A randomized, single-blind trial of 5% minoxidil foam once daily versus 2% minoxidil solution twice daily in the treatment of androgenetic alopecia in women

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Background: Although twice-daily application of propylene glycol–containing 2% minoxidil topical solution (MTS) stimulates new hair growth, higher concentrations of minoxidil in a once-daily, propylene glycol–free formulation may improve efficacy and reduce unpleasant side effects.

Objective: We sought to compare the efficacy, safety, and acceptability and to show noninferiority of once-daily 5% minoxidil topical foam (MTF) with twice-daily 2% MTS in women with androgenetic alopecia.

Methods: A total of 113 women with androgenetic alopecia were randomized to 24 weeks of treatment with 5% MTF or 2% MTS. The primary efficacy parameter was change from baseline in nonvellus target area hair count at week 24. Secondary end points included change in nonvellus target area hair width, overall efficacy by global photographic review as assessed by treatment-blinded evaluators and the subject herself, adverse events, and participants' assessment of product aesthetics.

Results: After 24 weeks, women randomized to 5% MTF once daily showed noninferior target area hair count and target area hair width and experienced greater, but nonsignificant, improvements in target area hair count, target area hair width, and overall efficacy by global photographic review than those randomized to 2% MTS used twice daily. 5% MTF was significantly superior to 2% MTS in participants' agreement with "the treatment does not interfere with styling my hair" ($P = .002$). Women randomized to 5% MTF experienced significantly lower rates of local intolerance ($P = .046$) especially in pruritus and dandruff compared with 2% MTS.

Limitation: Because of differences in the formulations tested, study participants were not blinded to treatment.

Conclusions: Once-daily 5% MTF is noninferior and as effective for stimulating hair growth as twice-daily 2% MTS in women with androgenetic alopecia and is associated with several aesthetic and practical advantages. (J Am Acad Dermatol 2011;65:1126-34.)

Key words: androgenetic alopecia; female pattern hair loss; hair preparations; hypertrichosis; minoxidil; topical administration; topical foam; topical solution.

Androgenetic alopecia (AGA) is the most common form of alopecia in men and women. Among healthy women, approximately 6% to 38% experience some degree of frontal and frontoparietal hair loss.[1,2] Currently, the only clinically validated medication approved for increasing hair density in women with AGA is minoxidil topical solution (MTS), with mostly licensing of the

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2% product form but also up to 5% in several countries. The exact mechanism of action of minoxidil is uncertain, but it has been suggested that it promotes hair growth by opening adenosine triphosphate-sensitive potassium channels and stimulating the synthesis of vascular endothelial growth factor in dermal papilla cells.[3] Hereby, the human hair follicle serves not only as a reservoir, but also as a major entry point for topically applied compounds.[4] Deposition of minoxidil has been similarly found in appendages and stratum corneum.[5] Although MTS is generally well tolerated, users occasionally experience pruritus, dandruff, and local intolerance (LI), most likely because of the fact that MTS contains propylene glycol, a potential skin irritant and with sensitizing occurrence of 2.3% to 3.5%.[6,7] Furthermore, some users report that MTS has a tendency to run off the scalp quickly, leaves the hair difficult to style, and leaves hair looking and feeling greasy. Finally, MTS is recommended for twice-daily application, which is impractical for many users and leads to participant noncompliance and reduced therapeutic efficacy.

CAPSULE SUMMARY

- To our knowledge, this is the first study to compare the efficacy of once-daily 5% minoxidil topical foam (MTF) with twice-daily 2% minoxidil topical solution in women with androgenetic alopecia.
- 5% MTF was as effective as 2% minoxidil topical solution for promoting hair growth and increasing hair width.
- 5% MTF was well tolerated, with rates of pruritus and dandruff significantly lower than for 2% minoxidil topical solution.
- Once-daily 5% MTF reduces unpleasant side effects and provides aesthetic and practical advantages.

These tolerability and product acceptability issues suggest that there is a need for once-daily formulations of minoxidil at equivalent or higher concentrations than currently available that do not contain propylene glycol and are easier to apply. In several countries all over the world, either 2% or up to 5% MTS has an approval for use in women. The use of higher concentrations of minoxidil in women is supported by results from an early study suggesting that concentrations higher than 2% could improve efficacy without increasing the rates of adverse events (AEs) when applying not more then 60 mg of minoxidil per day.[8] However, in a study on 381 women with AGA the topical application of 100 mg of minoxidil (5% MTS twice daily) per day showed higher rates of AEs compared with 40 mg of minoxidil (2% MTS twice daily).[9] Recently, a 5% minoxidil topical foam (MTF) formulation was found to be effective and safe in men with AGA when applied twice daily.[10] Among 180 participants randomized to 5% MTF in a 16-week, placebo-controlled study, 70.6% experienced an increase in hair growth compared with 42.4% of the 172 participants randomized to placebo. The incidence of pruritus was 1.1% in the 5% MTF group, which was lower than the 6% incidence rate observed in an earlier 16-week study of twice-daily 5% MTS.[11] The results from these studies demonstrated that 5% minoxidil formulations are safe and effective for the treatment of men with AGA. On the basis of these results, the 5% MTF formulation was approved by the US Food and Drug Administration in 2006 for over-the-counter use in men with AGA. Because 5% MTF twice daily was shown to be safe and effective in men and the aesthetically pleasing foam vehicle, we conducted a randomized, phase III study comparing the efficacy and safety of once-daily 5% MTF (50 mg of minoxidil per day) versus twice-daily 2% MTS (40 mg of minoxidil per day) in women with AGA.

METHODS

Study design

This was a 24-week, randomized, investigator-initiated and -blinded, 2-arm comparative study conducted at a single site to evaluate the efficacy and safety of once-daily 5% MTF versus twice-daily 2% MTS in women with AGA. The study design did not include a placebo arm on ethical grounds as there are a number of therapeutic options available to women with AGA and previous studies of minoxidil in women with AGA provide suitable and extensive comparative data on hair growth in participants receiving 2% MTS or placebo.[9,12,13] Furthermore, to maintain blinding with two very different active product formulations would have required two placebos furthering the ethical considerations and complications to the study design. The study protocol was approved by the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]) in Germany (European Union Drug Regulating Authorities Clinical Trials [EudraCT] number 2008-001770-33) (European Union Drug Regulating Authorities Clinical Trials). The trial was conducted from June 2008 through January 2009 in accordance with the principles of the Declaration of Helsinki (1996).

Participants

Women aged 18 years or older with Savin grade D3 to D6 female pattern AGA[14] and hair density less than

Abbreviations used:

AE: adverse event
AGA: androgenetic alopecia
GPR: global photographic review
LI: local intolerance
MTF: minoxidil topical foam
MTS: minoxidil topical solution
TAHC: target area hair count
TAHW: target area hair width

or equal to 220 hairs/cm^2 as measured by TrichoScan (Tricholog GmbH, Freiburg, Germany) were eligible to participate in the study. Study candidates were excluded if they had a Ferriman-Gallwey score greater than 6 (scores >8 indicate excess androgen production)[15] or were hypersensitive to minoxidil or other study product ingredients. Candidates were also excluded if they had received local scalp treatments during the last 4 weeks or systemic treatment during the last 3 months before study inclusion that could interfere with the study medications (ie, minoxidil, corticosteroids, Aminexil, medical shampoos, topical estrogens, ketoconazole, beta blocker, cimetidine, diazoxide, isotretinoin, or vitamin A intake >10,000 IU/d). Other exclusion criteria included: the use of nonbreathable wigs or hair transplants; participation in another study within the past 4 weeks; chemotherapy, radiation therapy, or laser therapy (on the scalp) within the last 6 months; pregnancy or desire to become pregnant; and the presence of other dermatologic disorders, severe medical conditions, or hair loss diseases. Women of childbearing potential were required to use safe contraception methods for at least 5 weeks before the study and throughout the study. Women using hormonal contraception methods were required to be on treatment for at least 6 months before the study and to continue the hormonal treatment throughout the study. All participants were required to provide signed informed consent before enrollment in the study. Participants were further required to maintain the same hairstyle, hair length, and hair color throughout the study and had to be willing and able to comply with the treatment plan, the mini-tattoo procedure at study entry, the visit schedule, and all scheduled laboratory tests and study procedures.

Participants were randomized (1:1) to treatment with either half a capful of 5% MTF applied once daily or 1 mL of 2% MTS applied twice daily. Application of half a capful of 5% MTF once daily provides a 50-mg daily dose of minoxidil, whereas application of 1 mL of 2% MTS twice daily provides a 40-mg daily dose of minoxidil. The MTF users were instructed to apply the daily dose of foam to the centroparietal region of the scalp and spread it partwise with the help of their fingertips. MTS users were instructed to spread 1 mL (about 6 sprays) of the solution twice daily in diverse partings of the scalp as described in the package insert (Regaine Frauen, Germany). Both groups were instructed to softly massage the product into the scalp and let it air dry before using hairstyling aids. They were also instructed not to wash or rinse their hair for the next 4 hours. Because of the differences in product formulations and application, the study was not blinded to the participants, although the study investigators were blinded to treatment. To ensure investigator blinding, participants were instructed to speak in the presence of an investigator only about "the product" and not to use the terms "foam" or "solution" or to mention how many times per day they used the study product. In addition, each participant was instructed to wash their hair before each study visit to avoid providing the study investigators with any indication as to which product they were using.

Efficacy assessments

Participants received a mini tattoo in the center of a designated target area of the scalp that was representative of the participant's thinning hair and a hair density assessment of the target area at baseline (week 0). The baseline hair assessment included a TrichoScan (Tricholog GmbH) to confirm study entry criteria ($\leq$ 220 nonvellus hairs/cm^2). A safety and compliance visit was scheduled at week 1. Efficacy and safety were evaluated at weeks 12 and 24.

Canfield Hair Metrix: Nonvellus target area hair count and nonvellus cumulative target area hair width

The primary efficacy end point of the study was the change from baseline in nonvellus ($\geq$ 30 μm in diameter) target area hair count (TAHC) (hairs/cm^2) at week 24. Nonvellus TAHC assessments and nonvellus target area hair width (TAHW) (cumulative mm/cm^2) assessments were performed at baseline and at weeks 12 and 24 in a designated target area of the scalp identified by the mini tattoo applied at baseline. The TAHC and TAHW assessments were performed using a 1.9-cm diameter circular template centered over the mini tattoo. Hair within the template was clipped to approximately 1 mm in length and dyed black with a standard hair color dying agent. Photographic imaging equipment was supplied by Canfield Scientific Inc (Fairfield, NJ) and was used to take macrophotographs of the shaved target area. It consisted of a Nikon D-SLR camera body (Nikon Corporation, Tokyo, Japan), Nikkor 60MM F2.8 lens (Nikon Corporation), and a Canfield Epiflash (Canfield Scientific Inc, Fairfield, NJ) with

a glass contact plate and was preset and locked for magnification, f-stop, and exposure control. The analysis of the hair count photographs was performed by Canfield's core imaging laboratory.[16] The same 1 cm^2 circular area was mapped among the baseline, week 12, and week 24 images using the dot tattoo as a reference. Each image was then assigned a definite tracking number and randomized before analysis. The compliant and validated Canfield Hair Metrix (Canfield Scientific Inc, Fairfield, NJ) image analysis application measured the average width along the hair fiber and a trained and validated imaging technician reviewed and accepted each of the measurements.[17,18] Only hairs with a diameter equal or greater than 30 μm were reported for TAHC (hairs/cm^2). The diameters of all nonvellus hairs (≥ 30 μm) in target region were summed and reported together (mm/cm^2).

Global photographic review

Global photographs of the midpattern of the scalp with hair parted in the center and combed away from the center part were taken at baseline, week 12, and week 24 using a Nikon D-SLR camera body (Nikon Corporation), Nikkor 60MM F2.8 lens (Nikon Corporation), and a Canfield IntelliFlash (Canfield Scientific Inc, Fairfield, NJ) mounted to a rotating arm on a stereotactic head positioning device (Canfield Scientific Inc) and was preset and locked for magnification, f-stop, and exposure control.[18] The photographs were standardized for lighting, camera angle, and position to the participant's head. Global photographic review (GPR) was conducted by 3 reviewers who were blinded to treatment group and pairing (eg, visit 1-visit 4), whereas the earlier photograph was shown left-handed. Photographs were evaluated in a blinded pairwise fashion at the end of the study using a 7-point evaluation scale for hair volume (−3 = greatly decreased, −2 = moderately decreased, −1 = slightly decreased, 0 = no change, +1 = slightly increased, +2 = moderately increased, and +3 = greatly increased). The reviewers compared the photographs taken at baseline with those taken at week 24; baseline and week 12; and weeks 12 and 24.

Participant questionnaires

At the end of the study (week 24), each participant completed 2 questionnaires. The first questionnaire consisted of a single question that assessed the change in hair volume and density from baseline ("Compared with baseline, how much change of hair volume/hair density do you observe?"). Participants were shown global photographs of their hair and scalp taken at baseline and week 24 and rated the change in volume with the same 7-point scale used by the study investigators during GPR. The second questionnaire consisted of 9 statements intended to assess the participant's perception of product aesthetics and consumer benefits. Participants were asked to indicate their level of agreement with each statement using a 7-point scale (7 = totally agree, 6 = mainly agree, 5 = rather agree, 4 = neither agree nor disagree, 3 = rather disagree, 2 = mainly disagree, and 1 = totally disagree). In general, the participants were asked to complete the second questionnaire before being presented with the first questionnaire and the global photographs of their hair at baseline and week 24.

Safety assessments

At screening, participants underwent a thorough physical examination of the scalp, integument, and cardiovascular and pulmonary systems, and a detailed medical history was recorded, including any known allergies and concomitant medications. A pregnancy test was administered at screening to all women with childbearing potential and at weeks 12 and 24 on an as-needed basis (eg, unknown status or suspicion of pregnancy). Safety evaluations were conducted at baseline and weeks 1, 12, and 24. Safety assessments included the recording of all AEs and indications of LI (eg, erythema, pruritus, burning/stinging, dryness, scaling) in 3 areas of the scalp: the designated target area, the entire area of hair thinning, and the entire scalp. Investigators were also asked to rate the severity (mild, moderate, or severe) of AEs and LIs and assess the relationship to study medication (excluded, unlikely, possible, probable, or certain). Facial hypertrichosis, a cosmetically unpleasing side effect associated with hair-stimulating medications, was assessed on the cheeks and in the temple region using a 4-point scale (none, mild, moderate, or severe). Plasma samples were collected at baseline and week 24 for determination of minoxidil levels. Minoxidil levels were also assessed any time a participant experienced an AE determined to be probably related to study medication. Participant compliance with the medication administration schedule was assessed at weeks 12 and 24 by weighing the participants' medication containers.

Statistical analysis

The sample size for the study was determined from historical data that show that the control effect in minoxidil hair growth studies (ie, the difference between 2% MTS twice daily and placebo) is approximately 15 hairs/cm^2. Therefore, to assure sensitivity to change in the current study, the tolerance margin was assumed to be half the historical control

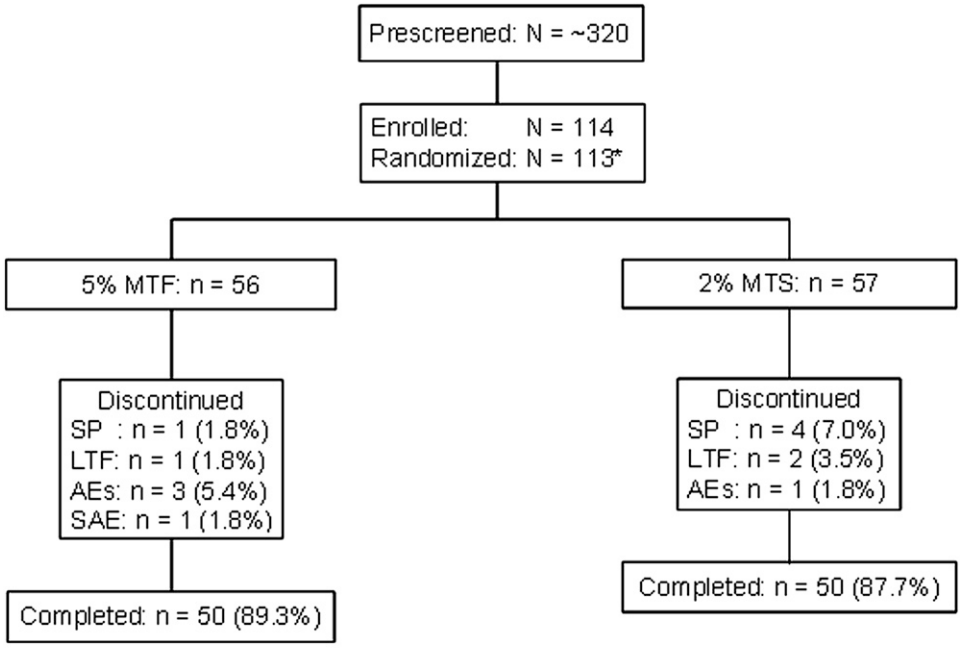

Fig 1. Participant disposition. One drug-unrelated serious adverse event (*SAE*) in 5% minoxidil topical foam (*MTF*) population. *AE*, Adverse event; *LTF*, lost to follow-up; *MTS*, minoxidil topical solution; *SP*, subject preference.

effect (ie, 7.5 hairs/cm^2). Based on data from previous studies, the common SD was assumed to be 20 hairs/cm^2. To demonstrate noninferiority of 5% MTF with power of 80% for 5% significance level, the minimum sample size required was 92, measured with PASW 2008 (Predictive Analysis SoftWare).

Assuming a discontinuation rate of 10% of the study participants, the minimum recruitment goal for the study was 102 participants. A sample size of 114 was designed.

Standard descriptive statistics were used to evaluate demographic, baseline, AE, and LI data. Differences between the groups in TAHC and TAHW were analyzed using Mann-Whitney U test. Noninferiority was shown by the confidence interval method with noninferiority test of the difference of two means.

GPR and participant questionnaire 1 were analyzed by the χ^2 test for homogeneity of proportions. For that, the GPR, median scores were determined for each pairwise comparison by the 3-member investigator panel. Analysis of participant questionnaire 2 was performed by Mann-Whitney U test.

All analysis was based on the intent-to-treat population, which included all randomized participants.

RESULTS

Participants

A total of 114 women with AGA in the centroparietal region were enrolled in the study (Fig 1). One enrolled participant was not randomized to treatment because of an existing pregnancy. The participants ranged from 23 to 75 years in age (mean: 49.9 years) (Table I; available online at http://www.eblue.org). The majority of participants were white (95.6%). The mean Savin hair density score at baseline was 4.13 in the 5% MTF arm and 3.84 in the 2% MTS arm. There was a higher proportion of participants with more extensive hair thinning (Savin scores of D5 or D6) in the 5% MTF group (n = 19) than in the 2% MTS group (n = 9). This resulted in somewhat lower mean TAHC and TAHW values at baseline in the 5% MTF group than in the 2% MTS group (Table I; available online at http://www.eblue.org). However, χ^2 analysis revealed that the two groups were not inhomogeneous (P = .161). Of the 113 participants randomized to treatment, 100 (88.5%) completed the 24-week study; for reasons for drop-out see Fig 1.

Efficacy

TAHC and TAHW. There was a roughly linear and parallel increase in nonvellus TAHC (Fig 2) and TAHW (Fig 3) in both treatment groups over the course of the study. With a margin of noninferiority of 7.5 hairs/cm^2 a significant noninferiority of the 5% MTF could be determined. The mean change from baseline in TAHC at week 24 (the primary efficacy outcome) was 31.9 hairs/cm^2 in the 5% MTF group

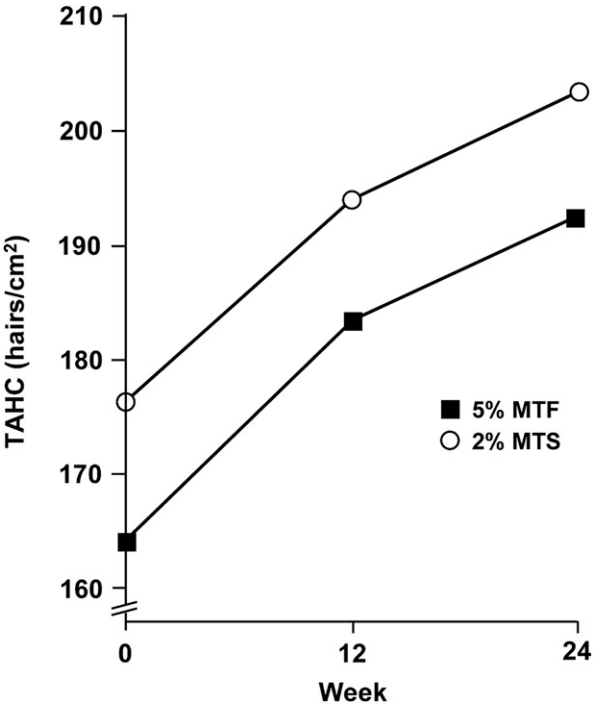

Fig 2. Nonvellus target area hair count (*TAHC*). *MTF*, Minoxidil topical foam; *MTS*, minoxidil topical solution.

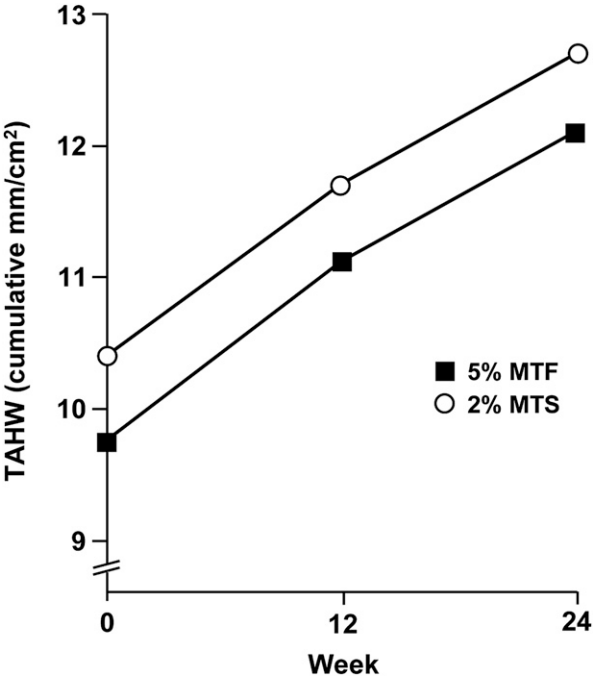

Fig 3. Nonvellus target area hair width (*TAHW*). *MTF*, Minoxidil topical foam; *MTS*, minoxidil topical solution.

and 28.4 hairs/cm^2 in the 2% MTS group (SD 19.13); this difference was not significant (P = .441). This represents a mean increase in hair count of 16.2% in the 5% MTF group and a 13.8% increase in the 2% MTS group. Not unexpectedly, increases in TAHC were lower in both treatment arms among participants with severe hair loss (ie, Savin grade D5 or D6) when compared with the increases observed in participants with less severe hair loss (Fig 4).

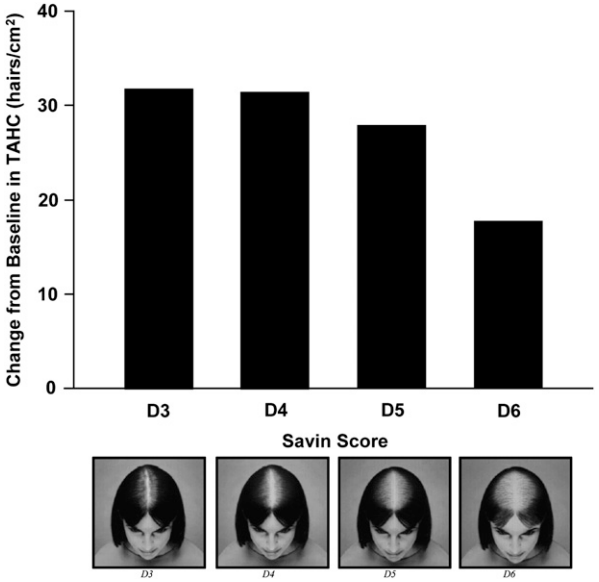

Fig 4. Nonvellus target area hair count (*TAHC*) at week 24 change from baseline is lower with increasing severity of Savin score among all participants randomized to 5% minoxidil topical foam or 2% minoxidil topical solution. Lowest TAHC is obtained in women with highest Savin score (D6) (Savin scale ranges from D1-D8, current study recruited women with Savin grade D3-D6).

Similar to the TAHC, the mean change from baseline in TAHW at week 24 was 2.49 mm/cm^2 in the 5% MTF arm and 2.33 mm/cm^2 in the 2% MTS arm (P = .497; SD 1.60). This represents a mean increase in hair density of 19.6% in the 5% MTF group and a mean increase of 17.8% in the 2% MTS group. The difference in TAHW between the two treatment groups was not significant. Just like TAHC a significant noninferiority of the TAHW for 5% MTF with a margin of 0.4 mm/cm^2 could be determined.

Global photographic review. Overall, the investigators reported that hair volume increased from baseline through week 24 in 67.7% of participants in the 5% MTF arm compared with 56.1% of participants in the 2% MTS arm (Fig 5, *A*). Hair volume decreased in 5.4% and 10.5%, respectively, of the participants randomized to 5% MTF and 2% MTS. Overall, there was no significant difference between the two treatment groups in the change from baseline in hair volume.

Participant questionnaires. Similar to the findings of the study investigators, the participants' impressions of change in hair volume at week 24

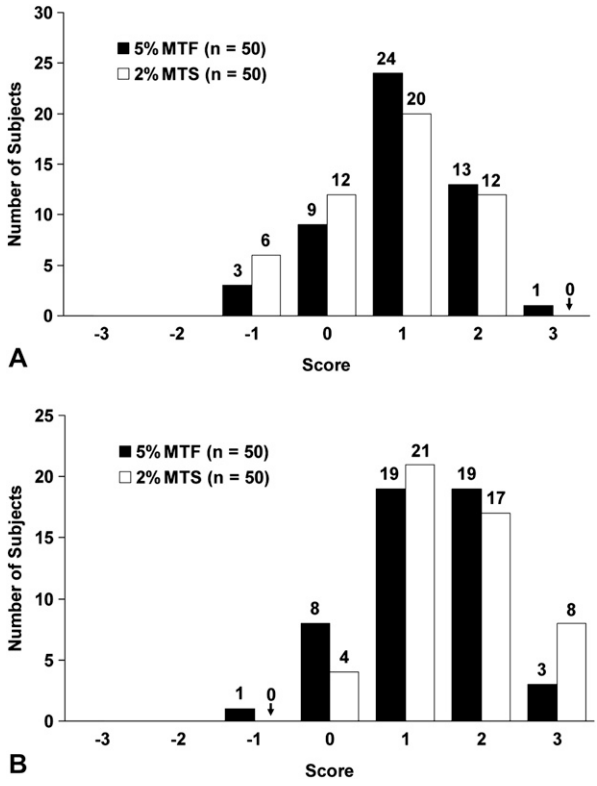

Fig 5. Global change in hair volume based on global photographs of scalp midpattern comparing baseline and week 24 by investigators' (**A**) and participants' (**B**) evaluation (−3 = greatly decreased, −2 = moderately decreased, −1 = slightly decreased, 0 = no change, +1 = slightly increased, +2 = moderately increased, and +3 = greatly increased). *MTF*, Minoxidil topical foam; *MTS*, minoxidil topical solution.

on the first questionnaire were not significantly different between the two treatment arms (Fig 5, *B*). At the end of the study, 73.2% of participants randomized to 5% MTF reported an increase in hair volume compared with 80.7% of participants randomized to 2% MTS. Only one participant receiving 5% MTF reported a decrease in hair volume. Overall, participants tended to rate the efficacy of both treatments somewhat higher in comparison with the investigators' ratings.

Statistical analysis of all 9 participants' ratings of the second questionnaire revealed no significant differences between all statements except for question 6 (Table II; available online at http://www.eblue.org). The latter statement ("The treatment does not interfere with styling my hair") demonstrated a significant difference ($P = .002$) between the two treatment groups. Among participants randomized to 5% MTF, 46.4% strongly agreed with the statement compared with 19.3% of participants randomized to 2% MTS (Fig 6).

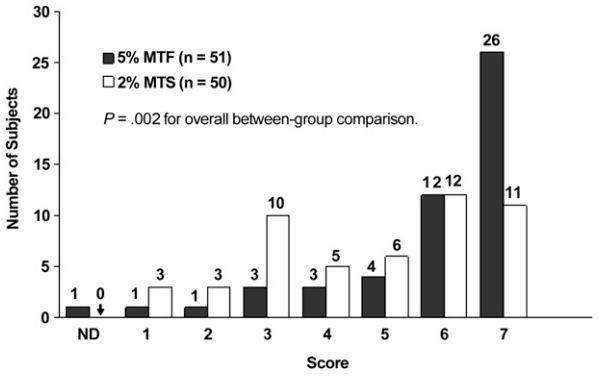

Fig 6. Distribution of responses to statement 6 of participants' questionnaire 2 ("The treatment does not interfere with styling my hair"). Responses range from 1 = totally disagree to 7 = totally agree. *MTF*, Minoxidil topical foam; *MTS*, minoxidil topical solution; *ND*, no data.

Safety and product acceptability

Adverse events. The incidence of AEs possibly related to study product including facial hypertrichosis (see below) was lower in the 5% MTF group (43 events) compared with the 2% MTS group (51 events). Hair shedding occurred in 17.5% of all participants in the 2% MTS group compared with 12.5% in the 5% MTF population. Headache, possibly related to study medication, was reported by 3.6% of the participants randomized to 5% MTF and by 7.0% of the participants randomized to 2% MTS. A slight breathlessness and nausea associated with the first application of study medication was reported by one of the participants randomized to 5% MTF (1.8%) and none of participants randomized to 2% MTS. Minor, distinct cardiovascular symptoms (palpitation, tachycardia) were reported by 1.8% of the participants in the 5% MTF group and 3.5% of the participants in the 2% MTS group. Swelling of the face and/or ear was reported by one participant in 2% MTS group. One participant in each group developed papules and pustules, whereas the participant in the 2% MTS group developed severe pruritus and dandruff in addition. One participant in the 5% MTF population also reported a maculopapular exanthema and unpleasant scalp tension (LI). The AE rates concerning dermatitis and pruritus at the integument, excluding the scalp, were higher in the 5% MTF group (3.6% and 8.9%) compared with the 2% MTS group (1.8% and 0%). Three of the 5 patients in the 5% MTF group only presented mild pruritus.

Three serious AEs were reported, none of which was related to study medication but one led to study discontinuation. Three participants (5%) in the 5% MTF group experienced AEs that led to discontinuation of treatment: severe pruritus of the integument (n = 1); maculopapular exanthema and unpleasant

scalp tension (n = 1); and severe pruritus and dandruff (n = 1). One participant in the 2% MTS group withdrew because of AEs (swelling of the ear, pruritus, dandruff, and headache).

The cosmetic AE rate was comparably low; problems reported on hairstyling occurred with the same prevalence of about 5% in each treatment arm.

Facial hypertrichosis. Hypertrichosis occurred in both groups with an increase of 1 on a 4—level scale (eg, from none-mild or moderate-severe), except for one patient in 5% MTF who presented a 2-level increase. Interestingly, frequency of manifestation of facial hypertrichosis in the sideburn area was significantly higher in the 2% MTS group compared with the 5% MTF group (2% MTS n = 15, 26%; 5% MTF n = 6, 11%; $P < .033$). However, in the temple region there were no significant differences between both groups (1-level increase: 2% MTS, n = 14, 25%; 5% MTF, n = 11, 20%; and 2-level increase: 5% MTF, n = 1, 2%).

Local intolerance. The total incidence of LI was significantly lower in the 5% MTF group ($P = .046$). The rate of mild-to-moderate scalp pruritus, as determined by the study investigators, was significantly lower in the 5% MTF group (16.1%) than in the 2% MTS group (36.8%; $P = .012$). In addition, the rate of dandruff was significantly lower in the 5% MTF group (5.4%) than in the 2% MTS group (17.5%; $P = .042$). The rates of other LIs were generally similar between the participants randomized to 5% MTF and those randomized to 2% MTS, including the rates of erythema (10.7% and 7.0%, respectively), burning/-stinging (10.7% and 10.5%), appearance of papules or pustules (5.4% and 1.8%), increased skin sensitivity (0% and 3.5%), tension of skin (5.4% and 1.8%), and scalp pain (0% and 1.8%). As mentioned previously, one participant in the 5% MTF group developed severe LI (pruritus and dandruff) that led to withdrawal from the study.

DISCUSSION

AGA may have significant impact for quality of life in female patients. Treatments to clinically improve scalp hair density and reduce midpattern thinning leading to improved scalp coverage are highly important for the affected women. This 24-week, randomized, investigator-initiated, blinded study compared a once-daily 5% MTF formulation with the twice-daily 2% MTS formulation currently available for treating women with AGA. Different aspects were analyzed: GPR by participants and investigators was an important tool to estimate clinical coverage of the scalp. All participants and the investigator separately evaluated the clinical outcome based on global photographs and a questionnaire. Overall, the investigators reported that hair volume increased from baseline through week 24 in 67.7% of participants in the 5% MTF group compared with 56.1% of participants in the 2% MTS group. More than two thirds of patients in both treatment groups reported an increase in hair volume compared with baseline based on GPR (first questionnaire). Interestingly participants' rating tended to be higher compared with blinded expert rating in both treatment groups, a finding that has also been reported in earlier clinical minoxidil trials.[9,10] Thus the subjective contentment of participants may lead to overestimation of the clinical effect. However, this shows that the overall impression of the clinical appearance is a highly important aspect for the patient.

A novel feature of the study was the use of the new Canfield Hair Metrix semiautomated digital analysis system for assessment of the changes from baseline in TAHC, and quantitative changes from baseline in TAHW. The results of the study demonstrate that once-daily 5% MTF is as effective as and noninferior to twice-daily 2% MTS for stimulating new hair growth. At the end of the study, TAHC and TAHW increased by 16.2% and 19.6%, respectively, in women randomized to 5% MTF compared with an increase of 13.8% and 17.8%, respectively, in women randomized to 2% MTS. We demonstrated a noninferiority of 5% MTF with a tolerance margin of 7.5 hairs/cm^2 for TAHC and 0.4 mm/cm^2 for TAHW.

Earlier studies investigating twice-daily 5% MTS in women with AGA had also demonstrated a good treatment response, however with a higher rate of facial hypertrichosis compared with our study.[9] This earlier study, which was performed over 48 weeks and was double blinded and placebo controlled, led to a TAHC increase of 17.3% for 5% MTS twice daily and 13.8% for 2% MTS twice daily in 381 women with AGA. Comparing our study results of a 24-week trial using once-daily 5% MTF with the earlier reports using twice-daily 5% MTS demonstrate comparable outcome parameters for TAHC (16.2% vs 17.3%).

Although the differences in the change from baseline in TAHC and TAHW between the two treatment arms were not significant in this study, there was a trend toward a greater efficacy with 5% MTF, which was confirmed by GPR: hair volume increased in 76% of the women randomized to 5% MTF compared with 64% of the women randomized to 2% MTS. Not unexpectedly, our results demonstrated that improvements in TAHC and TAHW are less pronounced in women with more severe hair loss than in women with lesser degrees of hair loss. This may have resulted in an underestimate of the comparative efficacy of 5% MTF with respect to the efficacy of 2% MTS. This is because of the fact that

despite the blinded, block-randomization procedure used to assign participants to the two treatment arms, the proportion of participants with pronounced hair loss (Savin grades D5 and D6) was markedly but not significantly greater in the 5% MTF group than in the 2% MTS group.

The significant lower rate of LI in the 5% MTF group compared with 2% MTS concurs with the tolerability of 5% MTF seen in the 5% MTF study in men.[10] Interestingly, we observed a lower incidence of AEs in the 5% MTF group, mainly because of the higher prevalence of facial hypertrichosis observed in the 2% MTS group (sideburns: 26%; temples: 25%) compared with 5% MTF (sideburns: 11%; temples: 22%). Shedding infrequently occurred in 5% MTF (12.5%) compared with 2% MTS (17.5%). Cosmetically, 5% MTF was found to be significantly superior to 2% MTS with respect to the statement "The treatment does not interfere with styling my hair." Taken together with the significantly lower rates of LI and lower rates of AEs observed in participants randomized to 5% MTF, we conclude that once-daily 5% MTF is an effective and safe product for improving hair growth in women with AGA. Furthermore, once-daily 5% MTF is significantly noninferior in efficacy and may offer advantages over twice-daily 2% MTS with respect to convenience of use, improved compliance, and better product acceptability.

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Table I. Demographics and baseline characteristics of randomized participants

Characteristic	5% MTF n = 56	2% MTS n = 57	Total n = 113
Age, y			
Mean	49.2	50.6	49.9
Range	23-68	25-75	23-75
Ethnicity, n (%)			
White	52 (92.3)	56 (98.2)	108 (95.6)
Oriental	2 (3.6)	1 (1.8)	3 (2.7)
Asian	1 (1.8)	0	1 (0.9)
Other	1 (1.8)	0	1 (0.9)
Savin score, n (%)			
Savin 3	15 (26.8)	20 (35.1)	35 (31.0)
Savin 4	22 (39.3)	28 (49.1)	50 (44.2)
Savin 5	16 (28.6)	7 (12.3)	23 (20.4)
Savin 6	3 (5.4)	2 (3.5)	5 (4.4)
TAHC, hairs/cm^2			
Mean (SD)	164.0 (43.05)	176.2 (44.91)	170.1
Median	161.0	175.0	165.0
TAHW, mm/cm^2			
Mean (SD)	9.74 (2.881)	10.41 (3.050)	10.08 (2.973)
Median	9.20	10.20	9.67

MTF, Minoxidil topical foam; *MTS*, minoxidil topical solution; *TAHC*, target area hair count; *TAHW*, target area hair width.

Table II. Participant questionnaire 2

	5% MTF								2% MTS								
Statements/rating	Missing	1 Totally disagree	2 Mainly disagree	3 Rather disagree	4 Neither agree nor disagree	5 Rather agree	6 Mainly agree	7 Totally agree	Missing	1 Totally disagree	2 Mainly disagree	3 Rather disagree	4 Neither agree nor disagree	5 Rather agree	6 Mainly agree	7 Totally agree	*P* value
S1: My hair looks thicker and fuller	6 10.7%	3 5.4%	2 3.6%	6 10.7%	6 10.7%	9 16.1%	13 23.2%	11 19.6%	7 12.3%	0	0	2 3.5%	8 14.0%	13 2.8%	17 29.8%	10 17.5%	.447
S2: I would continue to use the treatment	6 10.7%	2 3.6%	0	2 3.6%	2 3.6%	5 8.9%	12 21.4%	27 48.2%	7 12.3%	0	0	2 3.5%	2 3.5%	7 12.3%	9 15.8%	30 52.6%	.395
S3: I'm more satisfied with the appearance of my hair	6 10.7%	2 3.6%	2 3.6%	5 8.9%	9 16.1%	9 16.1%	11 19.6%	12 21.4%	7 12.3%	1 1.8%	0	4 7.0%	3 5.3%	15 26.3%	15 26.3%	12 21.1%	.764
S4: I feel I have more control over my thinning hair	6 10.7%	3 5.4%	0	7 12.5%	7 12.5%	11 19.6%	13 23.2%	9 16.1%	7 12.3%	0	2 3.5%	2 3.5%	7 12.3%	11 19.3%	19 33.3%	9 15.8%	.377
S5: Others have noticed an improvement in my hair	6 10.7%	8 14.3%	4 7.1%	2 3.6%	9 16.1%	13 23.2%	8 14.3%	6 10.7%	7 12.3%	1 1.8%	5 8.8%	4 7.0%	12 21.1%	10 17.5%	10 17.5%	8 14.0%	.471
S6: The treatment does not interfere with styling my hair	6 10.7%	1 1.8%	1 1.8%	3 5.4%	3 5.4%	4 7.1%	12 21.4%	26 46.4%	7 12.3%	3 5.3%	3 5.3%	10 17.5%	5 8.8%	6 10.5%	12 21.1%	11 19.3%	.002
S7: My hair is displeasingly greasy	6 10.7%	20 35.7%	7 12.5%	7 12.5%	7 12.5%	5 8.9%	1 1.8%	3 5.4%	8 14.0%	20 35.1%	6 10.5%	8 14.0%	6 10.5%	6 10.5%	3 5.3%	0	.690
S8: The treatment is easy to use	6 10.7%	1 1.8%	0	2 3.6%	3 5.4%	10 17.9%	15 26.8%	19 33.9%	7 12.3%	0	3 5.3%	3 5.3%	3 5.3%	6 10.5%	11 19.3%	24 42.1%	.793
S9: I feel better about myself	6 10.7%	2 3.6%	2 3.6%	1 1.8%	11 19.6%	6 10.7%	15 26.8%	13 23.2%	7 12.3%	0	1 1.8%	1 1.8%	9 15.8%	9 15.8%	14 24.6%	16 28.1%	.530

MTF, Minoxidil topical foam; *MTS*, minoxidil topical solution.