RESEARCH ARTICLE

The "NOMINAL" trial: Clinical efficacy, cosmetic acceptability, and local tolerability of topical 5% minoxidil lotion without propylene glycol: A 6-month, multicentre, real-life, prospective, assessor-blinded study in 196 subjects with hair loss.

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Abstract

Background and Trial Objectives:
A new propylene glycol (PG)-free 5% minoxidil (Mnx) (PG-Free-Mnx) lotion has been recently commercialized. Clinical efficacy and local tolerability have been, so far, documented in a limited number of patients. The aim of this study was to evaluate the clinical efficacy, cosmetic acceptability, and local tolerability of 6-month application of this new PG-Free Mnx lotion in a real-life situation.
Materials and Methods:
The NOMINAL (*NO-PG MINoxidil reAL life study*) trial was performed in 22 out-patients Italian dermatology clinics. A total of 196 subjects of both sexes with a diagnosis of androgenic alopecia (AGA) and female androgenic alopecia (FAGA) were enrolled in the trial, after their written informed consent. PG-Free-Mnx lotion was applied 1 ml twice daily for 6 months. Clinical efficacy was evaluated in an open fashion in all the enrolled subjects with a 5-grade scale score (from-2: severe worsening, to +2: very good improvement in comparison with baseline condition). In a subgroup of subjects (n=60) an assessor-blinded clinical efficacy evaluation has been also performed using high definition standardized and coded scalp global pictures at baseline, and after 6 months by an assessor unaware of the temporal sequence using a 3-grade score (from 0: no improvement to 3: very high improvement). Cosmetic acceptability evaluation was assessed using a 7-item questionnaire using a 10-point scale score, with score 1 meaning not at all and score 10 meaning the worst possible condition. Cosmetic acceptability and clinical efficacy were evaluated after 12 and 24 weeks of treatment. Global tolerability, assessed at week 24, was evaluated with a 4-grade scale score (from -1: very low tolerability to +2: very good tolerability).
Results:
All but seven (3.6%) subjects concluded the study. Clinical efficacy scores (open evaluation) were 0.8±0.7 and 1.0±0.7 at week 12 and 24, respectively. Good or very good clinical response (score +1 or +2) at week 12 and week 24 was observed in 64% and 74% respectively of the subjects with a similar response in women (75%) and men (73%). Baseline severity of AGA/FAGA was inversely correlated with the clinical response with a better outcome in subjects with AGA type II in comparison with subjects with types III/IV AGA. The clinical efficacy was confirmed by the assessor-blinded evaluation of the subgroup of 60 subjects' pictures at baseline (clinical score at baseline: 0.2±0.4 vs. 1.8±0.7 after 6 months; p=0.0001; absolute mean difference: 1.6; 95% CI: 1.1 to 2.0). Cosmetic acceptability score mean values were always <2 at each time-point evaluation, demonstrating good or very good acceptability. Global Tolerability score mean±SD value was 1.7±0.4 with 94% of the subjects reporting good or very good tolerability with no differences between men and women. No subjects reported severe or very severe (Tolerability score >7) burning, itching or redness sensations.
Conclusions:
This new PG-free lotion shows, in real-life conditions, a very good cosmetic acceptability and tolerability profile. Clinical efficacy, evaluated both in open and assessor-blinded fashions, was also documented, and it was in line with the available data of traditional Mnx formulations with propylene glycol.

Key Words: Androgenetic alopecia, Minoxidil, propylene glycol, real-life trial.

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Introduction

Androgenetic alopecia (AGA) is a common form of hair loss affecting both men and women[1]. This condition is characterized by the progressive loss of terminal hairs on the scalp with a characteristic distribution. The typical involved areas are the anterior scalp, the mid scalp, the temporal scalp, and the vertex. Epidemiological data show that AGA (Hamilton-Norwood III or above) is present in 48 percent of 266 healthy men (ages 18 to 49 years), including 16 percent of men between the ages of 18 and 29 years and 53 percent of men between the ages of 40 and 49 years[2]. AGA in men is also commonly associated with several other medical conditions, including coronary heart disease and enlargement of the prostate[3]. On the other hand, in women, female AGA (FAGA) is associated with an increased risk of polycystic ovary syndrome (PCOS). PCOS is characterized by a hormonal imbalance that can lead to irregular menstruation, acne, excess hair elsewhere on the body (hirsutism), and weight gain[4]. There are only two drugs authorized for the medical treatment of AGA and FAGA: 1 mg oral finasteride (only in men) and topical Minoxidil. Minoxidil (Mnx) 2 and 5% is a topical drug indicated for the treatment of androgenic alopecia (AGA/FAGA) both in men and women[5]. Mnx can counteract the sex hormone-dependent miniaturization process of hair follicle which characterizes AGA physiopathology[6]. The Mnx molecule could exert a vasodilation effect with a consequent positive action on the microcirculation of the scalp but at the same time favouring the cell cycle and cell proliferation, favouring at the hair follicle the anagen phase[7]. The clinical efficacy of Mnx in AGA is maintained only if the treatment is continued[8]. Therefore, long-term tolerability and safety are crucial aspects of AGA therapy with topical Mnx. Mnx 5% and 2% lotions commonly contain propylene glycol (PG), a solvent component able to enhance Mnx water solubility[9],[10]. PG is also a penetration enhancer of Mnx molecule, therefore contributing to the clinical efficacy[11]. PG could have, especially in the long-term, a negative effect on the skin barrier function. Several adverse reactions due to PG have been documented, like allergic contact dermatitis (6% of treated subjects), scalp dryness, irritation, burning and redness in subjects treated with classical PG-containing Mnx lotions[12]. The latter can be observed in up to 30% of Mnx-treated patients[13]. Rossi et al. in a recent review have reported that scalp pruritus and scaling are the most common side effects of Mnx lotions treatments[14]. A new propylene glycol (PG)-free 5% minoxidil (PG-Free-Mnx) lotion has been recently commercialized. Clinical efficacy and local tolerability have been, so far, documented in a limited number (n=30) of patients[15]. The aim of this study was to evaluate the clinical efficacy, cosmetic acceptability, and local tolerability of the 6-month application of this new PG-Free Mnx lotion in a real-life situation in a large sample of subjects.

Subjects and Methods

Study Design

The NOMINAL (NO-PG MINoxidil reAL life study) trial was a prospective multicentre open trial with an assessor-blinded efficacy evaluation, performed between January 2020 and February 2021, in 22 out-patients dermatology clinics which have enrolled, after their written informed consent, a total of 196 subjects of both sexes (106 men and 90 women, mean±SD age 41±15) with a diagnosis of mild to moderate AGA/FAGA.

Subjects

Men and women eligible for the inclusion in the trial were 18-65 years old with mild to moderate AGA/FAGA. Mild to Moderate AGA/FAGA was defined for men as a score of II-V on the Hamilton-Norwood scale[16] and as a score of I3-4 and II1-2 on the Ludwig Scale[17] for women. Subjects should be in good general health condition with no clinical evidence of systemic illnesses.PG-Free-Mnx lotion was applied 1 ml

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twice daily for 6 months on the scalp. The study was planned for the inclusion of at least 150 subjects. The product needed for the study conduction and evaluation was furnished for free by the Company selling the lotion (Cantabria Labs Difa Cooper).

Study Objectives

The clinical efficacy was evaluated in an open fashion in all the enrolled subjects with a 5-grade scale score (from-2: severe worsening, to +2: very good improvement). In a subgroup of subjects (n=60) an assessor-blinded clinical efficacy evaluation has been also performed using high definition standardized and coded pictures at baseline, and after 3 months by an assessor unaware of the temporal sequence using a 3-grade score (from 0: no improvement to 3: very high improvement). The subject's cosmetic acceptability evaluation was assessed using a 7-item questionnaire using a 10-point scale score with score 1 meaning not at all and 10 the worst possible condition. The 7-item questions were: 1) Application of the product is problematic; 2) After applying the product you noticed that the hair is more greasy; 3) After applying the product, you observed the presence of residues; 4) After applying the product, your skin feels drier; 5) You noticed the appearance of itching; 6) You have noticed the onset of burning; 7) You have noticed redness at the application site. Clinical efficacy and cosmetic acceptability were evaluated after 12 and 24 weeks of treatment. Global tolerability, assessed at week 24, was evaluated with a 4-grade scale score (from -1: very low tolerability to +2: very good tolerability).

Statistical Analysis

Statistical analysis was performed using GraphPad Prism statistical software ver. 9.1 (La Jolla, CA, USA). Continuous variables were expressed as mean±SD. The paired t-test and the Wilcoxon test were used for the analysis of the study outcomes. A P-value of <0.05 was considered significant. A formal calculation of sample size was not performed. For the clinical part of the study, the aim was to enrol at least 150 subjects.

Results

Table I shows the subjects' clinical and demographic characteristics at baseline. All but 7 (3.6%) subjects concluded the study. The reasons for these premature conclusions of Mnx lotion treatment were not related to reduce tolerability or safety issues. Clinical efficacy scores were 0.8±0.7 and 1.0±0.7 at week 12 and 24, respectively. Good or very good clinical response (score +1 or +2) at week 12 and 24 was observed in 64% (95% CI from 57% to 70%) and 74% (95% CI from 67% to 80%) of the subjects, respectively with a similar response in women (75%) and in men (73%) (*Figure 1*). Baseline severity of AGA/FAGA was inversely correlated with the clinical response with a better outcome in subjects with AGA types II in comparison with subjects with types III/IV AGA. The clinical efficacy was confirmed by the assessor-blinded evaluation of the subgroup of 60 subjects' pictures at baseline (clinical score at baseline: 0.2±0.4 vs. 1.8±0.7 after 6 months; p=0.0001; absolute mean difference: 1.6; 95% CI: 1.1 to 2.0) (*Figure 2*). *Figure 3* documents some global scalp pictures, utilized for the assessor-blinded subgroup evaluation, before and after treatment with the lotion in 9 subjects. Cosmetic acceptability score mean values were always <2 at each time-point evaluation, demonstrating good or very good acceptability. Global Tolerability score mean±SD value was 1.7±0.4 with 94% of the subjects reporting good or very good tolerability with no differences between men and women. Interestingly scalp irritation and low tolerability in this sample were reported in 2 subjects only (1%). Moderate or intense itching has been reported in 11% of treated subjects. The moderate or intense burning sensation was reported by 5.6%. No subjects reported severe or very severe (Tolerability score >7) burning, itching or redness sensations. No serious side effects were

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reported. No dropped out subjects because of drug-related local intolerance were observed.

Table I: Subjects' demographic and clinical characteristics at baseline

	Men	**Women**
Number	106	90
Age, mean±SD	35±15	46±16
Alopecia severity *Norwood-Hamilton scale (men), n(%)* N-H2 N-H3 N-H4 *Ludwig scale (women)n(%)* L1 L2 L3	 36 (34%) 54 (51%) 16 (15%)	 37 (41%) 35 (39%) 18 (20%)
Duration of alopecia (years)	2.3	1.5
Previous treatments N(%)	17 (16%)	20 (22%)

Figure 1: Percentage of subjects with good or very good clinical response (score 1 or 2) during PG-free minoxidil lotion treatment. Open evaluation in comparison with baseline (n=196).

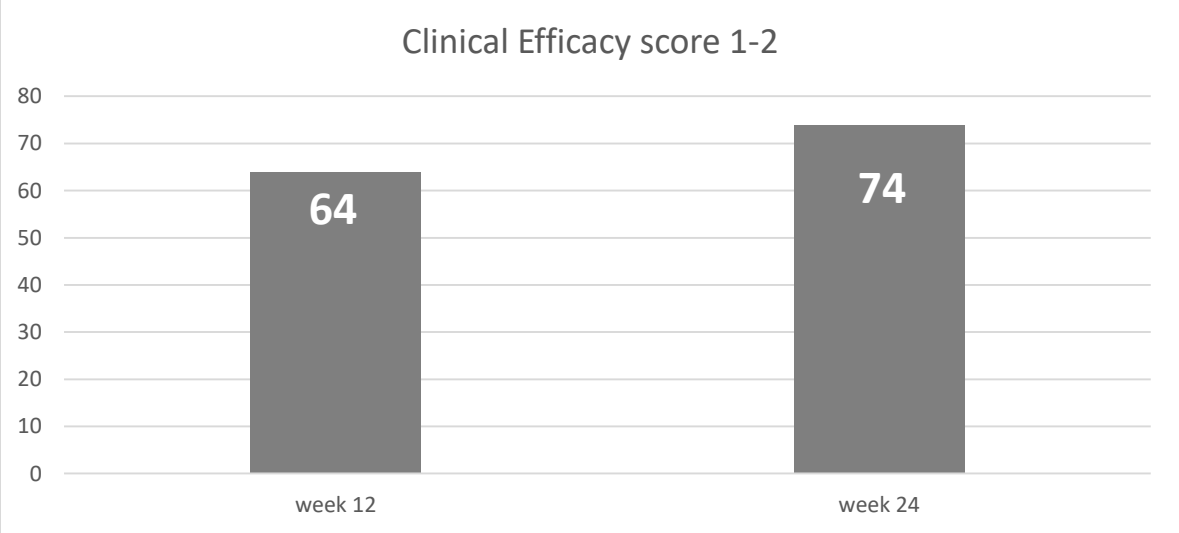

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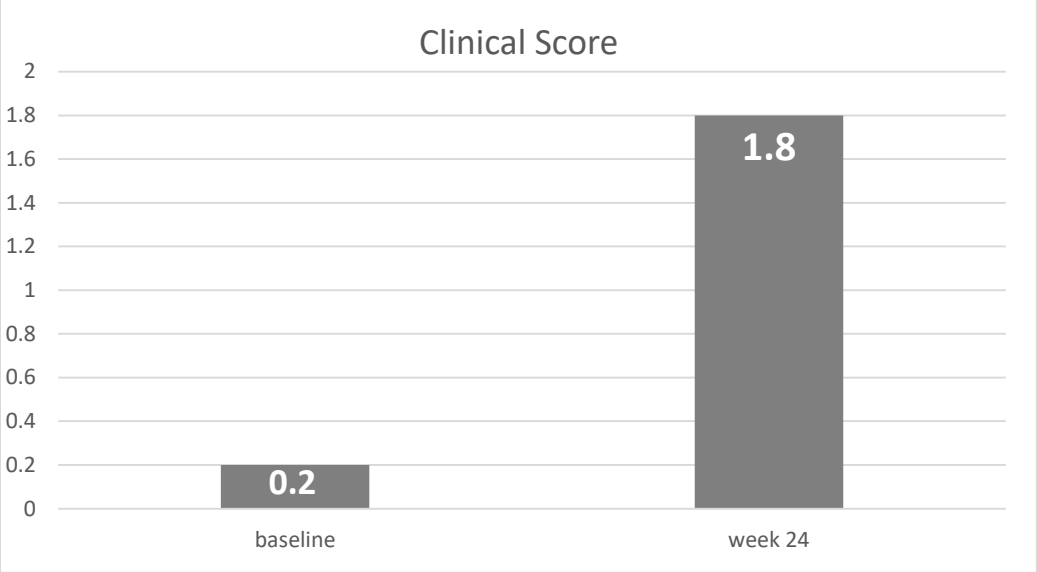
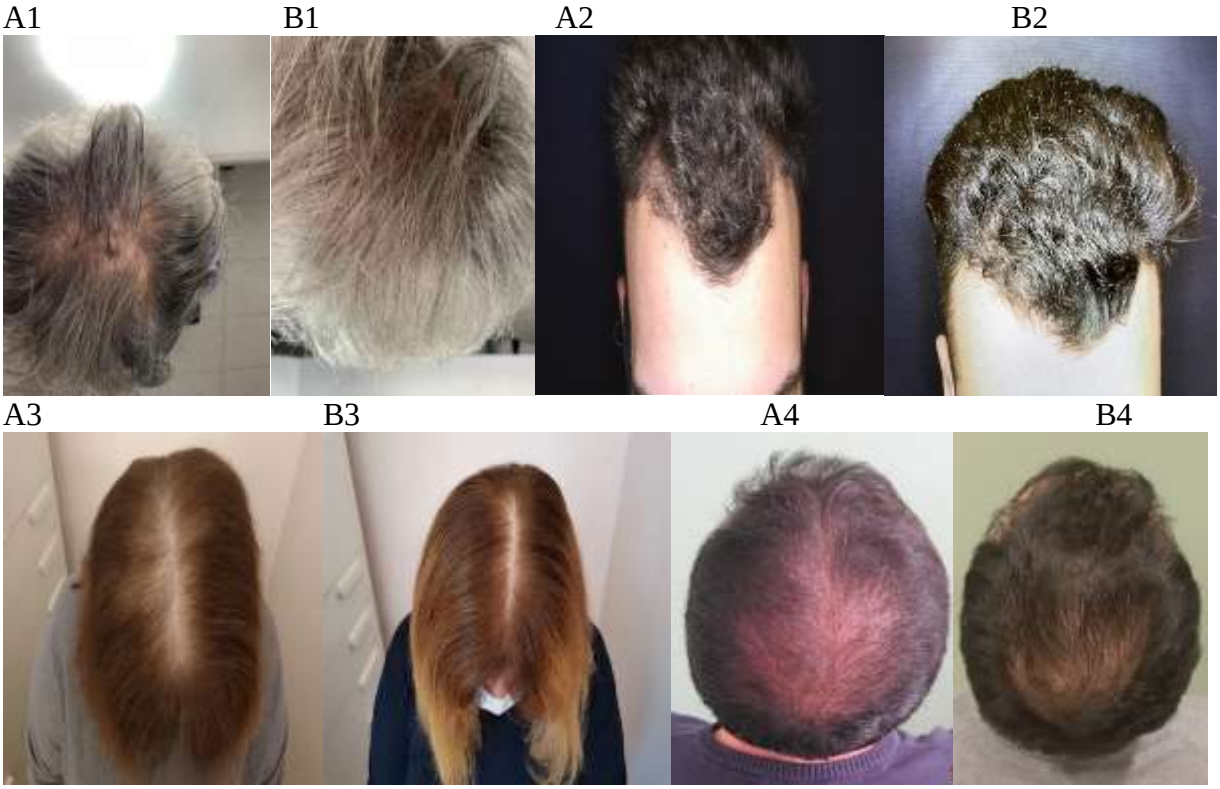
Figure 2: Clinical efficacy score (0: no improvement to 3: very high improvement). Assessor-blinded evaluation (n=60).



P=0.0001 week 24 vs. baseline

Figure 3: Global pictures of scalp of 9 subjects (A: baseline; B: week 24).



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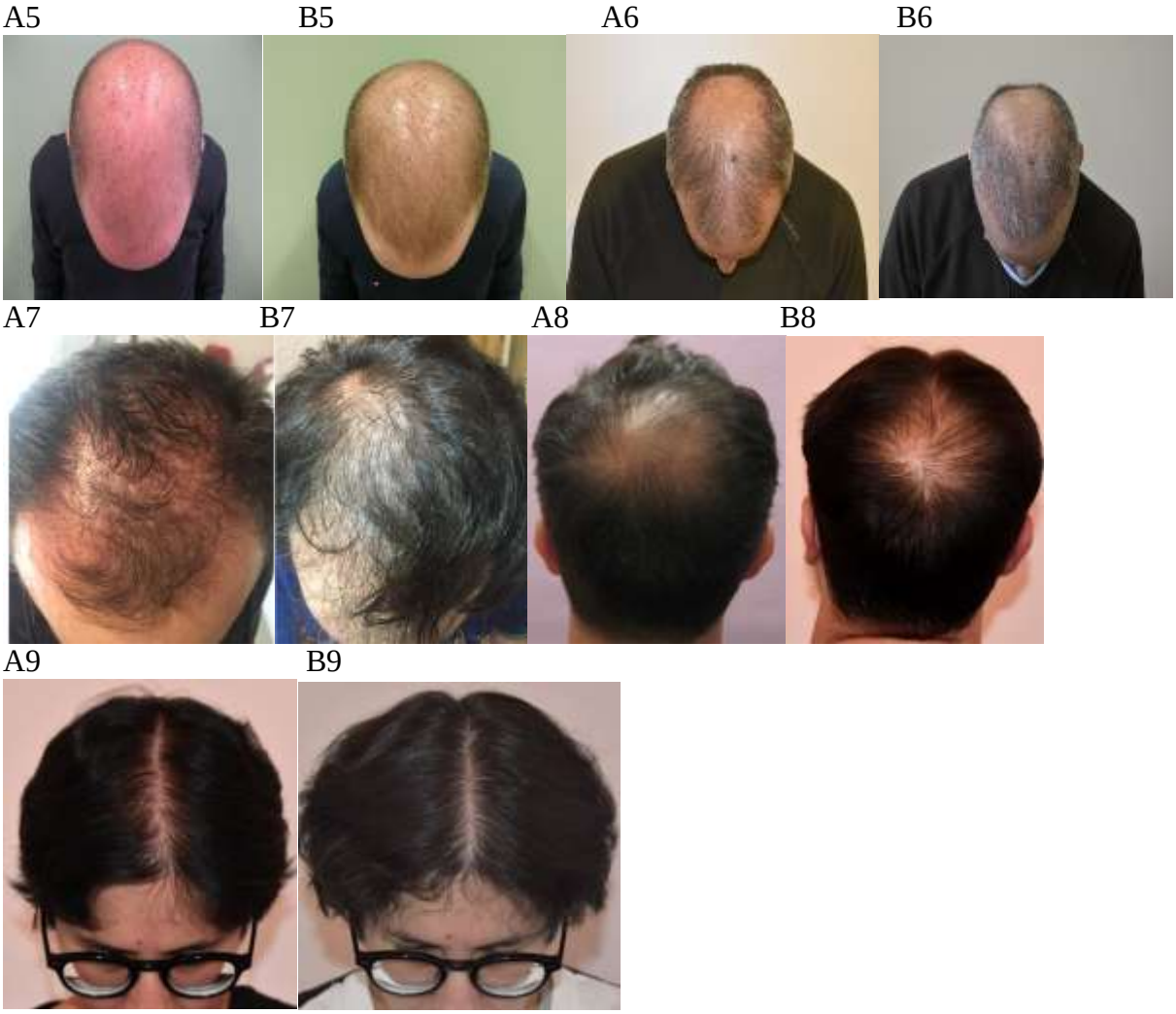

Discussion

AGA and FAGA are common chronic dermatological conditions with a relevant impact on self-esteem and quality of life of the affected subjects[18]. AGA is considered an androgen-dependent trait that requires a genetic predisposition. High levels of scalp Dihydrotestosterone (DHT), produced by the activity of 5-alpha reductase enzyme, contributes to follicular miniaturization (the transition of larger, terminal hair fibers to small vellus hair fibers) in susceptible AGA scalp areas[19]. DHT is a potent metabolite of testosterone and, compared with testosterone, has greater affinity for the androgen receptor[20]. Interfering with the miniaturization process of hair follicle should be considered the main pharmacological target for AGA treatment. The only AGA approved pharmacological treatments are topical minoxidil (MNX) and finasteride[21]. These therapeutic agents are the molecules most extensively studied for the treatment of AGA in men (Mnx and finasteride) and women (Mnx). Both drugs have demonstrated efficacy and high tolerability in placebo-controlled randomized trials, supporting their status as first-line agents[22]. Both treatments should be used chronically to maintain the improvement in hair count[23]. Minoxidil is used in lotions and foam formulations with 2% and 5% concentrations. Topical minoxidil is the mainstay pharmacological treatment for androgenic alopecia both in men and women[24]. The specific mechanism of action of topical minoxidil

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remains however to be fully explained. Mnx can positively affect follicular cells, enhancing hair growth and at the same time reducing hair loss[25]. Mnx solutions generally contain ethanol, water, and propylene glycol (PG). PG is widely used in dermatological and non-dermatological preparations[26]. PG favours the penetration of Mnx through the skin, but this is due to alteration of skin barrier function[27]; therefore, PG could induce skin irritation, especially in the long-term treatment[28]. Subjects treated with Mnx PG-containing lotions can suffer of skin irritation, itch and allergic contact dermatitis causing the interruption of the treatment[29]. Skin irritation is observed in up to 5% of subjects treated with Mnx foam, a formulation not containing propylene glycol[30]. Moderate-intense itching is reported in 25%-30% of Mnx classical lotion. A new propylene glycol (PG)-free 5% minoxidil (PG-Free-Mnx) lotion has been recently commercialized. Clinical efficacy and local tolerability have been documented in a prospective open-label study in 30 subjects with AGA[11]. The NOMINAL trial has evaluated clinical efficacy, cosmetic acceptability, and tolerability in a real-life condition in more than 190 AGA subjects. The present trial has demonstrated that in real-life condition in a population of more than 190 subjects 6-month treatment with PG-free 5% Mnx lotion is effective, well-tolerated with a good cosmetic acceptability. Some limitations should be taken in account in evaluating the results of our study. The study design was a prospective open not controlled trial. However, the NOMINAL trial should be considered as a "real-life" study evaluating the tolerability and the cosmetic impact of this new MNX formulation in the every-day clinical condition. In addition, the clinical efficacy was also evaluated in a subgroup (n=60) of patients with an assessor-blinded evaluation, increasing the internal validity of the results obtained.

Conclusion

This new PG-free lotion shows, in real-life conditions, a very good cosmetic acceptability and tolerability profile. Clinical efficacy, evaluated both in an open and assessor-blinded fashion, was also documented, and it was in line with the available data of traditional minoxidil formulations with propylene glycol.

Conflicts of interest.

Massimo Milani declares that he is employed by Cantabria Labs Difa Cooper. All the other authors have nothing to disclose.

Funding

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Authors' contributions

All the doctors of The NOMINAL study group contributed to the enrolment and the visits of the participating subjects. All authors had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. MP and KE performed the assessor blinded evaluation of the global pictures of the subgroup of 60 subjects. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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