopausal, menopausal, and postmenopausal women, affecting at least 50% of women by age 50.[1-5]The most recently published statistics show that by age 60, an estimated 80% of women experience hair loss.[6] Due to its perceived effect on female attractiveness, hair loss can have a significant psychological impact on affected individuals, leading to low self-esteem,[7] anxiety, and depression[8,9] and generally diminished quality of life.[9]

The hormonal changes of menopause are associated with a decrease in hair diameter and change in diameter distribution, increased miniaturization,[10,11] and decreased growth rate and time spent in the anagen phase.[12] Additional age-related changes in hair diameter and density that are independent of menopause, tend to occur at approximately the same time, compounding the perception of hair loss for middle-aged women.[12,13]

Current therapies often target sole causes, while research shows the underlying pathophysiology of hair loss and thinning to be multifactorial, caused by intrinsic and extrinsic factors including stress, hormonal shifts, inflammation, environmental insults, oxidative stress, nutritional compromise, and the natural aging process.[14] Treatment options are limited and mostly off-label. Minoxidil, the only FDA-approved drug indicated for the treatment of hair thinning and loss in women has potential side effects, and many women find it difficult to incorporate into daily haircare routines.[5,15] A nutraceutical formulation developed to provide a multi-targeted approach to thinning hair was evaluated in a randomized placebo-controlled study in women with self-perceived hair thinning.[5] Results showed significant and progressive improvements in hair growth and hair quality at 3 and 6-months compared to placebo.

More recently, an additional supplement was specifically formulated to provide a multi-targeted approach to thinning hair in women going through the menopausal transition (NUTRAFOL® Women's Balance, Nutraceutical Wellness Inc., New York, NY). The formulation features the patented Synergen Complex Plus®, a combination of standardized botanicals with clinically tested stress-adaptogenic, antioxidant, anti-inflammatory, dihydrotestosterone (DHT)-inhibiting, and hormone-balancing properties. These featured phytoactives include extracts of saw palmetto, maca, astaxanthin, curcumin, tocotrienols, and ashwagandha which are all bio-optimized for enhanced bioavailability.[15,16]

A prior publication detailing the results of the 6-month randomized, double-blind, placebo-controlled phase of this study demonstrated the ability of this novel nutraceutical supplement to significantly increase the number of terminal and vellus hairs, significantly reduce shedding, as well as improve blinded physician assessments and self-assessments of hair growth and quality.[16] The objective of this subsequent 6-month, open-label extension phase was to evaluate the continued safety and efficacy of this nutraceutical supplement for promoting and improving hair growth in perimenopausal, menopausal, and postmenopausal women with self-perceived thinning hair and assess potential long-term benefits on quality of life and menopausal symptoms.

MATERIALS AND METHODS

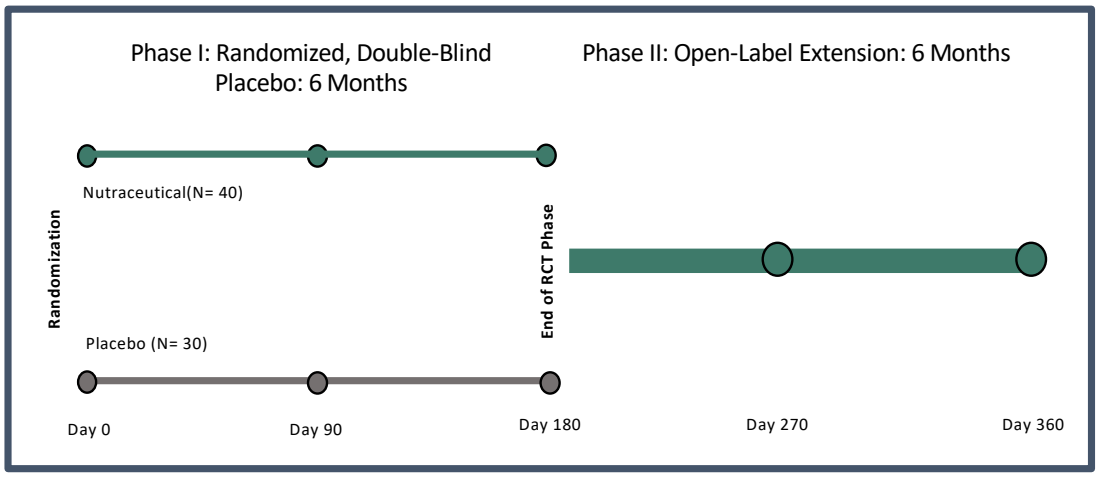
This study was approved by an institutional review board (IRB Company Inc, Buena Park, CA; now Advarra, Inc, Columbia, MD) and conducted in accordance with current standards for Good Clinical Practices as outlined in the United States FDA 21 CFR Part 50. Each subject provided written informed consent prior to participating in any study-related activities. ClinicalTrials.gov Identifier: NCT04048031.

The methods used in this study have been published in detail elsewhere.[16] Briefly, study subjects were healthy perimenopausal, menopausal, or postmenopausal women, 40 to 65 years old with Fitzpatrick I–IV photo skin types and self-perceived thinning hair. Selection criteria are listed in Table 1. Initially, 70 subjects were enrolled in the 6-month double-blind randomized placebo-controlled study (Phase I) which was completed by most active- (n=33) and placebo-treated subjects (n=27). After the day 180 evaluation, all 60 remaining subjects entered into a 6-month open-label extension study (Phase II). Subjects originally treated with the active supplement continued with their treatment and previously placebo-treated subjects were switched to treatment with the active supplement (Figure 1). The investigator and both subject groups all remained blinded to the original treatment received during Phase I until the full completion of Phase II.

TABLE 1.

Subject Selection Criteria	
Inclusion Criteria	**Exclusion Criteria**
• Females, age 40–65, who are perimenopausal, menopausal or post-menopausal in general good health • Self-perceived thinning hair as confirmed by the Investigator • Willing to maintain their normal hair shampooing frequency • Willing to add the provided oral supplement to their current daily routine • Agree not to substantially change their diet, medications, exercise, hair shampooing routines during the study • Agree to maintain a consistent frequency of haircut and color treatments for the duration of the study.	• Known allergy or sensitivity to any shampoo/conditioner. • Known stressful incident within the last six months • Recently started the use of hormone replacement therapy (HRT). • currently using any low-level laser therapy (LLLT) to treat thinning hair, or regular use of Minoxidil within the last 3 months • Use of prescription drugs known to affect the hair growth cycle within the last 6 months (eg, spironolactone, cyproterone acetate, finasteride, or any 5-alpha-reductase inhibitors) • Suffering from other hair loss disorders, such as alopecia areata, scarring alopecia, and telogen effluvium • History of burning, flaking, itching, and stinging of the scalp. • History of malignancy (except SCC and BCC skin cancers) or undergoing chemotherapy or radiation treatments. • Known history of autoimmune thyroid disease, any other thyroid disorder/abnormality or other autoimmune disorders that may interfere with the study treatment • Known history or recent blood work indicating iron deficiency, bleeding disorders or platelet dysfunction syndrome as well as subjects taking anticoagulant therapy, antiplatelet medications, more than one (1) 325 mg ASA on a daily basis or smokers with usage >20 cigarettes/day • Any medical condition, including dermatological conditions that may interfere with clinical evaluations • Use of any medications that are known to potentially cause hair loss or affect hair growth, as determined by the Investigator.

FIGURE 1. Twelve-month study design. Subjects were initially randomized to receive the nutraceutical supplement (N=40) or placebo (N=30) for 6 months. At that time, subjects previously treated with the supplement continued to take it while placebo-treated subjects were switched to the nutraceutical supplement for 6 additional months.



The clinical assessments for day 180, 270, and 360 evaluations were the same as those for the first 6 months, and included terminal, vellus, and total hair counts of a pre-specified target area on the scalp based on phototrichogram analysis via macrophotography (Canon Power Shot® G16 with 3GEN Dermlite FOTO Pro Dermoscopy DSRL lens), shed hair counts and standardized 2-dimensional global digital images (IntelliStudio®, Canfield Scientific; Parsippany, NJ). The blinded investigator completed Global Hair Growth and Global Hair Quality Improvement assessments. Subjects completed a Hair Satisfaction and Hair Quality Questionnaire, the Women's Hair Loss Quality of Life Questionnaire[17], and the Menopause Rating Scale Questionnaire[18] at each time point.

Comparative Analysis

The open-label extension phase first made comparative analyses of subjects who received active treatment during both study phases for the entire 12-month duration of the study. Comparisons were made at all timelines on days 90, 180, 270, and 360 vs baseline (day 0). The second comparative analyses were made for the group of subjects initially taking placebo. Comparisons were made between the first 6 months of those subjects taking placebo (Phase I: day 0, 90, 180) and the extension phase when the same subjects were taking the active nutraceutical (Phase II: day 180, 270, 360).

ANOVA for independent samples was used to compare demographics and baseline characteristics of each group, Tukey analysis was used to determine differences across time points and Student's t-tests was used for correlated samples to compare hair counts. A series of Chi-Square tests were performed to determine the significance of the Investigator Global Improvement and Subject Satisfaction assessments. All analyses were 2-tailed, where applicable, with α=0.05. Analyses were performed using a commercial statistical package (GraphPad Prism 8.4.3. San Diego, CA., Released 2020).

RESULTS

All 60 subjects completed the study per protocol through day 360 and completed the day 270 questionnaires; however, live assessments at day 270 could not be performed due to restrictions imposed by the COVID-19 pandemic, so only subjective assessments were collected virtually. Subjects in the active treatment group (n=33) and placebo group (n=27) had mean (SD) ages of 48.3 (10.5) years and 53.14 (5.7) years, respectively. There were no significant differences in subject age or other demographic or clinical characteristics across groups. There were no significant between-group differences in the quantity of alcohol consumed, diet, exercise, or stress, or any other parameters, except for a greater number of subjects taking thyroid medications among subjects in the active treatment group (n=12, 36%) vs. placebo subjects (n=2, 7%); however, a sub-analysis of covariance determined this difference had no impact on the primary endpoint.

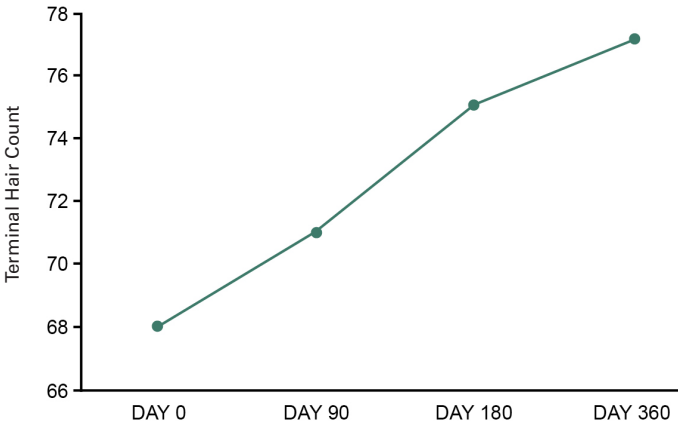
A similar number of subjects reported menopausal symptoms in the active supplement (n=15, 48%) and placebo groups (n=12, 44%). Subjects in the active supplement group reported they were perimenopausal (n=7, 24%), menopausal (n=8, 24%) or post-menopausal (n=17, 51%) while subjects in the placebo group were perimenopausal (n=6, 22%), menopausal (n=3, 11%) or post-menopausal (n=18, 67%).

Hair Counts and Global Assessments

Changes Over 12-months of Taking the Active Nutraceutical

Among subjects who received the active supplement for 12

FIGURE 2. Progressive and significant increases in mean terminal hair counts during 12 months of active treatment.



months, the mean number of terminal hairs progressively increased from 68.1 at day 0 to 77.2 at day 360, corresponding to a significant 13.4 % improvement (P<0.0001; Figure 2). The mean vellus hair counts significantly increased by 8.3% from day 0 to day 180 (P<0.05), but then decreased to baseline levels by day 360. The mean number of total hairs progressively increased from 78.4 at day 0 to 87.58 at day 360, representing a significant 11.7% improvement (P<0.0001). The mean baseline hair washing shed count progressively and significantly decreased by 43.2% (16.6 hairs) on day 180 (P<0.01), remaining stable through day 360 (P<0.01 vs baseline; Table 2).

Blinded investigator global hair assessments showed progressive and significant improvement among subjects receiving the active supplement over the entire 360 days. There was a statistically significant increase in Global Hair Growth Improvement ratings from 43% on day 90 to day 180 (P<0.001) and 25% from day 90 to day 360. Global Hair Quality Improvement scores significantly increased by 24% from day 90 to day 180 (P<0.05) and by 37% from day 90 to day 360 (P<0.005). Figure 3 shows improvements in hair growth and quality for representative subjects treated with the active product for 12 months.

FIGURE 3. These representative subjects were treated with the active product for 12 months. Images show visible clinical improvement and changes in macrophotographs of selected 1 cm^2 target areas.

Changes Within the Initial Placebo Group

When placebo group subjects were compared directly to the active group during Phase I of the study, there was no evidence of any change in the mean total or mean terminal hair counts and there was a small yet significant decrease in the mean vellus hair counts. The shed counts initially increased and then decreased at day 180 relative to baseline but did not reach statistical significance. Blinded investigator global hair assessments showed a non-significant increase in ratings for Hair Growth (22%) and Hair Quality (15%) Improvements.[16]

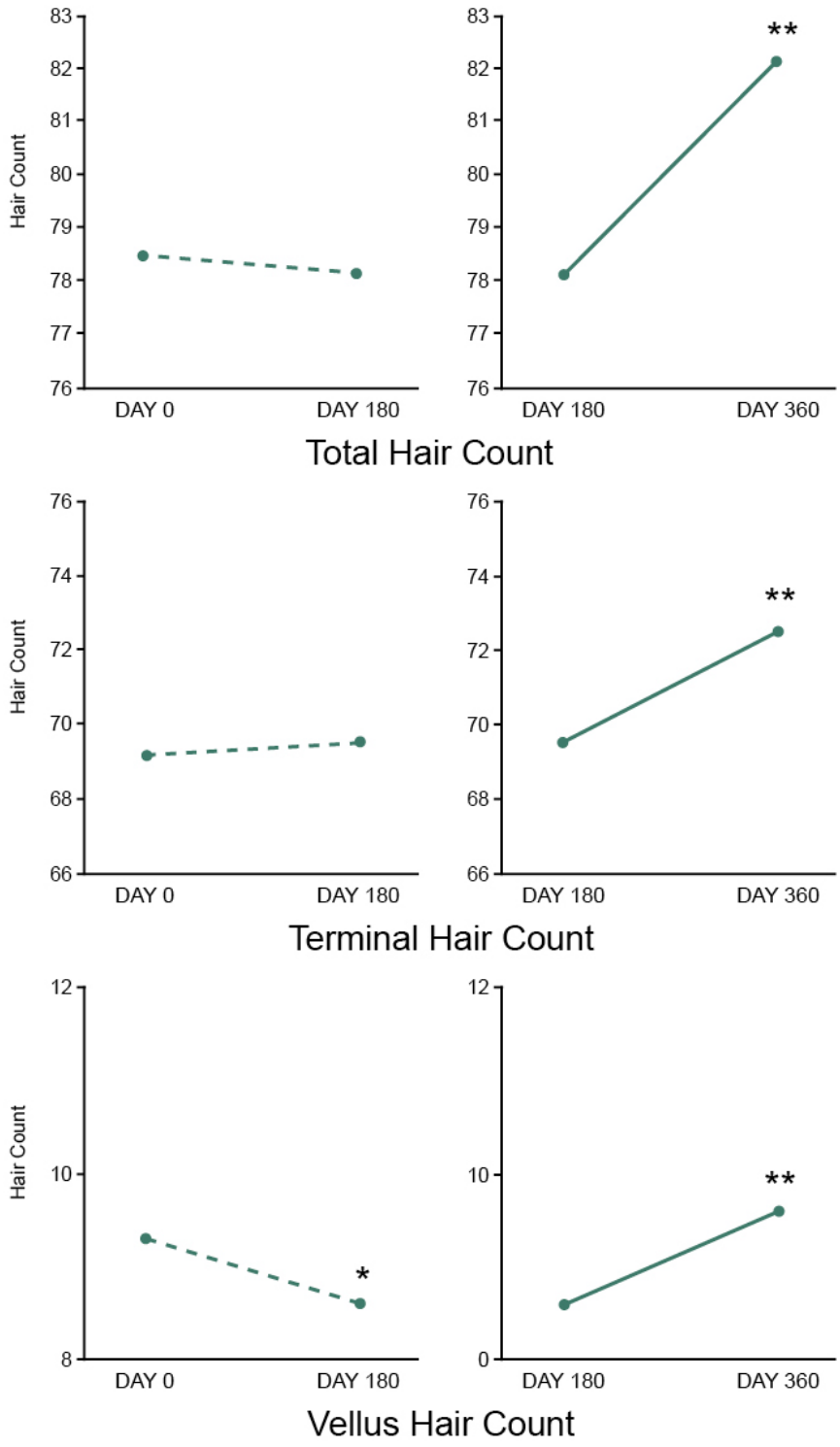
TABLE 2.

Changes in Hair Parameters Over 12-months of Taking the Active Nutraceutical

	Day 0	Day 90		Day 180		Day 360	
	Mean (SD)	Mean (SD)	Signif.	Mean (SD)	Signif.	Mean (SD)	Signif.
Total Hair Count	78.4 (7.4)	81.3 (8.4)	P=NS	86.3 (10.1)	P<0.01	87.6 (10.5)	P<0.0001
Terminal Hair Count	68.1 (6.5)	71.0 (7.5)	P<0.01	75.1 (9.1)	P<0.01	77.2 (9.6)	P<0.0001
Vellus Hair Count	10.3 (2.2)	10.3 (2.0)	P=NS	11.2 (1.6)	P<0.05	10.2 (1.4)	P<0.01
Shed Hair Count	38.2 (19.9)	26.7 (16.8)	P<0.01	22.6 (11.9)	P<0.01	22.3 (19.1)	P<0.001

NS, not significant.

FIGURE 4. Changes in terminal hairs counts, vellus hair counts, and total hairs counts during treatment with placebo for 6 months (left panel) and after switching to active treatment for 6 months (right panel).



*Denotes $P<0.05$, **denotes $P<0.005$.

Once placebo group subjects were switched to the active supplement and compared to when they were taking placebo, all hair counts increased significantly from day 180 to day 360: the mean terminal hair count increased by 4.3% (P<0.005), the mean total hair count increased by 5% (P<0.001), and the mean vellus count increased significantly by 11.6% (P<0.05; Figure 4). Furthermore, the mean change in total hair shed count significantly decreased from day 180 to Day 360 (-12.7) translating into a 39% decrease in shedding (P<0.0001). Blinded investigator Global Hair Growth improvement and Global Hair Quality Improvement scores increased significantly by 30% and 40%, respectively, across the 6-month evaluation period (for each, P<0.05).

Long-term Subjective Assessments

Hair Satisfaction Questionnaire

Chi-Square evaluations were conducted to evaluate the significance of the difference between the proportion of 'Satisfied' Subject Hair Satisfaction Ratings among subjects who took the active supplement for 12 continuous months. At day 0, not a single subject reported being 'Satisfied' with her hair; however, there was a significant increase in 'Satisfied' Hair Ratings across and between all evaluation periods for subjects who took the active supplement for 12 continuous months, culminating in 85% of subjects being 'Satisfied' with their hair (for each, P<0.05).

Hair Quality Self-assessment

Overall hair quality self-assessments agreed with the objective findings. From baseline until the end of the study, most subjects reported overall increased hair growth (81%), increased volume (84%), increased scalp coverage (78%), and increased amount of new hair (81%).

Women's Hair Loss Quality of Life Questionnaire

In general, items on the Women's Hair Loss Quality of Life Questionnaire showed positive changes from baseline until the end of the study. Notably, there was a ≥30% increased improvement for 'Feeling Embarrassed', 'Avoiding Social Gatherings', and 'Fearing Being the Center of Attention'. There was a ≥20% increase in improvement for 'Self-esteem', 'Being Self-Conscious', and 'Feeling Unattractive'.

Menopause Rating Scale Questionnaire

Almost all perimenopausal subjects (93%) reported experiencing baseline menopausal symptoms on the Lifestyle Questionnaire. Menopausal symptoms were notably more prevalent during the perimenopausal phase and progressively diminished for women in the menopausal (64%) and post-menopausal (23%) phases. The most frequently reported menopause symptom was hot flashes (61%) and most subjects reported symptom frequency as sporadic but a few experienced symptoms as often as 4 to 5 times weekly.

Subjects who reported experiencing menopausal symptoms at baseline and received the active supplement reported improvements and reductions in the severity of their menopausal symptoms throughout the 12-month period. Most symptoms that were rated as 'severe' or 'very severe' at baseline were either 'moderate', 'mild', or 'none' by day 360, including 'hot flashes', 'sleep problems', and 'depressive mood'. Furthermore, the symptoms of 'sexual problems,' 'irritability' and 'anxiety' showed a 44% improvement by ≥1-point in severity between day 0 and day 360. The most notable improvement occurred for 'physical and mental exhaustion' with a 56% improvement in severity.

Safety

No unanticipated adverse events were reported. Adverse events occurred in three subjects, two in the active group (nausea, bloating, diarrhea) and one in the placebo group (nausea, headache), during the first phase of the study. No adverse events were reported during Phase II.

DISCUSSION

This was a 12-month study to evaluate the efficacy and safety of a nutraceutical to promote hair growth in perimenopausal, menopausal, and postmenopausal women with self-perceived thinning hair. During the first 6-month double-blind, placebo-controlled phase of this study, women receiving the active supplement daily achieved significant improvements in hair growth and quality compared to placebo.[16] In fact, this active group showed significant increases in the number of terminal and vellus hairs, significantly reduced shedding, as well as improved blinded physician and subjective assessments of hair growth and quality. The subsequent 6-month open-label extension phase assessed the continued long-term safety and efficacy of the nutraceutical for promoting hair growth and quality, and potential benefits on quality of life and menopausal symptoms, as well as to evaluate overall efficacy for subjects previously treated with placebo when switched to the active supplement.

After a total of 12 months of treatment with the nutraceutical, subjects achieved significant and progressive increases in the number of total and terminal hairs, improvement followed by subsequent stabilization of vellus hair growth and hair shedding. Blinded investigator global hair growth and quality assessments, as well as subjects' self-assessments for hair growth, quality, and satisfaction also showed progressive and significant improvement over the year-long duration of the study. More specifically, the number of total hairs continued to improve for 12 months, suggesting that a maximum increase may not have been reached; however, the total hair count increase was driven mainly by continued increase in terminal hairs throughout 12 months. While vellus hair saw a significant increase in the first 6 months of use, there was more of a stabilization in growth

during the second phase of the study. Given the concomitant and continued increase in terminal hairs, this may indicate transition from vellus to terminal hair over time. Though overall shedding decreased significantly over 12 months, the most remarkable decrease was seen in the initial 6 months, indicating a possible return to healthy shedding patterns by 6 months of use and subsequent maintenance with continued therapy.

During the open-label phase of the study, subjects previously treated with placebo showed improvements in hair growth when placebo group transitioned to daily intake of the supplement. More precisely, they achieved significant increases in all hair counts and a significant decrease in shedding, as well as significant improvement in blinded investigator global hair and quality assessments. In contrast, while previously on placebo during the first phase, these subjects had a significant decrease in vellus hair counts, while showing no significant changes in terminal and total hair counts, or shedding.[16] Although a decrease in vellus hairs could point to a transition of vellus to terminal hairs, it could also indicate progressive change in hair during menopause normally marked by relative androgen dominance and miniaturization.[10,12] In the case of the placebo group in the initial phase of the study, the lack of concomitant increase in terminal hairs at the time suggested a progressive decline without intervention. It is known that androgens, particularly DHT, trigger miniaturization within genetically predisposed follicles, and that without intervention, miniaturization and hair loss tend to be progressive.[2,10,13] Interestingly, after switching to the nutraceutical, these subjects showed a pattern of improvement similar to those of the active group in Phase I of study. Notably, significant increase in all hair counts, including vellus, as well as a significant decrease in shedding. Based on both groups' initial 6 months of use, we can corroborate early results and efficacy of therapy and suggest a predictable pattern of improvement with daily use of the nutraceutical.

It is worth noting that for many patients enrolled in the study, the open-label phase coincided with the COVID-19 pandemic. Although no subject reported any symptoms or was diagnosed with COVID-19 during the study, it is very possible that subjects' hair might have been affected as a result of physical and emotional stress, and potentially impacting outcomes.[19-21] This could explain, at least in part, why the improvement in the placebo group that transitioned to active therapy was not as compelling as those initially seen in the active group during Phase I, and why the active group on continued therapy had stabilized in some parameters over the second 6-months of the study. Nevertheless, the results still showed significant and progressive improvements with 12 months of use, underscoring the observation that although the most dramatic improvements are seen within 3-6 months, hair growth and quality continuously increase over time, which speaks to continuity of care. Furthermore, a significant improvement from continued use was seen in women at different stages of menopausal transition, where we would otherwise expect a decline in hair health without intervention, as was witnessed in the placebo group during the first phase of the study until they were switched to the nutraceutical.

While the full etiology of female hair loss remains to be elucidated, we understand that multiple factors play a role.[4] The currently studied supplement is formulated with standardized nutraceuticals that have shown multimodal biological activity against multiple molecular factors of hair loss and more specifically, additional targets of hair thinning in women going through and beyond the menopausal transition.[16] These mechanisms and ingredients are detailed in previous publications[15,16,22] and briefly described here. The stress-adaptogen ashwagandha has been shown to improve symptoms of stress and lower elevated cortisol in stressed adults,[23] providing an option to address increased psycho-emotional stress as a factor in hair thinning for menopausal women. Saw palmetto, which has shown efficacy for hair loss and is well known for its anti-androgenic and DHT-inhibiting properties, was optimized in this formulation to address relative androgen dominance in menopausal women.[24-26] Maca root is likewise considered adaptogenic, exerting a positive effect on the balance of endogenous sex hormones, cortisol, and DHT through its numerous constituents and has been shown to improve menopausal symptoms.[27-30] Other key ingredients like curcumin, astaxanthin, and the tocotrienol/tocopherol complex are well known for their clinical anti-inflammatory, immunomodulatory and antioxidant properties.[15,31,32]

Combinations of these and other ingredients have shown clinical efficacy in addressing symptoms of hair thinning in both menopausal and non-menopausal women.[16,22] Additional benefits of the supplement reported in the current study included improvement in menopause symptoms such as hot flashes, sleep, and sexual problems, irritability, and mental and physical exhaustion. This may reflect the clinically studied properties of the individual ingredients discussed above.

Quality of life is significantly affected during the menopausal transition, while the emotional toll of associated symptoms including hair loss is high.[33,19,34] Throughout the study, quality of life measures such as self-esteem, feelings of embarrassment, and self-consciousness were shown to improve. This may be due to the properties of the nutraceutical significantly increasing hair growth and quality parameters or because of improvement in menopausal symptoms or both. Whilst there is a paucity of research on women going through menopause, it is important to consider clinical examination of options to better optimize management of symptoms during this time. To our knowledge, this is the first prospective study showing clinical efficacy of a nutraceutical hair supplement over 12 months, specifically

in improving hair growth in women with thinning hair in the menopausal transition.

CONCLUSION

The results of this 12-month study demonstrate that continued use of a novel nutraceutical provides significant incremental improvement over the beneficial effects achieved during the initial 6-month randomized, placebo-controlled phase. Continuous use may provide ongoing improvements in hair growth and exert a positive effect on secondary symptoms of menopause, as well as quality of life. There were no unanticipated adverse events reported and the supplement was well-tolerated over the year-long study duration.

DISCLOSURES

Drs Kogan and Raymond are employees of Nutraceutical Wellness, LLC, New York, NY. Dr Ablon has nothing to disclose. The study was conducted with a grant from Nutraceutical Wellness LLC, New York, NY.

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