Hindawi
Dermatologic Therapy
Volume 2023, Article ID 4582911, 10 pages
https://doi.org/10.1155/2023/4582911

Research Article

Comparison of a New 5% Minoxidil Foam and Rogaine® in the Treatment of Androgenetic Alopecia in Chinese Men: A Randomized, Double-Blind, Phase III, Equivalence Trial

Cheng Zhou,[1] Weixin Fan,[2] Jianfeng Zou,[3] Jianglin Zhang,[4] Hong Fang,[5] Zhongfa Lv,[6] Dingquan Yang,[7] Wei Lai,[8] Xinghua Gao,[9] Qinping Yang,[10] Aijun Chen,[11] Jing Lou,[12] Lili Zheng,[12] and Jianzhong Zhang[1]

[1]*Department of Dermatology, Peking University People's Hospital, Beijing, China*
[2]*Department of Dermatology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China*
[3]*Department of Critical Care Medicine, The Sixth Medical Center of PLA General Hospital, Beijing, China*
[4]*Department of Dermatology, Xiangya Hospital of Central South University, Changsha, China*
[5]*Department of Dermatology and STD, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*
[6]*Department of Dermatology and STD, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*
[7]*Department of Dermatology, China-Japan Friendship Hospital, Beijing, China*
[8]*Department of Dermatology and STD, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China*
[9]*Department of Dermatology, The First Hospital of China Medical University, Shenyang, China*
[10]*Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China*
[11]*Department of Dermatology and STD, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China*
[12]*Shenyang Sunshine Pharmaceuticals CO. Ltd., Shenyang, China*

Correspondence should be addressed to Jianzhong Zhang; zjianzhongpku@outlook.com

Received 26 October 2022; Revised 2 March 2023; Accepted 16 March 2023; Published 14 April 2023

Academic Editor: Althea East-Innis

Androgenetic alopecia (AGA) is a common cause of hair loss in adults. We aimed to compare the efficacy and safety of topical generic 5% new minoxidil foam (NMF) versus 5% minoxidil Rogaine® foam in male patients with AGA. A randomized, double-blind, controlled, phase III, equivalence trial in 10 centers in China between December 25, 2019, and June 28, 2021, was performed. In total, 417 men patients (≥18 years) with AGA were randomized to receive 5% NMF (211 patients) or 5% Rogaine® foam (206 patients) 1 g two times daily for 24 weeks. The primary outcome was the changes in nonvellus target area hair counts (TAHC) from baseline to week 24. Equivalence was concluded if the 95% confidence interval (CI) for the treatment difference between the 5% NMF and Rogaine® groups was within (−8.00, 8.00). After 24 weeks of treatment, the mean difference in the change of nonvellus TAHC between the 5% NMF group and the Rogaine® group was -3.85 ± 1.62 hair/cm^2 in full-analysis set (FAS) and -3.96 ± 1.68 hair/cm^2 in per-protocol set (PPS), and the 95% CI of mean difference was (−7.03, −0.67) in FAS and (−7.26, −0.66) in PPS. No significant differences were found between the two groups in hair diameter, the ratio of terminal hair to vellus hair, the global photographic assessment by investigators, and adverse events (all $P > 0.05$). 5% NMF is as effective as Rogaine® in increasing hair density and hair diameter in AGA patients and was found to be safe. This trial is registered with CTR20191708.

1. Introduction

Androgenetic alopecia (AGA), the most common cause of hair loss in adults, is characterized by the progressive miniaturization of hair follicles leading to the conversion of terminal hairs to vellus hairs [1, 2]. Epidemiologic evidence suggested that the prevalence of AGA was 40% in white men aged 20–50 years and 20% in white women aged 40 years

[3, 4]. In China, the prevalence of AGA was reported to be 21.3% in men and 6.0% in women, and the prevalence increased with age [5]. Although AGA is physiologically benign, it can cause negative psychological effects in both men and women including anxiety, depression, worries about aging, feelings of helplessness, and diminished attractiveness [6, 7].

AGA treatment mainly includes drug therapy and laser therapy. The minoxidil and finasteride are the only drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of AGA [8]. The efficacy of minoxidil for AGA has been demonstrated by multiple studies [8–11]. Currently, topical minoxidil is available in several formulations, including a 2% solution, a 5% solution, and a 5% foam [12]. The 5% minoxidil topical foam (Rogaine®, Johnson and Johnson, USA) has been shown to be effective in patients with AGA [13]. However, there is an unmet need for more economical treatment options in China due to access and treatment costs. Generic drugs have similar efficacy to licensed products but are less expensive and more accessible to patients [14]. The patent period of Rogaine® has ended, and a generic version of minoxidil has been reported [15]. The objective of this phase III study was to compare the efficacy and safety of a new 5% minoxidil foam versus Rogaine® in patients with AGA.

2. Methods

2.1. Study Design and Participants. This was a randomized, double-blind, controlled, multicenter, phase III trial conducted in 10 centers in China between December 25, 2019, and June 28, 2021. The study was approved by the ethics committee of each center and registered for clinical drug trials (http://www.chinadrugtrials.org.cn/, https://clinicaltrials.gov/ct2/show/CTR20191708). Written informed consent was obtained from all participants before the study was conducted. The inclusion criteria of participants were as follows: (1) men aged 18–49 years old; (2) diagnosed withAGA and classified as type III vertex, IV, and V by the Norwood–Hamilton classification or type I, II, and III by Ludwig baldness classification (some male patients had hair loss types consistent with female pattern baldness). The exclusion criteria were as follows: (1) allergyor intolerance to any ingredient in the study solutions; (2) participants with otherhair loss diseases, systemic or scalp diseases that may affect hair growth such as alopecia areata, scarring alopecia, bacterial or bacterial infections, seborrheic dermatitis, and psoriasis; (3) participants had used 5α-reductase inhibitors (e.g., finasteride and dutasteride) within 12 months and used drugs that may interfere with efficacy evaluation within 3 months; (4) participants with abnormal biochemical indicators such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 times the upper limit of normal value, serum creatinine >1.5 times the upper limit of normal value.

2.2. Interventions. All patients were randomly grouped into the 5% new minoxidil foam (NMF) group (trial group; 5% minoxidil foam, Zhejiang Wansheng Pharmaceutical Co., Ltd.) and the Rogaine® group (control group; 5% minoxidil foam, Johnson & Johnson). Participants were instructed to apply 1 g of the study product to the treated area twice a day (with a minimum of 8 hours between applications), not to exceed 2 g per day, for 24 weeks.

2.3. Assessment. The outcomes of this study were the efficacy and safety of 5% NMF. The primary efficacy endpoint was the changes in nonvellus (diameter > 30 μm) [13] target area hair counts (TAHC, hair/cm^2) from baseline to weeks 6, 12, 18, and 24 using the hair microscopic image analysis system. The follow-up time was 24 weeks after the start of the study. The circular area of the vertex balding scalp was selected as the target area for hair counting. Take a point 16–20 cm along the midline from the midpoint of the two points where the eyebrows start as the shaving point and record the position. At baseline and 6, 12, 18, and 24 weeks, the investigators used a circular hollow baffle centered on the marked point to cut hair in selected areas to 0.5–1 mm. The Medicam 800$_{HD}$ camera (FotoFinder Systems GmbH, Bad Birnbach, Deutschland) was used to take photographs of the target area, and the images were analyzed using the FotoFinder Universe software to automatically generate TAHC.

The secondary efficacy endpoints included the global photographic assessment by investigators and patients, changes in hair diameter, and changes in terminal hair to vellus hair ratio. The global photographs of alopecia in the apex region were taken using the Medicam 800HD camera at baseline and at weeks 6, 12, 18, and 24. Paired photographs (e.g., baseline vs. week 24) were assessed using a seven-point subscale by an expert panel of 3 dermatologists who were blinded to the treatment assignment. Participants were requested to assess their paired global photographs using the same seven-point scale. The seven-point subscale is rated as follows: marked decreased (−-3), moderate decreased (−-2), mild decreased (−-1), no change (0), mild increased (1), moderate increased (2), and marked increased (3).

Safety assessments included documentation of all adverse events, drug exposures, vital signs, and laboratory tests. Participants were recorded at baseline and at weeks 6, 12, 18, and 24 for any concurrent events and their potential correlation to the study drug and any symptoms of scalp irritation. Complete blood count, serum chemistry, urinalysis, and electrocardiogram were performed at baseline and weeks 12 and 24. Drug exposure includes the actual total drug dosage and duration of drug exposure for the study product.

2.4. Sample Size. The study by Olsen et al. showed that 5% minoxidil foam was used for the treatment of AGA after 16 weeks, and the mean change in TAHC increased by 16.2 hairs/cm^2 compared with the placebo [16]. The equivalent boundary of this study was set at 8 hairs/cm^2, the standard deviation of 22.5 hairs/cm^2, and a confidence level of 95% (two-sided test) to achieve a power of 80%. The distribution ratio between the trial group and the control group was 1 : 1. The minimum sample size for each group was calculated to

be 168 by PASS 16 software (NCSS, LLC, Kaysville, UT, USA). After considering a dropout rate of 20%, the sample size for each group was calculated to be 202. Therefore, the total sample size was considered to include 420 participants, with 210 participants in each group.

2.5. Randomization and Blinding. Eligible patients were randomly assigned to the trial and control groups in a ratio of 1 : 1 through the interactive web response system (IWRS). Patients and investigators were blinded to treatment assignments until the study was completed. The outer packaging of the test drug and the control drug is exactly the same, and the research drugs have been prefilled in the container.

2.6. Statistical Analysis. All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). P value <0.05 was considered statistically significant. The mean change of TAHC at 24 weeks after treatment was used as the primary efficacy endpoint, and the equivalence test between the trial drug (5% NMF) and the control drug (Rogaine®) was carried out. The covariance analysis model was used for equivalence testing. The change in TAHC after 24 weeks of treatment was used as the response variable, the TAHC at baseline was a covariate, the treatment group was used as a fixed effect, and the different centers were used as a random effect to estimate the difference in the mean change of TAHC between the trial group and control group and the 95% confidence interval (CI) of the mean difference. The 95% CI of the mean difference between the two groups satisfies the lower limit >−8 and the upper limit <8 in both the full-analysis set (FAS) and the per-protocol set (PPS), indicating the efficacy of the trial drug group is equivalent to that of the control drug group. Furthermore, the mixed-effects model repeated measures (MMRM) model was used for sensitivity analysis of the equivalence test after 24 weeks of treatment between the two groups. FAS is defined as all randomized subjects who had at least one application of study treatments and at least one post-treatment efficacy evaluation. The PPS is defined as all subjects without any major protocol deviation or other sources of bias for primary outcome analysis.

3. Results

3.1. Baseline Characteristics of Participants. A total of 420 male patients with AGA who met the study criteria were recruited, of whom 212 were assigned to the 5% NMF group and 208 to the Rogaine® group. At 24 weeks of follow-up, 8 patients in the 5% NMF group and 9 patients in the Rogaine® group were lost to follow-up. Finally, 211 patients in the 5% NMF group and 206 patients in the Rogaine® group were included in the analysis (Figure 1). Of the 417 patients in the FAS, 385 patients were eligible for the PPS. Table 1 demonstrates the baseline characteristics of patients, and the age of the patients ranged from 18 to 49 years. Age, BMI, grading of hair loss (Hamilton–Norwood scale and Ludwig scale), nonvellus TAHC, and hair diameter were similar between the 5% NMF group and the Rogaine® group at baseline (all $P > 0.05$).

3.2. Hair Density and Diameter. Table 2 shows the changes in nonvellus TAHC after 6, 12, 18, and 24 weeks of treatment. At baseline, the mean nonvellus TAHC was 112.74 ± 28.53 hair/cm^2 in the 5% NMF group and 116.26 ± 31.78 hair/cm^2 in the Rogaine® group. Both groups presented increased nonvellus TAHC over time, and the mean nonvellus TAHC was 127.59 ± 28.59 hair/cm^2 in the 5% NMF group and 134.26 ± 29.86 hair/cm^2 in the Rogaine® group at 24 weeks of treatment. Table 3 demonstrates the equivalence test of the 5% NMF group and the Rogaine® group in nonvellus TAHC index after 24 weeks of treatment. After 24 weeks of treatment, the mean difference in the change of nonvellus TAHC between the 5% NMF group and the Rogaine® group was 3.85 ± 1.62 hair/cm^2, and the 95% CI of the mean difference was (−7.03, −0.67) in the FAS. Similar results were found in the PPS, the mean difference was 3.96 ± 1.68 hair/cm^2, and the 95% CI of the mean difference was (−-7.26, −-0.66). The 95% CI for the mean difference between the two groups in both FAS and PPS met the clinically acceptable difference of this study (95% CI (−8.00, 8.00)), indicating that 5% NMF can be considered equivalent to Rogaine®. In addition, the sensitivity analysis using the MMRM model showed that the results of the equivalent test were robust (Supplement Table 1).

Changes in mean hair diameter after 6, 12, 18, and 24 weeks of treatment are shown in Figure 2. At baseline, the mean hair diameter was 0.054 ± 0.013 mm in the 5% NMF group and 0.056 ± 0.013 mm in the Rogaine® group. After 24 weeks of treatment, the mean hair diameter in the 5% NMF group and the Rogaine® group was 0.059 ± 0.014 mm and 0.060 ± 0.014 mm, respectively. Figure 3 shows the changes in the ratio of terminal hair to vellus hair after 6, 12, 18, and 24 weeks of treatment. The results demonstrated that the ratio of terminal hair to vellus hair increased with treatment time.

3.3. Global Photographic Assessment. The global photographic assessment was performed on 201 patients in the 5% NMF group and 199 patients in the Rogaine® group. After 24 weeks of treatment, 85 of 201 patients (42.3%) in the 5% NMF group and 83 of 199 patients (41.7%) in the Rogaine® group (5% NMF group vs. Rogaine® group; $P = 0.863$) were rated as improved by three dermatologists using the seven-point rating scale (Figure 4). In the self-evaluation, 186 of 201 patients (92.5%) in the 5% NMF group and 185 of 199 patients (93.0%) in the Rogaine® group (5% NMF group vs. Rogaine® group; $P = 0.464$) reported an improvement in their hair growth (Figure 5). Moreover, both 5% NMF and 5% Rogaine foam showed significant therapeutic effects on AGA after 24 weeks of treatment (Figure 6).

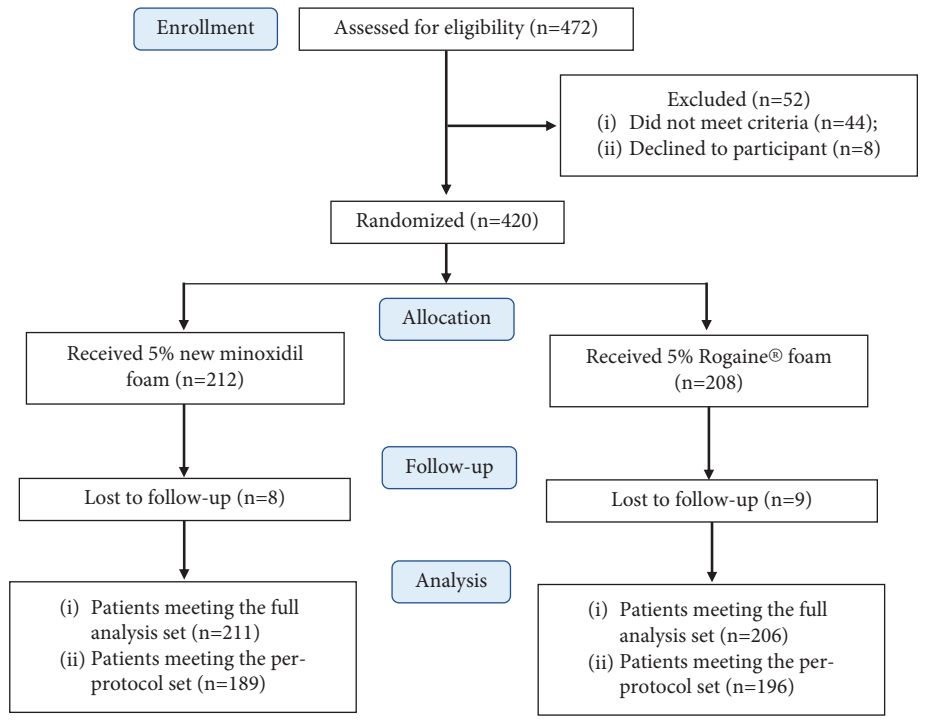

Figure 1: Participant flow diagram. NMF, new minoxidil foam. Full analysis set is defined as all randomized subjects who had at least one application of study treatments and at least one post-treatment efficacy evaluation. Per-protocol set is defined as all subjects without any major protocol deviation or other sources of bias for primary outcome analysis. For missing main efficacy indicators, data were populated using the last observation carried forward. The mixed-effects model-repeated measures (MMRM) were used for sensitivity analysis of the main efficacy indicators that were not populated.

Table 1: Participant demographics and baseline characteristics (based on FAS).

Characteristics	5% NMF group ($n = 211$)	Rogaine® group ($n = 206$)	P
Age, years, mean ± SD	32.70 ± 7.16	32.20 ± 7.27	0.4796
BMI, kg/m^2, mean ± SD	24.60 ± 3.07	24.45 ± 3.32	0.6321
Hamilton–Norwood scale, n (%)			0.3372
III vertex	90 (42.6)	95 (46.1)	
IV	74 (35.1)	60 (29.1)	
V	27 (12.8)	33 (16.0)	
Ludwig scale*, n (%)			0.7849
I	8 (3.8)	9 (4.4)	
II	10 (4.7)	7 (3.4)	
III	2 (0.9)	2 (1.0)	
Nonvellus TAHC, hair/cm^2, mean ± SD	112.74 ± 28.527	116.26 ± 31.776	0.2344
Hair diameter, mm, mean ± SD	0.054 ± 0.013	0.056 ± 0.013	0.1170
Duration of AGA, days, mean ± SD	160.0 ± 636.8	127.0 ± 415.5	<0.0001

Note. *These patients had hair loss types consistent with female pattern baldness (FPHL), so severity was assessed using the Ludwig baldness scale; FAS, full-analysis set; NMF, 5% new minoxidil foam; BMI, body mass index; TAHC, nonvellus (diameter > 30 μm) target area hair counts; AGA, androgenetic alopecia.

Table 2: Changes in nonvellus TAHC after 6, 12, 18, and 24 weeks of treatment compared with baseline.

Nonvellus TAHC, hair/cm^2, mean ± SD	FAS		PPS	
	5% NMF group ($n = 211$)	Rogaine® group ($n = 206$)	5% NMF group ($n = 189$)	Rogaine® group ($n = 196$)
Baseline	112.74 ± 28.53	116.26 ± 31.78	112.98 ± 28.43	115.59 ± 31.17
Week 6	117.78 ± 28.03	120.62 ± 30.82	117.65 ± 28.40	120.77 ± 30.28
Week 12	127.85 ± 28.88	131.60 ± 29.98	128.02 ± 29.06	132.19 ± 29.26
Week 18	130.06 ± 29.04	135.08 ± 29.85	130.55 ± 29.39	135.76 ± 29.02
Week 24	127.59 ± 28.59	134.26 ± 29.86	128.05 ± 28.53	134.18 ± 28.76

Note. FAS, full-analysis set; PPS, per-protocol set; NMF, 5% new minoxidil foam; TAHC, nonvellus target area hair counts.

Table 3: Equivalence test of nonvellus TAHC after 24 weeks of treatment.

Time	Variables	FAS		PPS	
		5% NMF group ($n = 211$)	Rogaine® group ($n = 206$)	5% NMF group ($n = 189$)	Rogaine® group ($n = 196$)
Baseline					
	Nonvellus TAHC, hair/cm^2, mean ± SD	112.74 ± 28.53	116.26 ± 31.78	112.98 ± 28.43	115.59 ± 31.17
Week 24					
	Nonvellus TAHC, hair/cm^2, mean ± SD	127.59 ± 28.59	134.26 ± 29.86	128.05 ± 28.53	134.18 ± 28.76
	Change of nonvellus TAHC, hair/cm^2, mean ± SD	14.85 ± 16.36	18.00 ± 19.16	15.07 ± 16.56	18.58 ± 19.17
	Mean difference, hair/cm^2, mean ± SE	−3.85 ± 1.62		−3.96 ± 1.68	
	95% CI of mean difference	(−7.03, −0.67)		(−7.26, −0.66)	

Note. The covariance analysis model was used for equivalence testing. FAS, full-analysis set; PPS, per-protocol set; NMF, 5% new minoxidil foam; TAHC, nonvellus target area hair counts.

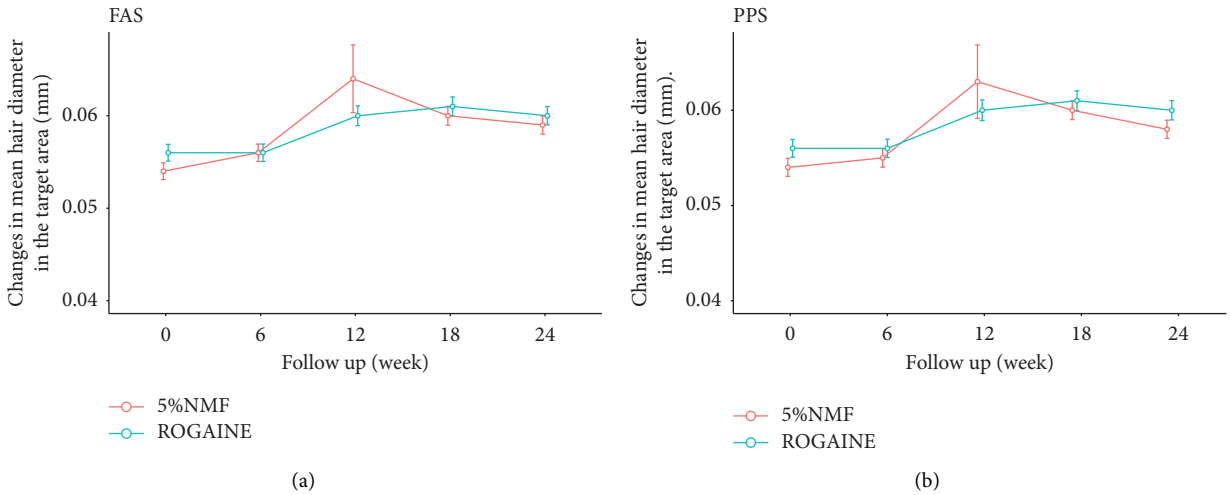

Figure 2: The mean change from baseline in hair diameter at week 6, week 12, week 18, and week 24 of the 5% new minoxidil foam (NMF) group and the Rogaine® group. (a) Full-analysis set (FAS) and (b) per-protocol set (PPS).

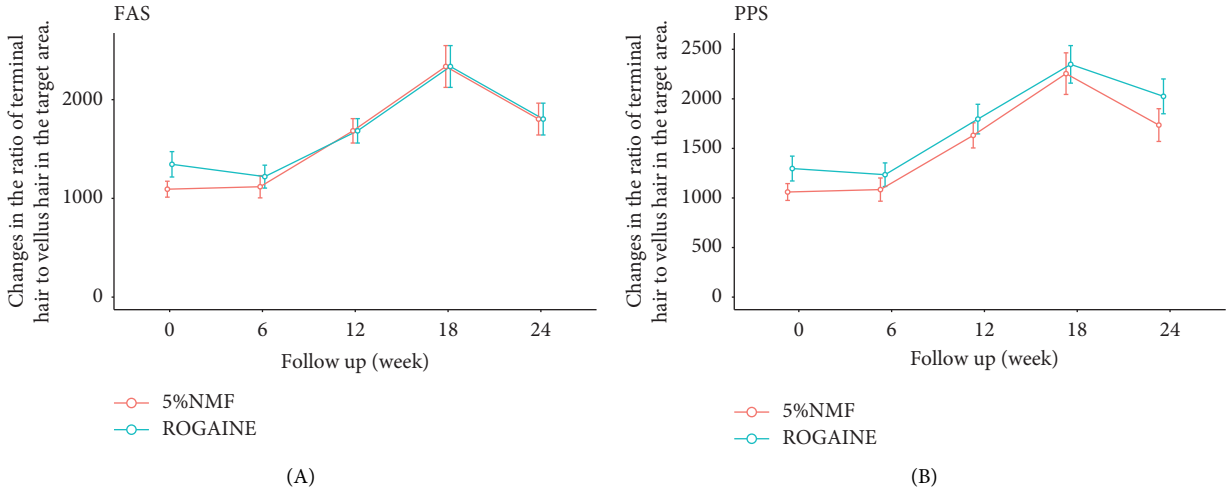

Figure 3: The mean change from baseline in terminal hair to vellus hair ratio at week 6, week 12, week 18, and week 24 of the 5% new minoxidil foam (NMF) group and the Rogaine® group. (A) Full-analysis set (FAS) and (B) per-protocol set (PPS).

3.4. Safety Assessment. Table 4 displays the adverse events of patients in the 5% NMF group and the Rogaine® group. During the study process, 111 of 212 patients (52.9%) in the 5% NMF group and 117 of 208 patients (55.7%) in the Rogaine® group observed adverse events. Adverse events occurred mainly in infections and skin diseases. No statistically significant differences were found between the 5% NMF group and the Rogaine® group in different types of adverse events (all $P > 0.05$).

4. Discussion

This randomized, double-blind, controlled, multicenter, phase III study compared the efficacy and safety of the generic 5% NMF and marketed comparator Rogaine® in patients with AGA. Our results demonstrated that the generic 5% NMF was equivalent to Rogaine® in efficacy and safety within a clinically acceptable difference after 24 weeks of treatment. 5% NMF was effective in improving hair density and diameter in patients with AGA.

Oral minoxidil has not been used to treat hair loss due to potential side effects of high doses of the drug (10–40 mg per day) such as sodium and fluid retention [10]. Topical minoxidil has been widely used as an effective treatment for hair loss in men with AGA [17–19]. Both 5% minoxidil topical solution and foam are used for the treatment of AGA in men. Compared to the minoxidil solution, the foam formulation contains no propylene glycol and is less irritating to the skin. The exact mechanism of action of minoxidil remains unknown [20]. The efficacy of minoxidil in patients with AGA may be related to its ability to shorten the telogen phase of the hair follicle, make the resting follicle to enter the anagen phase in advance, prolong the anagen phase, and increase the size of the hair follicle [20].

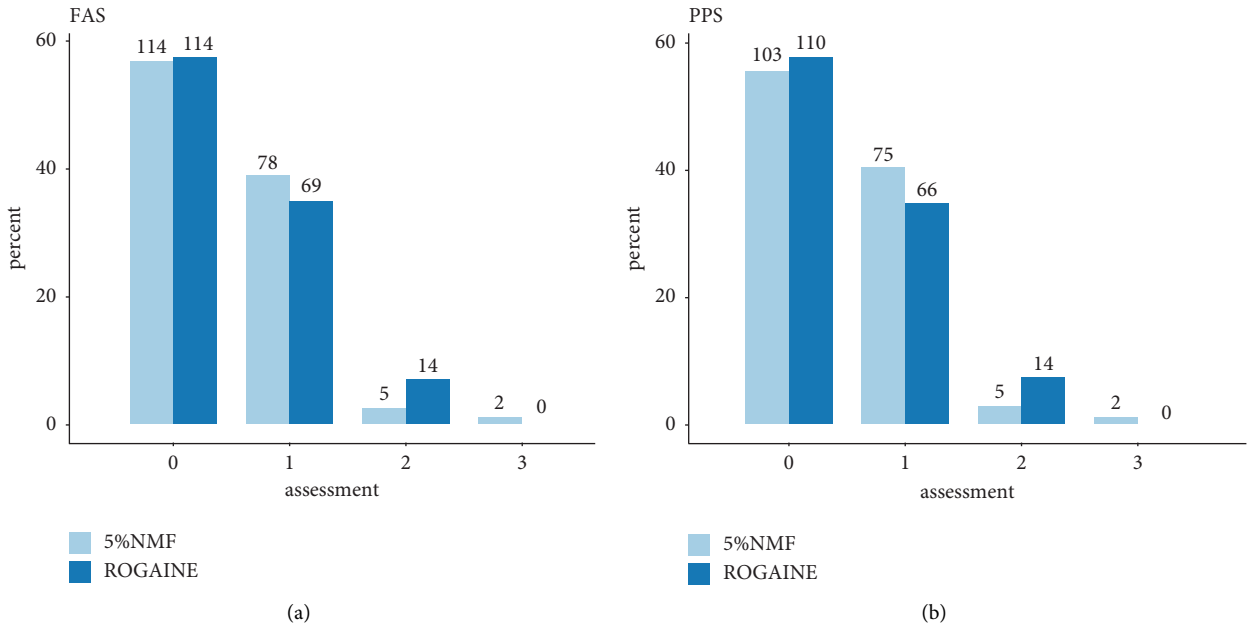

Figure 4: Global photographic assessment by investigators in the 5% new minoxidil foam (NMF) group and Rogaine® from baseline to week 24. (a) Full-analysis set (FAS) and (b) per-protocol set (PPS).

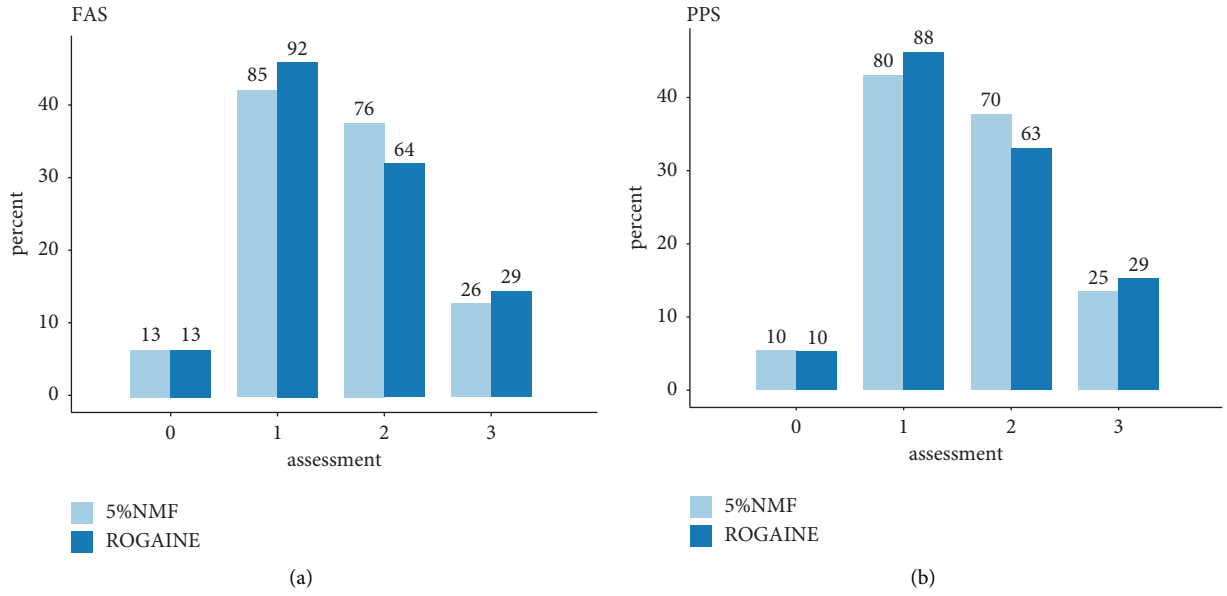

Figure 5: Global photographic assessment by patients in the 5% new minoxidil foam (NMF) group and Rogaine® from baseline to week 24. (a) Full-analysis set (FAS) and (b) per-protocol set (PPS).

Minoxidil directly promotes hair growth by stimulating dermal papilla and epithelial cells and indirectly stimulates adipose stem cells to secrete growth factors to promote hair growth [21]. Improvement in hair loss was observed approximately 6–8 weeks after the start of minoxidil treatment, with clinically significant improvements being reached at 12–16 weeks [20]. However, the effectiveness of minoxidil relies on continuous treatment and discontinuation of daily use may cause hair loss to reoccur. Our study assessed the difference in efficacy and safety between 5% NMF and Rogaine® over a 24-week treatment period. Our results indicated that 5% NMF was equivalent to Rogaine® in efficacy and safety within a clinically acceptable difference after 24 weeks of treatment.

Hair density and hair diameter are the main indicators to evaluate the effect of treatment. After 12 weeks of 5% NMF treatment, the patient's nonvellus TAHC and hair diameter improved significantly. There were no statistical differences between the 5% NMF group and Rogaine® group in the improvement of nonvellus TAHC at 6, 12, and 18 weeks after

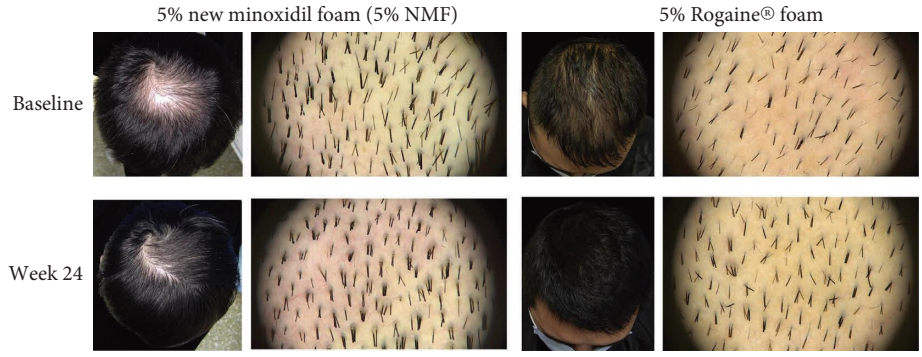

Figure 6: Baseline and week 24 global photographs and trichoscopic photographs of patients treated with topical 5% new minoxidil foam (NMF) versus topical 5% Rogaine® foam.

Table 4: Adverse events in the two groups of patients.

Adverse events	5% NMF group ($n = 212$)	Rogaine® group ($n = 208$)	P
Infection diseases, n (%)			0.6996
Upper respiratory tract infection	40 (18.9)	32 (15.4)	
Others	17 (8.0)	16 (7.7)	
Skin diseases, n (%)			0.2720
Folliculitis	39 (18.4)	30 (14.4)	
Hair loss	10 (4.7)	6 (2.9)	
Pruritus	6 (2.8)	7 (3.4)	
Others	6 (2.8)	6 (2.9)	
Gastrointestinal diseases, n (%)			0.6137
Diarrhea	17 (8.0)	14 (6.7)	
Others	9 (4.2)	4 (1.9)	
Laboratory tests, n (%)			0.6001
Elevated alanine aminotransferase	16 (7.5)	13 (6.3)	
Others	4 (1.9)	5 (2.4)	
Nervous system diseases, n (%)			0.3633
Headache	17 (8.0)	12 (5.8)	
Dizziness	8 (3.8)	7 (3.4)	
Others	7 (3.3)	2 (1.0)	
Respiratory, thoracic, and mediastinal disorders, n (%)			0.9584
Cough	14 (6.6)	14 (6.7)	
Others	5 (2.4)	8 (3.8)	
Total, n (%)	111 (52.9)	117 (55.7)	0.4235

treatment. Although, a statistical difference was found between the 5% NMF group and Rogaine® group in nonvellus TAHC at 24 weeks after treatment. However, the difference was within the equivalence difference interval assumed by the study (95% CI of mean difference, −8.00 to 8.00), suggesting that the efficacy of 5% NMF and Rogaine® could be considered equivalent. The sensitivity analysis using the MMRM model showed that the results of the equivalent test were robust. In addition, the ratio of terminal hair to vellus hair increased with treatment time, reaching a peak at 18 weeks after treatment. In the expert global photographic assessment, 42.3% of patients treated with 5% NMF and 41.7% of patients treated with Rogaine® were rated as having improved treatment. Our treatment improvement rate was similar to other studies using minoxidil foam (42.3% vs. 35%–67.7%) in the expert global photographic assessment [13, 19, 22]. Furthermore, our treatment improvement rate was low compared to studies using minoxidil solution (42.3% vs. ≥85%) in the expert global photographic assessment [11, 23]. The possible explanation was that minoxidil solution is more easily absorbed than foam, and the sample size of previous studies was too small (30 cases), which may have affected the representativeness of the results. However, compared with minoxidil solution, minoxidil foam has better convenience, improved compliance and product acceptability, and less irritation [13]. Although topical minoxidil is an effective option for the treatment of hair loss, many patients have poor compliance due to the necessity to use twice-daily medication and scalp stimulation. Several studies have evaluated the efficacy of minoxidil administered in different ways such as oral [24, 25], topical (solution and foam) [11, 12], and intradermal injection [26].

Dosage forms with good efficacy and compliance or a new treatment modality are needed in the future AGA treatment.

This study used a multicenter, large-sample phase III clinical trial to compare the equivalence of 5% NMF and Rogaine® in the treatment of AGA. However, several limitations of this study should be considered. First, this study lacks long-termfollow-up data and did not assess scalp dihydrotestosterone levels. Second, although our study included important assessments such as hair density and diameter, others indicators such as the proportion of follicular units with perifollicular hyperpigmentation and the average number of yellow dots can also be used to monitor treatment effects. Third, although we used anatomical landmarks to determine where trichological images were taken, more precise localization may rely on other modalities such as tattooing.

5. Conclusions

This multicenter, phase III trial compared changes in hair density, hair diameter, terminal hair to vellus hair ratio, global photographic assessment by investigators and patients, and adverse events between generic 5% NMF and marketed comparator Rogaine® in patients with AGA. The results clearly demonstrated that 5% NMF is as effective as Rogaine® in increasing hair density and hair diameter in AGA patients after 24 weeks of treatment. The 5% NMF has the potential to become a more accessible and economical treatment option for AGA patients in China.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Cheng Zhou, Weixin Fan, and Jianfeng Zou contributed equally to this work.

Supplementary Materials

Supplement Table 1. Sensitivity analysis of the equivalence test for non-vellus TAHC after 24 weeks of treatment using the MMRM model. (*Supplementary Materials*)

References

[1] Y. Kelly, A. Blanco, and A. Tosti, "Androgenetic alopecia: an update of treatment options," *Drugs*, vol. 76, no. 14, pp. 1349–1364, 2016.

[2] K. York, N. Meah, B. Bhoyrul, and R. Sinclair, "A review of the treatment of male pattern hair loss," *Expert Opinion on Pharmacotherapy*, vol. 21, no. 5, pp. 603–612, 2020.

[3] J. A. Ellis and R. D. Sinclair, "Male pattern baldness: current treatments, future prospects," *Drug Discovery Today*, vol. 13, no. 17-18, pp. 791–797, 2008.

[4] S. Heilmann, F. F. Brockschmidt, A. M. Hillmer et al., "Evidence for a polygenic contribution to androgenetic alopecia," *British Journal of Dermatology*, vol. 169, no. 4, pp. 927–930, 2013.

[5] T. L. Wang, C. Zhou, Y. W. Shen et al., "Prevalence of androgenetic alopecia in China: a community-based study in six cities," *British Journal of Dermatology*, vol. 162, no. 4, pp. 843–847, 2010.

[6] D. Stough, K. Stenn, R. Haber et al., "Psychological effect, pathophysiology, and management of androgenetic alopecia in men," *Mayo Clinic Proceedings*, vol. 80, no. 10, pp. 1316–1322, 2005.

[7] R. Sinclair, M. Patel, T. L. Dawson Jr. et al., "Hair loss in women: medical and cosmetic approaches to increase scalp hair fullness," *British Journal of Dermatology*, vol. 165, no. 3, pp. 12–18, 2011.

[8] A. Adil and M. Godwin, "The effectiveness of treatments for androgenetic alopecia: a systematic review and meta-analysis," *Journal of the American Academy of Dermatology*, vol. 77, no. 1, pp. 136–141.e5, 2017.

[9] J. R. Stoehr, J. N. Choi, M. Colavincenzo, and S. Vanderweil, "Off-Label use of topical minoxidil in alopecia: a review," *American Journal of Clinical Dermatology*, vol. 20, no. 2, pp. 237–250, 2019.

[10] M. Randolph and A. Tosti, "Oral minoxidil treatment for hair loss: a review of efficacy and safety," *Journal of the American Academy of Dermatology*, vol. 84, no. 3, pp. 737–746, 2021.

[11] P. Suchonwanit, P. Srisuwanwattana, N. Chalermroj, and S. Khunkhet, "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," *Journal of the European Academy of Dermatology and Venereology*, vol. 32, no. 12, pp. 2257–2263, 2018.

[12] A. K. Gupta, M. Talukder, M. Venkataraman, and M. A. Bamimore, "Minoxidil: a comprehensive review," *Journal of Dermatological Treatment*, vol. 33, no. 4, pp. 1896–1906, Jun 2022.

[13] U. Blume-Peytavi, K. Hillmann, E. Dietz, D. Canfield, and N. Garcia Bartels, "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," *Journal of the American Academy of Dermatology*, vol. 65, no. 6, pp. 1126–1134.e2, Dec 2011.

[14] M. Payette and J. M. Grant-Kels, "Generic drugs in dermatology: part I," *Journal of the American Academy of Dermatology*, vol. 66, no. 3, pp. 343.e1–8, 2012.

[15] U. Blume-Peytavi, Z. Issiakhem, S. Gautier et al., "Efficacy and safety of a new 5% minoxidil formulation in male androgenetic alopecia: a randomized, placebo-controlled, double-blind, noninferiority study," *Journal of Cosmetic Dermatology*, vol. 18, no. 1, pp. 215–220, 2019.

[16] E. A. Olsen, D. Whiting, W. Bergfeld et al., "A multicenter, randomized, placebo-controlled, double-blind clinical trial of a novel formulation of 5% minoxidil topical foam versus placebo in the treatment of androgenetic alopecia in men," *Journal of the American Academy of Dermatology*, vol. 57, no. 5, pp. 767–774, 2007.

[17] S. Varothai and W. F. Bergfeld, "Androgenetic alopecia: an evidence-based treatment update," *American Journal of Clinical Dermatology*, vol. 15, no. 3, pp. 217–230, 2014.

[18] V. Kanti, A. Messenger, G. Dobos et al., "Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men - short version," *Journal of the European*

Academy of Dermatology and Venereology, vol. 32, no. 1, pp. 11–22, 2018.

[19] V. Kanti, K. Hillmann, J. Kottner, A. Stroux, D. Canfield, and U. Blume-Peytavi, "Effect of minoxidil topical foam on frontotemporal and vertex androgenetic alopecia in men: a 104-weekopen-label clinical trial," *Journal of the European Academy of Dermatology and Venereology*, vol. 30, no. 7, pp. 1183–1189, 2016.

[20] A. G. Messenger and J. Rundegren, "Minoxidil: mechanisms of action on hair growth," *British Journal of Dermatology*, vol. 150, no. 2, pp. 186–194, 2004.

[21] N. Choi, S. Shin, S. U. Song, and J. H. Sung, "Minoxidil promotes hair growth through stimulation of growth factor release from adipose-derived stem cells," *International Journal of Molecular Sciences*, vol. 19, no. 3, p. 691, 2018.

[22] K. Hillmann, N. Garcia Bartels, J. Kottner, A. Stroux, D. Canfield, and U. Blume-Peytavi, "A single-centre, randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy and safety of minoxidil topical foam in frontotemporal and vertex androgenetic alopecia in men," *Skin Pharmacology and Physiology*, vol. 28, no. 5, pp. 236–244, 2015.

[23] P. Suchonwanit, W. Iamsumang, and S. Rojhirunsakool, "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," *American Journal of Clinical Dermatology*, vol. 20, no. 1, pp. 147–153, 2019.

[24] A. Villani, G. Fabbrocini, J. Ocampo-Candiani, A. Ruggiero, and S. S. Ocampo-Garza, "Review of oral minoxidil as treatment of hair disorders: in search of the perfect dose," *Journal of the European Academy of Dermatology and Venereology*, vol. 35, no. 7, pp. 1485–1492, 2021.

[25] J. Jimenez-Cauhe, D. Saceda-Corralo, R. Rodrigues-Barata et al., "Effectiveness and safety of low-dose oral minoxidil in male androgenetic alopecia," *Journal of the American Academy of Dermatology*, vol. 81, no. 2, pp. 648-649, Aug 2019.

[26] B. P. C. Uzel, G. H. S. Takano, J. C. N. Chartuni et al., "Intradermal injections with 0.5% minoxidil for the treatment of female androgenetic alopecia: a randomized, placebo-controlled trial," *Dermatologic Therapy*, vol. 34, no. 1, Article ID e14622, Jan 2021.