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A 4-month, open-label study evaluating the efficacy of eflornithine 11.5% cream in the treatment of unwanted facial hair in women using TrichoScan

Eflornithine 11.5% cream is an effective treatment for unwanted facial hair (UFH) in women with the effect on facial hair growth starting to be seen from 1 month after treatment initiation. TrichoScan is a validated method of assessing hair length, thickness, density, and growth rate using contact skin microscopy. The study aimed to evaluate the efficacy of eflornithine cream in women with UFH, as assessed by TrichoScan. In this open-label, single-centre study, 25 women (aged 25-63 years) applied eflornithine 11.5% cream to the upper lip twice daily for 4 months. Hair density, mean and cumulative hair length, mean hair thickness and hair growth rate were assessed at baseline and Month 1, 2 and 4 using TrichoScan. Eflornithine cream significantly decreased hair density from baseline to Month 1 (– 11.4 hairs/cm^2, p = 0.014), Month 2 (– 16.5 hairs/cm^2, p = 0.013) and Month 4 (– 12.05 hairs/cm^2, p = 0.05). In addition, cumulative hair length decreased from baseline to Month 1 (– 7.104 mm, p = 0.001), Month 2 (– 10.054 mm, p < 0.001) and Month 4 (– 8.061 mm, p = 0.001). There was also a significant decrease in hair growth rate. Mean hair thickness did not change significantly. Eflornithine 11.5% cream is an effective treatment for UFH in women with the effect on facial hair growth starting to be seen from 1 month after treatment initiation.

Key words: Eflornithine, hair, hirsutism, TrichoScan, unwanted facial hair

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Unwanted facial hair (UFH) is relatively common and is characterised by facial hair growth that is coarser, longer, or more profuse than the woman considers normal for her age. It is often a symptom of an underlying medical disorder. It has been shown that the amount of UFH considered unacceptable and distressing to the sufferer is much less than the criteria typically used by physicians to make a clinical diagnosis of facial hirsutism [1]. This is important as studies have shown that the presence of UFH has a tremendous negative impact on quality of life leading to low self-esteem and low self-confidence [2, 3].

There are several methods available to address unwanted hair growth. Commonly these include tweezing, shaving, waxing, and bleaching, with around 20% of women using one of these temporary methods at least once a week [4, 5]. More permanent approaches including electrolysis and laser hair removal are also available. Laser photo-epilation has become a popular choice for removing UFH, although its effectiveness can be variable [6], with only 50-90% of hairs being permanently removed [7-9]. Furthermore, laser hair removal is less efficacious against hair with thinner shaft diameters and ineffective on blond, grey and white hair [10]. In addition, it is a costly procedure and requires multiple treatments. Consequently, there remains a need for additional effective methods for managing UFH.

Eflornithine is an irreversible inhibitor of ornithine decarboxylase [11], a rate-limiting enzyme in the conversion of ornithine to the polyamine, putrescine [12]. Polyamines, such as putrescine, play a critical role in cell proliferation and the differentiation of many cells [13]. Inhibition of ornithine decarboxylase in the hair follicle slows hair growth [11]. Eflornithine 11.5% cream is indicated in the treatment of facial hirsutism in women. In randomised, double-blind, placebo-controlled studies, eflornithine cream has been shown to significantly reduce the growth of UFH in women, and to be well tolerated, both when used alone and when combined with laser treatment [14-16]. Eflornithine is thought to be suitable for all skin and hair types and is not anticipated to favour one particular hair shaft size over another [16].

Methods historically used to assess hair growth have tended to be time-consuming, costly and difficult to perform [17]. There was a need for an operator- and patient-friendly, reliable and sensitive method of monitoring hair growth and treatment response in the management of UFH. Such a tool must be able to assess hair growth rate, density and thickness. TrichoScan is a novel, reliable, well-validated

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method of quantitatively assessing these biological parameters of hair growth [17]. This technique combines epiluminescence microscopy (ELM) with automatic digital image analysis [17]. A good correlation between TrichoScan and manual evaluation of hair counts has been demonstrated. TrichoScan is more reproducible than manual evaluation, the margin of operator error is small and there is greater consistency in data collection compared with manual evaluation. TrichoScan has been shown to be a valuable tool in clinical trials assessing the efficacy of treatments for a number of conditions, including androgenetic alopecia, and facial hirsutism [18]. This open-label study was conducted to evaluate the efficacy of eflornithine 11.5% cream in the management of UFH in women, using TrichoScan to quantify the results.

Materials and methods

Subjects

Women aged ≥ 18 years with unwanted hair on the upper lip who attended the clinic were consecutively included in the study. Exclusion criteria were as follows: history of skin malignancy; pregnancy or lactation; known or suspected intolerance or hypersensitivity to the investigational products or any of its ingredients. The study was conducted in accordance with the Declaration of Helsinki, and reviewed and approved by an Independent Ethics Committee (Landesärztekammer Südbaden, Germany). Written informed consent was obtained from all patients. The study was listed under EudraCt Number: 2005-003537-41.

Study design

This was an open-label, single-centre, non-randomised study. The first subject was enrolled on 25 October 2005 and the last completed the study on 11 April 2006. The primary objective of the study was to evaluate the efficacy of twice-daily eflornithine 11.5% cream in women with UFH, using TrichoScan. The primary efficacy endpoint was mean hair density (hairs/cm^2). The secondary efficacy endpoints were mean and cumulative hair length (mm), mean hair thickness (μm), and hair growth rate (mm/day). Tolerability was assessed at the end of the study using a patient questionnaire. Patients were asked to judge tolerability according to a five-point scale, with 'excellent tolerability' being rated as a 1, 'very good' a 2, 'good' a 3, 'satisfactory' a 4, and 'not satisfactory' a 5.
All subjects were instructed to apply eflornithine 11.5% cream twice daily, according to the manufacturer's recommendation, to the upper lip area for a period of 4 months. During this time no other potentially permanent epilation was allowed including plucking (tweezing), electrolysis or laser epilation. Patients were, however, allowed to bleach or shave the hairs, and to continue to apply make-up and wash as normal. As this was an open-label study there was no protocol for randomisation or blinding. Subjects were instructed to bring their unused investigational product and empty used tubes to every visit.

Study equipment

For macroscopic imaging of the upper lip a stereotactic device *(figure 1)* was used to ensure that all patients were photographed consistently. This was accomplished with a chin and forehead holder. All images were taken with a Canon Powershot A95. This camera was controlled via a computer and the camera settings (use of flash, pixel number, compression etc) were predefined for both macroscopic images and TrichoScan images. After the macro-

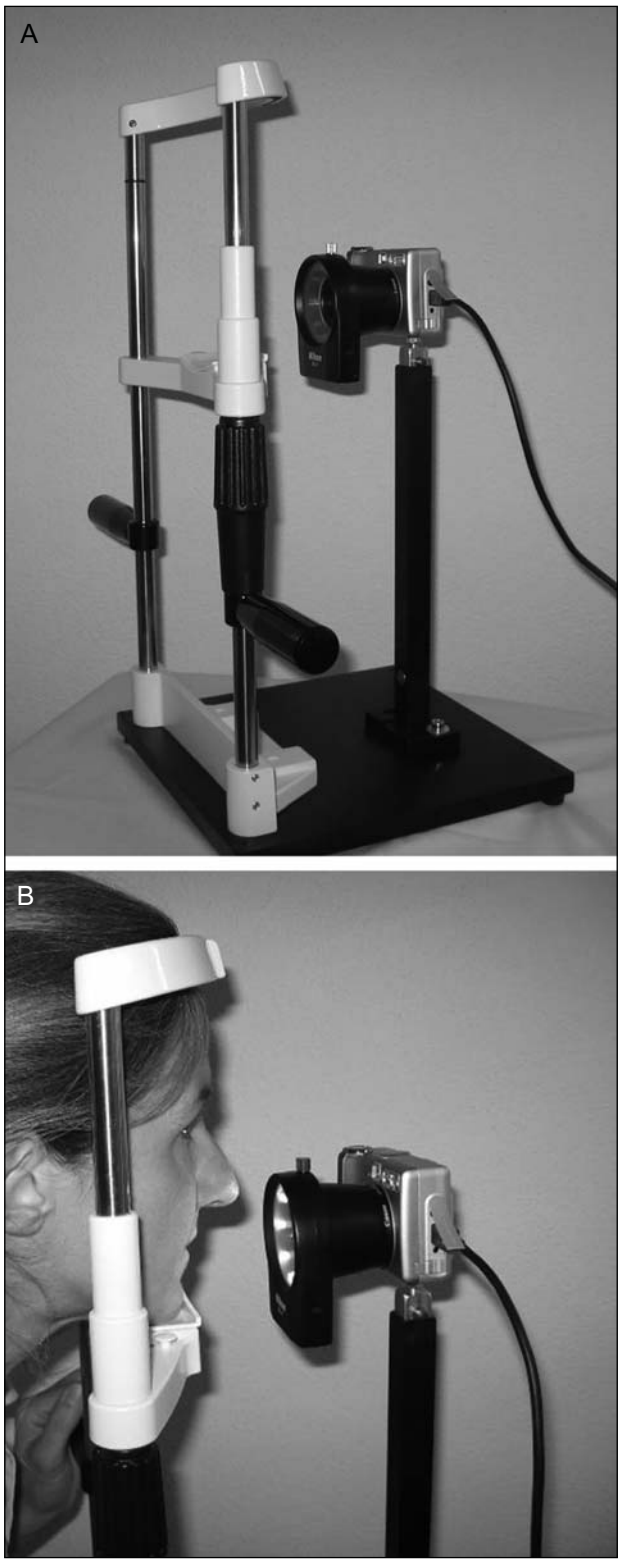

Figure 1. Stereotactic device used to produce reproducible macroscopic images of the upper lip.

Figure 2. Canon Powershot A95 equipped with optics for skin contact microscopy.

scopic image was taken the camera was detached from the device and an optic for skin-contact microscopy was attached *(figure 2)*.

TrichoScan assessments

Individuals were assessed at baseline, 1 month, 2 months and 4 months. Each assessment consisted of two visits. At the first visit the upper lip was shaved completely and TrichoScan images were taken for time recording. Subjects were instructed not to undergo laser epilation or electrolysis, or to shave or pluck their upper lip and to return to the investigation centre after 7 days for the second visit. At the second visit of each monthly assessment a macroscopic image was taken first and then a second TrichoScan image was taken. As grey or fair hairs have only limited contrast compared with skin, the area of the lip was dyed using hair dye (Just for Men, Brush in Colour Gel), which was mixed according to the manufacturer's instructions and applied for 5 minutes. It has been shown that dyed hairs produce the same imaging results as non-dyed hair [19]. The dye was then removed with an alcoholic tincture (Kodan Spray), and the area under investigation covered with one drop of corn oil to avoid air bubbles. TrichoScan images were then taken of the area between the lateral angle of the mouth and the tip of the nose ($2cm^2$ area) to obtain images of the upper lip and for microscopic assessment of the efficacy parameters. The images were then loaded onto the TrichoScan software for analysis.

Statistical analysis

The primary and secondary endpoints were assessed using the Wilcoxon test.

Results

In total, 25 women (aged 25-63 years old, mean 45.3 years) were enrolled in the study. Due to personal reasons unrelated to study medication, two patients dropped out of the study after 1 month of treatment and one after 2 months. TrichoScan images of the upper lip from one typical patient taken at baseline, Month 1 and Month 2 are shown in *figure 3*. Changes from baseline in hair density, mean hair length, cumulative hair length, mean hair thickness and hair growth rate over the 4-month treatment period are shown in *table 1*. Treatment with eflornithine 11.5% cream resulted in a statistically significant decrease in hair density as measured by TrichoScan from baseline to Month 1 (– 11.4 hairs/cm^2; p = 0.014), Month 2 (–16.5 hairs/cm^2; p = 0.013) and Month 4 (– 12.05 hairs/cm^2; p = 0.05, *figure 4*). In addition, mean hair length *(figure 5)* and cumulative hair length *(figure 6)* decreased significantly from baseline to Month 1 (– 0.084 mm; p = 0.005 and – 7.104 mm, respectively; p = 0.001) Month 2 (– 0.132 mm and – 10.054 mm, respectively p < 0.001); and Month 4 (– 0.122 mm and – 8.061 mm, respectively; p = 0.001). Eflornithine 11.5% cream also resulted in a significant decrease in hair growth rate from baseline to Month 1 (– 0.015 mm/day, p = 0.004), Month 2 (– 0.021 mm/day, p < 0.001) and Month 4 (– 0.017 mm/day, p < 0.001, *figure 7*). Mean hair thickness did not change significantly throughout the study period (*table 1*).

No patient withdrew from the study due to side-effects. The mean score from the tolerability questionnaire was 1.7, between excellent (1) and very good (2).

Discussion

In this study, eflornithine 11.5% cream applied twice daily for 4 months significantly reduced the growth of UFH, as measured by TrichoScan. The application of eflornithine 11.5% cream resulted in significant reductions in hair density, hair length and hair growth rate, with improvements starting to be seen with TrichoScan as early as 1 month after the start of treatment. It is important to note that the reductions in hair density as measured in this study are due to the slowing of hair growth by eflornithine, so that less hair is detectable at the time of the second TrichoScan visit at 7

Table 1. Mean difference in primary and secondary outcome measures during the 4-month treatment period

Variable	Month	Difference from baseline	p value
Density (hairs/cm^2)	1	– 11.419	0.014
	2	– 16.540	0.013
	4	– 12.045	0.058
Length mean (mm)	1	– 0.084	0.005
	2	– 0.132	< 0.001
	4	– 0.122	< 0.001
Cumulative length (mm)	1	– 7.104	0.001
	2	– 10.054	< 0.001
	4	– 8.061	0.001
Mean thickness (μm)	1	3.295	0.075
	2	1.177	0.540
	4	2.065	0.799
Growth rate (mm/day)	1	– 0.015	0.004
	2	– 0.021	< 0.001
	4	– 0.017	< 0.001

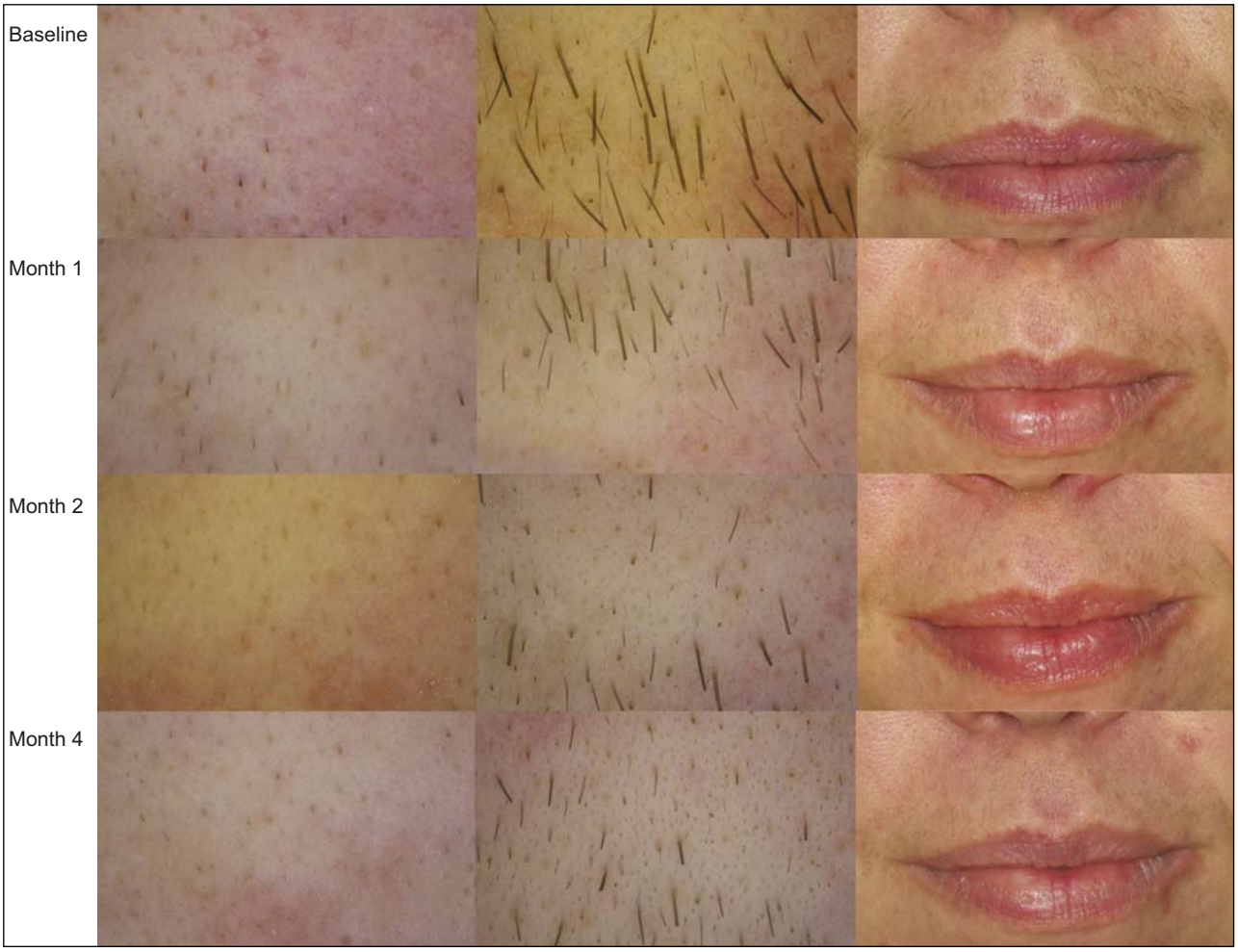

Figure 3. TrichoScan images at baseline, Month 1, Month 2 and Month 4 immediately after shaving for time recording and 7 days later. Note the reduction in overall hair length and hair density. This is reflected in hair density as seen in macroscopic images made 7 days after hair shaving.

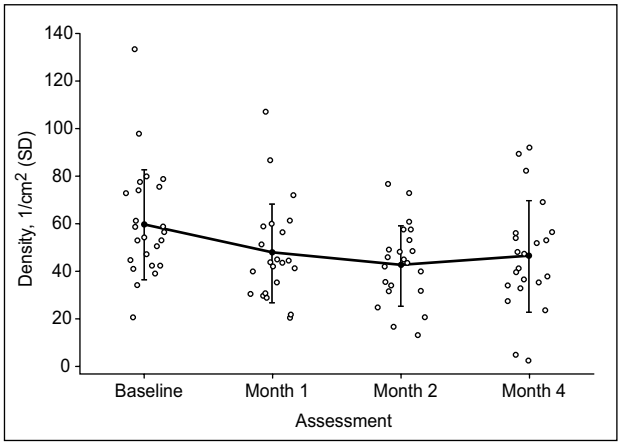

Figure 4. Change in hair density following treatment with eflornithine 11.5% cream, as assessed by TrichoScan.

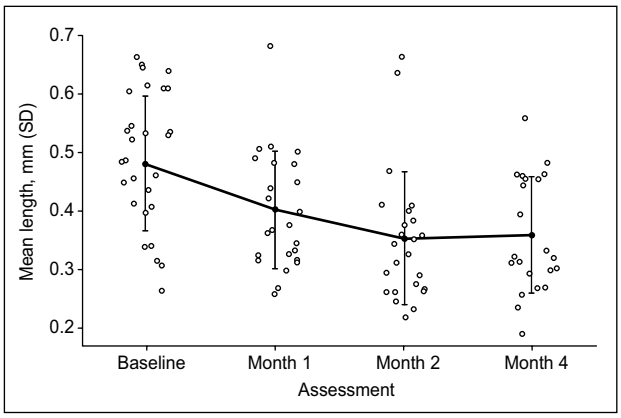

Figure 5. Mean hair length following treatment with eflornithine 11.5% cream, as assessed by TrichoScan.

days, rather than due to removal of hair. It should also be noted that, although the reductions in hair density, hair length and hair growth rate are seen as early as 1 month using TrichoScan imaging, physicians and patients may not notice visible improvements in UFH until 8 weeks of treatment. Eflornithine 11.5% cream was generally well tolerated. No patient withdrew because of lack of tolerability. These results support the findings of previous randomised, double-blind, controlled studies that have demonstrated the

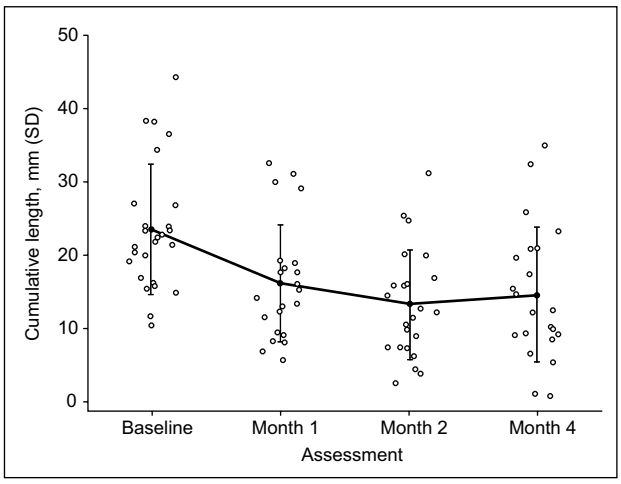

Figure 6. Cumulative hair length following treatment with eflornithine 11.5% cream, as assessed by TrichoScan.
SD: standard deviation.

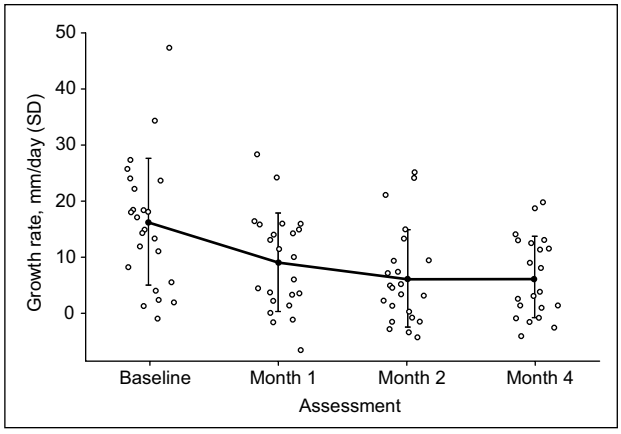

Figure 7. Change in hair growth rate following treatment with eflornithine 11.5% cream, as assessed by TrichoScan.

efficacy and safety of eflornithine 11.5% cream as monotherapy [14] and in combination with laser therapy [15, 16]. In two randomised, vehicle-controlled trials involving 596 women, 70% of eflornithine 11.5% cream-treated patients, compared with 41% of placebo-treated patients experienced some improvement in their condition, as assessed by the Physician's Global Assessment (PGA). Improvement was seen from 8 weeks after initiating treatment [14]. The present study demonstrates that eflornithine immediately starts working on the hair follicle to slow facial hair growth, providing encouragement to physicians and patients during the initial 8 weeks until the benefits of treatment are visibly seen.

Two small, randomised, double-blind, placebo-controlled studies have investigated the efficacy and safety of eflornithine cream combined with laser treatment versus laser treatment alone. In both studies, the addition of eflornithine cream to laser hair treatment resulted in a more rapid reduction of UFH, compared with laser treatment alone. Eflornithine was also well tolerated in both studies [15, 16]. Of note, in the current study, mean hair thickness was not affected by eflornithine cream, providing further reassurance that its use does not decrease the efficacy of simultaneous or subsequent laser therapy, which works best on coarse hair [10].

The effects of treatment in facial hirsutism can be difficult to measure. In this study, TrichoScan was shown to be a highly useful tool for evaluating the effectiveness of eflornithine 11.5% cream in the treatment of women with UFH. This method of evaluating hair growth has several advantages over standard techniques. Unlike other methods, TrichoScan has been well-validated and its reliability is investigator-independent, suggesting that it may be a more quantifiable method of evaluating hair growth than PGA [17]. Furthermore, TrichoScan is relatively simple and quick to perform, unlike other techniques that can be tedious and time-consuming [17]. In addition, the amount of equipment needed is small. Many dermatologists already have ELM-systems and would only need the TrichoScan software in order to use this method of evaluating hair growth in their practice. Of particular interest to the busy physician, TrichoScan can be performed following only 8-12 minutes of 'hands-on' experience [17].

In conclusion, eflornithine 11.5% cream was shown to be an effective treatment for the management of UFH in women. Using TrichoScan, the effect of eflornithine 11.5% cream on facial hair growth was starting to be seen from 1 month after initiation of treatment. Eflornithine 11.5% cream provides women with an effective treatment option for this distressing condition. Further studies should be initiated with greater numbers of patients to investigate further the effectiveness of TrichoScan in evaluating treatment responses in facial hirsutism. ■

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