

Efficacy and Safety of Minoxidil 5% Foam in Combination With a Botanical Hair Solution in Men With Androgenic Alopecia

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ABSTRACT

Androgenic alopecia (AGA) is the most common type of hair loss in men, characterized by hair miniaturization, hairline recession, and vertex balding. It affects approximately 50% of men, negatively affecting self-esteem and sociability. Topical minoxidil formulations are approved up to a 5% concentration for men, but patient adherence to treatment is challenged by gradual results that may be perceived as a lack of initial benefit. Herbal extracts, which are also believed to promote healthier-looking hair, have a long history of use in hair care formulations. The safety and efficacy of a twice-daily regimen of 5% minoxidil foam used in combination with a novel botanical hair solution was evaluated in a 12-week, multicenter, single-arm, open label study in 56 subjects with mild to moderate AGA. Assessments included investigator ratings of improvement and subject self-ratings of satisfaction. Investigator ratings indicated significant improvement in scalp hair coverage and perception of overall treatment benefit in as early as 4 weeks ($P<.001$). Subject self-ratings were significant for improved hair growth and hair appearance in as few as 4 weeks ($P<.05$). The regimen was well tolerated, and subjects indicated a high degree of satisfaction. Investigator and subject-assessed efficacy and subject satisfaction with this novel regimen provide clinicians with an effective treatment option for AGA that also provides a high level of patient satisfaction, which may help promote patient adherence to long-term treatment.

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INTRODUCTION

Male pattern hair loss (MPHL), also known as androgenic alopecia (AGA), is a progressive form of non-scarring hair loss with characteristic thinning/loss affecting the frontal, temporal, and vertex areas of the scalp.[1,2] Diagnosis is made by clinical evaluation of the scalp and a thorough medical history evaluation.[3] During the term of normal hair growth, 85% to 90% of the hair follicles are in a growth phase (anagen) which lasts for 2 to 7 years, and then they decelerate during a 2 to 3 week transition phase (catagen) when the hair follicle matrix cells associated with the dermal papilla (DP) undergo apoptosis (cell death). The remaining 10% to 15% of the hair follicles have progressed beyond anagen/catagen, into a rest phase (telogen). Telogen lasts for up to 3 months, and concludes with shedding of the hair shaft as growth of a new hair is initiated.[4]

Androgenic alopecia is characterized by the premature onset of catagen and a progressive shortening of the anagen phase. Over time this shift is reflected by accelerated hair shedding, a decreased ratio of terminal (long, thick, pigmented) hairs to vellus (short, thin, non-pigmented hairs), and an overall reduction in hair density.[5,6] AGA in men is associated with a progressive hereditary increase in conversion of testosterone to dihydrotestosterone (DHT) by type II 5-a-reductase.[7,8] When androgen receptors of the DP-associated cells are preferentially bound by DHT, absorption of vital nutrients is blocked and hair matrix cell proliferation becomes inhibited. This malnourishment is believed to trigger the premature onset of catagen, cell apoptosis, and progressive shortening of the anagen phase.[9-11] Microinflammation and altered prostaglandin metabolism within the hair follicle are also believed to contribute to premature DP apoptosis and follicular miniaturization by causing fibroplasia of the dermal sheath surrounding the hair follicle.[12]

Androgenic alopecia is the most common form of alopecia and is estimated to affect half of all men in the United States.[13] Typical onset occurs between 30 and 40 years of age, and by the age of 70 years up to 85% of men may be affected.[13,14] Although hair loss is primarily a cosmetic concern, hair contributes to outward appearance and social confidence, and patients seeking treatment for AGA are motivated by the psychological distress and negative impact that hair loss has on self-esteem and social self-confidence.[15] Currently, topical minoxidil (2% solution and 5% solution or foam) and oral finestramide (1mg) are the only US Food and Drug Administration (FDA)-approved medications for the treatment of male AGA.[16,17] Minoxidil's mode of action is androgen independent, and believed to promote hair growth by promoting the production of vascular endothelial growth factor, increasing the production of anti-inflammatory prostaglandin E2 (PGE2), and lengthening the duration of the anagen

phase.[18-20] Finasteride, an FDA-approved oral anti-androgen that inhibits type II 5-a-reductase activity, also promotes the anagen phase; however, the negative side effects attributed to DHT suppression such as erectile dysfunction and loss of libido are a cause of therapy withdrawal.[21-24]

Alternative options in topical treatments include herbal extracts, which ideally function in an androgen-independent manner, and have demonstrated efficacy in stimulating hair growth with little side effect. A wide variety of herbal extracts used for centuries in traditional Ayurveda, Chinese, and Unani culture have demonstrated benefit in promoting fuller healthier-looking hair as monotherapies and as adjunctive treatments to traditional hair loss treatments with fewer side effects.[25,26]

"The treatment of androgenic alopecia is long-term and requires patient adherence, so exploration of novel treatment options should evaluate patient satisfaction in addition to efficacy."

Other androgen-independent treatment options include platelet-rich plasma (PRP) scalp injections, which are believed to stimulate development of new hair follicles and promote neovascularisation using the pro-healing cytokines released from blood platelets such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), epidermal growth factor (EGF), and interleukin (IL)-1.[27,28] Although the results seen with PRP treatment for hair growth are promising, the long-term outcome has not yet been determined. In addition, low-level laser (light) therapy (LLLT) has been demonstrated to promote hair growth in men and women with AGA, although the long-term effects of low-level laser treatment on hair growth and maintenance have not yet been determined.[29] The most permanent treatment option, surgical hair transplantation, is an invasive procedure that favors the subgroup of patients with dense hair in the donor site (occipital scalp) and focal hair loss in the frontal and mid-frontal scalp.[30]

For patients affected by AGA, there is no permanent cure and the degree of hair loss progresses over time. The effect of hair loss impacts self-esteem, psychosocial functioning, and quality of life. The mainstay of treatment options for men is the twice-daily use of topical minoxidil. Because microinflammation may contribute to AGA, and existing commercial preparations of minoxidil can be irritating to some patients, it is important to explore treatment options that are compatible with minoxidil and provide an anti-inflammatory effect.[31] The need to explore additional safe and effective treatment options to supplement minoxidil monotherapy for AGA exists.

The treatment of AGA is long-term and requires patient adherence, so exploration of novel treatment options should evaluate patient satisfaction in addition to efficacy. On this basis, the current study evaluates the safety, efficacy, and subject satisfaction results with a topical regimen of topical minoxidil 5% foam used in combination with a botanical hair solution that may help promote hair growth in men with AGA. Investigator ratings show that the regimen significantly improved scalp hair coverage and provided overall benefit in as few as 4 weeks. Subject self-ratings showed significant improvement in hair growth and hair appearance, in as early as 4 and 6 weeks, respectively. The regimen was well tolerated, and subjects indicated a high degree of satisfaction.

METHODS

Participants

This clinical study protocol was reviewed and approved by an Institutional Review Board. At the baseline/screening visit, each participant's written informed consent was obtained. Main inclusion criteria included: males aged 18 to 60 years with presence of hair loss who exhibited MPHL/AGA (Norwood Scale III and IV), and a willingness to maintain the same hair style, color, and regimen throughout the study. Participants who had previously used minoxidil were considered for inclusion, but were limited to no more than half of the participants.

Primary exclusion criteria included: use of concomitant hair loss therapies or medications; use of blood pressure medication;

TABLE 1.

Subject Demographics	
	Subjects
N	56
Mean age, year (SD, range)	45.5 (9.7; 22-60)
Ethnicity/race, n (%)	
Native American or Alaskan Native	2 (3.6)
Asian	4 (7.1)
Black or African American	5 (8.9)
Hispanic or Latino	11 (19.6)
White	34 (60.7)
Fitzpatrick skin type, n (%)	
II	6 (10.7)
III	29 (51.8)
IV	17 (30.4)
V	4 (7.1)

SD, standard deviation.

FIGURE 1. Investigator ratings of scalp hair coverage and overall treatment benefit relative to baseline.

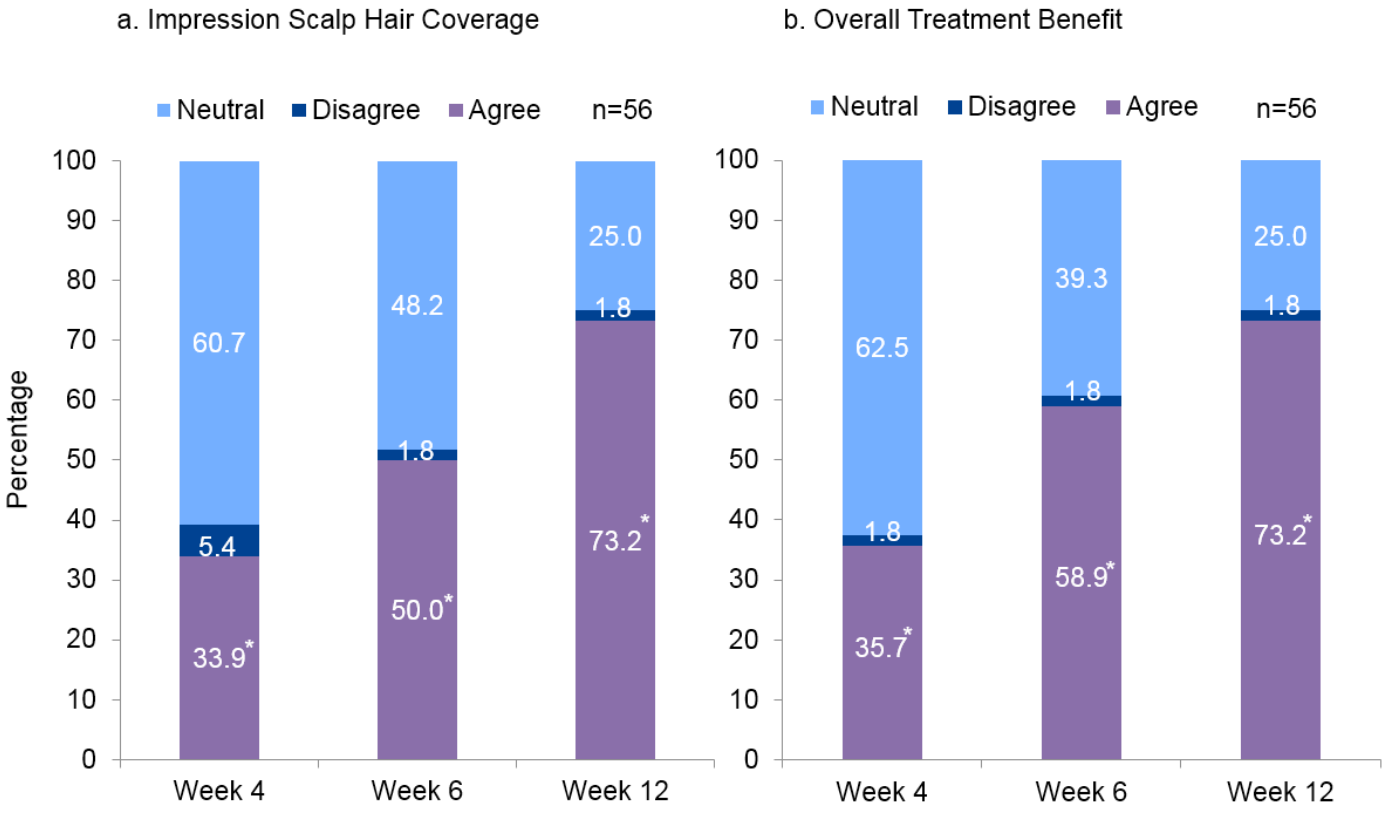


FIGURE 2. Representative photographs of subject improvement in scalp coverage at baseline and week 12.

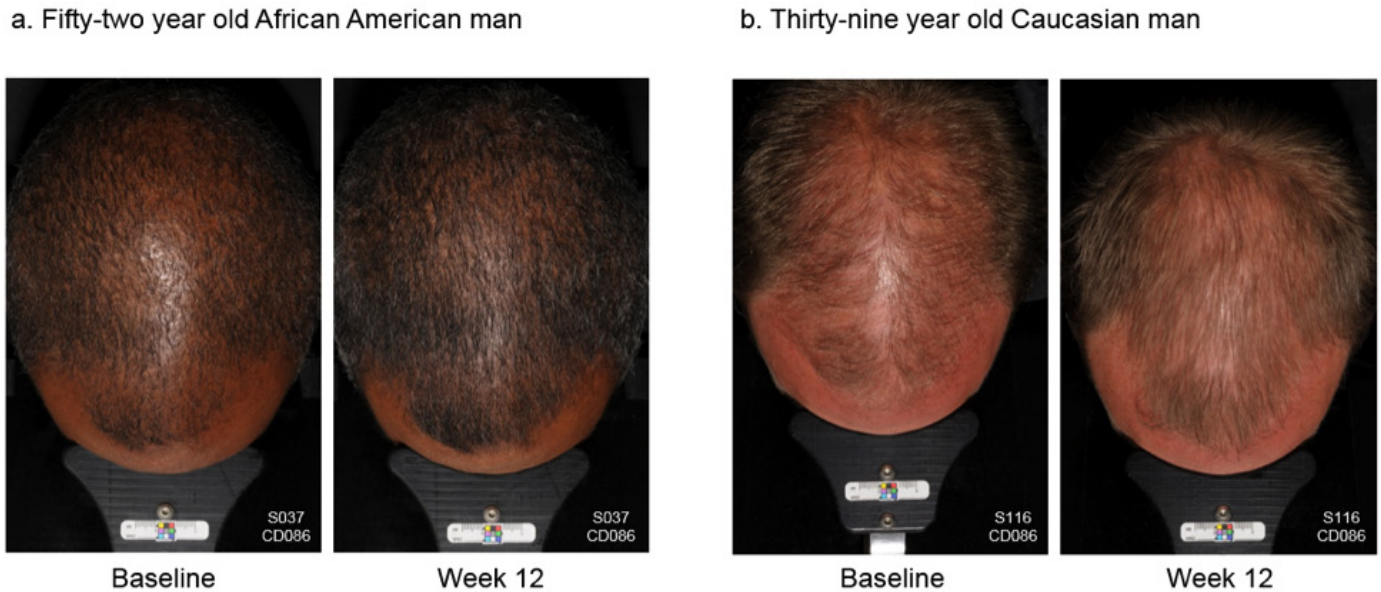
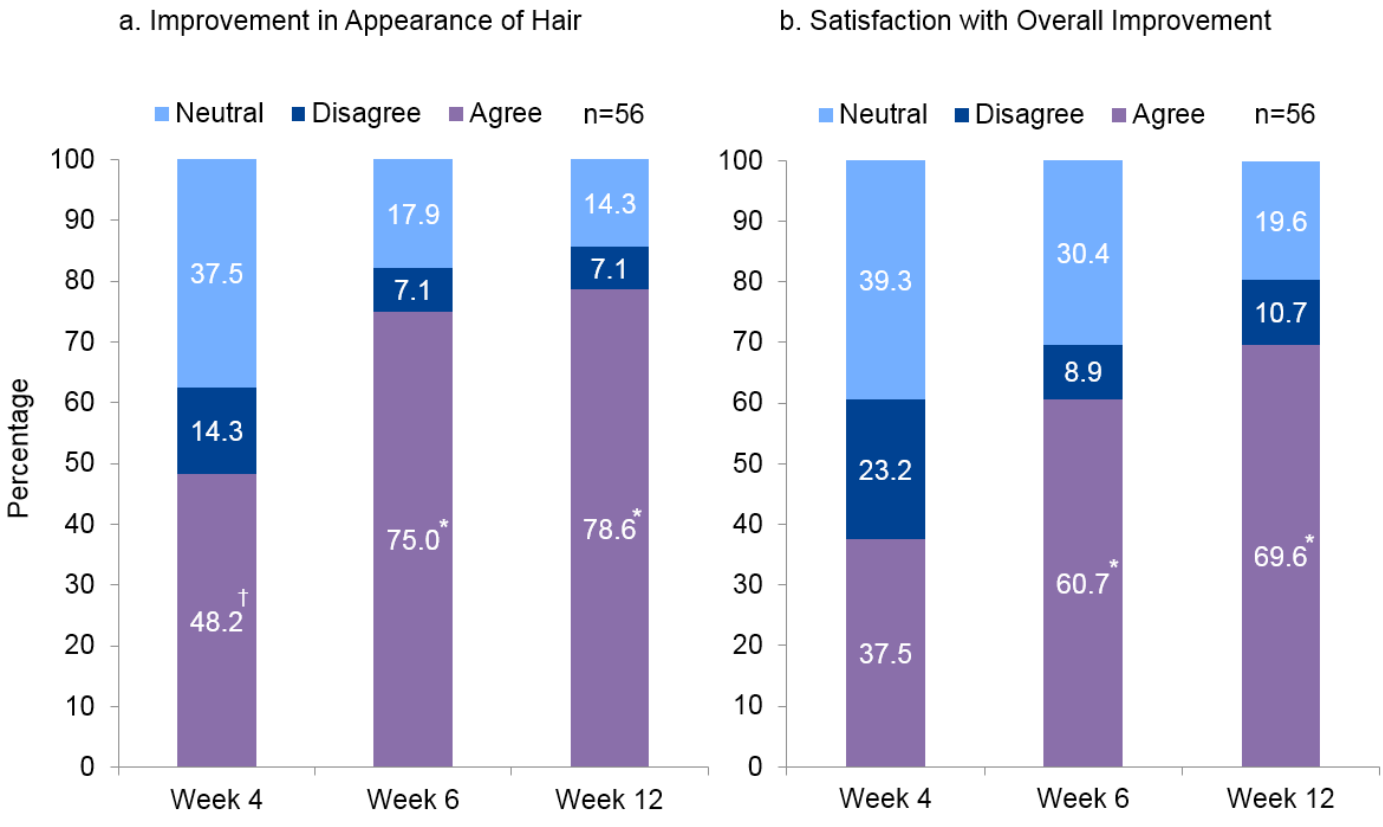


FIGURE 3. Subject self-ratings of appearance of hair and overall satisfactory improvement relative to baseline.



†*P* = .05 and **P* < .001 Agree vs. Disagree
Agree = rating of 5-7; Neutral = rating of 4; Disagree = rating of 1-3

history of hair transplant surgical procedures to the scalp; use of laser treatments, use within previous 6 months of over the counter medications known to affect hair growth cycles; active dermatological conditions (sebhorrheic dermatitis, psoriasis, atopic dermatitis, etc); a diagnosis of alopecia areata or scarring alopecia, and any participants employed by the study site or otherwise affiliated with the investigational research center.

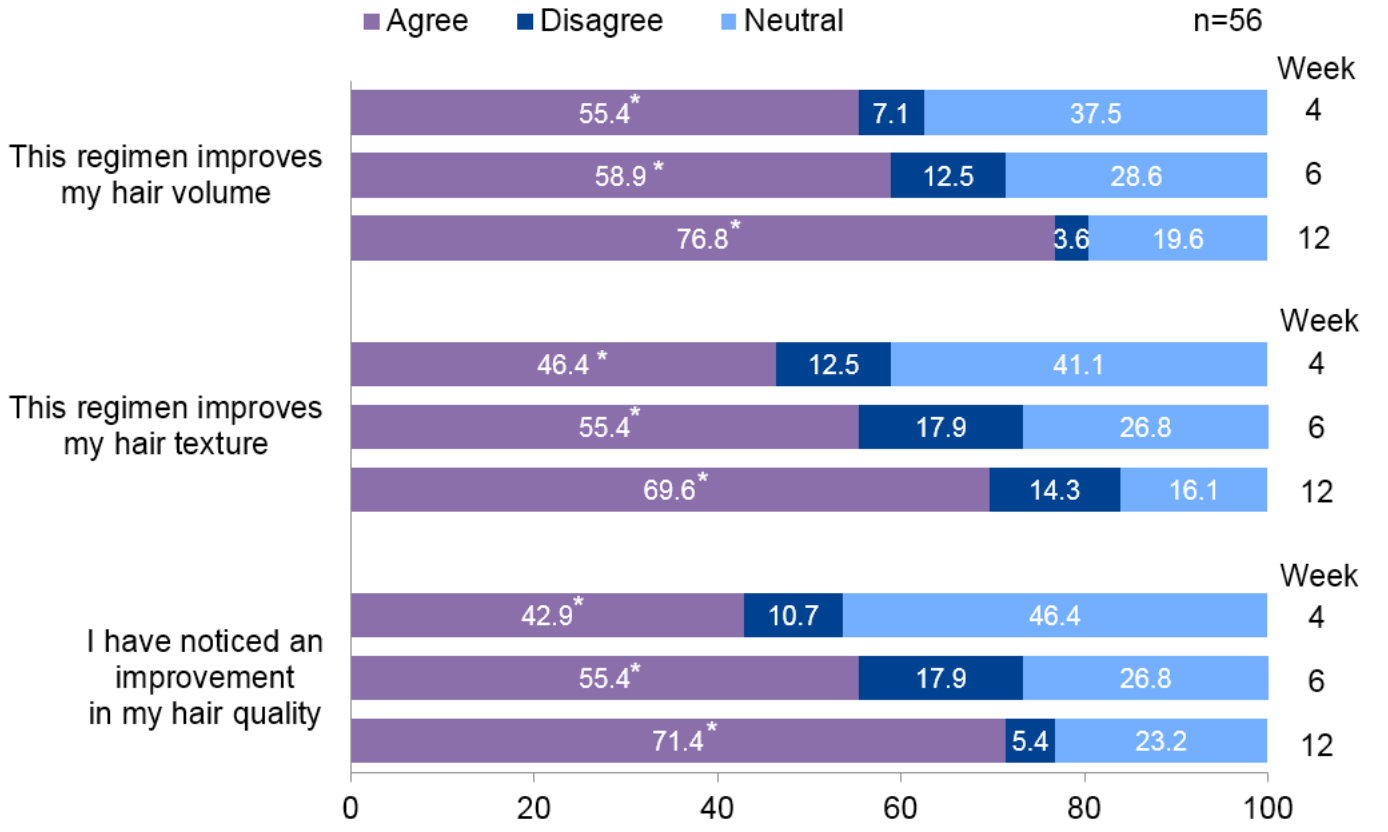
Study Design and Regimen

This was a multicenter, single-arm, open label study. The safety and efficacy of minoxidil 5% foam in a combined regimen with a botanical hair solution (BHS) was evaluated for 12 weeks. Subjects were instructed to use both products twice daily in a 2-step application process consisting of half a capful minoxidil 5% foam massaged onto the scalp in the hair loss area (wet or dry) and allowed to dry, followed by 5 to 10 sprays of the BHS applied to the entire scalp (wet or dry), with no subsequent wash step.

At the baseline/day 1 visit, a standardized global photograph of each subject's superior scalp and scalp vertex was collected, and participants were given a calculated supply of minoxidil 5% foam and the BHS (Galderma Laboratories, L.P., Fort Worth, TX). Investigator assessments of the subjects' global photographs were made using a 7-point Likert scale (1 = Entirely Disagree to 7 = Entirely Agree) to rate changes in hair thinning, hair growth, impression of scalp hair coverage, and overall treatment benefit at weeks 4, 6, and 12, relative to baseline. Subjects made self-assessments using a 7-point Likert scale (1 = Entirely Disagree to 7 = Entirely Agree) using a mirror to rate changes in their hair's appearance and overall treatment benefit at weeks 4, 6, and 12, relative to baseline.

For investigator and subject self-ratings, scores were transformed into a percentage and presented descriptively. Frequency and percentage of all response options were recorded and pooled as "Agree" (combining "Entirely Agree", "Mostly Agree", and "Somewhat Agree"), "Neutral" ("Neither Agree nor Disagree") and "Disagree" (combining "Entirely Disagree", "Mostly Disagree", and "Somewhat Disagree"). A Wilcoxon signed-rank was employed for the null hypothesis that the mean score is equal to 4 (neutral). A binomial (sign) test

FIGURE 4. Subject satisfaction at weeks 4, 6, and 12.



*$P \leq .001$ Agree vs. Disagree
Agree = rating of 1-2; Neutral = rating of 3; Disagree = rating of 4-5

was performed to test if the proportion of the combined agree responses was equal to the combined disagree responses for each applicable question.

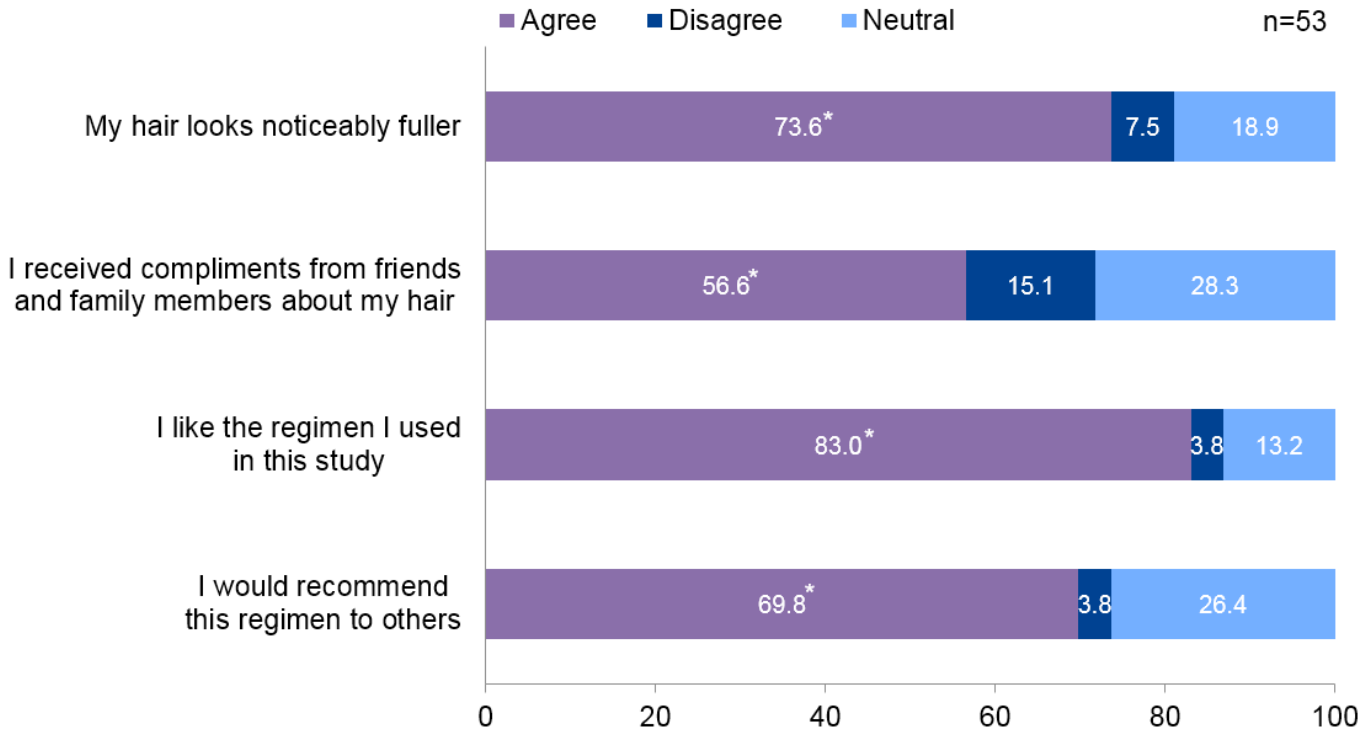
Subject satisfaction questionnaires were completed at weeks 4, 6, and 12 using a 5-point Likert response scale (1 = Strongly Agree to 5 = Strongly Disagree) to rate satisfaction with improvement in hair volume, texture, and quality as well as with the use of the regimen. Frequency and percentage of all response options were recorded and pooled as "Agree" (combining "Strongly Agree" and "Agree"), "Neutral" ("Neither Agree nor Disagree"), and "Disagree" (combining "Strongly Disagree" and "Disagree"). A binomial (sign) test was performed to test if the proportion of the combined agree responses was equal to the combined disagree responses for each applicable question. All statistical tests were 2-sided at significance level $\alpha = 0.05$.

RESULTS

A total of 56 male subjects between the ages of 22 and 60 with type III and IV Norwood hair loss pattern were included in the intent-to-treat (ITT) study population (Table 1).The mean age was 45.5 years, 60.7% of the subjects were Caucasian, 19.6% were Hispanic or Latino, and 8.9% were Black or African American. Investigator assessment ratings of subject photographs showed that the twice-daily regimen of minoxidil 5% foam in combination with BHS significantly improved scalp hair coverage and demonstrated overall treatment benefit at weeks 4, 6, and 12, relative to baseline ($P<.001$) (Figure 1). Representative photographs are shown in Figure 2. In addition, investigator ratings indicated significant improvement in hair growth (33.9% Agree vs 0% Disagree) ($P<.001$) at week 4, and hair thinning (50.0% Agree vs 1.8% Disagree) ($P<.001$) at week 6 (data not shown).

Subject self-assessment ratings indicated that a significant proportion of subjects agreed with improvement in the appearance of their hair and satisfaction with overall improvement at weeks 6 and 12, relative to baseline ($P<.05$) (Figure 3). In addition, subjects significantly agreed that they were satisfied with their hair growth (71.4% Agree vs 8.9% Disagree) and the hair on the top of their head (64.3% Agree vs 12.5% Disagree) ($P<.001$) as early as week 6 (data not shown).

FIGURE 5. Subject satisfaction at week 12.



*P < .001 Agree vs. Disagree
Agree = rating of 1-2; Neutral = rating of 3; Disagree = rating of 4-5

Subject satisfaction responses indicated that a significant proportion of subjects agreed regarding the improvement in their hair volume, texture, and quality at weeks 4, 6, and 12 ($P \leq .001$) (Figure 4). Subjects also agreed that their scalp felt better at week 4 (37.5% Agree vs 12.5% Disagree, $P<.05$) and week 6 (42.9% Agree vs 14.3% Disagree, $P<.05$) (data not shown). In addition, subject satisfaction responses indicated that a significant proportion of subjects agreed that their hair looked noticeably fuller, and reported having received compliments from others at week 12, relative to baseline ($P<.001$). Subjects also expressed strong agreement that they liked the regimen and that they would recommend the regimen to others ($P<.001$) (Figure 5).

Four adverse events (AEs) were reported during the course of the study. One AE described as pain on the crown of the head (1.7%) was considered related to the treatment regimen.

DISCUSSION

The results of this study demonstrate that a twice-daily regimen of minoxidil 5% foam in combination with BHS significantly improved scalp hair coverage and provided overall benefit to men with mild to moderate pattern hair loss in as early as 4 weeks, as rated by investigator and subjects. These results address several of the major limitations encountered with the treatment options currently available. The benefits observed by subjects early in the treatment period are important since the perception of benefit or lack of benefit is known to influence adherence to topical therapies such as minoxidil. Although potential side effects, such as pruritus have been reported with the use of the 5% minixidil, it was not reported by subjects in this study. Alternately, subjects significantly agreed at weeks 4 and 6 that their scalp felt better since beginning the regimen. Since this regimen functions in an androgen-independent manner, there is no concern of negative side effects that are associated with oral medications that alter androgen metabolism. This regimen was well tolerated, with only one AE considered as possibly related.

The lack of innovation in safe, effective, side-effect–free topical hair growth treatments is a limiting factor for clinicians and their patients. The adjunctive use of the BHS with minoxidil provides an additional option that satisfies current treatment limitations. Although hair loss is primarily a cosmetic concern, patients seeking treatment for hair loss are driven by their emotional distress and discomfort with their appearance. Research studies exploring the negative psychosocial consequences of hair loss indicate that effective treatments have a positive impact on self-confidence and social functioning.

Significant subject agreement with noticeably fuller-looking hair and having received compliments from others are important results, since these address the potential improvement of self-image, self-esteem, and social functioning, all variables that drive patients to seek relief and treatment for their hair loss. Ultimately, the high level of subject satisfaction with the benefits achieved by week 12, including improvement in hair volume, texture, and quality, was reflected by a significant proportion of subjects responding that they liked the study regimen, and that they would recommend it to others.

This study was limited by study design, as it was open-label, included no comparison with an active control regimen, and concluded at week 12. Additional studies designed with a longer duration, increased subject number, and active control may enhance the results obtained. Further study exploring the distinct benefit of the BHS in this regimen is necessary.

CONCLUSION

The aim of minoxidil treatment is to slow or stop the progression of hair loss and requires continuous use, therefore patient perception of treatment benefit and cosmetic acceptability are foundational in successful treatment. Important in these study results was the benefit reported by the subjects as well as the investigator as early as week 4. The favorable results demonstrated by the twice-daily use of minoxidil 5% foam in combination with the BHS suggest that this regimen is an effective treatment option for clinicians treating patients with AGA, and that it may also promote patient adherence to long-term minoxidil treatment recommendations.

DISCLOSURES

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