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The importance of dual 5?-reductase inhibition in the treatment of male pattern hair loss: Results of a randomized placebo-controlled study of dutasteride versus finasteride
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Background
Male pattern hair loss (MPHL) is a potentially reversible condition in which dihydrotestosterone is an important etiologic factor.

Objective
Our aim was to evaluate the efficacy of the type 1 and 2 5?-reductase inhibitor dutasteride in men with MPHL.

Methods
Four hundred sixteen men, 21 to 45 years old, were randomized to receive dutasteride 0.05, 0.1, 0.5 or 2.5 mg, finasteride 5 mg, or placebo daily for 24 weeks.

Results
Dutasteride increased target area hair count versus placebo in a dose-dependent fashion and dutasteride 2.5 mg was superior to finasteride at 12 and 24 weeks. Expert panel photographic review and investigator assessment of hair growth confirmed these results. Scalp and serum dihydrotestosterone levels decreased, and testosterone levels increased, in a dose-dependent fashion with dutasteride.

Limitations
The study was limited to 24 weeks.

Conclusion
Dutasteride increases scalp hair growth in men with MPHL. Type 1 and type 2 5?-reductase may be important in the pathogenesis and treatment of MPHL.

Abbreviations used: BPH, benign prostatic hyperplasia, DHT, dihydrotestosterone, MPHL, male pattern hair loss, PHL, pattern hair loss
Article Outline

Pattern hair loss (PHL) is a genetically determined, potentially reversible type of hair loss. It is limited largely to the top of the scalp and is characterized by recognizable patterns of hair loss in men and in some women. Miniaturization of the hair follicles and shortening of the anagen phase of hair growth occurs in involved hairs.1, 2, 3 Although testosterone is the major circulating androgen, to be maximally active in scalp hair follicles it must first be converted to dihydrotestosterone (DHT) by the enzyme 5?-reductase. The importance of DHT as an etiologic factor in male pattern hair loss (MPHL) is shown by the absence of this condition in men with a congenital deficiency of type 2 5?-reductase,4 and by varying amounts of hair regrowth in men with MPHL treated with finasteride, a selective type 2 5?-reductase inhibitor.5 A type 1 5?-reductase, which also metabolizes testosterone to DHT, is distinguished from the type 2 enzyme by its optimal pH range in vitro and its location and amount in different tissues.6 In the skin, type 1 5?-reductase is the principal isoenzyme in sebaceous and sweat glands.7, 8 The mRNA and protein for both isoenzymes have been found in hair follicles, although this is not a universal finding.9, 10, 11, 12 There is no recognized genetic deficiency of type 1 5?-reductase in humans to assess its role in MPHL, and a type 1 5?-reductase inhibitor has not previously been evaluated for its effect on MPHL.

Dutasteride (Avodart) inhibits both type 1 and type 2 5?-reductase13 and is approved at the 0.5-mg dose for treatment of symptomatic benign prostatic hyperplasia (BPH). It is approximately

3 times as potent as finasteride at inhibiting type 2 5?-reductase and more than 100 times as potent at inhibiting the type 1 enzyme.14 The objective of this study was to evaluate, in a dose-response manner, whether dual 5?-reductase inhibition leads to improved efficacy in the treatment of MPHL. This randomized, multicenter study compared 4 doses of dutasteride with finasteride and placebo. Outcome measures included scalp hair growth and scalp androgen (testosterone and DHT) concentrations.

Materials and methods

Subject selection

Men 21 to 45 years of age were eligible for this study (GSK study ARIA2004) if they had mild-to-moderate MPHL (IIIv, IV [including IVa] or V Hamilton-Norwood patterns15). They must never have used a 5?-reductase inhibitor or have used any medication for alopecia during the previous 6 months. They must have had no significant health problems and must not have taken any androgenic or antiandrogenic drugs during the previous 6 months. All men provided written consent, and the protocol and consent form were approved by local institutional review boards. The study was carried out at 21 centers in the United States.

Protocol

After an initial screening evaluation, which included a medical history, physical examination, and laboratory evaluation, eligible men were randomized to receive dutasteride (0.05, 0.1, 0.5, or 2.5 mg), finasteride (5 mg), or placebo daily for 24 weeks. To ensure 45 evaluable subjects per treatment arm (a total of 270 evaluable subjects), 416 eligible subjects were enrolled and randomized to treatment. Subjects were assigned to study treatment in accordance with a predetermined randomization schedule, with a block size of 6, generated by the Medical Data Sciences Department, GSK. During the trial the code was held by GSK, and both investigators and patients were blinded to dutasteride, finasteride, and placebo treatments. The 5-mg finasteride dose was used, rather than the 1-mg dose that has been approved for treatment of MPHL, because the 1-mg dose was not commercially available at the time of study initiation. Furthermore, the 5-mg dose of finasteride had previously been shown to have efficacy in MPHL at least as great as the 1-mg dose.16

Assessments

The primary efficacy measure was hair regrowth based on hair counts, determined by means of a macrophotographic technique. The secondary efficacy measures were exploratory assessment of hair count, panel assessment of improvement from baseline, investigators' assessment of improvement, subjects' global assessment of improvement, and stage of MPHL using the modified Hamilton-Norwood classification.

For determination of target area hair counts, the hair in a 1-inch diameter (0.79 square inch) circle at the leading edge of the vertex bald spot was clipped to a length of about 1 mm. Reproducibility of this area was assured by placing a central tattoo and using a plastic target area template. Macrophotographs of the target area were taken with a camera system developed by Canfield Scientific Inc (Fairfield, NJ).17 Using a validated method to count hair, a technician manually converted the photographs into a dot map of the hairs in the target areas, which was then converted to hair counts using a computer imaging system. Hair counts were measured at baseline and at 12 and 24 weeks.

For expert panel assessment of global changes in the amount of hair, photographs were taken of both the vertex and frontal scalp. A panel of experts (Drs Olsen, Savin and Whiting), blinded as to treatment, was shown pairs of photographs from baseline and either 12 or 24 weeks of treatment from each view. The panel graded the changes in hair growth on a 7-point rating scale: greatly, moderately, or slightly decreased; no change; slightly, moderately or greatly increased; ratings were converted to numbers (–3 to +3) for statistical analysis.

Investigator and subject assessments were done at baseline and at 12 and 24 weeks. For the investigator assessments, baseline photographs were provided for comparative purposes and the investigators used the same 7-point rating scale as already described for the expert photographic panel. The subjects were asked to rate changes in the size of the vertex spot, hair loss on top of the scalp, bitemporal recession, the amount of hair shedding, hair quality, and overall satisfaction with hair growth on a 3-point rating scale (improved, no change, or worse).

Serum testosterone and DHT levels were measured at baseline and at 6, 12, and 24 weeks during the treatment phase, at 36 weeks (12 weeks after treatment was stopped), and thereafter at follow-up visits approximately every 2 months until DHT levels rose to within 25% of baseline. Serum testosterone was measured by Covance Laboratories (Indianapolis, Ind) using a standard radioimmunoassay. Serum DHT was measured by PPD Pharmaco (Richmond, Va) using a combination of gas chromatography and mass spectrophotometry in order to measure the very low serum DHT levels in subjects treated with dutasteride.

Scalp testosterone and DHT concentrations were determined in 4-mm biopsy specimens taken at baseline and again at 24 weeks. The biopsy specimens were taken anterolateral to the leading edge of the vertex bald spot, adjacent to the target area for hair counts. Scalp testosterone and DHT were measured after tissue homogenization and ether extraction, using the same assay as for serum measurements.

Statistical methods
Descriptive statistics are expressed as the mean (or mean change from baseline) with one standard deviation or median percentage change from baseline. The primary population of subjects to be statistically analyzed was the intention-to-treat population. Analysis of the hair count change from baseline was performed using a general linear model with effects for treatment, investigator cluster, and baseline hair count. Analyses of the panel and investigator assessments of improvement (on the 7-point scale) were performed using a general linear model with effects for treatment and investigator cluster. Analysis of the panel assessment was based on the average of the ratings of the 3 experts. Analyses of the percentage change from baseline in serum and scalp DHT and testosterone were performed using the following general linear model: log (postbaseline/baseline) = log (baseline) + treatment. For summary and analysis purposes, concentrations reported as below the limit of quantification were set to the lower limit of detection of the assay.

Pairwise comparisons between the dutasteride and placebo groups were performed using t tests from the general linear model in a step-down manner through the following hierarchical dose hypotheses at the two-sided 0.05 level of significance: dutasteride 2.5 mg versus placebo, dutasteride 0.5 mg versus placebo, dutasteride 0.1 mg versus placebo, dutasteride 0.05 mg versus placebo. Pairwise comparisons between the dutasteride and finasteride groups were performed in a similar manner. The pairwise comparison between the placebo and finasteride

groups was performed and interpreted at the two-sided .05 level of significance. Correlations between efficacy and scalp androgen concentrations were evaluated across treatment groups using Spearman's rank correlation statistics. Statistical analyses were performed using both LOCF—last observation carried forward—and ‘at visit’ analyses, with similar results for both. The ‘at visit’ analyses are reported in this article.

Results

Demography

The randomization of 416 subjects from 21 centers began in December 1997 and ended in June 1998. A total of 416 subjects entered the study, with 390 completing 12 weeks and 374 completing 24 weeks of the study. Demographics are summarized in Table I. The mean age was 36.40 ± 6.05 years (range 21-45 years). Ninety-one percent of subjects were Caucasian, 2% were black, 2% were Asian, and 5% were American Hispanic. The stage of baldness was as follows: IIIv 41%, IV 31%, IVa 5%, and V 23%.

Table I.
Demographics

	Dutasteride (mg)						
	Placebo	0.05	0.1	0.5	2.5	Finasteride (5.0 mg)	Total
No. of subjects	64	71	72	68	71	70	416
Age (y)							
Mean	35.8	35.5	36.4	36.1	35.8	38.5	36.4
SD	6.15	5.83	6.48	6.31	5.89	5.34	6.05
Min:Max	23:45	21:45	22:45	21:45	23:45	22:45	21:45
Baseline hair count							
Mean	920.3	1000.6	907.8	927.5	971.5	902.1	938.5
SD	236.36	302.12	224.27	219.84	247.32	262.86	251.7
Min:Max	432:1471	262:1723	317:1371	462:1377	449:1562	219:1712	219:1723
No.	64	70	72	67	70	70	413
Age at first balding (y)							
Mean	25.5	25.3	26.0	27.3	25.8	26.9	26.1
SD	5.62	5.03	6.94	6.22	5.88	6.26	6.04
Min:Max	15:40	18:40	15:42	12:41	14:44	15:41	12:44
No.	64	69	72	68	71	70	414
Stage of MPHL, No. (%)							
III vertex	26 (41)	26 (37)	31 (43)	29 (43)	28 (39)	29 (41)	169 (41)
IV	20 (31)	29 (41)	19 (26)	21 (31)	24 (34)	18 (26)	131 (31)
IVa	3 (5)	3 (4)	4 (6)	3 (4)	1 (1)	5 (7)	19 (5)
V	15 (23)	13 (1	18 (25)	15 (22)	18 (25)	18 (26)	97 (23)

Min:Max, Minimum:maximum; MPHL, male pattern hair loss; SD, standard deviation.

Target areas were located at similar areas anterior to the vertex balding. The mean and range of baseline hair counts for patterns IIIv, IV, IVa, and V was 939 (range 219-1723). There were no

significant differences in the groups with respect to age, race or degree of baldness. Reasons for dropout included the following: withdrawal of consent (n = 20), adverse events (n = 11), lost to follow-up (n = 6), protocol violations and other reasons (n = 5). There were no significant differences in dropout rates among the treatment groups. The average compliance among the groups, as assessed by pill counts, was 94% to 99%.

Hair counts

Mean baseline hair counts in the 1-inch target area circle varied from 902.1 to 1000.6 hairs and were not significantly different between groups. During the 24 weeks of the study, mean hair counts in the placebo group decreased by 32.3 ± 59.2 hairs, while hair counts increased in all active treatment groups (Fig 1). Dutasteride 0.1–2.5 mg and finasteride groups were significantly different from placebo for mean change in hair count from baseline at 12 and 24 weeks (P < .001) as follows: placebo, –26.5 (n = 56) and –32.3 hairs (n = 50); dutasteride 0.1 mg, 55 (n = 63) and 78.5 hairs (n = 5; dutasteride 0.5 mg, 71.3 (n = 59) and 94.6 hairs (n = 61); dutasteride 2.5 mg, 99.9 (n = 62) and 109.6 hairs (n = 62); and finasteride group, 52.1 (n = 6 and 75.6 hairs (n = 66) (Fig 1). The mean hair count in the 2.5-mg dutasteride group was significantly greater than the finasteride group at both 12 weeks (P < .001) and 24 weeks (P = .009). At 24 weeks, the percentage of subjects with at least a 10% increase in hair counts was 0%, 17%, 38%, 48%, and 56% for placebo, 0.05, 0.1, 0.5 and 2.5 mg dutasteride, respectively, and 41% for finasteride.

Fig 1. Mean changes in hair counts after 12 and 24 weeks, compared with baseline, for placebo, datasteride (0.05-2.5 mg), and finasteride (FIN). , P <= .05; , P <= .001 compared with placebo; †, P <= .05; ‡, P <= .001 compared with finasteride.

Expert panel assessment of global photographs

The 3-member panel assessed paired photographs of baseline versus 12 and 24 weeks of treatment in both the vertex (Table II) and frontal (Table III) regions. Their assessments were given numeric values from –3 (greatly decreased compared with baseline) to +3 (greatly increased compared with baseline), in order to permit statistical analysis. In the vertex photographs, dutasteride (0.1, 0.5, and 2.5 mg) and finasteride showed significantly greater improvement than placebo (P < .001) at both 12 and 24 weeks (Fig 2, A). Dutasteride 0.5 mg showed a significantly greater improvement than finasteride at 24 weeks (P = .026), whereas dutasteride 2.5 mg showed significantly greater improvements than finasteride at both 12 and 24 weeks (P < .001). At 24 weeks, the mean expert panel score was –0.04, 0.19, 0.47, 0.84 and 1.01 points for placebo, 0.05-, 0.1-, 0.5-, and 2.5-mg dutasteride groups, respectively, and 0.62 points for finasteride (Fig 2, A). The percentages of patients judged to have improved hair growth (slightly to greatly increased) at 24 weeks in the vertex photographs were 2%, 15%, 39%, 63%, and 78% for placebo, 0.05-, 0.1-, 0.5 and 2.5-mg dutasteride groups, respectively, and 57% for finasteride (Table II). The panel assessments of the vertex photographs correlated with changes in hair counts assessed by macrophotography (r = 0.41, P < .001).

Table II.
Expert panel assessment of changes in vertex photographs at 12 and 24 weeks

	Moderately decreased		Slightly decreased		No change		Slightly increased		Moderately increased		Greatly increased	
	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24
Placebo	0	0	7	8	90	91	3	0	0	2	0	0
0.05 mg Dut	0	0	5	10	83	75	13	12	0	3	0	0
0.1 mg Dut	0	0	0	0	70	61	28	33	2	7	0	0
0.5 mg Dut	0	0	0	0	65	37	31	40	5	21	0	2
2.5 mg Dut	0	0	3	0	46	22	35	48	15	28	1	1
5.0 mg FIN	1	0	3	0	67	43	25	48	4	9	0	0

Dut, Dutasteride; FIN, finasteride; Wk, week.

Values denote percentage of patients in each category.

Table III.
Expert panel assessment of changes in frontal photographs at 12 and 24 weeks

	Moderately decreased		Slightly decreased		No change		Slightly increased		Moderately increased		Greatly increased	
	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24	Wk 12	Wk 24
Placebo	0	0	0	2	95	87	5	12	0	0	0	0
0.05 mg Dut	0	0	13	5	81	73	6	20	0	2	0	0
0.1 mg Dut	0	0	0	0	81	67	17	30	2	3	0	0
0.5 mg Dut	0	0	0	0	77	52	21	30	2	18	0	0
2.5 mg Dut	0	0	1	1	68	37	29	36	1	25	0	0
5.0 mg FIN	1	1	3	1	87	52	9	36	0	9	0	0

Dut, Dutasteride; FIN, finasteride; Wk, week.

Values denote percentage of patients in each category.

Fig 2. Mean expert panel ratings of photographs after 12 and 24 weeks, compared with baseline, for placebo, dutasteride (0.05-2.5 mg) and finasteride (FIN). Assessments were made of photographs of the vertex (A) and frontal (B) regions on a 7-point scale from –3 (greatly decreased) to +3 (greatly increased). , P <=.05; , P <= .001 compared with placebo; †, P <= .05; ‡, P <= .001 compared with finasteride.

In the frontal region, the dutasteride 0.1, 0.5, and 2.5 mg groups improved significantly more than placebo at both 12 and 24 weeks (Fig 2, B). Finasteride was not significantly different from placebo at 12 weeks (P = .69) but was at 24 weeks (P < .001). At 12 weeks, the improvement in the 0.5-mg dutasteride group (0.28 ± 0.40) and in the 2.5-mg dutasteride group (0.37 ± 0.46) was significantly greater than the finasteride group (0.09 ± 0.39, P = .009 and P < .001, respectively). At 24 weeks, the improvement in the 2.5-mg dutasteride group (0.85 ± 0.79) was also significantly greater than the finasteride group (0.51 ± 0.66, P = .002). The proportions of patients judged to have improved hair growth (slightly to greatly increased) at 24 weeks in the frontal photographs were 12%, 22%, 33%, 48%, and 61% for placebo, 0.05, 0.1, 0.5 and 2.5 mg dutasteride, respectively, and 45% for finasteride (Table III). The proportion of patients with moderate or greater increases was higher with dutasteride 0.5 and 2.5 mg than with finasteride for both vertex and frontal photographs.

Investigators' global assessment

As for the expert panel assessment, the investigator assessments of hair growth were given numerical values from –3 (greatly decreased compared with baseline) to +3 (greatly increased compared with baseline). At the vertex, mean investigator ratings showed improvement in hair growth for the placebo group compared with baseline (0.44 ± 0.73 and 0.52 ± 0.86 at 12 and 24 weeks, respectively) (Fig 3, A). At 12 weeks, only the 2.5-mg dutasteride group (1.14 ± 0.85) showed a significant increase in investigator rating compared with placebo (P < .001), and this group was also significantly more improved than the finasteride group (0.66 ± 0.87) (P = .001). For vertex hair growth at 24 weeks, investigator ratings of 1.23, 1.34, and 1.85 points were given for 0.1-, 0.5-, and 2.5-mg dutasteride groups, respectively, and 1.21 points for the finasteride group, which were all significantly greater ratings compared with placebo (P < .001). In addition, the 2.5-mg dutasteride group (1.85 ± 1.01) was significantly more improved than the finasteride group at 24 weeks (1.21 ± 0.94, P < .001). The expert panel assessment of hair growth correlated with investigator assessment at the vertex (r = 0.52, P < .001) and at the frontal area (r = 0.42, P < .001) for 24-week evaluations.

Fig 3. Mean investigator ratings of improvement in vertex (A) and frontal (B) hair growth after 12 and 24 weeks, compared with baseline, for placebo, dutasteride (0.05-2.5 mg) and finasteride (FIN). Assessments were made of changes in hair growth on a 7-point scale from –3 (greatly decreased) to +3 (greatly increased). , P <= .05; , P <= .001 compared with placebo; †, P <= .05; ‡, P <= .001 compared with finasteride.

At the frontal scalp, the investigator rating highlighted a modest improvement in the placebo group compared with baseline (0.18 ± 0.51 at 12 weeks and 0.31 ± 0.70 at 24 weeks) (Fig 3, B). At 12 weeks, only the 2.5-mg dutasteride group (0.85 ± 0.87) showed a significant increase in

investigator rating compared with placebo (P < .001). The 2.5-mg dutasteride group also showed a significant increase compared with finasteride (P < .001) at 12 weeks. At 24 weeks, dutasteride 0.1, 0.5, and 2.5 mg and finasteride groups showed significantly more improvement than the placebo group. The 2.5-mg dutasteride group (1.38 ± 0.93) was also significantly more improved than finasteride (0.83 ± 0.95, P < .001).

Subjects' assessment
In general, the 0.1-, 0.5-, and 2.5-mg dutasteride groups and the finasteride group provided numerically higher self-assessment scores than the placebo group for each parameter on the self-assessment questionnaire at 12 and 24 weeks. Only the 2.5-mg dutasteride and the finasteride groups at 24 weeks were consistently significantly greater than the placebo group for all parameters on the questionnaire (P < .05) (Table IV).

Table IV.
Percentage of men with improvement in scalp hair after 24 weeks according to answers to a self-assessment questionnaire

Dutasteride (mg)
Placebo 0.05 0.1 0.5 2.5 Finasteride (5.0 mg)
Size of vertex spot 31 58 57 52 69 61
Hair loss on top of scalp 29 55 52 40 63 51
Bitemporal recession 16 28 27 18 31 39
Hair shedding 47 67 63 56 74 64
Hair quality 36 47 47 45 60 57
Overall satisfaction 42 58 57 56 72 61

P < .05 compared with placebo, based on the overall distribution of answers (improved, no change, worse).

Serum and scalp androgen levels
Serum DHT concentrations in all dutasteride groups were suppressed significantly compared with placebo (P <= .001) in a dose-related manner, with the greatest median suppression at 24 weeks occurring in the 0.5-mg (92%) and 2.5-mg (96.4%) dutasteride groups (Fig 4, A). The 0.1-mg dutasteride and finasteride groups showed a similar median degree of DHT suppression at 24 weeks (69.8% and 73.0%, respectively). Serum testosterone levels rose significantly in all active treatment groups, increasing by a median of 27.5% in the 2.5-mg dutasteride group, compared with 10.4% in the finasteride group (Fig 4, B). In the 0.5-mg dutasteride group, the median increase at 24 weeks was 23.8%, which is similar to previous findings.14, 18 Serum DHT concentration was inversely correlated with target area hair count (r = –0.49, P < .001), panel assessment of the vertex photographs (r = –0.50, P < .001), and investigators' assessments of the vertex hair growth (r = –0.37, P < .001). Twelve weeks after termination of treatment (36 weeks), the mean serum DHT was not significantly different from the baseline value in the placebo, dutasteride 0.05 mg and 0.1 mg groups and the finasteride 5.0 mg group. However, at 36 weeks, serum DHT had not yet returned to baseline for patients receiving dutasteride 0.5 mg and 2.5 mg (–11.03 and –88.4 median difference from baseline, respectively). This is

summarized in Fig 4, A. In subjects whose serum DHT was not within 25% of the baseline value after 36 weeks, serum DHT was measured at approximately 2-month intervals until levels had returned to within 25% of the baseline value. Serum DHT returned to within 25% of baseline in a median of 86 days after treatment (range 71-307 days) for the dutasteride 0.5 mg group and in a median of 155 days (range 72-421 days) for the dutasteride 2.5 mg group.

Fig 4. Median percentage changes from baseline in serum dihydrotestosterone (DHT) and testosterone (T), for placebo, dutasteride (DUT) (0.05-2.5 mg), and finasteride (FIN). Treatment was stopped after 24 weeks. All active groups were significantly different from placebo for both parameters at 6, 12, and 24 weeks (P <= .001).

Scalp DHT concentrations in the dutasteride groups were also significantly suppressed compared with placebo in a dose-related manner. As with serum DHT, the 0.1-mg dutasteride and finasteride groups showed a comparable degree of scalp DHT suppression (32% and 41%, respectively). Scalp DHT decreased by 51% with 0.5-mg dutasteride and by 79% with 2.5-mg dutasteride. Scalp testosterone levels significantly increased in all active treatment groups compared with placebo, increasing by 23%, 39%, 99%, and 222% with 0.05-, 0.1-, 0.5 and 2.5-mg dutasteride, respectively, and 23% with finasteride. Change in scalp DHT concentration was inversely correlated with change in target area hair count (r = –0.27), panel assessments of the vertex (r = –0.39), and investigators' assessments of the vertex (r = –0.2; the P value was less than .001 for all 3 correlations. The relationship between mean percentage change in scalp DHT and mean change in hair count is shown in Fig 5.

Fig 5. Relationship between 24-week mean percentage change from baseline in scalp dihydrotestosterone (DHT) and mean change in hair count for placebo, dutasteride (DUT) (0.05-2.5 mg), and finasteride (FIN).

Safety and tolerability

There were no significant differences in total adverse events, serious adverse events, or withdrawals due to adverse events among any of the treatment groups, including placebo. In total, 11 subjects withdrew because of adverse events: 3 were in the placebo group (irritable bowel syndrome and impotency), 7 in the dutasteride 0.1 mg group (decreased libido, malaise and fatigue, mood disorders, skin disorders, injuries caused by trauma, and gastrointestinal- and neurology-related complaints) and 1 in the dutasteride 0.5 mg group (gastrointestinal discomfort and pain). Some subjects had more than one adverse event.

As questions have previously arisen concerning a possible impact of 5?-reductase inhibitors on sexual function, these adverse events were examined in greater detail and are summarized in Table V. Decreased libido was noted in 2 subjects in the placebo group, 2 subjects in each of the 0.05-mg and 0.1-mg dutasteride groups, 1 subject in the 0.5-mg dutasteride group, 9 subjects in the 2.5 mg dutasteride group, and 3 subjects in the finasteride group. Of the 9 subjects with decreased libido in the 2.5-mg dutasteride group, 4 resolved while receiving therapy; 1 resolved within 3 weeks and another within 8 weeks of stopping drug therapy; in 1 subject, decreased libido continued after therapy had been stopped and was presumed by the subject to be unrelated to the trial or drug therapy; 2 subjects switched to finasteride at the end of the active phase and were lost to follow-up (dutasteride was not commercially available at the time the study ended). None of these 9 subjects discontinued study therapy because of this side effect. There was no increase among the active treatment groups in the reported incidence of impotence, with 3 subjects in the placebo group, 2 subjects in the 0.05-mg dutasteride group, and one subject in the finasteride group reporting such difficulty. These sexual adverse events were characterized as either mild or moderate in severity and only one subject's withdrawal was thought to be as a result of this adverse event (ie, decreased libido—in the 0.1-mg dutasteride group; Table V). The only subject to develop gynecomastia was in the placebo group.

Table V.
Proportion of subjects experiencing the most frequent sexual AEs following randomization, proportion of sexual AEs resolving (and those resolved during therapy), and proportion of sexual AEs leading to withdrawal from the study

	Dutasteride (mg)				
Placebo	0.05	0.1	0.5	2.5	Finasteride (5.0 mg)
No. of subjects in group	64	71	72	68	71	70
Decreased libido, No. (%)	2 (3)	2 (3)	2 (3)	1 (1)	9 (13)	3 (4)
Resolved on therapy	2	0	1	0	4	0
Resolved off therapy	0	1	1	1	2	3
Leading to withdrawal, No.	0	0	1	0	0	0
Ejaculation disorders, No. (%)	0 (0)	0 (0)	3 (4)	1 (1)	1 (1)	2 (3)
Resolved on therapy	—	—	1	0	0	0
Resolved off therapy	—	—	1	1	1	2
Leading to withdrawal, No.	0	0	0	0	0	0
Impotence, No. (%)	3 (5)	2 (3)	0	0	0	1 (1)
Resolved on therapy	1	1	—	—	—	0
Resolved off therapy	2	1	—	—	—	1
Leading to withdrawal, No.	2	0	0	0	0	0

AEs, Adverse events.

AEs occurring in more than 2% of subjects in at least one treatment group.

Discussion

Dutasteride, the first dual 5?-reductase inhibitor, is currently approved for treatment of symptomatic BPH. It is about 3 times as potent as finasteride at inhibiting type 2 5?-reductase and more than 100 times as potent at inhibiting type 1 5?-reductase.14 Whereas 5-mg finasteride decreases serum DHT by about 70%,19 dutasteride can decrease serum DHT by more than 90%.20

In this phase II, dose-ranging study, 2.5-mg dutasteride was superior to 5-mg finasteride in improving scalp hair growth in men between ages 21 and 45 years with MPHL as judged by target area hair counts, expert panel assessment, and investigator assessment at 12 and 24 weeks. From the investigator assessment of hair growth, a significant effect was evident at 12 weeks with 2.5-mg dutasteride but not until 24 weeks with finasteride. The subjects' assessment was less sensitive to changes in hair growth: this may have been at least partially due to the fact that this assessment used only a 3-point scale, compared with the 7-point scale used for the expert panel and investigator assessments. The effect of 24-week treatment with 5-mg finasteride in this study was similar to that previously reported by Kaufman et al for 52-week treatment with 1-mg finasteride5 and 5-mg finasteride.21 Kaufman et al21 showed that for 1-year treatment with 5-mg finasteride, the mean change from baseline hair count in a 1 inch diameter target area was 95 compared with 75.6 in the same-sized target area in this study, and the change in serum DHT was –69.2% compared with –73% reported herein. The mean change from baseline target area hair count in the phase III study evaluating 1-year treatment with 1-mg finasteride daily was 107 per 1-inch diameter target area.5 The greater efficacy of 2.5-mg dutasteride shown herein supports the dual role of type 1 and type 2 5?-reductase in the pathogenesis of MPHL.

The results of this study also highlight the importance of scalp DHT in the pathogenesis of MPHL. The 2.5-mg dutasteride dose was consistently superior to 0.5-mg dutasteride in promoting scalp hair growth. The 2.5-mg dose was also better than the 0.5-mg dose at suppressing scalp DHT (79% vs 51%), whereas it was only marginally better at suppressing serum DHT (96% vs 92%). This difference in the dose-response of serum and scalp DHT to inhibition with dutasteride is likely to be due to the greater contribution of type 1 5?-reductase to scalp DHT concentrations. In comparison with dutasteride, finasteride reduced scalp DHT by only 41%, a value similar to the 34% reduction reported previously by Dallob et al.19 In another study, by Drake et al,22 5-mg finasteride reduced scalp DHT by 69%. There is no obvious reason why the results of the study by Drake et al should differ from the present study or that of Dallob et al. However, in the Drake study, there was no dose-response relationship among finasteride groups, with 0.01-mg finasteride showing no suppression of scalp DHT and 0.05-, 0.2-, 1 and 5-mg finasteride all showing about the same degree of suppression. The present study included a larger number of subjects and showed a complete dose-response for DHT suppression ranging from 26% in the 0.05 mg dutasteride group to 79% in the 2.5 mg dutasteride group. In this context, 5 mg finasteride suppressed scalp DHT to a similar degree as 0.1 mg dutasteride group (41% and 32%, respectively). Many of the clinical effects (hair count changes, global panel assessment, and investigator assessment) were also similar in these two groups, supporting the similarity in scalp suppression between 5-mg finasteride and 0.1-mg dutasteride.

Both dutasteride and finasteride were well tolerated in this phase II study, and no new safety concerns have arisen in any of the phase II and phase III studies of dutasteride given at doses up to 5 mg daily (the 5-mg dose was used in a phase II study for BPH). Concerning possible sexual adverse events, there was no evidence in the present study that either dutasteride or finasteride was associated with impotence. However, 9 men in the 2.5-mg dutasteride group complained of

decreased libido, compared with 1 man in the 0.5-mg dutasteride group and 3 men in the finasteride group. As with previous studies with finasteride, this adverse event was characterized as either mild or moderate in severity and often resolved with continuation of the medication. In the 4-year follow-up of the phase III trials in BPH, dutasteride (0.5 mg) was well tolerated and the incidence of the most common sexual adverse events was low and tended to decrease over time.23

It should be emphasized that the approved dose of dutasteride for treatment of BPH is 0.5 mg daily and that limited data are available on the safety of higher doses. Dutasteride is not approved for treatment of MPHL, and the beneficial effects of dutasteride in MPHL must be weighed against the possible adverse effects reported during use in BPH, such as gynecomastia, reduced sperm count, and drug-drug interactions (in particular, interactions with cytochrome P-450 isozyme, CYP 3A4 inhibitors), as detailed in the US labeling for Avodart.24

The serum half-life of finasteride is 6 to 8 hours.25 Dutasteride has a serum half-life of approximately 4 weeks, and this long half-life was evident in the persistent suppression of DHT with the 0.5-mg and 2.5-mg doses after dutasteride treatment was stopped. Because of this long half-life, men being treated with dutasteride should not donate blood until at least 6 months past their last dose to prevent administration to a pregnant female transfusion recipient.

In conclusion, 2.5-mg dutasteride, a dual 5?-reductase inhibitor, improved hair growth in balding men more rapidly and to a greater degree than finasteride, a selective type 2 inhibitor. Dutasteride was generally well tolerated. The results of this study demonstrate the significant additive effect of inhibiting both type 1 and type 2 5?-reductase in the treatment of MPHL.

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b Fairview University Medical Center, Minneapolis

c Baylor Hair Research and Treatment Center, Dallas

d The Stough Clinic, Hot Springs

e Clinical Development, GlaxoSmithKline, Research Triangle Park

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The Dutasteride Alopecia Research Team includes W. Bergfeld, Z. Draelos, F. E. Dunlap, T. Funicella, S. Kempers, A. W. Lucky, D. J. Piacquadio, V. Price, J. L. Roberts, R. C. Savin, J. S. Shavin, L. Stein, D. Thiboutot, E. Tschen, G. F. Webster, and G. D. Weinstein.

Three patients were initially labeled by the principal investigator as having Hamilton-Norwood pattern VII, but the mean target area hair count of the vertex, 1021 (range 473-1562) indicated that this pattern was incorrect. The first author reviewed the representative scalp photographs and reassigned all 3 as Hamilton-Norwood pattern V.

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Subject: Re: Dutasteride Studie, 24 wochen
Posted by H_U_82 on Mon, 04 Aug 2008 23:54:12 GMT
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ist das phase III ???

ich habe aber nur einen satz mit phase III gelesen irgendwo...ansonsten nur 1 und 2...

Subject: Re: Dutasteride Studie, 24 wochen
Posted by Moses on Tue, 05 Aug 2008 08:57:07 GMT
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nein ist Phase 2, ich ändere am besten Überschrift.

Subject: Re: Dutasteride Studie, 24 wochen
Posted by haarakiri1 on Thu, 02 Apr 2009 08:56:17 GMT
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Ich dachte die hätten abgebrochen?

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by Cynic on Thu, 02 Apr 2009 21:47:34 GMT
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Die hatten mal Phase3 abgebrochen.
Aber die haben sie in Korea Jan08 nachgeholt. Seit Jan09 werten sie aus.

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by pill on Fri, 15 May 2009 15:57:28 GMT
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Wenn der ganze Text ins Deutsche übersetzt wäre, ouuu Mann
Spiele mich auch mit dem Gedanken Dutasterid 2-3 Mal die Woche zu nehmen (je 0,5mg).
Täglich Fin bleibt.
Da Dutasterid beide DHT Typen hemmt, und dadurch auch der Front gut ankommen müsste
(da dort ja beide DHT-Typen aktiv sind), spricht ja auch nichts dagegen.
Die Dosis (2-3 mal die Woche) dürfte den Körper auch nicht allzuviel Schaden.

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by haarakiri1 on Tue, 26 May 2009 15:10:32 GMT
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Moses schrieb am Mon, 04 August 2008 22:34The importance of dual 5?-reductase inhibition in the treatment of male pattern hair loss: Results of a randomized placebo-controlled study of dutasteride versus finasteride
Elise A. Olsen, MDa, Maria Hordinsky, MDb, David Whiting, PhDc, Dow Stough, MDd, Stuart Hobbs, PharmDe, Melissa L. Ellis, PharmDe, Timothy Wilson, MSe, Roger S. Rittmaster, MDe

Durham and Research Triangle Park, North Carolina; Minneapolis, Minnesota; Dallas, Texas; and Hot Springs, Arkansas

Background
Male pattern hair loss (MPHL) is a potentially reversible condition in which dihydrotestosterone is an important etiologic factor.

Objective
Our aim was to evaluate the efficacy of the type 1 and 2 5?-reductase inhibitor dutasteride in men with MPHL.

Methods
Four hundred sixteen men, 21 to 45 years old, were randomized to receive dutasteride 0.05, 0.1, 0.5 or 2.5 mg, finasteride 5 mg, or placebo daily for 24 weeks.

Results
Dutasteride increased target area hair count versus placebo in a dose-dependent fashion and

dutasteride 2.5 mg was superior to finasteride at 12 and 24 weeks. Expert panel photographic review and investigator assessment of hair growth confirmed these results. Scalp and serum dihydrotestosterone levels decreased, and testosterone levels increased, in a dose-dependent fashion with dutasteride.

Limitations
The study was limited to 24 weeks.

Conclusion
Dutasteride increases scalp hair growth in men with MPHL. Type 1 and type 2 5?-reductase may be important in the pathogenesis and treatment of MPHL.

Abbreviations used: BPH, benign prostatic hyperplasia, DHT, dihydrotestosterone, MPHL, male pattern hair loss, PHL, pattern hair loss
Article Outline

• Copyright

Pattern hair loss (PHL) is a genetically determined, potentially reversible type of hair loss. It is limited largely to the top of the scalp and is characterized by recognizable patterns of hair loss in men and in some women. Miniaturization of the hair follicles and shortening of the anagen phase of hair growth occurs in involved hairs.1, 2, 3 Although testosterone is the major circulating androgen, to be maximally active in scalp hair follicles it must first be converted to dihydrotestosterone (DHT) by the enzyme 5?-reductase. The importance of DHT as an etiologic factor in male pattern hair loss (MPHL) is shown by the absence of this condition in men with a congenital deficiency of type 2 5?-reductase,4 and by varying amounts of hair regrowth in men with MPHL treated with finasteride, a selective type 2 5?-reductase inhibitor.5 A type 1 5?-reductase, which also metabolizes testosterone to DHT, is distinguished from the type 2 enzyme by its optimal pH range in vitro and its location and amount in different tissues.6 In the skin, type 1 5?-reductase is the principal isoenzyme in sebaceous and sweat glands.7, 8 The mRNA and protein for both isoenzymes have been found in hair follicles, although this is not a universal finding.9, 10, 11, 12 There is no recognized genetic deficiency of type 1 5?-reductase in humans to assess its role in MPHL, and a type 1 5?-reductase inhibitor has not previously been evaluated for its effect on MPHL.

Dutasteride (Avodart) inhibits both type 1 and type 2 5?-reductase13 and is approved at the 0.5-mg dose for treatment of symptomatic benign prostatic hyperplasia (BPH). It is approximately 3 times as potent as finasteride at inhibiting type 2 5?-reductase and more than 100 times as potent at inhibiting the type 1 enzyme.14 The objective of this study was to evaluate, in a dose-response manner, whether dual 5?-reductase inhibition leads to improved efficacy in the treatment of MPHL. This randomized, multicenter study compared 4 doses of dutasteride with finasteride and placebo. Outcome measures included scalp hair growth and scalp androgen (testosterone and DHT) concentrations.

Materials and methods

Subject selection

Men 21 to 45 years of age were eligible for this study (GSK study ARIA2004) if they had mild-to-moderate MPHL (IIIv, IV [including IVa] or V Hamilton-Norwood patterns15). They must never have used a 5?-reductase inhibitor or have used any medication for alopecia during the previous 6 months. They must have had no significant health problems and must not have taken any androgenic or antiandrogenic drugs during the previous 6 months. All men provided written consent, and the protocol and consent form were approved by local institutional review boards. The study was carried out at 21 centers in the United States.

Protocol

After an initial screening evaluation, which included a medical history, physical examination, and laboratory evaluation, eligible men were randomized to receive dutasteride (0.05, 0.1, 0.5, or 2.5 mg), finasteride (5 mg), or placebo daily for 24 weeks. To ensure 45 evaluable subjects per treatment arm (a total of 270 evaluable subjects), 416 eligible subjects were enrolled and randomized to treatment. Subjects were assigned to study treatment in accordance with a predetermined randomization schedule, with a block size of 6, generated by the Medical Data Sciences Department, GSK. During the trial the code was held by GSK, and both investigators

and patients were blinded to dutasteride, finasteride, and placebo treatments. The 5-mg finasteride dose was used, rather than the 1-mg dose that has been approved for treatment of MPHL, because the 1-mg dose was not commercially available at the time of study initiation. Furthermore, the 5-mg dose of finasteride had previously been shown to have efficacy in MPHL at least as great as the 1-mg dose.16

Assessments
The primary efficacy measure was hair regrowth based on hair counts, determined by means of a macrophotographic technique. The secondary efficacy measures were exploratory assessment of hair count, panel assessment of improvement from baseline, investigators' assessment of improvement, subjects' global assessment of improvement, and stage of MPHL using the modified Hamilton-Norwood classification.

For determination of target area hair counts, the hair in a 1-inch diameter (0.79 square inch) circle at the leading edge of the vertex bald spot was clipped to a length of about 1 mm. Reproducibility of this area was assured by placing a central tattoo and using a plastic target area template. Macrophotographs of the target area were taken with a camera system developed by Canfield Scientific Inc (Fairfield, NJ).17 Using a validated method to count hair, a technician manually converted the photographs into a dot map of the hairs in the target areas, which was then converted to hair counts using a computer imaging system. Hair counts were measured at baseline and at 12 and 24 weeks.

For expert panel assessment of global changes in the amount of hair, photographs were taken of both the vertex and frontal scalp. A panel of experts (Drs Olsen, Savin and Whiting), blinded as to treatment, was shown pairs of photographs from baseline and either 12 or 24 weeks of treatment from each view. The panel graded the changes in hair growth on a 7-point rating scale: greatly, moderately, or slightly decreased; no change; slightly, moderately or greatly increased; ratings were converted to numbers (–3 to +3) for statistical analysis.

Investigator and subject assessments were done at baseline and at 12 and 24 weeks. For the investigator assessments, baseline photographs were provided for comparative purposes and the investigators used the same 7-point rating scale as already described for the expert photographic panel. The subjects were asked to rate changes in the size of the vertex spot, hair loss on top of the scalp, bitemporal recession, the amount of hair shedding, hair quality, and overall satisfaction with hair growth on a 3-point rating scale (improved, no change, or worse).

Serum testosterone and DHT levels were measured at baseline and at 6, 12, and 24 weeks during the treatment phase, at 36 weeks (12 weeks after treatment was stopped), and thereafter at follow-up visits approximately every 2 months until DHT levels rose to within 25% of baseline. Serum testosterone was measured by Covance Laboratories (Indianapolis, Ind) using a standard radioimmunoassay. Serum DHT was measured by PPD Pharmaco (Richmond, Va) using a combination of gas chromatography and mass spectrophotometry in order to measure the very low serum DHT levels in subjects treated with dutasteride.

Scalp testosterone and DHT concentrations were determined in 4-mm biopsy specimens taken at baseline and again at 24 weeks. The biopsy specimens were taken anterolateral to the leading edge of the vertex bald spot, adjacent to the target area for hair counts. Scalp testosterone and DHT were measured after tissue homogenization and ether extraction, using the same assay as

for serum measurements.

Statistical methods
Descriptive statistics are expressed as the mean (or mean change from baseline) with one standard deviation or median percentage change from baseline. The primary population of subjects to be statistically analyzed was the intention-to-treat population. Analysis of the hair count change from baseline was performed using a general linear model with effects for treatment, investigator cluster, and baseline hair count. Analyses of the panel and investigator assessments of improvement (on the 7-point scale) were performed using a general linear model with effects for treatment and investigator cluster. Analysis of the panel assessment was based on the average of the ratings of the 3 experts. Analyses of the percentage change from baseline in serum and scalp DHT and testosterone were performed using the following general linear model: log (postbaseline/baseline) = log (baseline) + treatment. For summary and analysis purposes, concentrations reported as below the limit of quantification were set to the lower limit of detection of the assay.

Pairwise comparisons between the dutasteride and placebo groups were performed using t tests from the general linear model in a step-down manner through the following hierarchical dose hypotheses at the two-sided 0.05 level of significance: dutasteride 2.5 mg versus placebo, dutasteride 0.5 mg versus placebo, dutasteride 0.1 mg versus placebo, dutasteride 0.05 mg versus placebo. Pairwise comparisons between the dutasteride and finasteride groups were performed in a similar manner. The pairwise comparison between the placebo and finasteride groups was performed and interpreted at the two-sided .05 level of significance. Correlations between efficacy and scalp androgen concentrations were evaluated across treatment groups using Spearman's rank correlation statistics. Statistical analyses were performed using both LOCF—last observation carried forward—and ‘at visit’ analyses, with similar results for both. The ‘at visit’ analyses are reported in this article.

Results

Demography
The randomization of 416 subjects from 21 centers began in December 1997 and ended in June 1998. A total of 416 subjects entered the study, with 390 completing 12 weeks and 374 completing 24 weeks of the study. Demographics are summarized in Table I. The mean age was 36.40 ± 6.05 years (range 21-45 years). Ninety-one percent of subjects were Caucasian, 2% were black, 2% were Asian, and 5% were American Hispanic. The stage of baldness was as follows: IIIv 41%, IV 31%, IVa 5%, and V 23%.

Table I.
Demographics

	Dutasteride (mg)						
	Placebo	0.05	0.1	0.5	2.5	Finasteride (5.0 mg)	Total
No. of subjects	64	71	72	68	71	70	416
Age (y)							
Mean	35.8	35.5	36.4	36.1	35.8	38.5	36.4
SD	6.15	5.83	6.48	6.31	5.89	5.34	6.05

Min:Max 23:45 21:45 22:45 21:45 23:45 22:45 21:45
Baseline hair count
Mean 920.3 1000.6 907.8 927.5 971.5 902.1 938.5
SD 236.36 302.12 224.27 219.84 247.32 262.86 251.7
Min:Max 432:1471 262:1723 317:1371 462:1377 449:1562 219:1712 219:1723
No. 64 70 72 67 70 70 413
Age at first balding (y)
Mean 25.5 25.3 26.0 27.3 25.8 26.9 26.1
SD 5.62 5.03 6.94 6.22 5.88 6.26 6.04
Min:Max 15:40 18:40 15:42 12:41 14:44 15:41 12:44
No. 64 69 72 68 71 70 414
Stage of MPHL, No. (%)
III vertex 26 (41) 26 (37) 31 (43) 29 (43) 28 (39) 29 (41) 169 (41)
IV 20 (31) 29 (41) 19 (26) 21 (31) 24 (34) 18 (26) 131 (31)
IVa 3 (5) 3 (4) 4 (6) 3 (4) 1 (1) 5 (7) 19 (5)
V 15 (23) 13 (1 18 (25) 15 (22) 18 (25) 18 (26) 97 (23)

Min:Max, Minimum:maximum; MPHL, male pattern hair loss; SD, standard deviation.

Target areas were located at similar areas anterior to the vertex balding. The mean and range of baseline hair counts for patterns IIIv, IV, IVa, and V was 939 (range 219-1723). There were no significant differences in the groups with respect to age, race or degree of baldness. Reasons for dropout included the following: withdrawal of consent (n = 20), adverse events (n = 11), lost to follow-up (n = 6), protocol violations and other reasons (n = 5). There were no significant differences in dropout rates among the treatment groups. The average compliance among the groups, as assessed by pill counts, was 94% to 99%.

Hair counts
Mean baseline hair counts in the 1-inch target area circle varied from 902.1 to 1000.6 hairs and were not significantly different between groups. During the 24 weeks of the study, mean hair counts in the placebo group decreased by 32.3 ± 59.2 hairs, while hair counts increased in all active treatment groups (Fig 1). Dutasteride 0.1–2.5 mg and finasteride groups were significantly different from placebo for mean change in hair count from baseline at 12 and 24 weeks (P < .001) as follows: placebo, –26.5 (n = 56) and –32.3 hairs (n = 50); dutasteride 0.1 mg, 55 (n = 63) and 78.5 hairs (n = 5; dutasteride 0.5 mg, 71.3 (n = 59) and 94.6 hairs (n = 61); dutasteride 2.5 mg, 99.9 (n = 62) and 109.6 hairs (n = 62); and finasteride group, 52.1 (n = 6 and 75.6 hairs (n = 66) (Fig 1). The mean hair count in the 2.5-mg dutasteride group was significantly greater than the finasteride group at both 12 weeks (P < .001) and 24 weeks (P = .009). At 24 weeks, the percentage of subjects with at least a 10% increase in hair counts was 0%, 17%, 38%, 48%, and 56% for placebo, 0.05, 0.1, 0.5 and 2.5 mg dutasteride, respectively, and 41% for finasteride.

Fig 1. Mean changes in hair counts after 12 and 24 weeks, compared with baseline, for placebo, datasteride (0.05-2.5 mg), and finasteride (FIN). , P <= .05; , P <= .001 compared with

placebo; †, P <= .05; ‡, P <= .001 compared with finasteride.

Expert panel assessment of global photographs

The 3-member panel assessed paired photographs of baseline versus 12 and 24 weeks of treatment in both the vertex (Table II) and frontal (Table III) regions. Their assessments were given numeric values from –3 (greatly decreased compared with baseline) to +3 (greatly increased compared with baseline), in order to permit statistical analysis. In the vertex photographs, dutasteride (0.1, 0.5, and 2.5 mg) and finasteride showed significantly greater improvement than placebo (P < .001) at both 12 and 24 weeks (Fig 2, A). Dutasteride 0.5 mg showed a significantly greater improvement than finasteride at 24 weeks (P = .026), whereas dutasteride 2.5 mg showed significantly greater improvements than finasteride at both 12 and 24 weeks (P < .001). At 24 weeks, the mean expert panel score was –0.04, 0.19, 0.47, 0.84 and 1.01 points for placebo, 0.05-, 0.1-, 0.5-, and 2.5-mg dutasteride groups, respectively, and 0.62 points for finasteride (Fig 2, A). The percentages of patients judged to have improved hair growth (slightly to greatly increased) at 24 weeks in the vertex photographs were 2%, 15%, 39%, 63%, and 78% for placebo, 0.05-, 0.1-, 0.5 and 2.5-mg dutasteride groups, respectively, and 57% for finasteride (Table II). The panel assessments of the vertex photographs correlated with changes in hair counts assessed by macrophotography (r = 0.41, P < .001).

Table II.
Expert panel assessment of changes in vertex photographs at 12 and 24 weeks

Moderately decreased Slightly decreased No change Slightly increased Moderately increased Greatly increased
Wk 12 Wk 24 Wk 12 Wk 24 Wk 12 Wk 24 Wk 12 Wk 24 Wk 12 Wk 24 Wk 12 Wk 24
Placebo 0 0 7 8 90 91 3 0 0 2 0 0
0.05 mg Dut 0 0 5 10 83 75 13 12 0 3 0 0
0.1 mg Dut 0 0 0 0 70 61 28 33 2 7 0 0
0.5 mg Dut 0 0 0 0 65 37 31 40 5 21 0 2
2.5 mg Dut 0 0 3 0 46 22 35 48 15 28 1 1
5.0 mg FIN 1 0 3 0 67 43 25 48 4 9 0 0

Dut, Dutasteride; FIN, finasteride; Wk, week.

Values denote percentage of patients in each category.

Table III.
Expert panel assessment of changes in frontal photographs at 12 and 24 weeks

Moderately decreased Slightly decreased No change Slightly increased Moderately increased Greatly increased

Wk 12 Wk 24 Wk 12 Wk 24 Wk 12 Wk 24 Wk 12 Wk 24 Wk 12 Wk 24 Wk 12 Wk 24
Placebo 0 0 0 2 95 87 5 12 0 0 0 0
0.05 mg Dut 0 0 13 5 81 73 6 20 0 2 0 0
0.1 mg Dut 0 0 0 0 81 67 17 30 2 3 0 0
0.5 mg Dut 0 0 0 0 77 52 21 30 2 18 0 0
2.5 mg Dut 0 0 1 1 68 37 29 36 1 25 0 0
5.0 mg FIN 1 1 3 1 87 52 9 36 0 9 0 0

Dut, Dutasteride; FIN, finasteride; Wk, week.

Values denote percentage of patients in each category.

Fig 2. Mean expert panel ratings of photographs after 12 and 24 weeks, compared with baseline, for placebo, dutasteride (0.05-2.5 mg) and finasteride (FIN). Assessments were made of photographs of the vertex (A) and frontal (B) regions on a 7-point scale from –3 (greatly decreased) to +3 (greatly increased). , P <=.05; , P <= .001 compared with placebo; †, P <= .05; ‡, P <= .001 compared with finasteride.

In the frontal region, the dutasteride 0.1, 0.5, and 2.5 mg groups improved significantly more than placebo at both 12 and 24 weeks (Fig 2, B). Finasteride was not significantly different from placebo at 12 weeks (P = .69) but was at 24 weeks (P < .001). At 12 weeks, the improvement in the 0.5-mg dutasteride group (0.28 ± 0.40) and in the 2.5-mg dutasteride group (0.37 ± 0.46) was significantly greater than the finasteride group (0.09 ± 0.39, P = .009 and P < .001, respectively). At 24 weeks, the improvement in the 2.5-mg dutasteride group (0.85 ± 0.79) was also significantly greater than the finasteride group (0.51 ± 0.66, P = .002). The proportions of patients judged to have improved hair growth (slightly to greatly increased) at 24 weeks in the frontal photographs were 12%, 22%, 33%, 48%, and 61% for placebo, 0.05, 0.1, 0.5 and 2.5 mg dutasteride, respectively, and 45% for finasteride (Table III). The proportion of patients with moderate or greater increases was higher with dutasteride 0.5 and 2.5 mg than with finasteride for both vertex and frontal photographs.

Investigators' global assessment

As for the expert panel assessment, the investigator assessments of hair growth were given numerical values from –3 (greatly decreased compared with baseline) to +3 (greatly increased compared with baseline). At the vertex, mean investigator ratings showed improvement in hair growth for the placebo group compared with baseline (0.44 ± 0.73 and 0.52 ± 0.86 at 12 and 24 weeks, respectively) (Fig 3, A). At 12 weeks, only the 2.5-mg dutasteride group (1.14 ± 0.85) showed a significant increase in investigator rating compared with placebo (P < .001), and this group was also significantly more improved than the finasteride group (0.66 ± 0.87) (P = .001). For vertex hair growth at 24 weeks, investigator ratings of 1.23, 1.34, and 1.85 points were given

for 0.1-, 0.5-, and 2.5-mg dutasteride groups, respectively, and 1.21 points for the finasteride group, which were all significantly greater ratings compared with placebo (P < .001). In addition, the 2.5-mg dutasteride group (1.85 ± 1.01) was significantly more improved than the finasteride group at 24 weeks (1.21 ± 0.94, P < .001). The expert panel assessment of hair growth correlated with investigator assessment at the vertex (r = 0.52, P < .001) and at the frontal area (r = 0.42, P < .001) for 24-week evaluations.

Fig 3. Mean investigator ratings of improvement in vertex (A) and frontal (B) hair growth after 12 and 24 weeks, compared with baseline, for placebo, dutasteride (0.05-2.5 mg) and finasteride (FIN). Assessments were made of changes in hair growth on a 7-point scale from –3 (greatly decreased) to +3 (greatly increased). , P <= .05; , P <= .001 compared with placebo; †, P <= .05; ‡, P <= .001 compared with finasteride.

At the frontal scalp, the investigator rating highlighted a modest improvement in the placebo group compared with baseline (0.18 ± 0.51 at 12 weeks and 0.31 ± 0.70 at 24 weeks) (Fig 3, B). At 12 weeks, only the 2.5-mg dutasteride group (0.85 ± 0.87) showed a significant increase in investigator rating compared with placebo (P < .001). The 2.5-mg dutasteride group also showed a significant increase compared with finasteride (P < .001) at 12 weeks. At 24 weeks, dutasteride 0.1, 0.5, and 2.5 mg and finasteride groups showed significantly more improvement than the placebo group. The 2.5-mg dutasteride group (1.38 ± 0.93) was also significantly more improved than finasteride (0.83 ± 0.95, P < .001).

Subjects' assessment
In general, the 0.1-, 0.5-, and 2.5-mg dutasteride groups and the finasteride group provided numerically higher self-assessment scores than the placebo group for each parameter on the self-assessment questionnaire at 12 and 24 weeks. Only the 2.5-mg dutasteride and the finasteride groups at 24 weeks were consistently significantly greater than the placebo group for all parameters on the questionnaire (P < .05) (Table IV).

Table IV.
Percentage of men with improvement in scalp hair after 24 weeks according to answers to a self-assessment questionnaire

	Dutasteride (mg)					
Placebo	0.05	0.1	0.5	2.5	Finasteride (5.0 mg)
Size of vertex spot	31	58	57	52	69	61
Hair loss on top of scalp	29	55	52	40	63	51
Bitemporal recession	16	28	27	18	31	39
Hair shedding	47	67	63	56	74	64
Hair quality	36	47	47	45	60	57
Overall satisfaction	42	58	57	56	72	61

P < .05 compared with placebo, based on the overall distribution of answers (improved, no change, worse).

Serum and scalp androgen levels

Serum DHT concentrations in all dutasteride groups were suppressed significantly compared with placebo (P <= .001) in a dose-related manner, with the greatest median suppression at 24 weeks occurring in the 0.5-mg (92%) and 2.5-mg (96.4%) dutasteride groups (Fig 4, A). The 0.1-mg dutasteride and finasteride groups showed a similar median degree of DHT suppression at 24 weeks (69.8% and 73.0%, respectively). Serum testosterone levels rose significantly in all active treatment groups, increasing by a median of 27.5% in the 2.5-mg dutasteride group, compared with 10.4% in the finasteride group (Fig 4, B). In the 0.5-mg dutasteride group, the median increase at 24 weeks was 23.8%, which is similar to previous findings.14, 18 Serum DHT concentration was inversely correlated with target area hair count (r = –0.49, P < .001), panel assessment of the vertex photographs (r = –0.50, P < .001), and investigators' assessments of the vertex hair growth (r = –0.37, P < .001). Twelve weeks after termination of treatment (36 weeks), the mean serum DHT was not significantly different from the baseline value in the placebo, dutasteride 0.05 mg and 0.1 mg groups and the finasteride 5.0 mg group. However, at 36 weeks, serum DHT had not yet returned to baseline for patients receiving dutasteride 0.5 mg and 2.5 mg (–11.03 and –88.4 median difference from baseline, respectively). This is summarized in Fig 4, A. In subjects whose serum DHT was not within 25% of the baseline value after 36 weeks, serum DHT was measured at approximately 2-month intervals until levels had returned to within 25% of the baseline value. Serum DHT returned to within 25% of baseline in a median of 86 days after treatment (range 71-307 days) for the dutasteride 0.5 mg group and in a median of 155 days (range 72-421 days) for the dutasteride 2.5 mg group.

Fig 4. Median percentage changes from baseline in serum dihydrotestosterone (DHT) and testosterone (T), for placebo, dutasteride (DUT) (0.05-2.5 mg), and finasteride (FIN). Treatment was stopped after 24 weeks. All active groups were significantly different from placebo for both parameters at 6, 12, and 24 weeks (P <= .001).

Scalp DHT concentrations in the dutasteride groups were also significantly suppressed compared with placebo in a dose-related manner. As with serum DHT, the 0.1-mg dutasteride and finasteride groups showed a comparable degree of scalp DHT suppression (32% and 41%, respectively). Scalp DHT decreased by 51% with 0.5-mg dutasteride and by 79% with 2.5-mg dutasteride. Scalp testosterone levels significantly increased in all active treatment groups compared with placebo, increasing by 23%, 39%, 99%, and 222% with 0.05-, 0.1-, 0.5 and 2.5-mg dutasteride, respectively, and 23% with finasteride. Change in scalp DHT concentration was inversely correlated with change in target area hair count (r = –0.27), panel assessments of the vertex (r = –0.39), and investigators' assessments of the vertex (r = –0.2; the P value was less

than .001 for all 3 correlations. The relationship between mean percentage change in scalp DHT and mean change in hair count is shown in Fig 5.

Fig 5. Relationship between 24-week mean percentage change from baseline in scalp dihydrotestosterone (DHT) and mean change in hair count for placebo, dutasteride (DUT) (0.05-2.5 mg), and finasteride (FIN).

Safety and tolerability

There were no significant differences in total adverse events, serious adverse events, or withdrawals due to adverse events among any of the treatment groups, including placebo. In total, 11 subjects withdrew because of adverse events: 3 were in the placebo group (irritable bowel syndrome and impotency), 7 in the dutasteride 0.1 mg group (decreased libido, malaise and fatigue, mood disorders, skin disorders, injuries caused by trauma, and gastrointestinal- and neurology-related complaints) and 1 in the dutasteride 0.5 mg group (gastrointestinal discomfort and pain). Some subjects had more than one adverse event.

As questions have previously arisen concerning a possible impact of 5?-reductase inhibitors on sexual function, these adverse events were examined in greater detail and are summarized in Table V. Decreased libido was noted in 2 subjects in the placebo group, 2 subjects in each of the 0.05-mg and 0.1-mg dutasteride groups, 1 subject in the 0.5-mg dutasteride group, 9 subjects in the 2.5 mg dutasteride group, and 3 subjects in the finasteride group. Of the 9 subjects with decreased libido in the 2.5-mg dutasteride group, 4 resolved while receiving therapy; 1 resolved within 3 weeks and another within 8 weeks of stopping drug therapy; in 1 subject, decreased libido continued after therapy had been stopped and was presumed by the subject to be unrelated to the trial or drug therapy; 2 subjects switched to finasteride at the end of the active phase and were lost to follow-up (dutasteride was not commercially available at the time the study ended). None of these 9 subjects discontinued study therapy because of this side effect. There was no increase among the active treatment groups in the reported incidence of impotence, with 3 subjects in the placebo group, 2 subjects in the 0.05-mg dutasteride group, and one subject in the finasteride group reporting such difficulty. These sexual adverse events were characterized as either mild or moderate in severity and only one subject's withdrawal was thought to be as a result of this adverse event (ie, decreased libido—in the 0.1-mg dutasteride group; Table V). The only subject to develop gynecomastia was in the placebo group.

Table V.
Proportion of subjects experiencing the most frequent sexual AEs following randomization, proportion of sexual AEs resolving (and those resolved during therapy), and proportion of sexual AEs leading to withdrawal from the study

Dutasteride (mg)
Placebo 0.05 0.1 0.5 2.5 Finasteride (5.0 mg)

No. of subjects in group 64 71 72 68 71 70
Decreased libido, No. (%) 2 (3) 2 (3) 2 (3) 1 (1) 9 (13) 3 (4)
Resolved on therapy 2 0 1 0 4 0
Resolved off therapy 0 1 1 1 2 3
Leading to withdrawal, No. 0 0 1 0 0 0
Ejaculation disorders, No. (%) 0 (0) 0 (0) 3 (4) 1 (1) 1 (1) 2 (3)
Resolved on therapy — — 1 0 0 0
Resolved off therapy — — 1 1 1 2
Leading to withdrawal, No. 0 0 0 0 0 0
Impotence, No. (%) 3 (5) 2 (3) 0 0 0 1 (1)
Resolved on therapy 1 1 — — — 0
Resolved off therapy 2 1 — — — 1
Leading to withdrawal, No. 2 0 0 0 0 0

AEs, Adverse events.

AEs occurring in more than 2% of subjects in at least one treatment group.

Discussion

Dutasteride, the first dual 5?-reductase inhibitor, is currently approved for treatment of symptomatic BPH. It is about 3 times as potent as finasteride at inhibiting type 2 5?-reductase and more than 100 times as potent at inhibiting type 1 5?-reductase.14 Whereas 5-mg finasteride decreases serum DHT by about 70%,19 dutasteride can decrease serum DHT by more than 90%.20

In this phase II, dose-ranging study, 2.5-mg dutasteride was superior to 5-mg finasteride in improving scalp hair growth in men between ages 21 and 45 years with MPHL as judged by target area hair counts, expert panel assessment, and investigator assessment at 12 and 24 weeks. From the investigator assessment of hair growth, a significant effect was evident at 12 weeks with 2.5-mg dutasteride but not until 24 weeks with finasteride. The subjects' assessment was less sensitive to changes in hair growth: this may have been at least partially due to the fact that this assessment used only a 3-point scale, compared with the 7-point scale used for the expert panel and investigator assessments. The effect of 24-week treatment with 5-mg finasteride in this study was similar to that previously reported by Kaufman et al for 52-week treatment with 1-mg finasteride5 and 5-mg finasteride.21 Kaufman et al21 showed that for 1-year treatment with 5-mg finasteride, the mean change from baseline hair count in a 1 inch diameter target area was 95 compared with 75.6 in the same-sized target area in this study, and the change in serum DHT was –69.2% compared with –73% reported herein. The mean change from baseline target area hair count in the phase III study evaluating 1-year treatment with 1-mg finasteride daily was 107 per 1-inch diameter target area.5 The greater efficacy of 2.5-mg dutasteride shown herein supports the dual role of type 1 and type 2 5?-reductase in the pathogenesis of MPHL.

The results of this study also highlight the importance of scalp DHT in the pathogenesis of MPHL. The 2.5-mg dutasteride dose was consistently superior to 0.5-mg dutasteride in promoting scalp hair growth. The 2.5-mg dose was also better than the 0.5-mg dose at suppressing scalp DHT

(79% vs 51%), whereas it was only marginally better at suppressing serum DHT (96% vs 92%). This difference in the dose-response of serum and scalp DHT to inhibition with dutasteride is likely to be due to the greater contribution of type 1 5?-reductase to scalp DHT concentrations. In comparison with dutasteride, finasteride reduced scalp DHT by only 41%, a value similar to the 34% reduction reported previously by Dallob et al.19 In another study, by Drake et al,22 5-mg finasteride reduced scalp DHT by 69%. There is no obvious reason why the results of the study by Drake et al should differ from the present study or that of Dallob et al. However, in the Drake study, there was no dose-response relationship among finasteride groups, with 0.01-mg finasteride showing no suppression of scalp DHT and 0.05-, 0.2-, 1 and 5-mg finasteride all showing about the same degree of suppression. The present study included a larger number of subjects and showed a complete dose-response for DHT suppression ranging from 26% in the 0.05 mg dutasteride group to 79% in the 2.5 mg dutasteride group. In this context, 5 mg finasteride suppressed scalp DHT to a similar degree as 0.1 mg dutasteride group (41% and 32%, respectively). Many of the clinical effects (hair count changes, global panel assessment, and investigator assessment) were also similar in these two groups, supporting the similarity in scalp suppression between 5-mg finasteride and 0.1-mg dutasteride.

Both dutasteride and finasteride were well tolerated in this phase II study, and no new safety concerns have arisen in any of the phase II and phase III studies of dutasteride given at doses up to 5 mg daily (the 5-mg dose was used in a phase II study for BPH). Concerning possible sexual adverse events, there was no evidence in the present study that either dutasteride or finasteride was associated with impotence. However, 9 men in the 2.5-mg dutasteride group complained of decreased libido, compared with 1 man in the 0.5-mg dutasteride group and 3 men in the finasteride group. As with previous studies with finasteride, this adverse event was characterized as either mild or moderate in severity and often resolved with continuation of the medication. In the 4-year follow-up of the phase III trials in BPH, dutasteride (0.5 mg) was well tolerated and the incidence of the most common sexual adverse events was low and tended to decrease over time.23

It should be emphasized that the approved dose of dutasteride for treatment of BPH is 0.5 mg daily and that limited data are available on the safety of higher doses. Dutasteride is not approved for treatment of MPHL, and the beneficial effects of dutasteride in MPHL must be weighed against the possible adverse effects reported during use in BPH, such as gynecomastia, reduced sperm count, and drug-drug interactions (in particular, interactions with cytochrome P-450 isozyme, CYP 3A4 inhibitors), as detailed in the US labeling for Avodart.24

The serum half-life of finasteride is 6 to 8 hours.25 Dutasteride has a serum half-life of approximately 4 weeks, and this long half-life was evident in the persistent suppression of DHT with the 0.5-mg and 2.5-mg doses after dutasteride treatment was stopped. Because of this long half-life, men being treated with dutasteride should not donate blood until at least 6 months past their last dose to prevent administration to a pregnant female transfusion recipient.

In conclusion, 2.5-mg dutasteride, a dual 5?-reductase inhibitor, improved hair growth in balding men more rapidly and to a greater degree than finasteride, a selective type 2 inhibitor. Dutasteride was generally well tolerated. The results of this study demonstrate the significant additive effect of inhibiting both type 1 and type 2 5?-reductase in the treatment of MPHL.

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e Clinical Development, GlaxoSmithKline, Research Triangle Park

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Three patients were initially labeled by the principal investigator as having Hamilton-Norwood pattern VII, but the mean target area hair count of the vertex, 1021 (range 473-1562) indicated that this pattern was incorrect. The first author reviewed the representative scalp photographs and reassigned all 3 as Hamilton-Norwood pattern V.

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Bitte einmal auf Deutsch übersetzen!

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by Malte on Tue, 26 May 2009 20:56:46 GMT
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In conclusion, 2.5-mg dutasteride, a dual 5?-reductase inhibitor, improved hair growth in balding men more rapidly and to a greater degree than finasteride, a selective type 2 inhibitor. Dutasteride was generally well tolerated. The results of this study demonstrate the significant additive effect of inhibiting both type 1 and type 2 5?-reductase in the treatment of MPHL.

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by haarakiri1 on Wed, 27 May 2009 06:11:04 GMT
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Warum gibt es dann kaum Erfolgsberichte mit Dutasterid?

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by Ka$h on Wed, 27 May 2009 07:19:05 GMT
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Malte schrieb am Die, 26 Mai 2009 22:56In conclusion, 2.5-mg dutasteride, a dual 5?-reductase inhibitor, improved hair growth in balding men more rapidly and to a greater degree than finasteride, a selective type 2 inhibitor. Dutasteride was generally well tolerated. The results of this study demonstrate the significant additive effect of inhibiting both type 1 and type 2 5?-reductase in the treatment of MPHL.
halte ich alles für ein Gerücht... habe hier im Forum niemanden, aber auch niemanden im Kopf, der dieses Treatment langfristig "aushält" ...

das andere halte ich auch für ein Gerücht...

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by haarakiri1 on Wed, 27 May 2009 08:34:46 GMT
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Aus eigener Erfahrung:

"well tolerated" ja, allerdings hatte ich auch nur 0,5 mg alle 3-4 Tage.

"improving hair more than fin" definitiv nein, ich hatte das gefühl dass vor allem meine front richtig gelitten hat.

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by Improvement on Thu, 28 May 2009 22:52:35 GMT
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Hast Du Dutasterid vor Fin genommen, parallel oder danach ?

Subject: Re: Dutasteride phase II Studie, 24 wochen
Posted by Sssnake on Fri, 29 May 2009 03:58:30 GMT
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!3 Monate Dut haben auch mir nichts gebracht. Einnahmeschema Mo - Mi - Fr

Subject: Aw: Dutasteride phase II Studie, 24 wochen
Posted by Fin on Tue, 13 Apr 2010 21:43:37 GMT
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hier mal die Übersetzung:

Die Bedeutung der dualen 5?-Reduktase-Hemmung bei der Behandlung von männlichem Haarausfall: Ergebnisse einer randomisierten, Placebo-kontrollierten Studie mit Finasterid Dutasterid versus
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Hintergrund
Männlichen Haarausfall (MPHL) ist eine potenziell reversible Zustand, in dem Dihydrotestosteron ist ein wichtiger ätiologischer Faktor.

Ziel
Unser Ziel war es, die Wirksamkeit des Typs 1 und 2 5?-Reduktase-Hemmer Dutasterid bei Männern mit MPHL bewerten.

Methoden
Vierhundert sechzehn Männer, 21 bis 45 Jahre alt, wurden randomisiert und Dutasterid 0,05, 0,1, 0,5 oder 2,5 mg erhalten, 5 mg Finasterid oder Placebo täglich über 24 Wochen.

Ergebnisse
Dutasteride erhöhte Zielgebiet Anzahl der Haare im Vergleich zu Placebo in einer dosisabhängigen Weise und Dutasterid 2,5 mg überlegen war bei 12 und 24 Wochen Finasterid. Expert Panel fotografischen Überprüfung und Beurteilung der Ermittler Haarwachstum diese Ergebnisse bestätigt. Kopfhaut-und Serum-Dihydrotestosteron Niveau zurückgegangen, und der Testosteronspiegel erhöht, in einer dosisabhängigen Weise mit Dutasterid.

Einschränkungen
Die Studie wurde auf 24 Wochen begrenzt.

Abschluss
Dutasterid steigert Kopfhaut Haarwuchs bei Männern mit MPHL. Typ 1 und Typ-2-5?-Reduktase kann in der Pathogenese und der Behandlung von MPHL wichtig.

Abkürzungen: BPH, benigne Prostatahyperplasie, DHT, Dihydrotestosteron, MPHL, männlichem Haarausfall, PHL, Haarausfall
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Haarausfall (PHL) ist eine genetisch bedingte, potentiell reversible Form des Haarausfalls. Er ist weitgehend an die Spitze der Kopfhaut begrenzt ist und durch erkennbare Muster des Haarausfalls bei Männern gekennzeichnet und bei einigen Frauen. Miniaturisierung der Haarfollikel und die Verkürzung der Anagenphase des Haarwachstums tritt in hairs.1 beteiligt, 2, 3 Obwohl Testosteron ist das wichtigste zirkulierende Androgen, werden maximal aktiven Haarfollikel in der Kopfhaut ist zunächst zu Dihydrotestosteron umgewandelt werden (DHT) durch das Enzym 5?-Reduktase. Die Bedeutung von DHT als ätiologischer Faktor in männlichem Haarausfall (MPHL) ist durch das Fehlen dieser Bedingung Männer mit einem

angeborenen Mangel an Typ-2-5?-Reduktase, 4 und durch unterschiedliche Mengen an Nachwachsen der Haare bei Männern mit MPHL behandelt gezeigt mit Finasterid, ein selektiver Typ-2-5?-Reduktase Typ 1 A inhibitor.5 5?-Reduktase, das auch Testosteron in DHT umwandelt, ist aus dem Typ-2-Enzym, das durch seine optimale pH-Bereich unterschieden in vitro und seiner Lage und Höhe in verschiedenen Geweben. 6 In der Haut, ist Typ-1-5?-Reduktase Isoenzym der Auftraggeber in Talg-und Schweissdrüsen glands.7, 8 Die mRNA und Protein für beide Isoenzyme haben in den Haarfollikeln gefunden worden, obwohl dies nicht eine universelle finding.9, 10, 11 , 12, ist kein anerkanntes genetischen Mangel an Typ-1-5?-Reduktase in den Menschen, seine Rolle in MPHL bewerten, und ein Typ-1-5?-Reduktase-Inhibitor wurde bisher nicht auf ihre Auswirkungen auf MPHL bewertet worden.

Dutasterid (Avodart) hemmt sowohl Typ 1 und Typ-2-5?-reductase13 und ist an der 0,5-mg-Dosis zur Behandlung der symptomatischen benignen Prostatahyperplasie (BPH) zugelassen. Es ist etwa 3 mal so potent wie Finasterid hemmt bei Typ-2-5?-Reduktase und mehr als 100 mal so potent auf die Hemmung der Typ-1-enzyme.14 Das Ziel dieser Studie war es zu prüfen, in einer Dosis-Wirkungs-Weise, ob dualen 5? -Reduktase-Hemmung führt zu einer verbesserten Wirksamkeit bei der Behandlung von MPHL. Diese randomisierte, multizentrische Studie verglich 4 Dosen Dutasterid mit Finasterid und Placebo. Ergebnis enthaltenen Maßnahmen Haar und Kopfhaut Wachstum Androgene (Testosteron und DHT)-Konzentrationen.

Material und Methoden

Betrifft Auswahl
Männer 21 bis 45 Jahren wurden für diese Studie geeignet (GSK-Studie ARIA2004), wenn sie milder bis mittelschwerer MPHL (IIIV hatte IV [einschließlich IVa] oder V Hamilton-Norwood patterns15). Sie müssen nie ein 5?-Reduktase-Inhibitor verwendet wurden oder verwendet haben, irgendwelche Medikamente für Haarausfall in den vorangegangenen 6 Monaten. Sie müssen keine signifikanten gesundheitlichen Probleme gehabt haben und darf keine androgene oder antiandrogene Drogen während der letzten 6 Monate genommen haben. Alle Männer vorgesehen schriftlicher Zustimmung und Genehmigung des Protokolls und Form wurden von den lokalen Ethikkommissionen genehmigt. Die Studie wurde an 21 Zentren in den Vereinigten Staaten durchgeführt.

Protokoll
Nach einem ersten Screening-Auswertung, die eine Anamnese, körperliche Untersuchung und Laboruntersuchungen, in Frage kommenden Männer randomisiert und erhielten Dutasterid (0,05, 0,1, 0,5 oder 2,5 mg) wurden, Finasterid (5 mg) oder Placebo täglich über 24 Wochen inklusive . Um sicherzustellen, 45 auswertbaren Probanden pro Behandlungsgruppe (insgesamt 270 auswertbaren Patienten), wurden 416 in Frage kommen sollten aufgenommen und randomisiert einer Behandlung. Anhand zugeordnet wurden zur Behandlung nach Studie mit einem vorgegebenen Zeitplan Randomisierung, mit einer Blockgröße von 6, die durch das Medical Data Sciences Department, GSK. Während des Prozesses der Code von GSK abgehalten wurde, und die beiden Ermittler und die Patienten wurden geblendet zu Dutasterid, Finasterid und Placebo-Behandlungen. Die 5-mg-Dosis Finasterid verwendet wurde, statt der 1-mg-Dosis, die für die Behandlung von MPHL genehmigt worden, weil die 1-mg-Dosis wurde nicht kommerziell erhältlich zum Zeitpunkt der Studie beginnen. Darüber hinaus hatte die 5-mg-Dosis von Finasterid zuvor gezeigt worden, um die Wirksamkeit bei MPHL mindestens so

groß wie die 1-mg dose.16

Assessments
Der primäre Wirksamkeits-Maßnahme wurde das Nachwachsen der Haare auf der Grundlage Haare zählt, durch ein macrophotographic Technik bestimmt. Die sekundäre Wirksamkeit Maßnahmen wurden explorative Beurteilung der Anzahl der Haare, Panel Bewertung der Verbesserung gegenüber dem Ausgangswert, Ermittler Beurteilung der Verbesserung, Themen "globale Beurteilung der Besserung und Stadium der MPHL mit dem modifizierten Hamilton-Norwood Klassifikation.

Zur Bestimmung der Zielbereich Haarzählungen, das Haar in einem 1-Zoll Durchmesser (0,79 Quadratzentimeter) Kreis an der Vorderkante des Vertex Glatze wurde zu einer Länge von etwa 1 mm abgeschnitten. Reproduzierbarkeit dieses Gebiet wurde durch die Anbringung eines zentralen Tätowierung und mit einem Kunststoff-Zielgebiet Vorlage gesichert. Makroaufnahmen des Zielbereichs wurden mit einem Kamera-System von Canfield Scientific Inc (Fairfield, NJ) .17 Mit einer validierten Methode zur Anzahl der Haare, ein Techniker manuell konvertiert die Bilder in einem Punkt der Karte von den Haaren in den Zielgebieten, entwickelt werden, die Anschließend wurde die Haare zählt mit einem Computer Imaging System umgestellt. Haarzählungen wurden zu Studienbeginn gemessen und bei 12 und 24 Wochen.

Für Expertengremium Bewertung der globalen Veränderungen in der Menge der Haare, waren Fotografien der beiden Vertex-und Kapillitium frontal getroffen. Ein Expertengremium (DRS Olsen, Savin und Wittling), geblendet, um die Behandlung, konnte gezeigt werden, Paare von Fotografien vom Ausgangswert und entweder 12 oder 24 Wochen der Behandlung aus jedem Blick. Die Jury bewertet die Änderungen in das Haarwachstum auf einer 7-Punkte-Skala: stark, mittel oder leicht zurückgegangen; keine Veränderung; leicht, mäßig oder stark zugenommen; Ratings wurden in Zahlen umgewandelt (-3 bis +3) für die statistische Analyse.

Investigator und vorbehaltlich Einschätzungen wurden zu Studienbeginn durchgeführt und bei 12 und 24 Wochen. Für die Ermittler Einschätzungen wurden Baseline-Fotos für Vergleichszwecke zur Verfügung gestellt und die Ermittler verwendet den gleichen 7-Punkte-Skala, wie bereits für den Fachmann fotografischen Panel beschrieben. Die Probanden wurden Wechselkursveränderungen in der Größe der Knoten vor Ort, Haarausfall auf der Kopfhaut, bitemporalen Rezession gebeten, den Betrag von Haarausfall, Haar-Qualität, und die allgemeine Zufriedenheit mit dem Haarwuchs auf einem 3-Punkt-Rating-Skala (verbesserte , keine Veränderung, oder noch schlimmer).

Serum-Testosteron und DHT-Spiegel wurden zu Studienbeginn gemessen und bei der 6, 12 und 24 Wochen während der Behandlungsphase, bei 36 Wochen (12 Wochen nach der Behandlung gestoppt wurde), und danach in Folgebesuchen ca. alle 2 Monate, bis DHT-Spiegel stieg innerhalb von 25% des Ausgangswertes. Serum-Testosteron wurde von Covance Laboratories (Indianapolis, Ind.) mit einem Standard-Radioimmunoassay gemessen. Serum DHT wurde von PPD Pharmako (Richmond, VA) mit einer Kombination von Gaschromatographie und Massenspektrometrie Spektrophotometrie, um die sehr niedrigen Serum-DHT-Spiegel bei Patienten mit Dutasterid behandelt vermessen.

Scalp Testosteron und DHT-Konzentrationen wurden in 4-mm-Biopsien bei Studienbeginn getroffen und bestimmt wieder bei 24 Wochen. Die Biopsien wurden anterolateralen an der

Vorderkante des Vertex Glatze, angrenzend an das Zielgebiet für die Haare zählt. Scalp Testosteron und DHT Gewebe wurden nach Homogenisierung und Ätherextraktion gemessen, mit dem gleichen Test wie für Serum-Messungen.

Statistische Methoden
Beschreibende Statistik sind als die mittlere (mittlere Veränderung vom Ausgangswert berechnet) mit einer Standardabweichung oder Median prozentuale Veränderung gegenüber dem Ausgangswert. Der primäre Population von Patienten, um statistisch ausgewertet wurde, war die Intention-to-treat-Population. Die Analyse der Anzahl der Haare Veränderung vom Ausgangswert wurde mit einem allgemeinen linearen Modell mit Wirkung für die Behandlung, Investigator-Cluster, und Baseline Haare zu zählen. Analysen des Panels und Einschätzungen der Ermittler Verbesserung (auf der 7-Punkte-Skala) wurden mit einem allgemeinen linearen Modell mit Wirkung für die Behandlung und Ermittler Cluster. Die Analyse der Panel Bewertung stützte sich auf den Durchschnitt der Bewertungen der 3 Experten. Analysen der prozentuale Veränderung gegenüber dem Ausgangswert im Serum und Kopfhaut DHT und Testosteron wurden mit den folgenden allgemeinen linearen Modell: log (postbaseline / Ausgangswert) = log (Baseline) + Behandlung. Für Zusammenfassung und Analyse Zwecke, berichtete Konzentrationen unterhalb der Bestimmungsgrenze wurden an die untere Nachweisgrenze des Tests festgelegt.

Paarweisen Vergleiche zwischen den Dutasterid und Placebo-Gruppen wurden mit t-Tests aus dem allgemeinen linearen Modell in einer Step-down Weise durch die folgenden hierarchischen Dosis Hypothesen an der zweiseitige 0,05 Ebene von Bedeutung: Dutasterid 2,5 mg versus Placebo, 0,5 mg Dutasterid versus Placebo, 0,1 mg Dutasterid versus Plazebo, 0,05 mg Dutasterid versus Placebo. Paarweisen Vergleiche zwischen den Dutasterid und Finasterid Gruppen wurden in ähnlicher Weise durchgeführt. Der paarweise Vergleich zwischen den Gruppen mit Placebo und Finasterid wurde durchgeführt und interpretiert die zweiseitige ,05-Ebene von Bedeutung. Korrelationen zwischen Wirksamkeit und Kopfhaut Androgen-Konzentrationen waren in den Behandlungsgruppen ausgewertet mittels Spearman-Rangkorrelation Statistiken. Statistische Analysen wurden durchgeführt mit beiden LOCF-last observation carried forward-und 'unter' Analysen, mit ähnlichen Ergebnissen für beide. Die 'unter' Analysen werden in diesem Artikel berichtet.

Ergebnisse

Demografie
Die Randomisierung von 416 Probanden aus 21 Zentren begann im Dezember 1997 und im Juni 1998 endete. Insgesamt 416 Probanden in die Studie aufgenommen, mit 390 Abschluss 12 Wochen und 374 über 24 Wochen der Studie. Bevölkerungsentwicklung sind in Tabelle I. Das mittlere Alter betrug 36,40 ± 6,05 Jahre (Bereich 21-45 Jahre). Ninety-ein Prozent der Probanden waren Kaukasier, 2% waren schwarz, 2% waren Asiaten, und 5% waren amerikanische Hispanic. Das Stadium der Kahlköpfigkeit war wie folgt: IIIV 41%, IV 31%, 5% IVa, V und 23%.

Tabelle I.
Bevölkerungsentwicklung

Dutasterid (mg)
Placebo 0,05 0,1 0,5 2,5 Finasteride (5,0 mg) Total
Anzahl der Probanden 64 71 72 68 71 70 416
Alter (y)
Mean 35,8 35,5 36,4 36,1 35,8 38,5 36,4
SD 6,15 5,83 6,48 6,31 5,89 5,34 6,05
Min: Max 23:45 21:45 22:45 21:45 23:45 22:45 21:45
Baseline Haarzählung
Mean 920,3 1000,6 907,8 927,5 971,5 902,1 938,5
SD 236,36 302,12 224,27 219,84 247,32 262,86 251,7
Min: Max 432:1471 262:1723 317:1371 462:1377 449:1562 219:1712 219:1723
Nr. 64 70 72 67 70 70 413
Alter auf den ersten Glatzenbildung (y)
Mean 25,5 25,3 26,0 27,3 25,8 26,9 26,1
SD 5,62 5,03 6,94 6,22 5,88 6,26 6,04
Min: Max 15:40 18:40 15:42 12:41 14:44 15:41 12:44
Nr. 64 69 72 68 71 70 414
Stage von MPHL, Anzahl (%)
Vertex III 26 (41) 26 (37) 31 (43) 29 (43) 28 (39) 29 (41) 169 (41)
IV 20 (31) 29 (41) 19 (26) 21 (31) 24 (34) 18 (26) 131 (31)
IVa 3 (5) 3 (4) 4 (6) 3 (4) 1 (1) 5 (7) 19 (5)
V 15 (23) 13 (1 18 (25) 15 (22) 18 (25) 18 (26) 97 (23)

Min: Max, Minimum: Maximum; MPHL, männlichem Haarausfall, SD, Standardabweichung.

Zielgebiete wurden auf ähnlichen Gebieten befinden anterior bis zum Scheitel kahl. Der Mittelwert und die Bandbreite des Ausgangswertes Haarzählungen nach Mustern IIIV war IV, IVa, V und 939 (Bereich 219-1723). Es gab keine signifikanten Unterschiede in den Gruppen in Bezug auf Alter, Rasse oder der Grad der Kahlheit. Gründe für Ausbildungsabbrüche umfasste Folgendes: Widerruf der Zustimmung (n = 20), verlor Nebenwirkungen (n = 11), das Follow-up (n = 6), Protokoll Verletzungen und anderen Gründen (n = 5). Es gab keine signifikanten Unterschiede in der Abbrecherquoten unter den Behandlungsgruppen. Die durchschnittliche Übereinstimmung zwischen den Gruppen, wie Pille zählt bewertet, lag bei 94% bis 99%.

Haarzählungen
Mean Baseline Haar zählt in der 1-Zoll-Zielgebiet Kreis von 902,1 bis 1000,6 Haare vielfältig und unterschied sich nicht signifikant zwischen den Gruppen. Während der 24 Wochen der Studie, meine Haare zählt in der Placebo-Gruppe sank um 32,3 ± 59,2 Haare, Haare, während in allen aktiven Behandlungsgruppen (Abb. 1) erhöhte zählt. Dutasteride 0,1-2,5 mg Finasterid und Gruppen unterschieden sich signifikant von Placebo für die mittlere Veränderung in der Menge der Haare gegenüber dem Ausgangswert um 12 und 24 Wochen (P <.001) wie folgt: Placebo, -26,5 (n = 56) und -32,3 Haare (n = 50); Dutasterid 0,1 mg, 55 (n = 63) und 78,5 Haare (n = 5; Dutasterid 0,5 mg, 71.3 (n = 59) und 94,6 Haare (n = 61); Dutasterid 2,5 mg, 99,9 (n = 62) und 109,6 Haare (n = 62); und Finasterid-Gruppe, 52.1 (n = 6 zu 75,6 Haare (n = 66) (Abb. 1). Die durchschnittliche Anzahl der Haare in der 2,5-mg Dutasterid-Gruppe war signifikant höher als der Finasterid-Gruppe sowohl auf 12 Wochen (p <.001) und 24 Wochen

(P = ,009). Nach 24 Wochen betrug der Prozentsatz der Patienten mit mindestens einer 10% igen Anstieg der Haarzählungen 0%, 17%, 38%, 48% und 56% für Plazebo, 0,05, 0,1, 0,5 und 2,5 mg Dutasterid bzw. 41% und für Finasterid.

Fig 1. Mittlere Veränderungen in Haarzählungen nach 12 und 24 Wochen, verglichen mit einem Ausgangswert, mit Placebo, datasteride (0,05-2,5 mg) und Finasterid (FIN). , P <= ,05;, P <= ,001 im Vergleich zu Placebo; †, P <= ,05; ‡, P <= ,001 mit Finasterid verglichen.

Expert Panel Bewertung der globalen Fotografien
Das 3-köpfige Jury bewertete Fotos von Baseline versus 12 und 24 Wochen der Behandlung in beiden Scheitel (Tabelle II) und frontalen (Tabelle III) Regionen gekoppelt. Ihre Einschätzungen wurden numerische Werte aus gegebenen -3 (stark zurückgegangen im Vergleich zum Ausgangswert) auf +3 (stark im Vergleich zum Ausgangswert) erhöht, um statistische Analysen zu ermöglichen. In der Ecke Fotografien zeigten Dutasterid (0,1, 0,5 und 2,5 mg) und Finasterid signifikant größere Verbesserung als unter Placebo (p <.001) an beiden 12 und 24 Wochen (Abb. 2, A). 0,5 mg Dutasterid zeigten eine signifikant stärkere Verbesserung als Finasterid bei 24 Wochen (P = ,026), während Dutasterid 2,5 mg signifikant größere Verbesserungen als Finasterid bei beiden 12 und 24 Wochen (P <.001). Nach 24 Wochen betrug die durchschnittliche Expertengremium der Gäste -0,04, 0,19, 0,47, 0,84 und 1,01 Punkte für Plazebo, 0.05-, 0.1-, 0.5-und 2.5-mg Dutasterid Gruppen, jeweils und 0,62 Punkte für Finasterid (Abb. 2 , A). Die Prozentsätze der Patienten beurteilt verbessert das Haarwachstum (leicht zu stark erhöht haben) nach 24 Wochen in die Ecke Fotografien wurden 2%, 15%, 39%, 63% und 78% für Plazebo, 0.05-, 0.1-, 0.5-und 2,5 mg Dutasterid Gruppen, jeweils 57% und für Finasterid (Tabelle II). Das Panel Einschätzungen der Vertex Fotografien mit Veränderungen im Haar korreliert Grafen von macrophotography bewertet (r = 0,41, p <.001).

Tabelle II.
Expert Panel Beurteilung von Änderungen im Scheitel Fotografien bei 12 und 24 Wochen

	Mäßig leicht zurückgegangen		Keine Änderung		sank leicht		erhöht		Mäßig stark zugenommen		haben zugenommen	
	Wk 12	WK 24	Wk 12	WK 24	WK 24	Wk 12	Wk 12	WK 24	WK 24	Wk 12	Wk 12	WK 24
Placebo	0	0	7	8	90	91	3	0	0	2	0	0
0.05 mg Dut	0	0	5	10	83	75	13	12	0	3	0	0
0,1 mg Dut	0	0	0	0	70	61	28	33	2	7	0	0
0,5 mg Dut	0	0	0	0	65	37	31	40	5	21	0	2
2,5 mg Dut	0	0	3	0	46	22	35	48	15	28	1	1
5,0 mg FIN	1	0	3	0	67	43	25	48	4	9	0	0

Dut, Dutasteride; FIN, Finasterid, Wk, Woche.

Werte bezeichnen Prozentsatz der Patienten in jeder Kategorie.

Tabelle III.
Expert Panel Bewertung von Veränderungen in frontalen Aufnahmen bei 12 und 24 Wochen

	Mäßig leicht zurückgegangen		Keine Änderung		sank leicht		erhöht		Mäßig stark zugenommen		haben zugenommen	
Wk	12	WK 24	Wk 12	WK 24	WK 24	Wk 12	Wk 12	WK 24	WK 24	Wk 12	Wk 12	WK 24
Placebo	0	0	0	2	95	87	5	12	0	0	0	0
0.05 mg Dut	0	0	13	5	81	73	6	20	0	2	0	0
0,1 mg Dut	0	0	0	0	81	67	17	30	2	3	0	0
0,5 mg Dut	0	0	0	0	77	52	21	30	2	18	0	0
2,5 mg Dut	0	0	1	1	68	37	29	36	1	25	0	0
5,0 mg FIN	1	1	3	1	87	52	9	36	0	9	0	0

Dut, Dutasteride; FIN, Finasterid, Wk, Woche.

Werte bezeichnen Prozentsatz der Patienten in jeder Kategorie.

Abb. 2. Mean Expertengremium Bewertungen von Fotos nach 12 und 24 Wochen, verglichen mit einem Ausgangswert, mit Placebo, Dutasterid (0,05-2,5 mg) und Finasterid (FIN). Einschätzungen wurden von Fotografien des Vertex (A) und frontal gestellt (B) Regionen auf einer 7-Punkte-Skala von -3 (stark gesunken) bis +3 (stark erhöht). , P <= ,05;, P <= ,001 im Vergleich zu Placebo; †, P <= ,05; ‡, P <= ,001 mit Finasterid verglichen.

In der Stirngegend, verbesserte sich die Dutasterid 0,1, 0,5 und 2,5 mg-Gruppe signifikant mehr als unter Placebo bei beiden 12 und 24 Wochen (Abb. 2, B). Finasteride unterschied sich nicht signifikant von Placebo nach 12 Wochen (P = ,69), wurde aber nach 24 Wochen (P <.001). Nach 12 Wochen war die Verbesserung in der 0,5 mg Dutasterid-Gruppe (0,28 ± 0,40) und in der 2,5-mg Dutasterid-Gruppe (0,37 ± 0,46) signifikant größer als der Finasterid-Gruppe (0,09 ± 0,39, P = ,009-und P < .001, jeweils). Nach 24 Wochen, die Verbesserung der 2,5-mg Dutasterid-Gruppe (0,85 ± 0,79) war ebenfalls deutlich höher als der Finasterid-Gruppe (0,51 ± 0,66, P = .002). Der Anteil der Patienten beurteilt verbesserten Haarwuchs (leicht bis stark erhöht haben) nach 24 Wochen in den frontalen Aufnahmen wurden 12%, 22%, 33%, 48% und 61% für Plazebo, 0,05, 0,1, 0,5 und 2,5 mg Dutasterid bzw. 45% und für Finasterid (Tabelle III). Der Anteil der Patienten mit mäßiger oder größere Steigerungen höher war mit Dutasterid 0,5 und 2,5 mg als mit Finasterid sowohl für Vertex-und frontalen Aufnahmen.

Investigators "umfassenden Beurteilung
Als für das Expertengremium Einschätzung der Ermittler Einschätzungen des Haarwachstums wurden numerische Werte aus gegebenen -3 (stark zurückgegangen im Vergleich zum Ausgangswert) bis +3 (stark im Vergleich zum Ausgangswert) erhöht. An der Ecke, meine Bewertungen Ermittler zeigten eine Verbesserung des Haarwachstums für die Placebo-Gruppe im Vergleich zum Ausgangswert (0,44 ± 0,73 und 0,52 ± 0,86 bei 12 und 24 Wochen, jeweils) (Abb. 3, A). Nach 12 Wochen zeigte nur der 2,5-mg Dutasterid-Gruppe (1,14 ± 0,85) einen signifikanten Anstieg in Ermittler-Bewertung im Vergleich zu Placebo (p <.001), und diese Gruppe wurde ebenfalls signifikant stärker verbessert als die Finasterid-Gruppe (0,66 ± 0,87) (P = .001). Für Vertex Haarwachstum bei 24 Wochen, waren Ermittler Bewertungen von 1,23, 1,34, und 1,85 Punkte für 0.1-, 0.5-und 2.5-mg Dutasterid Gruppen, jeweils und 1,21 Punkte für die Finasterid-Gruppe, die alle wesentlich größer waren abgegebenen Bewertungen im Vergleich zu Placebo (p <.001). Darüber hinaus wurde der 2,5-mg Dutasterid-Gruppe (1,85 ± 1,01) signifikant mehr verbessert als die Finasterid-Gruppe nach 24 Wochen (1,21 ± 0,94, p <.001). Das Expertengremium Beurteilung des Haarwachstums korreliert mit Prüfer die Bewertung auf dem Scheitel (r = 0,52, p <.001) und an der Stirnfläche (r = 0,42, p <.001) für 24-wöchigen Auswertungen.

Abb. 3. Mean Ermittler Bewertungen der Verbesserung der Scheitelpunkt (A) und frontalen (B) Haarwuchs nach 12 und 24 Wochen, verglichen mit einem Ausgangswert, mit Placebo, Dutasterid (0,05-2,5 mg) und Finasterid (FIN). Einschätzungen wurden von Veränderungen in den Haarwuchs auf einer 7-Punkte-Skala von -3 (stark abgenommen hat) bis +3 (stark vergrößert). , P <= ,05;, P <= ,001 im Vergleich zu Placebo; †, P <= ,05; ‡, P <= ,001 mit Finasterid verglichen.

In der frontalen Kopfhaut, unterstrich die Ermittler Rating eine leichte Verbesserung in der Placebo-Gruppe im Vergleich zum Ausgangswert (0,18 ± 0,51 nach 12 Wochen und 0,31 ± 0,70 nach 24 Wochen) (Abb. 3, B). Nach 12 Wochen zeigte nur der 2,5-mg Dutasterid-Gruppe (0,85 ± 0,87) einen signifikanten Anstieg in Ermittler-Bewertung im Vergleich zu Placebo (p <.001). Die 2,5-mg Dutasterid-Gruppe zeigte auch einen signifikanten Anstieg im Vergleich mit Finasterid (p <.001) nach 12 Wochen. Nach 24 Wochen, Dutasterid 0,1, 0,5 und 2,5 mg Finasterid und Gruppen zeigten eine signifikant größere Verbesserung als die Placebo-Gruppe. Die 2,5-mg Dutasterid-Gruppe (1,38 ± 0,93) war ebenfalls deutlich mehr verbessert als Finasterid (0,83 ± 0,95, p <.001).

Anhand Einschätzung
Im Allgemeinen, wenn die 0.1-, 0.5-und 2.5-mg Dutasterid Gruppen und der Finasterid-Gruppe numerisch höhere Self-Assessment Scores als die Placebo-Gruppe für jeden Parameter über die Self-Assessment Fragebogen an 12 und 24 Wochen. Nur der 2,5-mg Dutasterid und Finasterid Gruppen nach 24 Wochen waren durchweg deutlich größer als die Placebo-Gruppe für alle Parameter auf dem Fragebogen (P <.05) (Tabelle IV).

Tabelle IV.
Anteil der Männer mit Verbesserungen im Kopfhaar nach 24 Wochen nach Antworten auf eine Self-Assessment Fragebogen

Dutasterid (mg)
Placebo 0,05 0,1 0,5 2,5 Finasteride (5,0 mg)
Größe des Vertex Spot 31 58 57 52 69 61
Haarausfall auf der Kopfhaut 29 55 52 40 63 51
Bitemporalen Rezession 16 28 27 18 31 39
Haarausfall 47 67 63 56 74 64
Haarqualität 36 47 47 45 60 57
Allgemeine Zufriedenheit 42 58 57 56 72 61

P <.05 verglichen mit Placebo, bezogen auf die gesamte Verteilung der Antworten (verbessert, keine Veränderung, noch schlimmer).

Serum und Kopfhaut Androgenspiegel
Serum-DHT-Konzentrationen in allen Gruppen signifikant Dutasterid verglichen mit Placebo (P <= 001) in einer dosisabhängigen Weise unterdrückt, mit der größten Median 24 Wochen Unterdrückung vorkommenden in der 0,5-mg (92%) und 2,5-mg (96,4 %) Dutasterid Gruppen (Abb. 4, A). Die 0,1-mg Finasterid und Dutasterid Gruppen zeigten eine ähnliche mittlere Grad der Unterdrückung DHT nach 24 Wochen (69,8% bzw. 73,0%, beziehungsweise). Serum Testosteronspiegel stieg signifikant bei allen aktiven Behandlungsgruppen mit einem Plus von einem Median von 27,5% in der 2,5-mg Dutasterid-Gruppe, verglichen mit 10,4% in der Finasterid-Gruppe (Abb. 4, B). In der 0,5 mg Dutasterid-Gruppe betrug die mediane Anstieg nach 24 Wochen waren 23,8%, was gegenüber den Vorjahren ist findings.14, 18
Serum-DHT-Konzentration war invers korreliert mit der Anzahl der Haare Zielgebiet (r = -0,49, p <.001) , Panel Bewertung der Vertex Fotografien (r = -0.50, p <.001), und den Ermittlern die Einschätzungen des Vertex Haarwuchs (r = -0,37, p <.001). Zwölf Wochen nach Beendigung der Behandlung (36 Wochen), die mittlere Serum-DHT war nicht signifikant verschieden von der Grundlinie Wert in der Placebogruppe, Dutasterid 0,05 mg und 0,1 mg Finasterid Gruppen und der 5,0 mg-Gruppe. Jedoch bei 36 Wochen hatten Serum-DHT noch nicht zum Ausgangswert bei Patienten, die Dutasterid 0,5 mg und 2,5 mg (-11,03 und -88,4 mediane Differenz gegenüber dem Ausgangswert, jeweils) zurückgegeben. Dies ist zusammengefasst in Abb. 4, A. Bei Patienten, deren Serum-DHT wurde nicht innerhalb von 25% des Ausgangswertes nach 36 Wochen, Serum-DHT wurde auf ca. 2-Monats-Abständen gemessen, bis Ebenen musste innerhalb von 25% des Baseline-Wert zurückgegeben. Serum DHT kehrte innerhalb von 25% des Ausgangswertes in ein Durchschnittseinkommen von 86 Tagen nach der Behandlung (Bereich 71-307 Tage) für die Dutasterid 0,5 mg-Gruppe und in einem Median von 155 Tage (Bereich 72-421 Tage) für die Dutasterid 2,5 mg-Gruppe .

Abb. 4. Median prozentuale Veränderung gegenüber dem Ausgangswert im Serum Dihydrotestosteron (DHT) und Testosteron (T), für Placebo, Dutasterid (DUT) (0,05-2,5 mg) und Finasterid (FIN). Die Behandlung wurde nach 24 Wochen beendet. Alle aktiven Gruppen unterschieden sich signifikant von Placebo für beide Parameter bei 6, 12 und 24 Wochen (P <= 001).

Kopfhaut DHT-Konzentrationen in der Dutasterid Gruppen waren ebenfalls signifikant im Vergleich zu Placebo in einer dosisabhängigen Weise unterdrückt. Wie bei den Serum-DHT, der 0,1-mg Finasterid und Dutasterid Gruppen zeigten ein vergleichbares Maß an Unterdrückung Kopfhaut DHT (32% bzw. 41%, beziehungsweise). Kopfhaut DHT Rückgang von 51% mit 0,5-mg Dutasterid und von 79% mit 2,5-mg Dutasterid. Scalp Testosteronspiegel deutlich in allen aktiven Behandlungsgruppen im Vergleich zu Placebo erhöht, erhöht um 23%, 39%, 99% und 222% mit 0,05-, 0.1-, 0.5-und 2.5-mg Dutasterid bzw. 23% und mit Finasterid. Ändern Sie in der Kopfhaut DHT-Konzentration war invers korreliert mit Veränderungen im Zielgebiet Haarzählung (r = -0,27), Panel Einschätzungen der Scheitelpunkt (r = -0,39), und den Ermittlern die Einschätzungen der Scheitelpunkt (r = -0,2; der P-Wert weniger als ,001 für alle 3 Korrelationen. Die Beziehung zwischen der durchschnittlichen prozentualen Veränderung in der Kopfhaut DHT und mittlere Veränderung in der Menge der Haare ist in Abb. 5 dargestellt.

Abb. 5. Verbindungen zwischen 24-wöchigen mittlere prozentuale Veränderung gegenüber dem Ausgangswert in der Kopfhaut Dihydrotestosteron (DHT) und mittlere Veränderung der Anzahl der Haare in der Placebogruppe, Dutasterid (DUT) (0,05-2,5 mg) und Finasterid (FIN).

Sicherheit und Verträglichkeit
Es gab keine signifikanten Unterschiede in der gesamten unerwünschten Ereignisse, schwerwiegende unerwünschte Ereignisse oder Auszahlungen aufgrund von unerwünschten Ereignissen unter einer der Behandlungsgruppen, einschließlich Placebo. Insgesamt zogen sich 11 Personen wegen unerwünschter Ereignisse: 3 wurden in der Placebo-Gruppe (Reizdarmsyndrom und Ohnmacht), 7 in der Dutasterid 0,1 mg-Gruppe (verminderte Libido, Unwohlsein und Müdigkeit, affektive Störungen, Erkrankungen der Haut, verursacht durch Verletzungen, Traumata und Magen-Darm-und Neurologie-Beschwerden) und 1 in der Dutasterid 0,5 mg-Gruppe (Magen-Darm-Beschwerden und Schmerzen). Einige Probanden hatten mehr als ein unerwünschtes Ereignis.

Wie zuvor aufgetretenen Fragen über eine mögliche Auswirkungen der 5?-Reduktase-Inhibitoren auf die sexuelle Funktion, standen diese unerwünschten Ereignisse näher untersucht und sind in Tabelle V. verminderte Libido war im 2-Fächer in der Placebo-Gruppe bei 2 Probanden in jeder der darauf hingewiesen die 0,05-mg und 0,1 mg Dutasterid-Gruppen, 1 Thema in der 0,5-mg Dutasterid-Gruppe, 9 Fächer in der 2,5 mg

Dutasterid-Gruppe und 3 Fächer in der Finasterid-Gruppe. Von den 9 Patienten mit verminderter Libido in der 2,5-mg Dutasterid-Gruppe, 4 gelöst, während der Therapie; 1 innerhalb von 3 Wochen behoben und eine weitere innerhalb von 8 Wochen zu stoppen Arzneimitteltherapie; in 1 unterliegen, verminderte Libido weiter nach der Therapie gestoppt worden war und vermutlich durch den Gegenstand in keinem Zusammenhang mit der Prüfung oder medikamentöse Therapie; 2-Fächer wechselte am Ende der aktiven Phase Finasterid und gingen verloren to follow-up (Dutasterid wurde nicht im Handel erhältlich zum Zeitpunkt der Studie beendet). Keines dieser Studie 9 Patienten abgesetzt Therapie aufgrund dieser Nebenwirkung. Es wurde kein Anstieg bei den aktiven Behandlungsgruppen in der Inzidenz der Ohnmacht, mit 3 Fächern in der Placebo-Gruppe bei 2 Probanden und in der 0,05-mg Dutasterid-Gruppe und ein Fach in der Finasterid-Gruppe Berichterstattung so schwer. Diese sexuelle Nebenwirkungen waren entweder als leicht oder mäßig im Schweregrad und nur ein Thema der Rückzug geprägt war gedacht als ein Ergebnis dieser unerwünschten Ereignisse (dh, verminderte Libido-in der 0,1-mg Dutasterid-Gruppe; Tabelle V). Die nur unter Gynäkomastie entwickeln, wurde in der Placebo-Gruppe.

Tabelle V.
Anteil der Patienten erleben die häufigste sexuelle AEs nach Randomisierung Anteil der sexuellen AEs zu lösen (und während der Therapie gelöst), und der Anteil des sexuellen AEs führt zu Rückzug aus der Studie

Dutasterid (mg)					
Placebo	0,05	0,1	0,5	2,5	Finasteride (5,0 mg)
Anzahl der Probanden in Gruppe	64	71	72	68	71	70
Verminderte Libido, Anzahl (%)	2 (3)	2 (3)	2 (3)	1 (1)	9 (13)	3 (4)
Beschlossen auf Therapie	2	0	1	0	4	0
Beschlossen off-Therapie	0	1	1	1	2	3
Führende bis zum Entzug, Nr.	0	0	1	0	0	0
Ejakulation Erkrankungen, Anzahl (%)	0 (0)	0 (0)	3 (4)	1 (1)	1 (1)	2 (3)
Beschlossen auf Therapie	-	-	1	0	0	0
Beschlossen off-Therapie	-	-	1	1	1	2
Führende bis zum Entzug, Nr.	0	0	0	0	0	0
Impotenz, Anzahl (%)	3 (5)	2 (3)	0	0	0	1 (1)
Beschlossen auf Therapie	1	1	-	-	-	0
Beschlossen off-Therapie	2	1	-	-	-	1
Führende bis zum Entzug, Nr.	2	0	0	0	0	0

AEs, Unerwünschte Ereignisse.

AEs bei mehr als 2% der Probanden in mindestens einer Behandlungsgruppe.

Diskussion

Dutasterid, das erste Dual-5?-Reduktase-Inhibitor, wird derzeit zur Behandlung der symptomatischen BPH genehmigt. Es ist etwa 3 mal so potent wie Finasterid hemmt bei

Typ-2-5?-Reduktase und mehr als 100 mal so potent hemmt bei Typ-1-5?-reductase.14 Die 5-mg Finasterid sinkt Serum-DHT um etwa 70%, kann 19 Dutasterid Rückgang Serum DHT um mehr als 90% ,20

In dieser Phase II, Dosisfindungsstudie, 2,5 mg Dutasterid überlegen war 5-mg Finasterid bei der Verbesserung der Kopfhaut das Haarwachstum bei Männern im Alter zwischen 21 und 45 Jahren mit MPHL durch Zielgebiet Haarzählungen, Expertengremium Bewertung beurteilt, und Prüfarzt Bewertung auf 12 und 24 Wochen. Von der Ermittler Beurteilung des Haarwachstums, einen signifikanten Effekt war nach 12 Wochen mit 2,5-mg Dutasterid aber erst 24 Wochen mit Finasterid evident. Die Themen "Beurteilung war weniger empfindlich auf Veränderungen im Haarwuchs: Dies kann zumindest teilweise auf die Tatsache zurückzuführen, dass diese Einschätzung nur ein 3-Punkte-Skala, im Vergleich mit dem 7-Punkte-Skala für die Fachjury und Forscher verwendeten Bewertungsmethoden wurden . Die Wirkung der 24-wöchigen Behandlung mit 5 mg Finasterid-in dieser Studie war ähnlich wie bereits berichtet von Kaufman et al für die 52-wöchige Behandlung mit 1 mg finasteride5-und 5-mg finasteride.21 Kaufman et AL21 zeigten, dass für 1 - jährigen Behandlung mit 5 mg Finasterid-, die mittlere Veränderung vom Ausgangswert Anzahl der Haare in einem 1 Zoll Durchmesser Zielgebiet 95 wurde verglichen mit 75,6 in der gleichen Größe Zielgebiet in dieser Studie, und die Veränderung der Serum-DHT war -69,2%, verglichen mit -73% berichteten hier. Die mittlere Veränderung vom Ausgangswert Zielgebiet Anzahl der Haare in der Phase III Studie zur Bewertung 1-Jahres-Behandlung mit 1 mg Finasterid-täglich 107 pro 1-Zoll-Durchmesser Ziel area.5 Die höhere Wirksamkeit von 2,5 mg Dutasterid-hier gezeigten unterstützt das duale Rolle vom Typ 1 und Typ 2 5?-Reduktase in der Pathogenese der MPHL.

Die Ergebnisse dieser Studie auch auf die Bedeutung der Kopfhaut DHT in der Pathogenese der MPHL. Die 2,5-mg-Dosis wurde konsequent Dutasterid überlegen 0,5 mg Dutasterid bei der Förderung der Kopfhaut das Haarwachstum. Die 2,5-mg-Dosis war auch besser als die 0,5-mg-Dosis auf die Unterdrückung der Kopfhaut DHT (79% vs 51%), während es nur marginal besser unterdrücken Serum-DHT (96% vs 92%) war.

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