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Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

SYNOPSIS

Study number: SPD488-401	**Study drug:** Eflornithine hydrochloride

Title of the study: A 24-week randomised, double-blind, placebo-controlled study to evaluate the atrophogenic potential of eflornithine in the treatment of women with excessive facial hair

Investigators:
Multicentre study

Countries involved: France, Germany and Spain

Study centres:

Five centres participated in the study.

Coordinating Principal Investigator: Professeur [redacted] France.

Publications (reference):

None

Study period:	**Clinical phase:** IV
29 October 2004 (first patient enrolled) 04 July 2005 (last patient completed)	

Objectives:

Primary

The primary objective of this study was to evaluate the atrophogenic potential of twice-daily application of eflornithine 11.5% cream in the treatment of women with excessive facial hair growth, by measuring change in total skin thickness of treated areas on the face from baseline, as measured by ultrasound at Week 24, compared to placebo cream.

Secondary

- To globally assess pre- and post-treatment skin biopsies for qualitative histological changes pertaining to photodamage and skin atrophy
- To assess histological changes in the epidermis (thickness, architecture and cellular morphology)
- To assess histological and histochemical changes in the dermis (procollagen I formation and elastic tissue damage)
- To assess skin thickness measured by ultrasound after 12 weeks' treatment
- To assess efficacy using the Physician Global Assessment (PGA) and Subject Self-Assessment Questionnaire (SSAQ)
- To assess the safety profile in terms of adverse events (AEs).

Methodology:

This was a multicentre, randomised, double-blind, placebo-controlled study. The study consisted of a screening visit (Visit 1) and a treatment period lasting 24 weeks. An individual's study participation could last up to 25 weeks.

Number of patients (total and for each treatment arm):

Treatment was allocated using a 1:1 ratio for eflornithine:placebo

	Placebo	Eflornithine	Total
Planned	39	39	78
Randomised	40	40	80
Withdrawn	0	1	1
Completed	40	39	79
Safety population	40	40	80
ITT	40	39	79
PP	30	30	60

ITT = Intent-to-treat, PP = Per Protocol

Diagnosis and main criteria for admission:

The main inclusion criteria stated that patients should be females aged 18-85 years, of skin phototype I-IV, with a clinical diagnosis of facial hirsutism/excessive facial hair. Patients should customarily remove facial hair two or more times per week and have a total of at least 20 terminal hairs on the upper lip and chin.

Eligibility criteria excluded conditions such as severe inflammatory acne, significant facial scarring, connective tissue disorders, a history of skin malignancy, and excluded the use of topical medications on the face, systemic and topical treatment with phenytoin, retinoids or corticosteroids, and the use of electrolysis, laser or epilation to remove hair within 6 weeks before start of study.

Test product, dose and mode of administration, batch no.:

Eflornithine hydrochloride 11.5% cream was applied twice daily to all affected areas on the face and under the chin. The treatment area on the face was extended to include an adjacent flat area on the lateral aspect of the face. In addition, patients also applied study medication to a 6cm x 4cm area on the dorsal aspect of the forearm. One batch of eflornithine 11.5% cream was used during the study (batch number [redacted]

Duration of treatment:

- Duration of screening period: up to 1 week
- Duration of enrolment period: 67 days
- Duration of treatment period: 24 weeks.

Reference therapy, dose and mode of administration, batch no.:

Placebo cream was applied twice daily to all affected areas on the face and under the chin. The treatment area on the face was extended to include an adjacent flat area on the lateral aspect of the face. In addition, patients also applied study medication to a 6cm x 4cm area on the dorsal aspect of the forearm. One batch of placebo cream was used during the study (batch number [redacted]

Criteria for evaluation:

Safety

- Primary safety variable

  Percentage change from baseline in skin thickness of treated areas of the face at Week 24, as measured by ultrasonography.

- Secondary safety variables
  - Change from baseline in skin thickness of treated areas of the face at 12 weeks, as measured by ultrasonography
  - Changes from baseline in dermal and epidermal histology (from the forearm biopsies at Week 24)
  - AEs
  - Vital signs
  - Physical examination.

  Epidermal histology evaluated: keratinocytic atypia (present or absent), melanocytic atypia (present or absent), stratum corneum (normal, thin, thick orthokeratosis or thick parakeratosis), stratum granulosum

(normal, absent or thick) and stratum spinulosum (normal, acanthosis or papillomatosis), pre- and post-treatment measurements (direct measurement and ratio area/length), epidermal inflammatory changes (none, spongiosis, exocytosis, apoptotic bodies or spongiosis/exocytosis). Dermal histology evaluated: elastosis (grade 0-3), elastin (normal, abnormal, increased or decreased), pro-collagen I positive fibroblast count and intensity of pro-collagen I expression in fibroblasts (scale 0-3), papillary dermal thickness (normal, reduced or increased), pre- and post-treatment measurements: direct measurement and ratio area/length, dermal inflammatory changes (grade 0-4).

Efficacy

- PGA

  The Investigator assessed length of hair (a function of hair growth rate), density (the number of visible terminal hairs per unit area) and darkening of skin (the apparent increase in pigmentation which is commonly referred to as a "5 o'clock shadow") as clear/almost clear (no, or nearly no, visible terminal hair on the treated areas of the face. No, or nearly no, darkening in the appearance of the facial skin due to terminal hair), marked improvement (a considerable decrease in the visibility of terminal hair on the treated areas of the face. Only minimal darkening in the appearance of the facial skin due to terminal hair), improved (a clinically apparent decrease in visibility of terminal hair on the treated areas of the face. Noticeable lightening in the appearance of the facial skin due to terminal hair) or no improvement/worse (no decrease, or worsening, in visibility of terminal hair on the treated areas of the face. No improvement, or worsening, in darkening of the facial skin due to terminal hair).

- SSAQ

  The patient answered six questions by making a single vertical mark on a 100mm Visual Analogue Scale (VAS) that best represented how she felt at that time. The left extreme of the line (0) represented the best possible response to the question; the right extreme of the line (100mm) represented the worst possible response. The six questions were: How much are you bothered by your facial hair? How uncomfortable does your facial hair make you feel when you meet new people? How uncomfortable does your facial hair make you feel when you go to work or class? How uncomfortable does your facial hair make you feel when you go to social gatherings, dine out in a public restaurant, go to the supermarket or other public place? How uncomfortable does your facial hair make you feel in exchanges of affection (such as in an intimate situation with your partner)? How much are you bothered by the time you spend removing, treating or concealing your facial hair?

Statistical methods:

Safety

Summary statistics (ie, n, mean, median, SD, minimum and maximum) of percentage change from baseline in mean total skin thickness at 12 and 24 weeks, were calculated by treatment group for the PP population. The mean percentage change of the thickness of the skin from baseline to Week 24 was assessed by analysis of variance (ANOVA), with treatment as a factor in the model. A two-sided 95% confidence interval (CI) for the treatment difference (eflornithine 11.5% cream minus placebo) was constructed from the estimates for the mean and the standard error from the ANOVA model. Eflornithine 11.5% cream was said to be non-inferior to placebo if the lower limit of the confidence interval was smaller than δ% as depending on the estimated standard deviation. Furthermore, the difference in treatment effect at each centre was explored by examining the treatment x centre interaction term in an ANOVA with centre and treatment arm as the main effects.

Summary statistics of the changes from baseline in dermal and epidermal histology from the forearm biopsies at Week 24 were calculated for the ITT population, for each treatment group.

The frequency of treatment-emergent AEs was calculated for each body system, by preferred term and by treatment group. The severity of AEs and the relationship to the investigational product were summarised for each System Organ Class (SOC) and preferred term by treatment group.

Withdrawals from the study were summarised by treatment group.

Baseline demography data were summarised for the safety, ITT and PP populations.

Efficacy

The PGA parameters were dichotomised into 'success' (marked improvement or clear/almost clear) and 'failure' (improved or no improvement/worse). The proportion of patients achieving success was tabulated over time by treatment arm for the ITT population.

Summary statistics of the six SSAQ scores over time, by treatment arm are presented for the ITT population.

Summary – Results:

Patient demographics

The mean/median age in the safety population were 46.4/45.0 and 43.9/43.5 years for placebo and eflornithine, respectively. In the PP population, the mean/median ages were 44.8/42.0 and 44.6/45.0 years for placebo and eflornithine, respectively. Age ranged from 21-76 years in the placebo group and 20-74 years in the eflornithine group. The two treatment groups were also comparable with regard to weight and height.

Patients in the placebo group had skin phototypes I-IV and patients in the eflornithine group had skin phototypes II-IV. The most common individual skin phototype in both treatment groups was phototype II, which was recorded in 40% and 50% of the placebo and eflornithine groups, respectively (safety population).

Concurrent conditions were reported at baseline for 26 (65.0%) and 32 (80.0%) of the placebo- and eflornithine-treated patients, respectively. The most common conditions were in the Social circumstances SOC (menopause) seen in five (12.5%) patients in the placebo group and eight (20.0%) patients in the eflornithine group. Other common individual conditions included hypertension and hypothyroidism (10% to 17.5% of each group). There were no marked differences between the two treatment groups with regard to baseline concurrent conditions.

Safety results

Exposure to study medication was not appreciably different between the two treatment groups. The mean/median duration of treatment was 168.0/169.0 and 166.5/169.0 days in the placebo and eflornithine groups, respectively (safety population). The total number of patient days of treatment was 6718 for placebo and 6659 for eflornithine.

Primary Safety Variable: Change in skin thickness

The percentage change in total skin thickness at Week 24 (primary safety variable) and at Week 12 (a secondary safety variable) is shown for the PP population in the following table.

Total skin thickness at Week 12 and Week 24 (PP population)

	Week 12				Week 24			
	Placebo N=30		Eflornithine N=30		Placebo N=30		Eflornithine N=30	
	Actual (mm)	Change from baseline (%)	Actual (mm)	Change from baseline (%)	Actual (mm)	Change from baseline (%)	Actual (mm)	Change from baseline (%)
Mean	1.52	0.97	1.64	-0.57	1.51	0.45	1.60	-2.93
SD	0.27	6.53	0.25	8.27	0.26	10.25	0.25	6.28
Median	1.47	0.67	1.59	0.25	1.40	0.39	1.53	-1.82
Min	1.1	-15.6	1.2	-15.3	1.1	-22.9	1.2	-20.2
Max	2.0	15.4	2.3	32.0	2.1	21.9	2.2	5.5
95% CI for diff				-5.40, 2.30				-7.77, 1.02
Point estimate				-1.55				-3.37
P value				0.4241				0.1293

When analysed by ANOVA, there was no significant difference in percentage change in skin thickness between the eflornithine and placebo groups at Week 24 in the PP population (p=0.1293). The lower limit of the 95% CI for the difference was within the -8% cut-off that defined non-inferiority. There was also no significant difference in percentage change in skin thickness between the groups at Week 12 in the PP population (p=0.4241) or at Weeks 12 and 24 for the safety population (p=0.5126 and p=0.5627, respectively). In all cases, the lower limit of the 95% CI for the difference was within the -8% cut-off.

The ANOVA model including centre and treatment revealed a significant treatment by centre interaction; in one of the centres, there was a much greater reduction in skin thickness from baseline to Week 24 with placebo than eflornithine treatment. However, the assumptions of this model were examined and the inclusion of centre found to be inappropriate. In the PP population, five sites recruited 60 patients. The median number of patients per site

was 10 (range 6 – 20). Based on the low, and unequal, numbers of patients at most centres and the large variability observed in the data, it was determined that the main effect of centre should not be included in the model as treatment group means adjusted for differences within a centre would not be robust.

Biopsy

In the epidermal layers at baseline and Week 24, all patients, had normal stratum granulosum and stratum spinulosum and the vast majority of patients in both treatment groups had a normal stratum corneum. No abnormalities were seen in keratin or melanin-producing cells in either of the two treatment groups at baseline or Week 24. No epidermal inflammation was seen at baseline. At Week 24 in the eflornithine group, two patients had spongiosis and one patient had spongiosis/exocytosis.

In the dermis at baseline, three patients in the placebo group and two in the eflornithine group had Grade 1 inflammatory changes and one patient in the eflornithine group had Grade 2 inflammatory changes. At Week 24, this had increased to five patients in the placebo group and eight in the eflornithine group with Grade 1 dermal inflammatory changes, and two eflornithine patients with Grade 2 or Grade 3 inflammatory changes.

There were no marked differences between epidermal and dermal thickness between the two treatment groups. The mean epidermal thicknesses at baseline/Week 24 were 53/54 and 54/55µm in the placebo and eflornithine groups, respectively. The mean dermal thickness at baseline/Week 24 was 2410/2306 and 2498/2342µm in the placebo and eflornithine groups, respectively. There were no marked differences between epidermal and dermal area/length ratio between the two treatment groups. The mean epidermis area/length ratio at baseline/Week 24 was 52.7/59.0 and 53.3/60.7 in the placebo and eflornithine groups, respectively. The mean dermis area/length ratio at baseline/Week 24 was 1467.7/1435.2 and 1598.7/1376.9 in the placebo and eflornithine groups, respectively.

The majority of patients (73-74%) had normal elastosis at baseline. At Week 24, the percentage of patients with normal elastosis had fallen to 47.5% and 53.8% with placebo and eflornithine, respectively. All patients had normal elastin at baseline and at Week 24. The mean pro-collagen I positive fibroblast count at baseline/Week 24 was 2.183/3.393 and 2.062/2.422 for the placebo and eflornithine groups, respectively. At baseline, the intensity of pro-collagen I expression in fibroblasts was graded ‘2’ or '3' in 62.5% of placebo and 61.6% of eflornithine patients. At Week 24, the majority of patients had a grade of ‘1’ (55.0% and 59.0% of the placebo and eflornithine groups, respectively).

Adverse events

In total, 56 patients (70.0%) experienced one or more AEs: 29 patients (72.5%) in the eflornithine group and 27 (67.5%) in the placebo group. The most common AEs (MedDRA classification) were those classed as Infections and infestations. Within this SOC, the most common individual events were nasopharyngitis (10.0% of placebo group and 20.0% of eflornithine group) and Herpes simplex (12.5% and 5.0%, respectively). The most common individual events within the Skin and subcutaneous tissue disorders SOC were acne and pruritus, each of which was reported for placebo-treated patients only (5.0% and 10.0%, respectively). The majority of AEs were mild or moderate in severity. [redacted]
All severe AEs were considered unrelated to study treatment.

A minority of patients experienced treatment-related AEs. In total, 10 (12.5%) patients experienced at least one treatment-related AE: four (10.0%) patients in the eflornithine group and six (15.0%) in the placebo group. The most common treatment-related AEs (MedDRA classification) were those classed as Infections and infestations. Within this SOC, the most common individual event was folliculitis, which was reported for 2.5% of the placebo group and 5.0% of the eflornithine group.

There were no deaths and no patients were withdrawn due to AEs. Three SAEs were reported in two patients and were considered unrelated to treatment. [redacted] There were no significant abnormalities noted in the physical examination or vital signs at Week 24.

Adverse events (irrespective of relationship to treatment) reported for ≥ 5% of one or both groups are shown in the following table.

AEs reported for at least 5% of one or both groups

SOC/Preferred Term	Placebo N=40		Eflornithine N=40	
	n	%	n	%
Number of patients with any adverse event	27	67.5	29	72.5
Gastrointestinal disorders				
Gastrointestinal disorder	0	0.0	2	5.0
Infections and infestations				
Bronchitis	2	5.0	3	7.5
Cystitis	2	5.0	0	0.0
Folliculitis	1	2.5	2	5.0
Gastroenteritis	1	2.5	2	5.0
Herpes simplex	5	12.5	2	5.0
Influenza	1	2.5	2	5.0
Nasopharyngitis	4	10.0	8	20.0
Pharyngitis	2	5.0	1	2.5
Rhinitis	0	0.0	3	7.5
Musculoskeletal and connective tissue disorders				
Back pain	3	7.5	2	5.0
Nervous system disorders				
Headache	3	7.5	2	5.0
Psychiatric disorders				
Depression	1	2.5	2	5.0
Respiratory, thoracic and mediastinal disorders				
Cough	3	7.5	0	0.0
Skin and subcutaneous tissue disorders				
Acne	2	5.0	0	0.0
Pruritus	4	10.0	0	0.0
Surgical and medical procedures				
Bunion operation	2	5.0	0	0.0
Vascular disorders				
Hypertension	0	0.0	2	5.0

Efficacy results:

PGA (ITT Population)

The PGA demonstrated success with regard to length of hair and darkening of skin in a greater number and percentage of patients in the eflornithine group than in the placebo group at Weeks 4, 12 and 24, and at Weeks 12 and 24 with regard to density. After 24 weeks of treatment, success was noted in 28.2% of the eflornithine group compared with 7.5% of the placebo group for length of hair and density and 20.5% in the eflornithine group versus 12.5% in the placebo group for darkening of skin.

SSAQ (ITT Population)

The mean VAS scores for all questions decreased (improved) from baseline to Week 24 in both the placebo and eflornithine groups (see next table); however, the decreases were greater in the eflornithine group. The reductions in the mean scores at Week 24 for Questions 1-6 ranged from 5.4 to 11.2 for the placebo group and 9.2 to 16.7 for the eflornithine group.

Question		Placebo N=40			Eflornithine N=39		
		Baseline	Week 24	Difference between means	Baseline	Week 24	Difference between means
1	"How much are you bothered by your facial hair?"	75.5	69.0	-6.5	71.2	58.2	-13.0
2	"How uncomfortable does your facial hair make you feel when you meet new people?"	79.0	71.6	-7.4	73.7	61.7	-12.0
3	"How uncomfortable does your facial hair make you feel when you go to work or class?"	75.1	67.5	-7.6	71.4	62.2	-9.2
4	"How uncomfortable does your facial hair make you feel when you go to social gatherings, dine out in a public restaurant, go to the supermarket or other public place?"	74.4	68.8	-5.6	71.8	59.1	-12.7
5	How uncomfortable does your facial hair make you feel in exchanges of affection (such as in an intimate situation with your partner)?"	74.1	62.9	-11.2	71.2	61.1	-10.1
6	How much are you bothered by the time you spend removing, treating or concealing your facial hair?"	68.9	63.5	-5.4	66.5	49.8	-16.7

Conclusion

This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.

Date of report

26 October 2005