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ORIGINAL RESEARCH ARTICLE

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

Poonkiat Suchonwanit[1] · **Wimolsiri Iamsumang**[1] · **Salinee Rojhirunsakool**[1]

Abstract

Background The relationship between female pattern hair loss (FPHL) and androgenic hormones is not well established, but some evidence indicates oral finasteride may be efficacious in FPHL. Use of a topical formulation has been proposed to minimize unwanted effects.

Objectives Our objective was to compare the efficacy and safety of topical 0.25% finasteride combined with 3% minoxidil solution and 3% minoxidil solution as monotherapy in the treatment of FPHL.

Methods This was a prospective, randomized, double-blind study in 30 postmenopausal women with FPHL. Each participant was randomized to receive either topical 0.25% finasteride combined with topical 3% minoxidil or topical 3% minoxidil solution as monotherapy for 24 weeks. To determine efficacy, the hair density and diameter was measured and global photographic assessment was conducted at baseline and 8, 16, and 24 weeks. Side effects and serum dihydrotestosterone levels were also evaluated.

Results By 24 weeks, hair density and diameter had increased in both groups, and finasteride/minoxidil was significantly superior to minoxidil solution in terms of hair diameter ($p = 0.039$). No systemic side effects were reported. However, serum dihydrotestosterone levels in the finasteride/minoxidil group significantly decreased from baseline ($p = 0.016$).

Conclusion A topical combination of 0.25% finasteride and 3% minoxidil may be a promising option in the treatment of FPHL with an additional benefit of increasing hair diameter. Nevertheless, as it may be absorbed percutaneously, it should be reserved for postmenopausal women.

Trial Registration clinicaltrials.in.th; identifier TCTR20160912002.

Key Points

The efficacy of oral finasteride in female pattern hair loss (FPHL) has been reported. Topical formulations of finasteride have been developed in an attempt to minimize systemic adverse effects.

Our study revealed the efficacy of topical finasteride/minoxidil in the treatment of FPHL; the combination treatment also increased hair diameter over topical minoxidil alone.

Topical finasteride/minoxidil may be a promising treatment option in FPHL. However, given the possibility of systemic absorption, it should be reserved for postmenopausal women with no personal or family history of breast cancer.

✉ Poonkiat Suchonwanit
poonkiat@hotmail.com

[1] Division of Dermatology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand

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1 Introduction

Female pattern hair loss (FPHL) is a common cause of non-scarring alopecia in women, occurring in 6% of women aged < 50 years and increasing with age to 38% in those aged ≥ 70 years [1, 2]. It is characterized by progressive hair thinning over the crown with preservation of the frontal hairline and is caused by transformation of terminal hair to miniaturized hair and a shortening of the anagen phase in each hair cycle [3]. As the relationship between FPHL and androgens and genetics is unclear, unlike the established link in men, it has been proposed that the term "androgenetic alopecia" (AGA) be replaced with FPHL [1, 4].

The US FDA has approved topical minoxidil 2% solution and 5% foam as treatments, and they are now widely used in women with FPHL [5]. Nonetheless, treatment outcomes remain unsatisfactory in some patients, and the condition may lead to social anxiety and embarrassment. Finasteride, a selective type II 5-α-reductase inhibitor approved by the FDA for the treatment of male AGA, can be considered as a treatment option [6]. The teratogenic effects of finasteride have limited its use in women, but it is now more commonly prescribed as an alternative therapy. Reports of the efficacy of oral finasteride for FPHL are conflicting. Several uncontrolled studies have shown a positive treatment response [7–10], but a multicenter, double-blind, placebo-controlled, randomized study of finasteride 1 mg daily in 137 postmenopausal women with FPHL revealed no significant efficacy [11]. To minimize its potential side effects, a topical formulation has been proposed [12].

Mazzarella et al. [13] conducted a single-blind, placebo-controlled study evaluating the efficacy of topical 0.005% finasteride in 52 balding women and men and reported a significant decrease in hair shedding. Nevertheless, determining the true value of topical finasteride in FPHL was difficult because the study did not include a subgroup analysis of the women [13]. In 2012, another study reported greater efficacy from 0.1% finasteride combined with 3% minoxidil than from 3% minoxidil alone in male AGA [14]. Subsequent studies also confirmed the efficacy of topical finasteride without significant systemic untoward effects, but data were exclusively in men [15, 16]. A 0.25% concentration was proposed in 2014 because of its optimal pharmacokinetic and pharmacodynamic properties [17]. Most recently, a randomized, double-blind, controlled study demonstrated that topical 0.25% finasteride plus 3% minoxidil resulted in significantly increased hair density and diameter over 3% minoxidil alone in male AGA [18].

Although several studies have shown topical finasteride to be an effective option in male AGA, its efficacy in the treatment of FPHL remains inconclusive. However, no study has evaluated the efficacy and safety of topical finasteride combined with topical minoxidil compared with topical minoxidil as monotherapy in FPHL. Therefore, the objective of our study was to evaluate the efficacy and safety of topical 0.25% finasteride plus 3% minoxidil (FMX) compared with topical 3% minoxidil (MX) in the treatment of FPHL.

2 Methods

2.1 Study Design, Participants, and Interventions

This was a pilot, randomized, double-blind, controlled trial to evaluate the efficacy and safety of topical FMX versus topical MX in women with FPHL. The study was approved by the Mahidol University Institutional Review Board for Ethics in Human Research on 16 September 2015 (protocol number 09-58-20, clinicaltrials.in.th identifier: TCTR20160912002), and written informed consent was provided by each patient before enrollment. The date of first enrollment was 22 September 2015.

The sample size was determined based on data from a previous study of FPHL in a Thai population [3]. The mean difference in hair density from baseline to week 24 between the FMX and MX group was assumed to be 28 hairs/cm^2. To achieve a power of 80% with a level of significance of 5% and to account for a withdrawal rate of 20%, the minimum sample size required was 22.

We enrolled 30 postmenopausal women diagnosed with FPHL, Ludwig classification type I, II, or III. Exclusion criteria included use of topical or systemic drugs with hair growth-promoting properties within 12 months, patients with systemic or scalp diseases that may affect hair growth, or a history of allergic reaction to any ingredients in the study solution. The study was conducted over 24 weeks, and follow-up visits were scheduled every 8 weeks.

All subjects were randomized using a random number table to receive either FMX or MX. Investigators and subjects were blinded to treatment until study completion. Subjects were asked to apply 1 ml of the study solution on the balding area twice daily. Topical FMX and MX were supplied in identical bottles labeled with a container number and dosing and storage instructions. Subjects were asked to return their remaining study solution at every follow-up visit, and product accountability was performed throughout the study. All returned study solutions and containers were processed according to medical waste management guidelines. Subjects were also required to maintain the same hair style, color, and length throughout the study.

2.2 Assessments

Efficacy and safety were assessed at each visit. The primary efficacy endpoint was evaluated by measuring changes in hair density and diameter from baseline to week 24. Trichoscopic photography (Folliscope®; LeadM, Seoul, Korea) of the 1 cm^2-sized target section of the balding area was used to determine hair density and diameter. For reproducibility, the target area was determined by a combination of two techniques. First, a flexible clear plastic sheet was applied to the scalp. Then, two or more scalp lesions such as nevi or hemangiomas were permanently marked on the plastic sheet as reference points. Second, the target area was confirmed by the intersection point of three distances from fixed anatomical locations (left tragus, right tragus, and tip of the nose).

The secondary efficacy endpoint was a global photographic assessment by investigators and subjects. Photographs were taken with a Nikon D5100 digital single-lens reflex camera (Nikon Corporation, Tokyo, Japan). Three dermatologists who were blinded to the treatment independently conducted clinical assessments. Photographs at baseline were compared with those from 24 weeks after treatment using a seven-point rating scale: greatly decreased (−3), moderately decreased (−2), slightly decreased (−1), no change (0), slightly increased (+1), moderately increased (+2), and greatly increased (+3).

Adverse events, change in sexual function, and vital signs were monitored and breast examinations conducted to assess safety and tolerability throughout the study. Additional assessments included serum dihydrotestosterone (DHT) levels and basic laboratory panels, including complete blood count, liver function test, blood urea nitrogen, and serum creatinine, taken at baseline and at week 24.

2.3 Statistical Analysis

Statistical analysis was performed using the SPSS statistical package (SPSS® 18.0 for Windows; SPSS Inc., Chicago, IL, USA). Differences in demographic data and seven-point rating scales were measured with Chi-squared and unpaired *t* tests. Fleiss' kappa was used to evaluate agreement among the three independent investigators. The significances of changes in hair density and diameter between the two treatment groups were determined using analysis of variance (ANOVA) and Fisher's protected least significant difference test. Changes in serum DHT levels between the two groups were evaluated with Wilcoxon's rank-sum test. A p value <0.05 was considered statistically significant.

3 Results

Of the 30 enrolled participants, 29 completed the 24-week study protocol, and one withdrew from the MX group because they were unable to attend follow-up. Demographics and efficacy were analyzed using an intention-to-treat analysis, whereas safety data were analyzed with a per-protocol analysis. No statistical differences in demographic data were found between the groups (Table 1).

3.1 Hair Density and Diameter

At baseline, mean ± standard deviation hair counts were 102.5 ± 22.7 hairs/cm^2 in the FMX group and 98.1 ± 19.0 in the MX group. Both groups showed increased hair counts over time, but changes had no statistical difference ($p=0.88$ between the two treatments according to ANOVA; Fig. 1). At the initial visit, the mean hair diameter was 56.3 ± 10.3 and 58.4 ± 13.5 μm in the FMX and MX groups, respectively. Increased hair diameter was observed in both groups but was significantly superior with FMX compared with MX at 24 weeks after treatment. The mean increase at 24 weeks was 11.9 μm for FMX and 7 μm for MX ($p=0.02$, according to ANOVA; Fig. 2).

3.2 Global Photographic Assessment

After 24 weeks of treatment, 14 (93.3%) of 15 FMX-treated participants and 12 (85.7%) of 14 MX-treated participants were rated as improved by three dermatologists using the seven-point rating scale (Fig. 3). Fleiss' kappa showed moderate agreement (0.54) among the three independent

Table 1 Participant demographics and baseline characteristics

Characteristic	FMX group ($N=15$)	MX group ($N=15$)
Age (years)	56.8 ± 6.6	59.8 ± 7.7
Duration of FPHL (years)	8.5 ± 6.8	9 ± 8.6
Family history of AGA		
Yes	13	12
No	2	3
Ludwig type		
I	5	4
II	8	8
III	2	3
Hair density (hair/cm^2)	102.5 ± 22.7	98.1 ± 19
Hair diameter (μm)	56.3 ± 10.3	58.4 ± 13.5

Data are presented as mean ± standard deviation or n unless otherwise indicated

AGA androgenetic alopecia, *FMX* topical 0.25% finasteride and 3% minoxidil, *FPHL* female pattern hair loss, *MX* topical 3% minoxidil

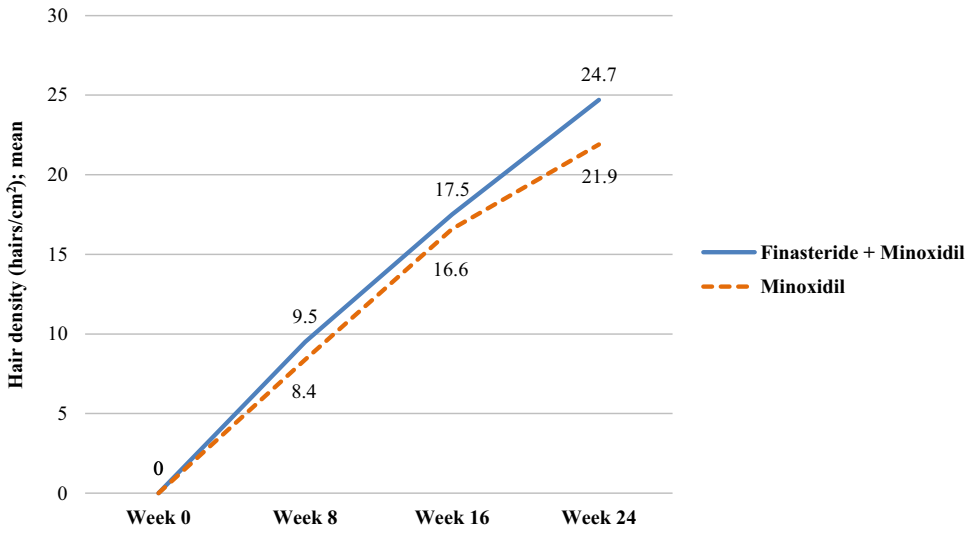

Fig. 1 Differences in hair density in both treatment groups at weeks 8 ($p=0.72$), 16 ($p=0.86$), and 24 ($p=0.66$)

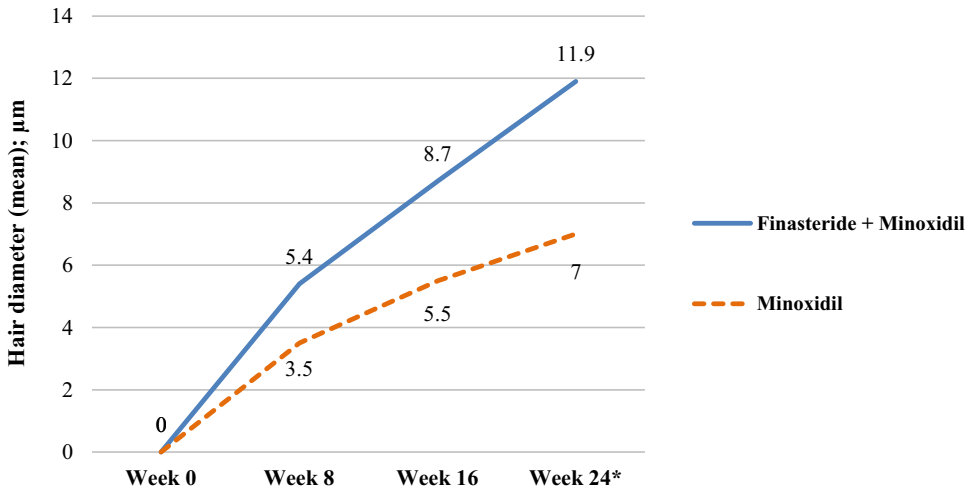

Fig. 2 Differences in hair diameter in both treatment groups at weeks 8 ($p=0.36$), 16 ($p=0.21$), and 24 ($p=0.039$*). *Indicates statistical significance

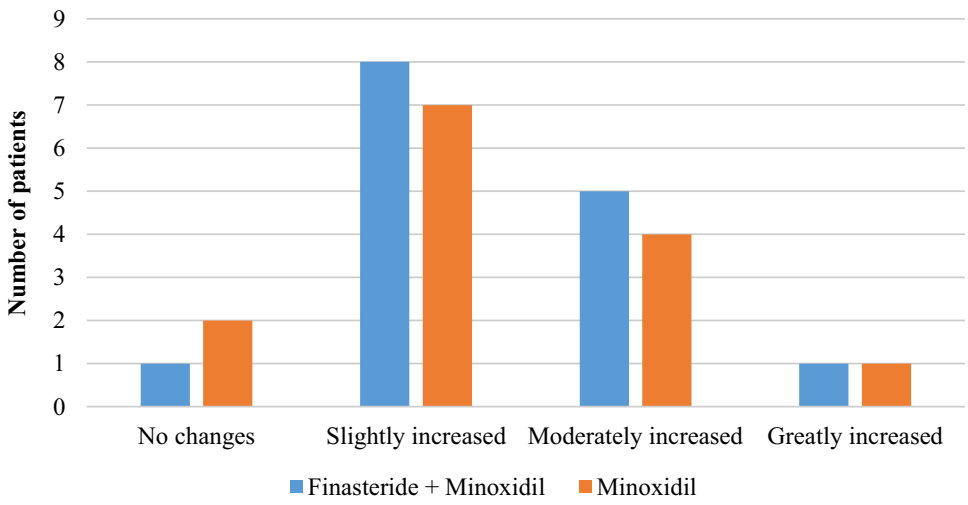

Fig. 3 Seven-point rating scale used by investigators in both groups ($p=0.87$)

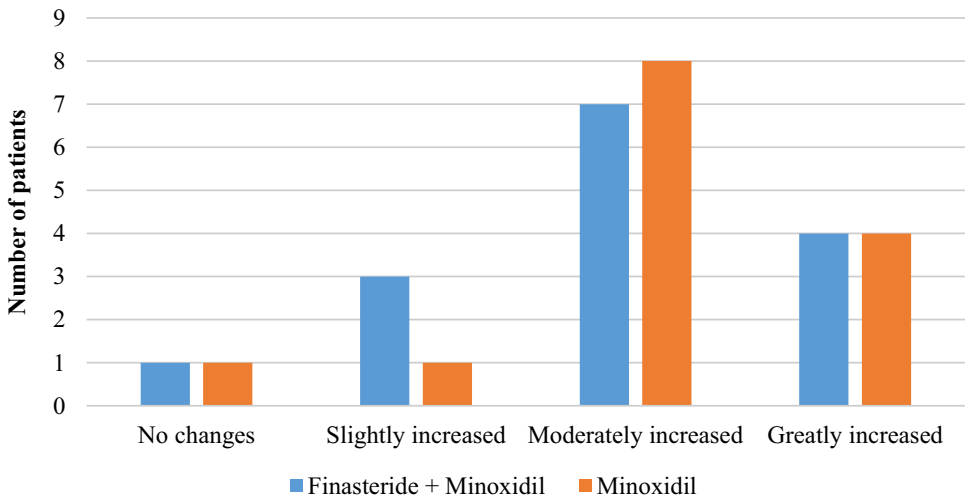

Fig. 4 Seven-point rating scale used by participants in both groups ($p = 0.84$)

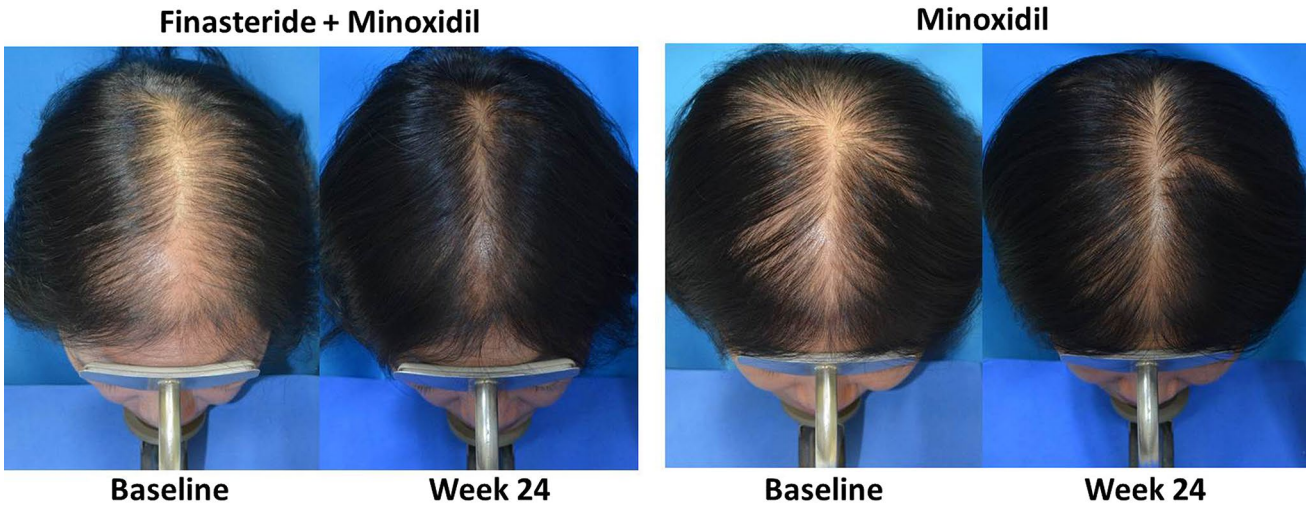

Fig. 5 Baseline and week 24 global photographs of patients treated with topical 0.25% finasteride combined with 3% minoxidil solution versus topical 3% minoxidil solution

investigators. In total, 14 (93.3%) of 15 participants in the FMX group and 13 (92.9%) of 14 in the MX group reported improvement in their condition via self-evaluation on a seven-point rating scale (Fig. 4). Nevertheless, there was no statistical significance between the two treatment groups for any type of evaluation (Fig. 5).

3.3 Safety Assessment

No serious side effects or sexual problems were reported. Minimal local side effects were reported, but this did not differ significantly between the groups. Two patients from each group reported pruritus, and one patient in the MX group reported irritation. All laboratory results in both treatment groups were within normal ranges. Serum DHT levels remained normal in both groups throughout the study, but changes from baseline in serum DHT levels at 24 weeks were statistically significant in the FMX group ($p = 0.016$) (Table 2).

Table 2 Differences in plasma dihydrotestosterone levels in participants

DHT levels	FMX group	MX group	*p* value
Baseline	153 (67 to 1040)	166 (59 to 726)	0.645
Week 24	111 (68 to 743)	189 (30 to 922)	0.23
Differences	−51 (−297 to 25)	−19 (−484 to 694)	0.016*

Data are presented in pg/ml as median (range)

DHT dihydrotestosterone, *FMX* topical 0.25% finasteride and 3% minoxidil, *MX* topical 3% minoxidil

*Statistical significance between two treatments

4 Discussion

Until recently, minoxidil solution has been the only drug approved by the FDA for the treatment of FPHL [5]. Although its mechanism remains unclear, it has been proven to improve hair growth in women with FPHL with or without hyperandrogenism [19]. Unfortunately, a number of patients do not experience a satisfactory outcome. Women receiving oral finasteride have reported side effects including sexual dysfunction, dizziness, allergic reactions, elevated liver enzymes, and depression; the topical formulation was developed in an effort to minimize these [20].

The efficacy of topical finasteride in FPHL was first noted in 1997 by Mazzarella et al. [13] and was also reported in several subsequent studies, but only in male AGA [12]. The overall outcomes with topical finasteride, either as monotherapy or in combination with topical minoxidil, were promising. It was generally well-tolerated, with only mild local adverse events reported. To the best of our knowledge, our study was the first to evaluate the efficacy and safety of finasteride combined with minoxidil solution in FPHL. We discovered that FMX was more efficacious in terms of increasing hair diameter and was significantly superior to MX at 24 weeks after treatment. This is supported by the superiority of FMX over MX in preferential recruitment of non-vellus hair follicles in a latent phase (telogen or kenogen) into an anagen phase rather than vellus to terminal hair transformation [21]. With long-term application, a greater hair diameter potentially results in greater hair volume and better cosmetic outcomes. Increased hair density was greater with FMX than with MX, but no statistical differences were found.

Regarding clinical evaluation, global photographic assessment scores by the three dermatologists and the participants did not differ significantly between the two treatment groups. This lack of clinical significance may be because women with FPHL tend to need treatment for longer than alopecic men: Yeon et al. [7] reported a significant increase in hair density after 12 months of oral finasteride, indicating that FMX may require longer to demonstrate significant clinical improvement. Furthermore, it seems that women with FPHL require a higher dose of oral finasteride, usually 2.5–5 mg daily, to achieve appreciable outcomes [7–9]. Greater concentration is thus expected to yield more clinical improvement.

With respect to safety, FMX-treated patients reported only minimal local reactions, including pruritus and irritation, similar to those receiving MX. Nevertheless, a significant decrease in serum DHT levels suggested percutaneous drug absorption. Furthermore, as a previous pharmacokinetic study of 0.25% finasteride solution demonstrated systemic absorption of the topical formulation [17], it should only be used in postmenopausal women to avoid possible teratogenic effects. Another concern regarding finasteride use in women is that conditions resulting in relative estrogen excess or lack of androgen are associated with an increased risk of breast cancer. Women with a personal or family history of breast cancer should avoid finasteride [22]. These results extend our knowledge of FMX in the treatment of FPHL and highlight its efficacy and safety in enhancing hair growth, particularly hair diameter.

The small sample size and relatively short follow-up period in this study were limitations. Study duration should be adequate to appropriately determine efficacy and safety. We recommend further investigations with more participants, a longer duration, and different finasteride concentrations to evaluate clinical outcomes. Since most women tend to experience negative psychological consequences from FPHL, future studies should also assess psychological status and quality of life. Moreover, the ecotoxicological effects on the environment of finasteride should be further investigated given the possibility of endocrine disruption in non-human animals [18].

5 Conclusion

FMX may be considered a promising option for the treatment of FPHL as it had an additional benefit over MX as monotherapy in terms of increasing hair diameter. However, the possibility of systemic absorption means it should be reserved for postmenopausal women with no personal or family history of breast cancer.

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Compliance with Ethical Standards

Trial registration clinicaltrials.in.th; identifier TCTR20160912002.

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Conflict of interest PS, WI, and SR have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval This study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonization—Good Clinical Practice and local regulatory requirements. The study was reviewed and approved by the appropriate independent ethics committees, and written informed consent was obtained from all subjects prior to study initiation. This study was approved by the MU-IRB (Mahidol University Institutional Review Board) on 16 September 2015 (Protocol number 09-58-20).

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