Efficacy and safety of topical finasteride spray solution for male androgenetic alopecia: a phase III, randomised, controlled clinical trial

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Abstract

Background Oral finasteride is a well-established treatment for men with androgenetic alopecia (AGA), but long-term therapy is not always acceptable to patients. A topical finasteride formulation has been developed to minimize systemic exposure by acting specifically on hair follicles.

Objectives To evaluate the efficacy and safety of topical finasteride compared with placebo, and to analyse systemic exposure and overall benefit compared with oral finasteride.

Methods This randomised, double-blind, double dummy, parallel-group, 24-week study was conducted in adult male outpatients with AGA at 45 sites in Europe. Efficacy and safety were evaluated. Finasteride, testosterone, and dihydrotestosterone (DHT) concentrations were measured.

Results Of 458 randomised patients, 323 completed the study and 446 were evaluated for safety. Change from baseline in target area hair count (TAHC) at Week 24 (primary efficacy endpoint) was significantly greater with topical finasteride than placebo (adjusted mean change 20.2 *vs* 6.7 hairs; $p < 0.001$), and numerically similar between topical and oral finasteride. Statistically significant differences favouring topical finasteride over placebo were observed for change from baseline in TAHC at Week 12 and investigator-assessed change from baseline in patient hair growth/loss at Week 24. Incidence and type of adverse events, and cause of discontinuation, did not differ meaningfully between topical finasteride and placebo. No serious adverse events were considered treatment related. As maximum plasma finasteride concentrations were >100 times lower, and reduction from baseline in mean serum DHT concentration was lower (34.5 *vs* 55.6%), with topical versus oral finasteride, there is less likelihood of systemic adverse reactions of a sexual nature related to a decrease in DHT with topical finasteride.

Conclusion Topical finasteride significantly improves hair count compared to placebo and is well tolerated. Its effect is similar to that of oral finasteride, but with markedly lower systemic exposure and less impact on serum DHT concentrations.

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Introduction

Androgenetic alopecia (AGA), or male pattern baldness, is a genetically determined disorder caused by susceptibility of hair follicles to androgenic miniaturization, occurring most commonly at the scalp vertex.[1] The condition affects more than half of men under 50 years of age.[2] Even clinically imperceptible hair loss has been correlated with decreased quality of life.[3] Men predisposed to AGA have an increased rate of conversion of testosterone to dihydrotestosterone (DHT) within the hair follicle, a process involving type II 5α-reductase.[4] Finasteride, a synthetic anti-androgen that inhibits type II 5α-reductase, was approved initially in tablet form for the treatment of male AGA.[5]

The clinical efficacy of oral finasteride for treating AGA is well established. Long-term studies of oral finasteride 1 mg in men with AGA demonstrated slower progression of hair loss or enhanced hair growth, compared with baseline and/or placebo, as early as 3 months after treatment start and extending for 5-10 years.[6–10] Although oral finasteride is generally well tolerated,[5] in some patients 5α-reductase inhibition is associated with sexual adverse effects (erectile dysfunction, ejaculation problems, decreased libido),[11] and increased risk of depression,[12] prompting health authorities in some countries to include warnings in the product labelling.[13]. Topical administration of finasteride offers potential to reduce systemic effects related to its mechanism of action by preferentially inhibiting 5-α reductase in the scalp, as has been suggested in recent years.[14]

Preliminary results regarding topical application of finasteride for treatment of AGA were promising. In a testosterone-induced alopecia albino mouse model, higher follicular density and anagen:telogen ratios were observed in the group treated with topical finasteride 2% solution.[15] In humans, topical finasteride application for the treatment of AGA was first explored by Mazarella and colleagues in a study involving 52 patients (28 males) with AGA. Beginning from six months, a progressive and significant decrease in the rate of hair loss was observed in the topical finasteride versus placebo group, with no significant changes in plasma levels of total testosterone, free testosterone, and DHT between treatment groups.[16]

Phase I-II studies of finasteride 0.25% topical solution in male volunteers demonstrated that a once daily application of up to 200 µL (4 sprays of 50 µL, each delivering 0.144 mg/spray to non-overlapping areas) exerted a maximal effect on scalp DHT concentrations with less reduction of serum DHT compared with higher doses.[17,18]

The current phase III study aimed to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of topical finasteride (0.25% solution applied once daily in a volume between 50 µL and 200 µL) compared with placebo and to assess the overall patient benefit of topical finasteride relative to oral finasteride at 24 weeks.

Materials and Methods

Patients and methods

This was a multicentre, randomised, double-blind, double-dummy, parallel-group, placebo-controlled study in men with AGA (Clinicaltrials.gov identifier: NCT03004469).[19]

Eligible patients were male outpatients aged 18-40 years with mild to moderate vertex male pattern hair loss according to a modified Norwood/Hamilton classification scale (III vertex, IV or V).[20] Main exclusion criteria were: abrasion or abnormalities to the scalp; hair transplant or hair weaving; clinically relevant abnormal laboratory values; hypersensitivity or allergy; recent history of local infections of the head; history of infertility or difficulty fathering children; history of relevant significant disease; active seborrheic dermatitis; history of varicocele; concurrent use of corticosteroids, anabolic steroids or over-the-counter 'hair restorers'; use of drugs with anti-androgenic properties within 6 months; treatment in the past year with minoxidil, zidovudine, cyclosporine, diazoxide, phenytoin, systemic interferon, psoralens, streptomycin, penicillamine, benoxaprofen, tamoxifen, phenothiazines, cytotoxic agents, finasteride or dutasteride; and light or laser treatment of the scalp within the last 3 months.

The experimental drug was topical finasteride 0.25% w/w (concentration of 2.275 mg/ml) delivered using a spray applicator with a plastic cone that prevents product dispersion in the air (Figure 1). Each actuation delivers 50 µL of solution, equivalent to 0.114 mg of finasteride. The topical placebo comparator contained the same excipients as the experimental solution (ethanol, propylene glycol, hydroxypropyl chitosan and purified water) and was identical in appearance to and indistinguishable from active treatment. Oral finasteride 1 mg was the reference drug for systemic exposure and was provided as film-coated tablets (Propecia®, Merck, Kenilworth, NJ, USA) over-encapsulated to maintain study blinding. The matching oral placebo was an inert powder-filled capsule indistinguishable from the oral reference drug.

Using a computer-generated list, eligible patients were randomly allocated in a 2:2:1 ratio to one of three treatment arms: topical finasteride and oral placebo ('topical finasteride' arm), topical placebo and oral placebo ('placebo' arm), or topical placebo and oral finasteride ('oral finasteride' arm).

All patients applied topical spray each morning to a dry scalp, at the dose recommended by the study doctor (1–4 sprays, or 50–200 µL of solution depending on the extent of hair loss). The first spray was applied over a target 1 cm^2 circular area in the scalp vertex, marked by a small dot tattoo to identify it for repeated efficacy assessments. Additional sprays (2–4), if recommended by the study doctor, were applied to cover the rest of the baldness area. The topical spray solution was to be left in place for at least 6–8 hours, then washed off with shampoo.

Baseline assessments were performed at screening (Week −2). Patients were randomised on Day 1 and treated for 24 weeks. Assessments and study procedures were performed at Weeks 4, 8, 12, and 24. A follow-up visit took place at Week 28. In the event of early termination, patients were followed up at the early termination visit.

Patients maintained a diary of daily compliance. Bottles and blister packs of study medications were returned and assessed by investigators for compliance.

Efficacy assessment

At screening, standardised colour global photographs of the scalp vertex were taken with the head in a stereotactic positioning device to confirm the Hamilton Norwood inclusion criterion. For patients fulfilling inclusion and exclusion criteria at the baseline visit, investigators selected a circular 1 cm^2 area in the anterior leading edge of the thinning area on the vertex as the target area. Hairs in this area were clipped to approximately 1 mm in length and a small dot tattoo was placed in the centre of the circle of clipped hairs to allow for subsequent accurate identification. Macrophotographs were taken of this target area at baseline, Week 12 and Week 24 using an established validated technique as a basis for counting hairs on the digital images.[21]

The primary efficacy variable was the change from baseline in target area hair count (TAHC) at Week 24 as assessed on the macrophotographs. Main secondary efficacy variables were: change from baseline in TAHC at Week 12; change from baseline in target area hair width (TAHW) at Week 24; patient-assessed scores on the Male Hair Growth Questionnaire (MHGQ; 7 items regarding treatment efficacy and satisfaction with appearance)[22] at Week 24; investigator-assessed change from baseline in patient hair growth/loss at the vertex (on a 7-point scale from −3 = greatly decreased to +3 = greatly increased) at Week 24; and blinded-assessor evaluation of change from baseline in patient hair growth/loss at the vertex (on a 7-point scale from −3 = greatly decreased to +3 = greatly increased) at Week 24. Study investigators examined patients' scalps directly at follow-up visits. The blinded assessor (an experienced independent dermatologist) was limited to making assessments on global photographs with reference to the baseline photograph.

Safety assessment

Treatment emergent adverse events (TEAEs) were recorded. Investigators assessed their severity, seriousness, and causal relationship to study treatment. Patients were monitored by physical examination, vital signs and body weight. Routine haematology, blood chemistry and urinalysis were conducted. Investigators used the Severity Score for Skin Irritation scale[23] to assess local tolerability at the application site from Week 4 to Week 28. Patients completed the self-administered Sexual Dysfunction Questionnaire (International Index of Erectile Function, version 2)[24] at each visit from Week 4 to Week 28.

PK and PD assessment

The plasma PK profiles of finasteride following topical application and oral administration, and any impact of treatment on serum DHT concentrations (PD), were assessed by analysing blood samples collected at randomisation and at Weeks 4, 8, 12, 24 and 28 (post-treatment). Samples were taken at approximately 1 h (+ 30 min) post-dose when maximum finasteride plasma concentrations after oral administration were expected to be reached. finasteride and DHT analyses were performed according to the 'OECD Principles of Good Laboratory Practices' for testing of chemicals using previously fully-validated bioanalytical methods.[25] finasteride concentrations in plasma, and DHT concentrations in serum, were determined using supported-liquid extraction followed by analysis using high performance liquid chromatography followed by tandem mass spectrometric detection. Lower limits of quantification were established at 4 pg/mL and 2 ng/dL for plasma finasteride and serum DHT, respectively.

Statistical analysis

A total of 450 patients were to be randomised in a 2:2:1 allocation ratio, allowing for 20% attrition. A group sample size of 144 patients in the topical finasteride arm and placebo arm was calculated to achieve 99% power to detect the superiority of topical finasteride versus placebo for the primary endpoint, with a significance level (alpha) of 0.05 using a two-sided two-sample t-test. A group sample size of approximately 72 patients in the oral finasteride arm was calculated to achieve a power close to one to reject the null hypothesis of an equal decrease in serum DHT between oral finasteride and topical finasteride with an alpha of 0.05 using a two-sided two-sample equal-variance t-test.

The intention-to-treat (ITT) population was defined in the study protocol as all patients with valid measurements for the primary efficacy variable at baseline and on treatment. The per protocol (PP) population was defined as all patients in the ITT population who did not take prohibited medications and who completed the study without any major protocol violations. The safety population consisted of all randomised patients who received at least one application of study drug. The modified ITT (mITT) population was defined *a posteriori*, as all randomised patients who received at least one application of study drug, and was therefore equivalent to the safety population.

The main efficacy analyses were based on the ITT population. Analyses performed on the PP population were considered supportive. Post hoc sensitivity analyses for efficacy were performed on the ITT population for endpoints dependent on the baseline macrophotograph (i.e. TAHC, TAHW), and on the mITT population for endpoints not dependent on the baseline hair count (i.e. investigator and blinded-assessor assessments of patient hair growth/loss change; MHGQ). Post hoc analyses applied a multiple imputation with jump-to-reference approach, assuming the same result as that observed in the placebo group, to handle missing data from patients who withdrew early or did not have a valid macrophotograph. This conservative method assumes that a patient with missing values follows a profile equivalent to that of a patient in the reference group which, in this case, was the placebo group.

The primary efficacy variable, change from baseline in TAHC at Week 24, was analysed using the SAS PROC MIXED procedure and summarised descriptively. Data were fitted by a mixed linear model for repeated measures with treatment, centre, visit, and treatment-by-visit interaction as fixed effects, and baseline hair count as a covariate. Correlation between two repeated measurements (over the post-baseline visits) was modelled. Maximum likelihood estimates of the treatment mean difference were computed at Week 24 together with associated two-sided 95% confidence intervals (CI) calculated using the Newton-Raphson algorithm implemented in the SAS Mixed Procedure. A two-sided test p-value ≤ 0.05 was considered statistically significant. The same statistical approach was used for secondary efficacy variables. All computations were performed using the SAS® version 9.4 statistical software package.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local laws and regulations of participating countries. The study protocol, patient information sheet and informed consent form were reviewed and approved by independent ethics committees. All patients provided written informed consent prior to participation. Procedures were enacted to ensure patient confidentiality and data protection.

Results

Participating sites and patient populations

Patients were enrolled at 45 sites in five countries: Belgium (4 sites), Germany (18 sites), Spain (8 sites), Hungary (6 sites), and Russian Federation (9 sites). The study took place between August 2016 and March 2018.

Patient disposition is shown in Figure 2. A total of 458 patients were randomised to treatment (189 to topical finasteride, 184 to placebo, 85 to oral finasteride) and 323 patients completed the study. Percentages of patients not completing the study, and reasons for discontinuation, were similar among treatment groups. Overall, 250 patients (54.6%) had evaluable hair count measurements from the macrophotographs both at baseline and on treatment and formed the ITT population. A total of 446 patients formed the safety (and mITT) population.

Patient demographics and baseline characteristics

Demographic details and baseline hair loss pattern in the ITT population are shown in Table 1. Mean age was approximately 32 years and about half of patients in each group had type III vertex pattern hair loss. Mean TAHC at baseline was similar among treatment groups: 201.0 ± 67.6 hairs for topical finasteride, 204.8 ± 67.2 hairs for placebo and 201.9 ± 72.9 hairs for oral finasteride. Mean TAHW at baseline was also similar, with values of 44.4, 46.3, and 46.0 μm, respectively. Treatment groups were broadly similar with respect to other demographic variables (including alcohol and tobacco use) and baseline characteristics.

Efficacy analyses

At Week 24, the adjusted mean change from baseline in TAHC was significantly greater with topical finasteride than with placebo (20.2 *vs* 6.7 hairs; p < 0.001), and was numerically similar to that with oral finasteride (21.1 hairs) (Figure 3). The post hoc sensitivity analysis produced robust results with the same conclusion: the adjusted mean change from baseline in TAHC at Week 24 was significantly greater with topical finasteride than placebo (16.3 *vs* 6.3 hairs; p = 0.012) and numerically similar to that with oral finasteride (18.7 hairs) (Figure 4).

At Week 12, a statistically significant increase from baseline in TAHC relative to placebo was observed with topical finasteride (Figure 3). Changes from baseline in other secondary

efficacy outcomes in the ITT population are summarised in Table 2. The adjusted mean change from baseline to Week 24 in TAHW indicated negligible changes with any study treatment. At Week 24, the patient-assessed MHGQ score for the item 'overall assessment' was similar across treatment groups. The investigator-assessed adjusted mean change from baseline to Week 24 in patient hair growth/loss at the vertex was statistically significantly greater with topical finasteride than placebo (0.8 *vs* 0.3, p < 0.001) and was numerically similar to that with oral finasteride (0.7). Blinded-assessor evaluation of patient hair growth/loss at the vertex indicated no to minimal change from baseline in any group at Week 24.

To assist in interpreting the clinical relevance of the findings, a post hoc sensitivity analysis was performed on the mITT/safety population. For MHGQ and investigator and blinded-assessor evaluations of the change in patient hair growth/loss, results were dichotomised into 'responder' and 'non-responder' categories, where response for each item was defined as showing any degree of improvement. The percentage of responders with respect to investigator assessment, blinded-assessor assessment, and three items of the MHGQ were significantly greater with topical finasteride than placebo (Table 3).

Safety assessment

The percentage of patients with TEAEs in the topical finasteride group was similar to that in the placebo group and lower than that in the oral finasteride group (Table 4). Most TEAEs (96.9%) were mild or moderate in intensity. Ten patients reported treatment-emergent serious AEs of which none was considered by investigators to be related to study medication.

Incidences of treatment-related TEAEs were 9.9%, 6.6% and 11.9% in the topical finasteride, placebo, and oral finasteride groups, respectively. Withdrawal rates due to treatment-related TEAEs were 2.8% and 2.2% in the topical finasteride and placebo groups, respectively, and 7.1% in the topical finasteride group. Treatment-related TEAEs reported by ≥ 3 patients in

any of the topical finasteride, placebo or oral finasteride groups were: pruritus (2.2% *vs* 0.6% *vs* 1.2% of patients, respectively), erythema (2.2%, 0%, and 0%, respectively), and loss of or reduction in libido (0.6%, 2.8% and 4.8%, respectively).

There were no clinically meaningful changes from baseline, or differences among treatment groups, in mean values for haematology, serum chemistry and urinalysis results.

Incidence rates of skin irritation as evaluated using the Severity Score for Skin Irritation scale were < 1% in all treatment groups.

There were no significant differences between topical finasteride and placebo in mean scores for any item on the Sexual Dysfunction Questionnaire at Week 12 or Week 24. Mean scores for all items were similar between topical finasteride and oral finasteride at Week 12 and Week 24.

Treatment-related sexual adverse events (sexual dysfunction, erectile dysfunction, libido decreased, loss of libido) were reported in 2.8% *vs* 3.3% *vs* 4.8% of patients treated with topical finasteride, placebo, or oral finasteride. Discontinuations due to treatment-related sexual adverse events were reported in 0% *vs* 1.1% *vs* 2.4% of patients, respectively.

PK and PD analyses

Mean ± SD maximum plasma finasteride concentrations were 36.5 ± 45.9 pg/mL with topical finasteride and 7166 ± 12,744 pg/mL with oral finasteride at Week 12; and were 48.0 ± 87.2 pg/mL and 5029 ± 4182 pg/mL, respectively, at Week 24.

Mean serum DHT concentrations in the placebo group remained unaffected during the study (range: 38.5 to 39.8 ng/dL). Mean serum DHT concentrations at Week 24 were 34.6% lower than at baseline in the topical finasteride group (25.75 *vs.* 39.32 ng/dL, respectively), and were 55.6% lower than at baseline in the oral finasteride group (15.75 *vs.* 35.50 ng/dL, respectively). The adjusted mean difference in the change from baseline in serum DHT

concentrations was statistically significant between topical finasteride and placebo ($p < 0.05$), and between topical finasteride and oral finasteride ($p < 0.05$), at each of Weeks 4, 8, 12 and 24 (Figure 5).

The lower impact of topical finasteride on DHT levels was not accompanied by any shift from normal to high plasma testosterone concentrations for patients in this group; this was also the case for the placebo group. In the oral finasteride group, this shift occurred in four (6.7%) patients.

Discussion

Although oral finasteride has proven effective in treating AGA, the occurrence of adverse effects has been a point of concern. Since the 1990s, interest had shifted towards topical application of finasteride to improve the risk-to-benefit ratio, as summarised in a recent systematic review.[14] To test the hypothesis, this 24-week phase III study used a robust design, incorporating placebo and active control arms and a double dummy technique to maintain blinding.

A statistically significantly greater improvement in hair count at the scalp vertex was demonstrated with topical finasteride over placebo, with an effect evident at 12 weeks. The efficacy of topical finasteride was numerically similar to that of oral finasteride. Of interest was that the increase in hair count was not accompanied by any appreciable change in hair width compared to baseline values in any treatment group (see Table 2). As such, hair width may not be of utility as an endpoint to monitor treatment effect. At study end, the change in patient hair growth/loss at the vertex significantly favoured topical finasteride versus placebo when assessed by the investigator, and was numerically similar between topical and oral finasteride. Small discrepancies, ranging from 0.2 to 0.6 on the 7 point scale, were observed between assessments made by the investigator and blinded evaluator which may be due to the way in which these assessments were generated. Investigators were able to examine the

patient more closely at follow-up visits with the option to touch the hair and scalp and part the hair. In contrast, the blind assessor had access only to two-dimensional photographs which could be compared with the baseline image. Although the investigators' assessment was more favourable, there is no suggestion that investigators were biased towards a more positive opinion of treatment success with topical finasteride, since assessments were made under blinded conditions. With regard to patients' own perception of treatment success, as reflected in responses to the MHGQ, even in this relatively short term study over 24 weeks it is interesting that patients reported statistically significant improvement in three of the six items on the questionnaire. Post hoc sensitivity analyses demonstrated the consistency and robustness of the main analysis.

While there was a trend towards more treatment-related skin and application site reactions (e.g. pruritus, erythema) with topical finasteride than with placebo or oral finasteride, events that occurred were mainly mild or moderate in intensity. Incidences of skin irritation as assessed by the Severity Score for Skin Irritation scale were low ($< 1\%$) in all treatment groups.

Some patients treated with oral finasteride may experience adverse effects potentially related to the circulating plasma concentration of drug required to achieve effective concentrations at the scalp. There is ongoing debate whether, in some cases, use of oral finasteride 1 mg/day to treat male pattern hair loss may be associated with irreversible sexual dysfunction and severe depression.[26–29] As demonstrated in the current study, maximum mean plasma finasteride concentrations were more than 100-fold lower with the topical versus oral formulation, and the impact on serum DHT concentrations after 24 weeks' treatment was statistically significantly lower with topical versus oral finasteride (reductions of 34.6% and 55.6%, respectively). While this does not exclude the possibility of systemic adverse events related to decreased DHT in both groups, the probability is lower with topical than oral finasteride. A trend was evident for fewer treatment-related sexual adverse events, and associated treatment discontinuations, in the topical versus oral finasteride group.

European evidence-based guidelines recommend topical minoxidil and oral finasteride for AGA and suggest low-level laser light therapy as an ancillary therapy.[30] Although follicular unit transplantation (FUT) and non-surgical methods such as platelet-rich plasma (PRP)[31] and microneedling with PRP[32] have been developed, current European guidelines suggest FUT only in combination with oral finasteride as a treatment option for AGA.[30] Stem cell procedures are in development for patients resistant to other therapies.[33] The availability of topical finasteride provides an additional treatment option that is effective and generally well tolerated.

The main finding of the study was that the change from baseline in hair count was significantly greater with topical finasteride than placebo, and similar to that observed with oral finasteride. This result was achieved with markedly lower systemic exposure to finasteride and less impact on serum DHT concentrations compared with oral finasteride. Topical finasteride was well tolerated and had a safety profile not meaningfully different from that of placebo. As such, topical finasteride appears to be a useful option for treatment of AGA in men. Further studies would be useful to demonstrate the long-term efficacy of topical finasteride. Understanding the reasons for the relatively high number of treatment discontinuations and negligible changes from baseline to end of treatment in certain subjective measures such as patient-assessed MHGQ score for 'overall assessment' and blinded-assessor evaluation of patient hair growth/loss may assist in designing future studies.

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Tables

Table 1. Demographics and baseline characteristics (ITT population).

Characteristic	Topical finasteride (N = 105)	Placebo (N = 97)	Oral finasteride (N = 48)
Age (years), mean (SD)	32.5 (5.4)	31.8 (4.9)	32.3 (5.5)
Weight (kg), mean (SD)	83.6 (17.5)	84.3 (14.6)	83.3 (12.4)
Caucasian, n (%)	103 (98.1)	96 (99.0)	46 (95.8)
Male pattern baldness†, n (%)			
Type III vertex	50 (47.6)	45 (46.4)	26 (54.2)
Type IV	27 (25.7)	31 (32.0)	14 (29.2)
Type V	28 (26.7)	20 (20.6)	8 (16.7)
Other	0 (0.0)	1 (1.0)	0 (0.0)

† According to the Norwood/Hamilton Scale.

ITT, intention to treat; SD, standard deviation.

Table 2. Changes from baseline in secondary efficacy variables (ITT population).

Variable	Topical finasteride (N = 105)	Placebo (N = 97)	Oral finasteride (N = 48)
Hair width, μm [adjusted mean (SE)]			
Week 24	−0.81 (0.35)	−1.53 (0.37)	0.72 (0.47)
Self-administered MHGQ overall score† [adjusted mean (SE)]			
Week 24	2.8 (0.75)	3.0 (0.95)	2.9 (0.89)
Investigator-assessed change in patient hair growth/loss‡ [adjusted mean (SE)]			
Week 24	0.8 (0.09)***	0.3 (0.09)	0.7 (0.12)
Blinded-assessor change in patient hair growth/loss‡ [adjusted mean (SE)]			
Week 24	0.2 (0.09)	0.1 (0.09)	0.3 (0.12)

† Assessed on a 5-point scale from 1 = very satisfied to 5 = very dissatisfied.

‡ Assessed on a 7-point scale from −3 = greatly decreased to +3 = greatly increased.

*** p <0.001 versus placebo.

ITT, intention to treat; MHGQ, Male Hair Growth Questionnaire; SE, standard error.

Table 3. Percentage of responders for secondary endpoints at Week 24: post hoc sensitivity analysis (safety population).

Responders[a]	Topical finasteride (N = 181)	Placebo (N = 181)	Oral finasteride (N = 84)	p-value (topical finasteride *vs* placebo)
Investigator assessment (%)	42.0	27.6	35.7	< 0.005
Blinded-assessor assessment (%)	26.0	16.0	28.6	0.02
MHGQ – patient assessment (%)				
Smaller bald spot	29.3	21.0	31.0	0.069
Hair appearance	40.9	28.7	36.9	0.015
Hair growth	39.8	32.0	31.0	0.12
Slow down hair loss	41.4	31.5	40.5	< 0.05
Satisfaction – front hair line	21.6	11.1	17.9	0.007
Satisfaction – head top	26.0	19.3	23.8	0.13

Overall change	26.5	19.9	25.0	0.13

^a Response for each parameter was defined as showing any degree of improvement.

MHGQ, Male Hair Growth Questionnaire.

Table 4. Frequency of treatment emergent adverse events (TEAEs) in the safety population.

	Topical finasteride (N = 181)	Placebo (N = 181)	Oral finasteride (N = 84)	Total (N = 446)
Patients with TEAEs, n (%)	75 (41.4)	76 (42.0)	41 (48.8)	192 (43.0)
Mild	59 (32.6)	60 (33.1)	33 (39.3)	152 (34.1)
Moderate	32 (17.7)	31 (17.1)	19 (22.6)	82 (18.4)
Severe†	4 (2.2)	3 (1.7)	2 (2.4)	9 (2.0)
Patients with TEAEs leading to study discontinuation, n (%)	5 (2.8)	4 (2.2)	6 (7.1)	15 (3.4)
Patients with treatment-related TEAEs‡, n (%)	18 (9.9)	12 (6.6)	10 (11.9)	40 (9.0)
Patients with treatment-related TEAEs leading to study discontinuation	4 (2.2)	2 (1.1)	2 (2.4)	8 (1.8)
Patients with treatment-emergent serious AEs	4 (2.2)	5 (2.8)	1 (1.2)	10 (2.2)
Patients with treatment-related serious AEs	0	0	0	0

† Cases of unknown intensity were assumed to be severe.

‡ Includes AEs considered related or possibly related to study drug and AEs with unknown or missing relationship to study drug.

Figure legends

Figure 1. Finasteride 0.25% spray applicator and mode of administration on the scalp.

Figure 2. Patient disposition. AE, adverse event; ITT, intention to treat.

Figure 3. Adjusted mean change from baseline in target area hair count in the vertex at Week 12 and at Week 24 (primary efficacy endpoint) in the intention to treat population. *** $p < 0.001$ versus placebo. SE, standard error.

Figure 4. Baseline and Week 24 macrophotograph of a patient treated with finasteride 0.25% topical solution who was rated as showing marked improvement (Canfield Scientific, Inc., Parsippany, NJ).

Figure 5. Mean serum dihydrotestosterone (DHT) concentrations during treatment for 24 weeks with topical finasteride, placebo, or oral finasteride. The difference in mean values from baseline to Week 24 is shown at the end of each line. * $p < 0.05$ versus placebo and oral finasteride at all time points; ** $p < 0.05$ versus placebo at all time points. Note: error bars indicate standard deviation.

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                          │     Randomised       │
                          │    (N = 458)         │
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┌─────────────────┐         ┌─────────────────┐         ┌─────────────────┐
│ Topical         │         │    Placebo      │         │ Oral finasteride│
│ finasteride     │         │   (N = 184)     │         │   (N = 85)      │
│  (N = 189)      │         │                 │         │                 │
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Topical finasteride	Placebo	Oral finasteride
Discontinued: 61 (32.3%)	Discontinued: 49 (26.6%)	Discontinued: 25 (29.4%)
AE, n=6	AE, n=4	AE, n=6
Lack of efficacy, n=1	Lack of efficacy, n=0	Lack of efficacy, n=1
Lost to follow-up, n=23	Lost to follow-up, n=14	Lost to follow-up, n=6
Non-compliance, n=2	Non-compliance, n=0	Non-compliance, n=0
Protocol deviation, n=0	Protocol deviation, n=0	Protocol deviation, n=1
Patient withdrawal, n=29	Patient withdrawal, n=27	Patient withdrawal, n=10
Other, n=0	Other, n=4	Other, n=1

ITT population (N = 105)	ITT population (N = 97)	ITT population (N = 48)

Legend:
- Topical finasteride
- Placebo
- Oral finasteride

2.25% *vs* baseline

-34.52% *vs* baseline *

-55.63% *vs* baseline **

Y-axis: Serum DHT concentration (ng/dL)

X-axis: Time (weeks)