Finasteride in the treatment of men with frontal male pattern hair loss

Background. Finasteride, a specific inhibitor of type 11 5a-reductase, decreases serum and scalp dihydrotestosterorie and has been shown to be effective in men with vertex male pattem hair loss.
Objective: This study evaluated the efficacy of finasteride 1 mg/day in men with frontal (anterior/mid) scalp hair thinning.
Methods: This was a 1-year, double-blind, placebo-controlled study followed by a 1-year open extension. Efficacy was assessed by hair counts (I CM2 circular area), patient and investigator assessments, and global photographic review.
Results: There was a significant increase in hair count in the frontal scalp of finasteride-treated patients (P < .00 1), as well as significant improvements in patient, investigator, and global photographic assessments. Efficacy was maintained or improved throughout the second year of the study. Finasteride was generally well tolerated.
Conclusion: In men with hair loss in the anterior/mid area of the scalp, finasteride 1 mg/day slowed hair loss and increased hair growth.

Male pattern hair loss, or androgenetic alopecia, is a common condition with both genetic and hormonal origins. Typically, there is progressive loss **and thinning of hair in an** easily recognizable pattem of bitemporal and anterior/mid scalp recession or vertex thinning. Although the rate of hair loss varies in individual men, the cyclical process is slow, such that over several years, terminal hairs

are gradually replaced by progressively finer and less pigmented miniaturized hairs.

Although the genetic component is still being elucidated, the essential involvement of androgens has been known for more than 50 years. It is now clear that dihydrotestosterone rather than testosterone is the principal androgen responsible for male pattern hair loss. This was confirmed by the observation that men with inherited type 11 5a-reductase deficiency have low levels of dihydrotestosterone and normal to high levels of testosterone, but do not experience male pattern hair loss. Furthermore, it has been shown that baseline dihydrotestosterone levels are higher in balding scalp versus hairy scalp.

Finasteride, a specific inhibitor of the human type II 5a-reductase enzyme, has been shown to reduce both serum and scalp skin dihydrotestosterone levels in balding men. Recent data have also demonstrated that finasteride 1mg/day increases scalp hair in men with vertex thinning. Because hair loss in the frontal (anterior/mid) region of the scalp is highly visible, and therefore important to patients, this study was undertaken to assess the efficacy and safety of finasteride in men with frontal (anterior/mid) scalp thinning.

PATIENTS AND METHODS

Study design

This was a multicenter, double-blind, placebo-controlled study conducted at 45 investigational sites in the United States. The study was approved by the institutional review board at each center, and all men gave written informed consent. After a 2-week, single-blind placebo run-in period, each subject was randomized to receive either oral finasteride 1 mg or placebo once daily for 12 months. All men who elected to enter the open extension received finasteride 1 mg daily during a second year of study.

The primary end point, hair count, was assessed in a blinded manner at months 6, 12, and 24. Individual photographs of the anterior/mid scalp were obtained at months 6, 12, and 24, and were reviewed in a blinded manner by a panel of expert dermatologists at the end of the trial. Investigator and patient assessments, obtained with a validated questionnaire, were obtained every 3 months during the first year and every 6 months thereafter.

Subjects were instructed to maintain the same hair style, and to refrain from dyeing their hair or using any hair enhancement products or procedures throughout the study. A standard shampoo (Neutrogena T/Gel, Neutrogena Corp, Los Angeles, Calif) was given to all subjects to use throughout the study period.

Patient selection

Men were eligible for enrollment into the study if they were between 18 and 40 years of age, in good physical and mental health, and had typical male pattem hair loss with modified Norwood/Hamilton grade II, grade II vertex, IIa, III, or III vertex pattern hair loss as well as recent or ongoing mild to moderate thinning of their hair in the frontal area of the scalp. The frontal area of the scalp was defined as those areas anterior to the vertex.

Evaluation procedures

Hair counts. Hair counts were obtained from computer assisted scans of standardized macrophotographs of clipped hair in a defined target area (1 cm2), centered on a tattoo located in the anterior or mid area of the scalp. Macrophotographs were converted into dot maps of each visible hair by trained technicians, validated for precision, and blinded to patient, treatment, and time.

Patient self-assessment. Patient self-assessment of hair growth was determined by means of a validated self-administered questionnaire comprising 6 questions, each of which asked the patient about a specific aspect of their hair compared with the start of the study (appearance of hair, growth of hair, slowing down hair loss, satisfaction with appearance of their hair, satisfaction with the frontal hairline, and satisfaction with their hair overall).

Investigator assessment. Investigators assessed each patient by means of a 7-point scale to answer the following question: "As the investigator, how would you subjectively rate the patient's hair at this time point compared to baseline?" The options for the investigator were as follows: don't know, -3 = greatly decreased, -2 = moderately decreased, -1 = slightly decreased, 0 = no change, 1 = slightly increased, 2 = moderately increased, 3 = greatly increased.

Global photographic assessment. Standardized global photographs of the anterior/mid area of the scalp were taken, before clipping the patient's hair for the macrophotographs, by means of a stereotactic device in which the patient's head was placed to ensure consistency of patient positioning and photographic distance. Before the global photographs were taken, the patient's hair was combed in a consistent manner for each patient so that the balding area could be optimally viewed. At the end of the study, an expert panel of 3 dermatologists evaluated hair growth or loss from baseline by comparing baseline with follow-up photographs of each subject by means of the same scale as the investigator assessment.

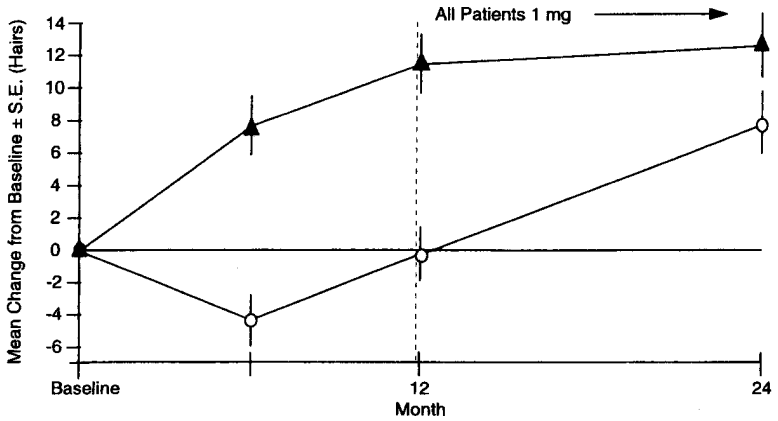

Fig 1. Hair count mean change from baseline (--t 1 SE) during 1-year double-blind study and second-year open extension in cohort of men who entered the open extension portion.
/\ - Finasteride 1 mg for 12 months followed by finasteride 1 mg for another 12 months;
O - placebo for 12 months followed by finasteride for 12 months.

Table 1. Baseline characteristics of men randomized

	Finasteride 1 mg (n = 166)	Placebo (n = 160)
Age (y) (mean± SE)	33 ± 0.4	32 ± 0.4
Age (y) at which hair loss began (mean ± SE)	26 ± 0.6	25 ± 0.4
No. (%) of patients with family history*	132(80.5)	128(82.1)
Baseline hair count (mean ± SE) t	211 ± 4	219 ± 4
No. (%) of patients with hair loss pattern t		
Grade II vertex	30 (18.1)	40 (25)
Grade IIa	8 (4.8)	5 (3.1)
Grade II vertex	30 (18.1)	39 (24.4)
Grade III	27 (16.3)	35 (21.9)
Grade III vertex	71 (42.8)	41 (25.6)

*Family history = Parents or siblings with androgenetic alopecia.
t Measured in a 1-cm2 circle in anterior mid-scalp.
f According to a modified Norwood-Hantilton scale.

Photographic procedures. Separate cameras (Nikon N-6006 camera with a Nikon 60 min f2.8 lens) with a CSI Twin Flash (Canfield Scientific, Inc, Fairfield, NJ) and separate rolls of film (Kodak KR-64 35 mm slide) were used for the macro and global photographs. Film emulsion, lighting, framing, exposure, and reproduction ratios were held constant. Photographs were processed at Qualex Laboratories, Fairlawn, New Jersey, and returned to Canfield Scientific, Inc for technical evaluation and quality assurance.

Statistical analysis

Twelve-month hair count were the primary efficacy endpoint of the study and were assessed by evaluating the change from baseline in all subjects (intention-to-treat population).

Analysis of variance (ANOVA) was used to compare the change from baseline among treatment groups. The analysis of hair counts in men who continued into the second year of the study (open extension) included all men with, a hair count at month 24. The patient self-assessment questionnaire was analyzed by means of the global test of treatment differences across all 6 questions as well as by evaluating individual questions. The investigator and global photographic assessments were analyzed by means of the rating scores at each time point. In addition, the percent of subjects with a positive self-assessment, investigator assessment, or global photographic assessment (defined as responses representing improvement) was determined.

RESULTS

Baseline characteristics

A total of 326 men with active mild to moderate hair loss/thinning in the frontal area enrolled in the study. Approximately 50% of the men also had some degree of vertex hair loss. The 2 treatment groups were similar in terms of all baseline characteristics (Table 1). Eighty-nine percent of finasteride-treated subjects and 86% of placebo-treated subjects completed the 1-year double-blind trial. Dropouts in both treatment groups were predominantly because of loss of follow-up (4% in each

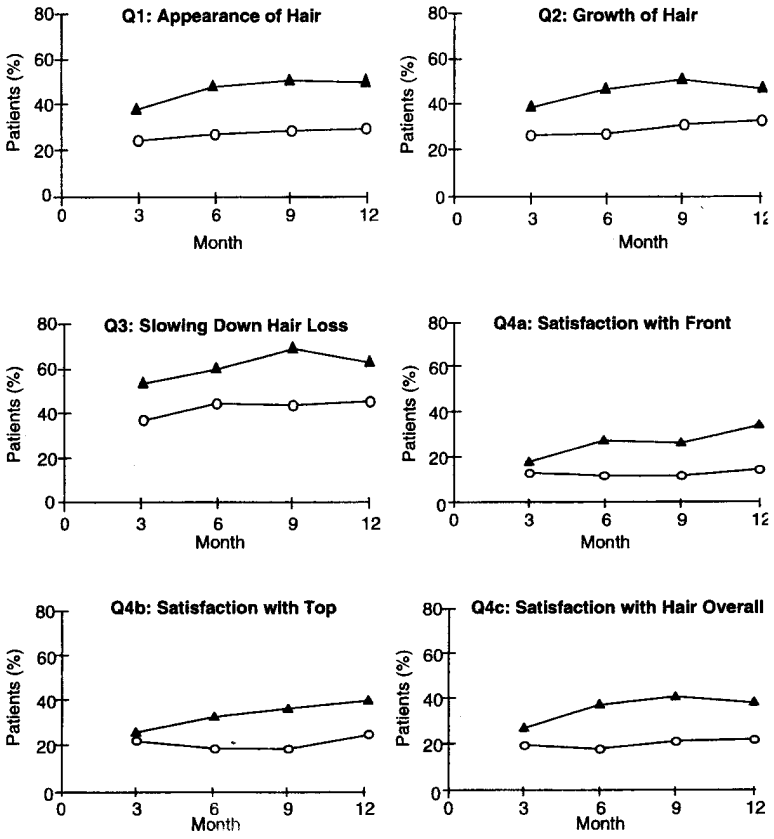

Fig 2. Percent of patients with positive self-assessment for each question over time during 1-year double-blind study. /\ - Finasteride 1 mg; O - placebo.

treatment group). Two patients (1.2%) in the finasteride group discontinued because of lack of efficacy. Two hundred fifty-six men enrolled into the second year (open extension portion) of the trial (133 from the finasteride group and 123 from the placebo group).

Hair count

Over the course of the first year of the study, mean hair count in a 1cm 2 circular area increased by 9.6 ± 1.5 hairs (mean ± SE) in the finasteride treated group and decreased by 2.0 6± 1.5 hairs) in the placebo group (11.6 ± 2.0 hair difference, P < .001). At month 12, 70% of finasteride-treated patients demonstrated no further frontal hair loss by hair count (ie, hair count was either increased or unchanged), whereas 56% of placebo-treated patients continued to lose hair (ie, had a decrease in hair count). The improvement in mean hair count was seen at the first assessment (month 6) and was maintained through 24 months in those men who continued receiving finasteride therapy in the open extension (Fig 1).

Patient self-assessment

The global test analysis of all 6 questions of the patient self-assessment questionnaire demonstrated significantly greater efficacy for the finasteride group than the placebo group as early as the first assessment (month 3; $P < .011$), and at all subsequent time points ($P < .001$). Individually, questions 1 (appearance of hair) and 3 (slowing down hair loss) demonstrated significant improvement for men in the finasteride group as early as month 3 compared with the placebo group ($P < .050$). By month 6, and continuing through to the end of the study, there was a significant ($P < .050$) difference between the treatment groups in all 6 individual questions. In addition, the percent of subjects with a positive self-assessment was consistently higher in the finasteride group for each question at all time points (Fig 2). The greatest positive response

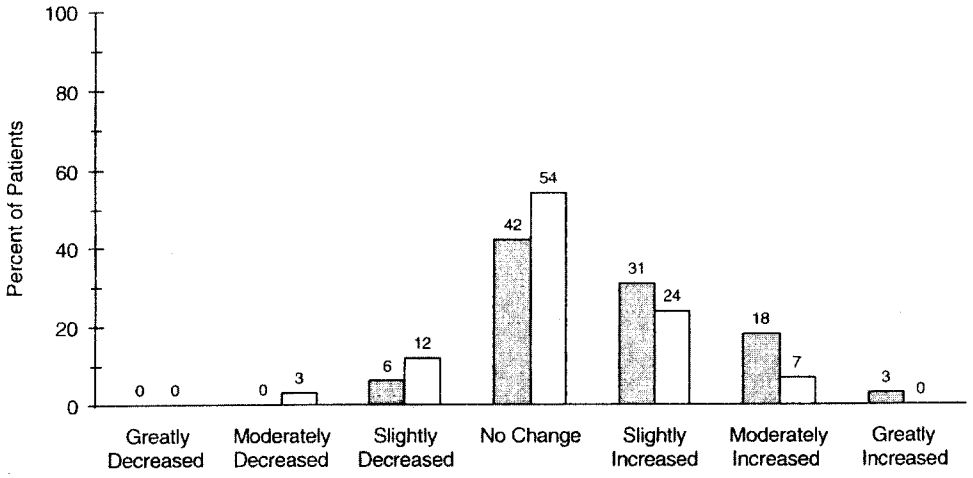

Fig 3. Percent of patients with positive investigator assessment at month 12 of double blind study. *Shaded box,* Finasteride 1 mg, n = 156*; Open box,* placebo, n = 154.

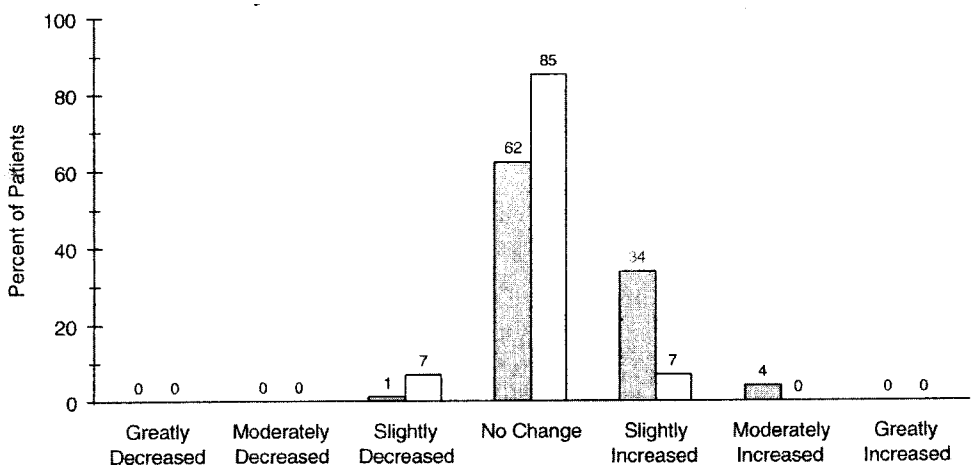

Fig 4. Percent of patients with positive global photograph assessment at month 12 of double-blind study. *Shaded box,* Finasteride 1 mg, n = 155; *Open box,* placebo, n = 150.

to finasteride (65%) at month 12 was seen in question 3, effectiveness in slowing hair loss. During the second year open extension of the study there was continued improvement with use of finasteride (data not shown).

Investigator clinical assessment

The investigator assessment of hair growth demonstrated significantly greater efficacy for the finasteride group over the placebo group at all time points ($P < .001$) beginning at month 3. The magnitude of the effect of finasteride and the difference from placebo increased over time, and the percent of subjects rated by the investigator as having improved hair growth also increased through out the study. By month 12, 52% of subjects in the finasteride group were rated as improved compared with 3 1 % of those in the placebo group (Fig 3). Further improvements in investigator assessments were seen through the second year open extension portion of the study (data not shown).

Global photographic assessment

Analysis of global photographs demonstrated

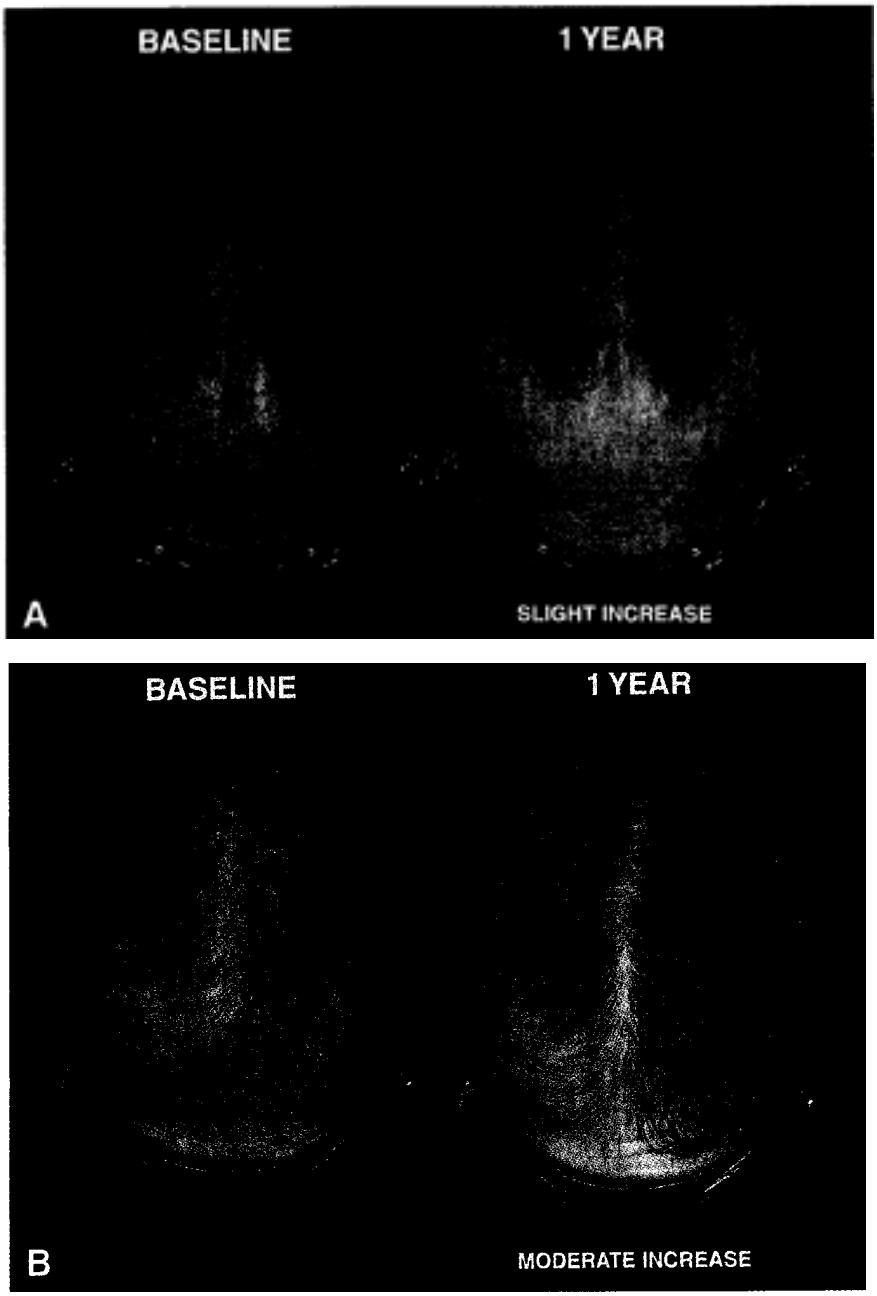

Fig 5. Baseline and month 12 global photographs of men treated with finasteride rated as having (A) slightly or (B) moderately increased hair growth from baseline by expert panel review.

significant improvement in men treated with finasteride compared with those treated with placebo at months 6 and 12 ($P < .00\ 1$). By month 12, 37% of men in the finasteride group were rated as improved compared with 7% in the placebo group (Fig 4). These improvements were maintained through the second year of the study. Fig 5 provides examples of patients receiving finasteride at baseline and after 1 year who were rated as having slightly or moderately increased hair compared with baseline.

Safety

Over the course of the study, finasteride was generally well tolerated. There was no significant increase in clinical or laboratory adverse experiences in the finasteride group compared with

placebo. The only drug-related adverse experiences were sexual adverse effects, and were reported in approximately 2% of men in both treatment groups (2 patients in each treatment group reported decreased libido, 1 patient in the placebo group reported an ejaculation disorder, and 1 patient in the finasteride group reported impotence). No patients discontinued because of a sexual adverse event, and for most patients the adverse experience resolved while continuing in the study. There was no increase in any drug-related adverse experience reported through the second year of treatment.

DISCUSSION

During the past 50 years, the causes of male pattern hair loss have been more clearly defined, including its polygenic nature and association with androgens. It is now clear that dihydrotestosterone is important in the pathogenesis of this condition, because men with an inherited deficiency of 5a-reductase and decreased dihydrotestosterone levels do not experience bitemporal recession or androgenetic alopecia, and finasteride has been shown to be efficacious in the treatment of men with vertex hair loss. The present study extends these findings by demonstrating efficacy in the anterior and mid area of the scalp.

Although the present study was designed specifically to look at the efficacy in men with frontal scalp hair loss, approximately half of the patients enrolled also had some degree of vertex hair loss, consistent with the concept that male pattern hair loss presents as a continuum of thinning areas in many men. Thus men included in this study represented a large range of patterns of balding, including men with thinning in one or more different areas of the scalp.

Scalp hair counts at month 12 revealed that men treated with finasteride had a relative mean increase of 12 hairs in a 1-cm2 circular area compared with placebo. When considering the results in men with vertex hair loss (demonstrating a 107 hair difference from placebo in a 5.1 cm2 area at the leading edge of the vertex bald spot), this may appear to be less of an improvement. However, hair count data from vertex and frontal hair loss studies cannot be directly compared because of the differences in these studies in both the location of the counting area as well as the baseline hair density. In general, the lower the baseline hair density, the greater the increase in scalp hair with finasteride. Men enrolled in the present study had hair counts determined in areas of mild to moderate thinning in the frontal (anterior and mid) area of the scalp (mean baseline hair count = 215 hairs/cm2), in regions where the clipped/tattooed target area for hair counting could be cosmetically concealed to avoid embarrassment during the study. On the other hand, men in the vertex studies had hair counts determined at the anterior leading edge of the bald spot, with lower hair density at baseline (mean baseline hair count = 876 hairs/5.1 cm2, or approximately 172 hairs/cm2). Therefore, it is not surprising that the relative increase in hair count would be higher in the vertex studies than in the frontal hair loss study.

The significance of the improvement in hair count seen with finasteride was substantiated by the improvements seen in the patient self-assessment questionnaire. Approximately 50% of the men on finasteride noted improvement in the appearance of their hair, and almost 70% of men reported slowing of their hair loss. In addition, patient satisfaction with their hair, a difficult parameter to change in any condition visible to patients, also improved over the course of the study. The patient assessment results of this study were remarkably similar to those seen in the vertex studies, attesting to the cosmetic significance of the hair count changes in such a visible area of the scalp. Both the investigator assessment and the independent photographic review by a panel of dermatologists demonstrated superiority of finasteride over placebo, and supported the cosmetic improvements noticed by patients during the study.

Although the improvements in hair count were seen as early as 6 months in the present study and were maintained over the course of 24 months in those patients who enrolled into the open extension, the more subjective assessments continued to show improvements over time. It appears that finasteride acts initially to slow down the miniaturization of hairs and to stimulate hair growth. With continued therapy, the newly grown hairs become longer and thicker. Because hair cycling is a slow process, it is not surprising that these effects improve slowly over time. Finasteride is directed at correcting the underlying pathophysiology of androgenetic alopecia; it therefore follows that the initial effects continue to improve over time.

In this study, there were no adverse effects seen significantly more often with finasteride than placebo. It is noteworthy that in other larger studies, the percent of patients with any drug-related sexual adverse experience was higher in men receiving finasttride than placebo (3.8% vs. 2.0% in the finasteride versus placebo groups). These side effects cleared in men who stopped taking finasteride, and disappeared in most men who continued taking fmasteride.

In summary, this study in men with hair loss in the anterior and/or mid areas of the scalp demonstrates that fmasteride increases hair counts and results in significant improvements in scalp hair noticeable to the patient, investigator, and an expert panel of dermatologists reviewing global photographs. Improvements in the appearance of hair as well as slowing of hair loss were noted by men receiving finasteride as early as 3 months into the study. Additionally, maintenance or improvement of the effects of finasteride were seen in those men who continued for up to 24 months of therapy. Finally, finasteride therapy was generally well-tolerated over the course of the study. The results of this study extend the efficacy of finasteride I mg to men with male pattern hair loss and thinning in the frontal (anterior/mid) area of the scalp.