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A novel finasteride 0.25% topical solution for androgenetic alopecia: pharmacokinetics and effects on plasma androgen levels in healthy male volunteers

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Key words
androgenetic alopecia – finasteride – dihydrotestosterone

Abstract. Objective: Finasteride, a selective inhibitor of type 2 5-α reductase isoenzyme, inhibits the conversion of testosterone to dihydrotestosterone (DHT) and is indicated in the treatment of male androgenetic alopecia. The study objective was to evaluate a newly developed finasteride 0.25% topical solution in comparison to the marketed finasteride 1 mg tablet, with respect to finasteride pharmacokinetics and suppressive effects on plasma DHT. Methods: 24 healthy men with androgenetic alopecia were randomized in a single center, open-label, parallel-group, exploratory study, and received either multiple scalp applications of the topical solution b.i.d. or oral doses of the reference tablet o.d. for 7 days. Plasma finasteride, testosterone and DHT concentrations were determined. Results: After multiple doses, mean (± SD) finasteride C_{max} and AUC_{0-t} corresponded to 0.46 ± 0.28 ng/mL and 6.64 ± 7.50 ng/mL×h for the topical solution and to 6.86 ± 1.78 ng/mL and 57.93 ± 29.38 ng/mL×h for the tablet. Plasma DHT was reduced by ~ 68 – 75% with the topical solution and by ~ 62 – 72% with the tablet. No relevant changes occurred for plasma testosterone with either treatment. No clinically significant adverse events occurred. Conclusions: A strong and similar inhibition of plasma DHT was found after 1 week of treatment with the topical and tablet finasteride formulations, albeit finasteride plasma exposure was significantly lower with the topical than with the oral product ($p < 0.0001$).

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Introduction

Androgenetic alopecia, or male pattern baldness, is characterized by progressive patterned hair loss from the scalp and is recognized as a physically and psychologically untoward medical condition [1, 2, 3]. The basis of androgenetic alopecia in men is a progressive decrease in the density of terminal hair and a concurrent increase in the density of short, non-pigmented hair. This effect is attributed to miniaturization of the hair follicle, which is associated with a substantial reduction in hair diameter [4]. Although the mechanism of these changes has not been definitively established, male pattern baldness is known to depend on the presence of the androgen dihydrotestosterone (DHT) [5] and on genetic predisposition [1, 6]. DHT is formed by testosterone (Figure 1) through the action of the 5-α reductase enzyme. Dallob et al. [7] reported that in untreated men with androgenetic alopecia, mean (± SEM) DHT levels were significantly higher in bald (7.37 ± 1.24 pmol/g) compared to hair-containing (4.20 ± 0.65 pmol/g) scalp, whereas there was no difference in mean testosterone levels.

Finasteride (Figure 1), a potent selective inhibitor of type 2 5-α reductase isoenzyme, was initially developed for the treatment of benign prostate hyperplasia in a 5 mg dose and is presently authorized and marketed as a 1 mg dose tablet for the treatment of male pattern baldness [8]. In published studies, doses of 0.05 – 5 mg finasteride, orally administered once a day (o.d.) for 42 days, blocked the conversion of testosterone to DHT, resulting in 60 – 70% reduction in serum, prostate and scalp DHT levels [9]. The clinical effectiveness of finasteride was evaluated in well-controlled clinical trials that monitored 1,879 men with androgenetic alopecia, demonstrating that treatment with oral finasteride for 5 years, as opposed to placebo, resulted in hair loss reduction [10, 11]. A systemic review by Mella et al. [12] concluded that daily use of oral finasteride (1 mg tablet) increases hair count and improves patient and investigator assessment of hair appearance.

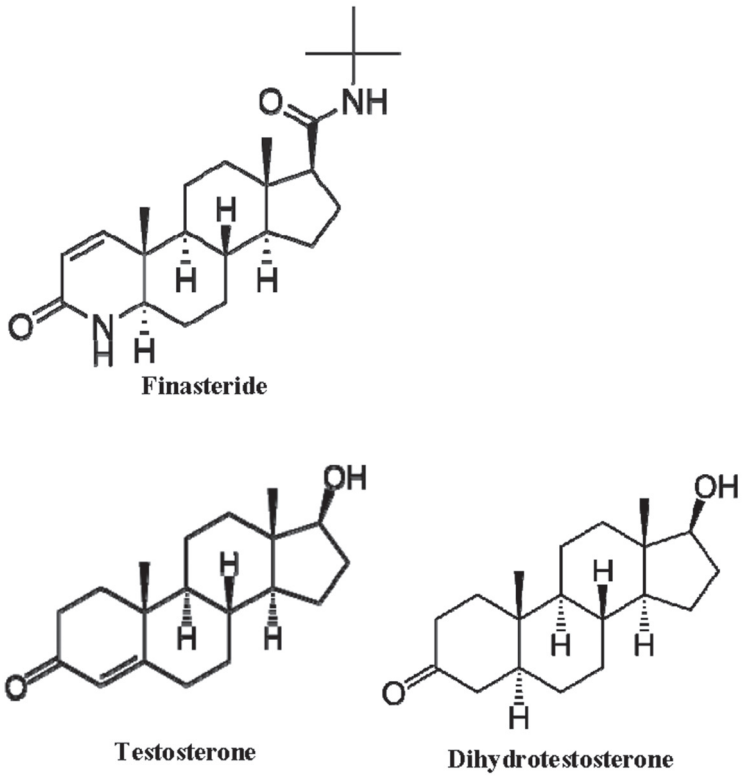

Figure 1. Chemical structure of finasteride [(5α,17β)-N-(1,1-dimethylethyl)-3-oxo-(5α,17β)-4-azaandrost-1-ene-17-carboxamide], testosterone [(17β)-17-Hydroxyandrost-4-en-3-one] and dihydrotestosterone (5α-androstan-17β-ol-3-one).

To maintain therapeutic benefits, oral finasteride must be taken long-term on a daily basis. Generally finasteride is well tolerated with long-term use, although sexual adverse effects have been consistently reported [1, 13]. In multiple double-blind randomized controlled trials, finasteride has been associated with a small but significant amount of sexual dysfunctions, including decreased libido (1.8%), erectile dysfunction (1.3%), ejaculation disorders (0.8 – 1.2%), and orgasm disorders (0.4%) [12, 14, 15, 16]. Recently, it has been shown that sexual side effects could be persistent and at times might be associated with anxiety and depression [15].

It is biologically plausible that a lack of plasmatic DHT or another 5α-reduced hormone may be responsible for a decrease in libido and/or orgasm [17]. Persistent symptoms of erectile dysfunction include difficulty in getting an erection, difficulty in maintaining an erection and low sexual desire and are likely to be caused by finasteride suppression of DHT, a hormone that plays an important role in erectile physiology. Animal and human studies have confirmed that oral finasteride and other 5-α-reductase inhibitors can have an adverse effect on erectile response. While lowering body DHT levels may correct hair loss, problems may arise because this sex hormone is important for maintaining the structural integrity of nerves, smooth muscle, connective tissue and signaling pathways in the penis [18, 19].

Topical finasteride formulations, in comparison with the marketed oral tablet, might potentially reduce some of the systemic side effects related to the mechanism of action of finasteride, due to expected preferential inhibition of the 5-α reductase enzyme in the scalp.

A topical formulation of finasteride 0.25% solution (namely P-3074) has recently been selected among different finasteride formulations on the basis of its optimal performance in the hairless rat skin model [20, 21, 22] in terms of finasteride transdermal permeation and skin retention. This novel formulation contains hydroxypropyl chitosan (HPCH), which acts as a film-forming agent maintaining a balanced amount of finasteride at the surface of the scalp, for enough time to allow the active compound to penetrate through the skin layers.

The present exploratory study in male volunteers with androgenetic alopecia was designed to determine the pharmacokinetic profile of finasteride, after single and multiple dose administration of finasteride 0.25% topical solution, in comparison with finasteride 1 mg oral tablet. The effect of the two treatments on plasma DHT and plasma testosterone concentrations after single dose and at the end of the 7-day treatment was also investigated.

Subjects and methods

Subjects

Study participants were healthy men, aged 18 – 65 years, with at least stage II androgenetic alopecia on the Hamilton-Norwood classification scale [23]. All men were in good physical health, as assessed at study entry by medical history and physical examination, including electrocardiogram (ECG) recording, vital signs measurement and routine laboratory blood and urine assays,

according to the study inclusion criteria. Exclusion criteria included skin damage, such as abrasions, hyperkeratosis or any abnormal findings on the scalp. Subjects were not enrolled if they had participated in other clinical trials or donated blood in the past three months, or if they were on any previous or concomitant medications in the 2 weeks preceding the study. The study was approved by an independent Ethics Committee, Canton Ticino, Switzerland, and was performed at CROSS Research S.A., Phase I Unit, Switzerland, in accordance with the Declaration of Helsinki and the harmonized European standards of Good Clinical Practice (ICH E6 1.24).

Study design and procedures

This was a single center, open-label, randomized, parallel-group, pharmacokinetic, pharmacodynamic, exploratory study. After providing written informed consent, 24 healthy male subjects with androgenetic alopecia were randomly allocated to finasteride 0.25% topical solution (Polichem S.A., Switzerland (Test)) or finasteride 1 mg oral tablet – (Propecia®, MSD S.A., Switzerland (Reference)) treatment groups in a 1 : 1 ratio. The randomization list was computer-generated by the Biometry Department of CROSS Metrics S.A., Switzerland, using the PLAN procedure of the validated SAS for Windows Version 9.1.3 Service Pack 4.

In the test treatment group, a single dose of finasteride topical solution was applied to the shaved scalp in the morning of day 1, and then b.i.d. from day 2 to the morning of day 8, for a total of 14 applications (1 mL (2.275 mg)/application). Reference formulation (1 mg tablet) was orally administered o.d. for 7 days, i.e., from the morning of day 1 to the morning of day 7. In both treatment groups, blood samples were collected at pre-dose (0 h) and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours after the first single dose and at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 36 hours after the last multiple dose. Finasteride was determined in all plasma samples, while testosterone and DHT were dosed at pre-dose and 6, 12, and 24 hours after single dose, and at pre-dose and 6, 12, 24, and 36 hours after multiple doses.

Local tolerability at the application site was assessed by the investigator and the subjects (test treatment group only) before and 4 hours after the first drug application and before each morning and evening application, up to the morning of day 8. Adverse events were recorded throughout the study. Safety assessments also included physical examinations, ECG, routine laboratory tests and vital signs check.

Analytical methods

Plasma concentrations of finasteride were determined at Nikem Research S.r.l., Italy, using a validated UPLC-MS/MS method, published by Phapale et al. [24], with a quantification range of 0.25 – 10 ng/mL. Plasma concentrations of DHT and testosterone were determined at ABL Analytical Biochemical Laboratory, the Netherlands, using a validated LC-MS/MS method with a validated range of 0.05 – 20 ng/mL. Validation of the two methods was compliant with the method validation guidelines [25]. Finasteride samples were stable for at least 1 month at –80 °C. Plasma DHT and testosterone samples were stable after 66 days at ≤ –18 °C. Accuracy and precision were within 15% of the nominal values (20% at the lower quantification limit) for both methods.

Pharmacokinetic evaluation

Finasteride pharmacokinetic parameters were measured and calculated after single and multiple doses, by non-compartmental analysis, using the validated software WinNonlin version 5.2 (Pharsight Corporation, USA) at CROSS Research S.A., Switzerland. The following pharmacokinetic parameters were calculated from the measured concentrations: maximum plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), area under the concentration-time curve from time 0 hours to the last observed concentration time t, calculated with the trapezoidal method ($AUC_{0–t}$), area under the concentration-time curve extrapolated to infinity ($AUC_{0–\infty}$; single dose only), and half-life ($t_{1/2}$; single dose only).

Table 1. Demographic profile of the study of healthy male volunteers with androgenetic alopecia. Safety population.

Parameter	Finasteride 0.25% topical solution n = 12	Finasteride 1 mg tablet n = 12
Race Caucasian	 12 (100.0%)	 12 (100.0%)
Age (years) Mean ± SD (range)	39.4 ± 8.3 (26 – 50)	42.8 ± 9.0 (31 – 58)
Body weight (kg) Mean ± SD (range)	77.3 ± 12.3 (51.0 – 96.0)	79.2 ± 8.9 (64.0–93.0)
Body mass Index (kg/m^2) Mean ± SD (range)	24.9 ± 2.6 (18.7 – 27.7)	25.7 ± 3.1 (19.6 – 29.9)
Systolic blood pressure (mmHg) Mean ± SD (range)	116.2 ± 13.0 (100 – 138)	120.2 ± 13.1 (104 – 138)
Diastolic blood pressure (mmHg) Mean ± SD (range)	73.0 ± 6.8 (60 – 84)	77.8 ± 8.3 (66 – 88)
Heart rate (bpm) Mean ± SD (range)	61.2 ± 6.2 (52 – 76)	58.8 ± 5.8 (50 – 68)

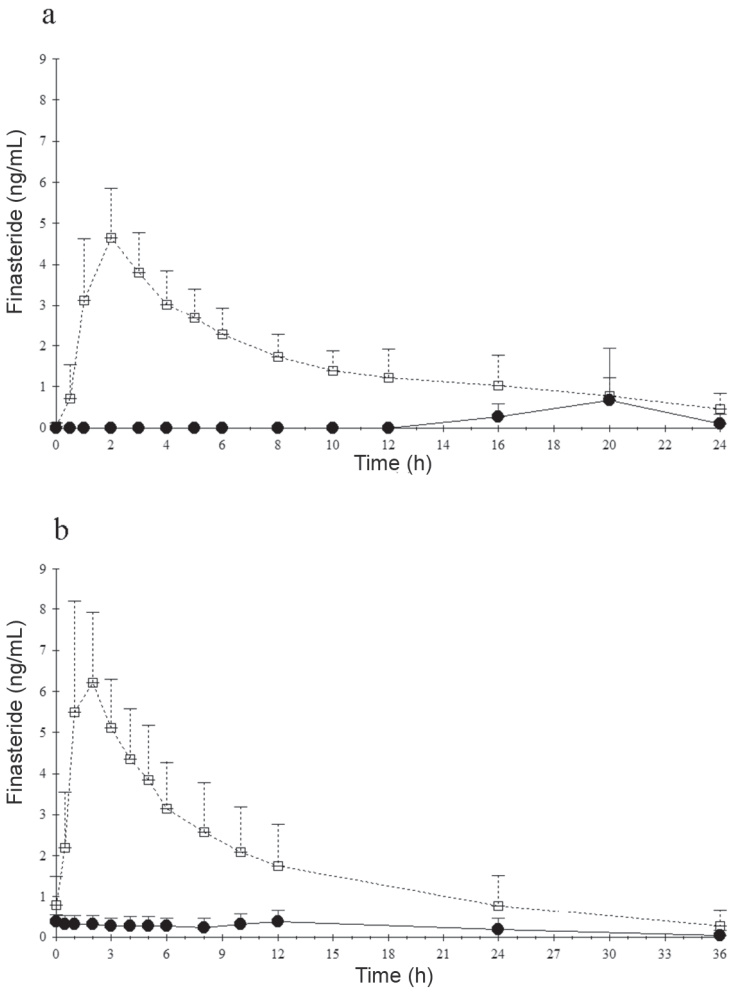

Figure 2. Mean (+ SD) plasma finasteride concentration (ng/mL) vs. time profiles after single (a) and multiple (b) administration of finasteride 0.25% (2.275 mg) topical solution b.i.d. (● solid line) or finasteride 1 mg oral tablet o.d. (□ dotted line). Linear scale. Bars represent standard deviation.

Pharmacodynamic evaluation

DHT and testosterone plasma concentrations were evaluated. Changes from baseline in DHT and testosterone levels after single and multiple doses were calculated and presented as percentage of inhibition.

Sample size and statistical methods

Considering the explorative and descriptive nature of the study, no formal power calculation was performed. Plasma finasteride pharmacokinetic parameters and DHT and testosterone concentrations at each sampling time were compared between the two study treatments using an independent sample t-test.

Results

24 eligible healthy male volunteers with androgenetic alopecia were randomized in the study, 12 of them to the finasteride 0.25% topical solution treatment group and 12 to the finasteride 1 mg tablet treatment group. The first subject was screened on 22 August 2011 and the last completed the trial on 06 September 2011. All the randomized subjects completed the study and were included in the safety analysis. One subject in the test treatment group was excluded from the pharmacokinetic and pharmacodynamic analyses for a major protocol violation, i.e., previous intake of finasteride. Demographic characteristics of the men randomized in the study are presented in Table 1.

Pharmacokinetics

Finasteride pharmacokinetic profiles after single and multiple administrations of the two investigational products are shown in Figure 2. Finasteride pharmacokinetic parameters are presented in Table 2.

Finasteride plasma rate and extent of absorption were much lower with the topical solution than with the oral reference tablet, as indicated by the C_{max} and AUC values of the two formulations (Table 2). After single administration of the topical formulation,

Table 2. Plasma finasteride pharmacokinetic parameters for finasteride 0.25% (2.275 mg) topical solution and finasteride 1 mg oral tablet.

	Single dose		Multiple dose	
PK parameter	Finasteride 0.25% topical solution n = 11	Finasteride 1 mg tablet n = 12	Finasteride 0.25% topical solution n = 11	Finasteride 1 mg tablet n = 12
C_{max} (ng/mL)	0.78 ± 1.25	4.92 ± 1.24	0.46 ± 0.28	6.86 ± 1.78
t_{max} (h)	20.0 (16.0 – 24.0)[a]	2.0 (1.0 – 3.0)	5.25 (0.0 – 12.0)[c]	2.0 (1.0 – 2.0)
AUC_{0-t} (ng/mL× h)	2.56 ± 3.50	38.07 ± 12.88	6.64 ± 7.50	57.93 ± 29.38
$AUC_{0-\infty}$ (ng/mL×h)	NC	46.59 ± 18.84[b]	NC	66.59 ± 32.93
$t_{1/2}$ (h)	NC	8.40 ± 3.79[b]	NC	8.91 ± 3.91

Values are arithmetic means ± SD, except for t_{max}: Median (range). [a]n = 6; [b]n = 8; [c]n = 10; NC = Not calculated.

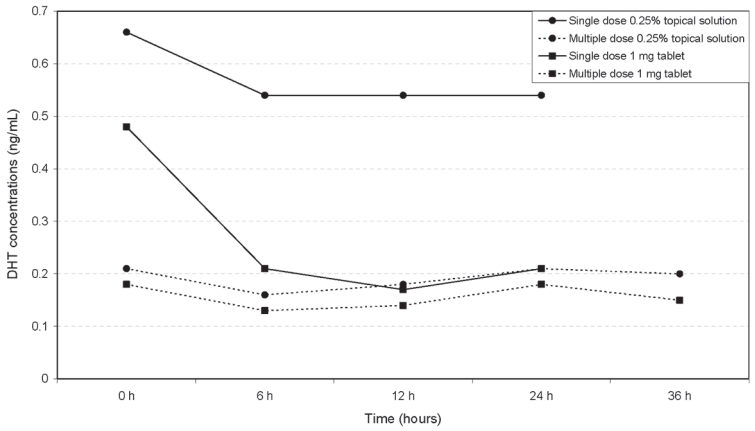

Figure 3. Dihydrotestosterone plasma concentrations vs. time profiles after single and multiple administration of finasteride 0.25% (2.275 mg) topical solution b.i.d. (● circle) or finasteride 1 mg oral tablet o.d. (■ square). Linear scale.

plasma finasteride levels were below the lower quantification limit of the analytical assay at most assessment times, except for sporadic very low concentrations detected between 16 and 24 hours post-dose for 5 of the 11 subjects included in the analysis (Figure 2), resulting in a median t_{max} of 20 hours (Table 2). Multiple applications of the topical solution b.i.d. for 1 week resulted in detectable finasteride concentrations in most samples, although at very low levels. Mean C_{max} and AUC values obtained after multiple administration of the topical solution were, in fact, ~ 15 and 9 times lower than the mean C_{max} and AUC_{0-t} calculated after the last multiple dose of the reference formulation. As expected, differences in finasteride C_{max} and AUC values between test and reference formulations were statistically significant ($p < 0.0001$).

No clear absorption and elimination phases were available from the individual pharmacokinetic profiles for the topical formulation, and thus the extrapolated parameters $t_{1/2}$ and $AUC_{0-\infty}$ could not be calculated.

Pharmacodynamics – effects on plasma androgens

Mean baseline plasma DHT levels were 0.66 ± 0.18 and 0.48 ± 0.13 ng/mL for the topical solution and the reference tablet, respectively. Mean baseline plasma testosterone levels were 6.24 ± 1.55 ng/mL for the solution and 5.69 ± 1.91 ng/mL for the tablet.

After single dose (day 1), a clear suppressive effect on plasma DHT was evident with the oral tablet at all post-dose assessment times (~ 56 – 64% reduction), whereas the reduction in plasma DHT caused by the topical formulation was much less pronounced (~ 18 – 19%) (Figure 3, Table 3). On day 1 there was a significant difference between treatments in plasma DHT levels at all post-dose assessment times ($p < 0.0001$).

Notably, after multiple dose treatment, plasma DHT was reduced by 67.95 – 75.19% after administration of finasteride 0.25% topical solution b.i.d., and by 61.87 – 71.97% after administration of the 1 mg tablet o.d. (Table 3). No significant difference between the two treatments in DHT levels was present at pre-dose, 6 hours and 24 hours after the last multiple dose ($p \geq 0.1092$). At 12 and 36 hours post-dose the differences were only marginally significant ($p \leq 0.0434$). These results confirm a considerable and similar inhibition of DHT after 1 week treatment with the finasteride 0.25% topical solution b.i.d and the oral 1 mg tablet o.d.

Table 3. Percentage of change (%) in DHT levels from pre-dose (baseline) to post-dose values for finasteride 0.25% (2.275 mg) topical solution and finasteride 1 mg oral tablet

Change from baseline (%)				
	Single dose		Multiple dose	
Time (h)	Finasteride 0.25% topical solution n = 11	Finasteride 1 mg tablet n = 12	Finasteride 0.25% topical solution n = 11	Finasteride 1 mg tablet n = 12
Pre-dose	0.00	0.00	–67.95	–61.87
6	–19.45	–56.36	–75.19	–71.97
12	–18.11	–63.73	–72.19	–70.40
24	–18.81	–55.79	–68.78	–63.28
36	NA	NA	–69.95	–68.07

NA = Not applicable (determinations were up to 12 hours after single dose).

Changes from baseline in plasma testosterone after 1 week of treatment were –18.8 – +8.7% with the topical formulation and –19.8 – +12.5% with the reference tablet. A marked inter-individual variation in response was observed within each group. No significant differences in testosterone levels between treatments were observed ($p \geq 0.3748$ and $p \geq 0.0844$ for the single and multiple doses, respectively).

Local tolerability and safety

Local tolerability of the topical formulation was excellent, with no signs or symptoms detected at the scalp application site throughout the study. No clinically significant adverse events occurred.

Discussion

In this exploratory pharmacokinetic and pharmacodynamic study in healthy men with androgenetic alopecia, administration on the scalp of the newly developed finasteride 0.25% topical solution (1 mL) b.i.d. for 1 week decreased plasma DHT to levels comparable to those obtained with the reference 1 mg tablet administered o.d., despite the nearly negligible systemic absorption with the test formulation. Plasma DHT was in fact reduced by ~ 68 – 75% after multiple scalp application of the 0.25% topical solution b.i.d., and by ~ 62 – 72% after multiple administration of the 1 mg tablet o.d.

The results obtained in the present study are consistent with the data reported in the literature. Ohtawa et al. [26] showed that after multiple oral administrations of 5, 10, 20, 50, and 100 mg finasteride, serum DHT was significantly reduced and remained suppressed up to 7 days after the final dosing. Roberts et al. [27] found that an effect on serum DHT levels was demonstrated for finasteride doses ≥ 0.2 mg/day, with the 1 mg and 5 mg dose regimens showing the same inhibitory effect of 60 – 70%. This finding was confirmed by Rosner's work [13], which reported that oral administration of 1 mg and 5 mg finasteride results in approximately equal changes in serum, prostatic and scalp DHT. In a large clinical study by Drake et al. [9], serum DHT was reduced by 49.5% after administration of finasteride at 0.05 mg/day and by ~ 70% after 0.2 – 5 mg/day for 42 days. Notably, finasteride C_{max} and $AUC_{0–24h}$ following single administration of the 0.2 mg oral tablet were 0.56 ng/mL and 2.19 ng/mL×h, as compared to values of 9.89 ng/mL and 49.29 g/mL×h for the 1 mg tablet [28]. Mean C_{max} and $AUC_{0–24h}$ values after single dose of the 0.2 mg tablet were ~ 18 and 22.5 times lower than the mean C_{max} and $AUC_{0–24h}$ calculated for the 1 mg dose. Drake et al. [9] also reported that, despite the lower systemic exposure with the 0.2 mg formulation with respect to the 1 mg tablet, the effect on serum DHT was the same for the two doses and corresponded to 70%, similarly to the result obtained in our study.

It is worth pointing out that there were no statistically significant differences in hair counts using patient estimates, physician estimates and global photographic assessment between the 0.2 and the 1 mg doses [27, 29].

As previously reported by some authors [6, 7, 8, 9, 13, 26, 30], during the study no relevant changes occurred for plasma testosterone with either treatment. However,

a 10 – 15% increase in serum testosterone, which remained within the physiological range, was previously observed after long-term treatment with 5 mg finasteride [31]. In the study by Drake et al. [9], significant increases in median serum testosterone levels from baseline were observed in the placebo group, and in the 0.01, 0.05, and 1 mg finasteride groups but not in the 0.2 and 0.5 mg dose groups.

Results of the present study confirmed a favorable local tolerability of the topical solution after 1-week applications on the scalp. However, safety profiles of the two study products could not be properly investigated because the subjects were treated for only 1 week, as opposed to the long-term treatments (months or years) commonly used in the clinical practice. Topical finasteride applications clearly induced a systemic decrease in DHT at the multiple dose regimen investigated in the present study despite the limited sample size of this exploratory study. Further studies at different dose regimens, e.g., once a day applications and/or lower volumes, will be conducted in order to evaluate whether substantial and selective decreases in scalp DHT, as opposed to plasma DHT, could be obtained at lower doses of this locally acting formulation.

The doses of the investigational products were administered at the clinical center, assuring 100% compliance with study treatment. The study end-points were based on objective assessments, i.e., the determination of finasteride, testosterone and DHT levels in study samples by blinded analysts. To increase the reliability of the study end-points, the subjects were confined in the clinical center under the supervision of clinical staff during the entire treatment and evaluation period.

Conclusions

In conclusion, we found a strong and similar inhibition of plasma DHT after multiple doses of the topical and tablet formulations. As expected, finasteride systemic exposure was significantly lower with the topical than the oral product. Considering these findings, it would be interesting to investigate the effects of P-3074 on DHT levels in plasma and scalp biopsies at different dose regimens, e.g., multiple applications o.d. and/or lower volumes, in order to further investigate whether the novel topical formulation could offer an effective and safe alternative for androgenetic alopecia treatment in men.

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Conflict of interest

Maurizio Caserini and Renata Palmieri are employees of Polichem S.A., which funded this study. Milko Radicioni, Chiara Leuratti and Ottavia Annoni are employees of CROSS Research S.A. The relationship between the Sponsor and CROSS Research S.A. was regulated by financial agreements.

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