ORIGINAL ARTICLE

A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia

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Background: Dihydrotestosterone is the main androgen causative of androgenetic alopecia, a psychologically and physically harmful condition warranting medical treatment.

Objective: We sought to compare the efficacy and safety of dutasteride (type 1 and 2 5-alpha reductase inhibitor) with finasteride (type 2 5-alpha reductase inhibitor) and placebo in men with androgenetic alopecia.

Methods: Men aged 20 to 50 years with androgenetic alopecia were randomized to receive dutasteride (0.02, 0.1, or 0.5 mg/d), finasteride (1 mg/d), or placebo for 24 weeks. The primary end point was hair count (2.54-cm diameter) at week 24. Other assessments included hair count (1.13-cm diameter) and width, photographic assessments (investigators and panel), change in stage, and health outcomes.

Results: In total, 917 men were randomized. Hair count and width increased dose dependently with dutasteride. Dutasteride 0.5 mg significantly increased hair count and width in a 2.54-cm diameter and improved hair growth (frontal view; panel photographic assessment) at week 24 compared with finasteride ($P = .003$, $P = .004$, and $P = .002$, respectively) and placebo (all $P < .001$). The number and severity of adverse events were similar among treatment groups.

Limitations: The study was limited to 24 weeks.

Conclusions: Dutasteride increased hair growth and restoration in men with androgenetic alopecia and was relatively well tolerated. (J Am Acad Dermatol 10.1016/j.jaad.2013.10.049.)

Key words: 5-alpha reductase; 5-alpha reductase inhibitors; androgenetic alopecia; dutasteride; finasteride; male pattern baldness; male pattern hair loss; treatment.

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Androgenetic alopecia is a common, androgen-induced pattern of progressive hair loss in genetically predisposed individuals, with prevalence rates and type varying according to factors such as ethnicity.[1-6] The psychosocial impact of androgenetic alopecia may negatively affect a patient's quality of life,[7-10] causing patients to seek treatment, while published literature suggests that androgenetic alopecia can cause indirect physical harm to some patients, such as sunburn as a result of hair loss and exposure to ultraviolet light, thus warranting medical intervention.[11]

CAPSULE SUMMARY

- Dihydrotestosterone is the principal androgen causative of androgenetic alopecia.
- Dutasteride 0.5 mg/d significantly increased hair count in a 2.54-cm diameter at week 24 compared with finasteride and placebo. Adverse events were similar across treatment groups.
- Dutasteride may provide an alternative treatment option for men with androgenetic alopecia.

Topical minoxidil and oral finasteride (1 mg/d) have been approved by the US Food and Drug Administration for the treatment of male androgenetic alopecia. Finasteride, a type 2 5-alpha reductase (5AR) inhibitor (5ARI), significantly improves hair growth,[12] slows hair loss versus placebo,[13-15] and is the most commonly used treatment for the condition.[16] 5AR is involved in the pathogenesis of androgenetic alopecia, as it converts testosterone to dihydrotestosterone,[17] the principal androgen causative of the condition in men.[18] 5AR exists as 3 isoenzymes: types 1, 2, and 3.[19-21] Type 1 is mainly located in the skin, including the hair follicles and sebaceous glands,[22,23] whereas type 2 is predominantly found in male genitalia, including the prostate, but is also present in the inner root sheath of hair follicles.[17]

In 2009, dutasteride 0.5 mg, a type 1 and 2 5ARI, was approved in Korea for the treatment of androgenetic alopecia based on the results of a phase III, 6-month study showing a significant increase in hair growth versus placebo.[24] As a dual 5ARI, dutasteride may demonstrate improved efficacy in the treatment of androgenetic alopecia versus a type 2 5ARI only, given the relevant tissue distribution of type 1 5AR. In a phase II, 24-week dosing study, dutasteride 2.5 mg increased hair growth in Caucasian men more rapidly and to a greater extent versus finasteride 5 mg.[25]

This study reports the first phase III trial data, to our knowledge, comparing the efficacy, safety, tolerability, and health outcomes of different dutasteride doses with finasteride and placebo in the treatment of androgenetic alopecia.

METHODS

Study design

This was a randomized, double-blind, double-dummy, parallel-group, 29-week study conducted at 39 centers (academic and private) in 9 countries (Argentina, Chile, Japan, Mexico, Philippines, Peru, Russian Federation, Taiwan, and Thailand). A screening period (up to 3 weeks) was followed by 24 weeks of treatment and a 2-week follow-up period (Clinicaltrials.gov identifier: NCT01231607).

Patients were randomized (1:1:1:1:1 ratio) to dutasteride 0.02, 0.1, or 0.5 mg/d; finasteride 1 mg/d; or matched placebo using a randomized schedule generated by GlaxoSmithKline's RandAll system. Randomization was stratified by study center with a block size of 5.

GlaxoSmithKline, investigators/treating physicians, and patients were blinded to treatment allocation until study completion, or until patient withdrawal from the study, because of a serious adverse event (SAE).

Study participants

Eligible men were aged 20 to 50 years with androgenetic alopecia classified as type III vertex, IV, or V (excluding types IV and V anterior) using the Norwood–Hamilton classification.[26] Subjects had to maintain the same hair color and style for the study duration. Exclusion criteria included serum testosterone levels less than 250 ng/dL, unstable liver disease (except chronic stable hepatitis B and C), history of malignancy within prior 5 years (except basal or squamous cell carcinoma of the skin), prostate cancer before the age of 50 years in a first-degree relative, breast cancer or clinical breast examination suggestive of malignancy, or serum prostate-specific antigen level greater than 2.0 ng/mL. Additional exclusion criteria were global hair thinning (including female-pattern hair loss), hair loss not caused by androgenetic alopecia, scarring of the scalp, including prior hair transplantation or scalp reduction, or any other condition/disease of the scalp/hair.

The protocol was approved by relevant ethics committees or institutional review boards. Each patient provided written informed consent before study procedures.

Abbreviations used:

5AR: 5-alpha reductase
5ARI: 5-alpha reductase inhibitor
AE: adverse event
HGI: Hair Growth Index
HGSS: Hair Growth Satisfaction Scale
IPAQ: Investigator Photographic Assessment Questionnaire
SAE: serious adverse event

Assessments

The primary efficacy end point was change from baseline in hair count within a 2.54-cm diameter circle at the vertex at 24 weeks (hair growth), using a validated macrophotographic technique.[27] If baseline macrophotographs were unsuitable, subjects were reassessed. Secondary end points included: hair growth (change from baseline in hair count within a 2.54-cm diameter circle [12 weeks] and 1.13-cm diameter circle [12 and 24 weeks] at the vertex); hair restoration (change from baseline in hair width and terminal hair [defined as thickness of ≥ 60 μm] count within a 2.54- and 1.13-cm diameter circle at the vertex [12 and 24 weeks]); panel (3 dermatologists) global photographic assessment of improvement at the vertex and frontal views (from baseline to week 24); and investigator assessments, including satisfaction with treatment by the Investigator Photographic Assessment Questionnaire (IPAQ) for vertex and frontal views (12 and 24 weeks) and change in androgenetic alopecia stage according to Norwood–Hamilton scale (screening, and 12 and 24 weeks).

Subjects' perceived change in hair growth and satisfaction with hair appearance were assessed by the validated, 3-questioned Hair Growth Index (HGI) (7-point scale from "much less hair" to "much more hair") and the validated, 5-questioned Hair Growth Satisfaction Scale (HGSS) (7-point scale from "very dissatisfied" to "very satisfied") at 12 and 24 weeks. Sexual problems were assessed using the validated, 3-questioned Problem Assessment Scale of the Sexual Function Inventory at 6, 12, and 24 weeks.

Adverse events (AEs), vital signs, clinical laboratory tests, breast examinations, and prostate-specific antigen levels were monitored during the study.

Statistical analyses

Assuming a 20% postrandomization drop-out rate, 900 subjects would be needed at randomization to have 715 completers (143 completers per treatment group), providing 90% power to test noninferiority of a single dutasteride dose versus finasteride at the 1-sided 0.00835 significance level, with a 35-hair noninferiority margin. In all, 715 completers also provided more than 99% power at the 2-sided 0.0167 significance level to detect superiority (difference of 100 hairs) of dutasteride over placebo and finasteride.

To adjust for multiple comparisons, each dutasteride dose was compared with placebo in a superiority test. If superior, a noninferiority test was conducted comparing the dutasteride dose with finasteride. If noninferior, a superiority test was conducted comparing the dutasteride dose with finasteride. The overall significance level did not exceed .0501.

The intent-to-treat population (all randomized subjects) was used for efficacy, safety, and health outcomes analyses. The per-protocol population (protocol-compliant subjects) was used to confirm the noninferiority analysis results for the primary end point. All efficacy and health outcomes analyses were performed using the last observation carried forward principle. For the primary and secondary end points of hair growth and restoration, along with total HGSS and Problem Assessment Scale of the Sexual Function Inventory scores, a general linear analysis model adjusting for treatment, cluster, and baseline value was used. A general linear analysis model with effects for treatment and cluster was used to compare median panel assessment, IPAQ, and total HGI scores. A Fisher exact test was used to compare AEs, SAEs, drug-related AEs, and AEs leading to study drug or study withdrawal between treatment groups.

RESULTS

Fig 1 shows subject disposition throughout the study (October 2010 to February 2012). The intent-to-treat population contained 917 patients, of which 761 completed the study. Subject demographics and baseline characteristics were similar across treatment groups (Table I). Ninety percent of subjects were compliant with their study treatment (assessed by pill count), taking 75% to 125% of their assigned study drug.

Hair growth

In all, 764 baseline macrophotographs were used in the efficacy assessments of hair growth and restoration, of which 71 (9%; range 11-16 per group) were taken after start of treatment.

Hair count (2.54-cm diameter). The increase in baseline hair count was superior in the dutasteride 0.1, dutasteride 0.5 mg, and finasteride groups versus placebo at week 24 (all $P < .001$) (Fig 2, *A*). Dutasteride 0.1 and 0.5 mg were noninferior to

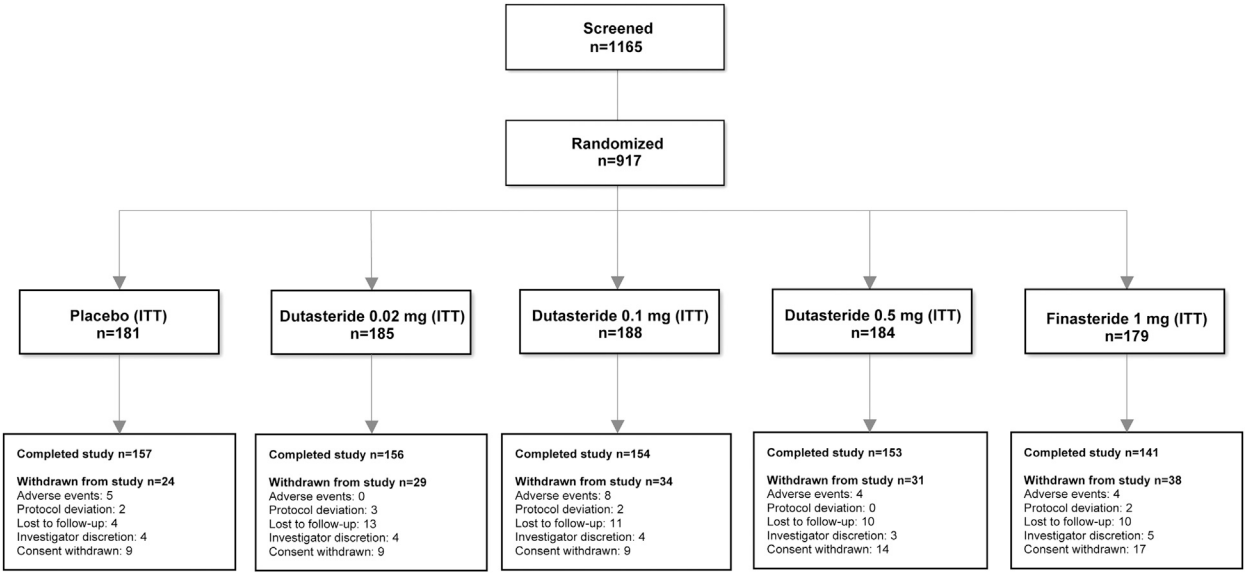


Fig 1. Subject disposition. *ITT*, Intent to treat.

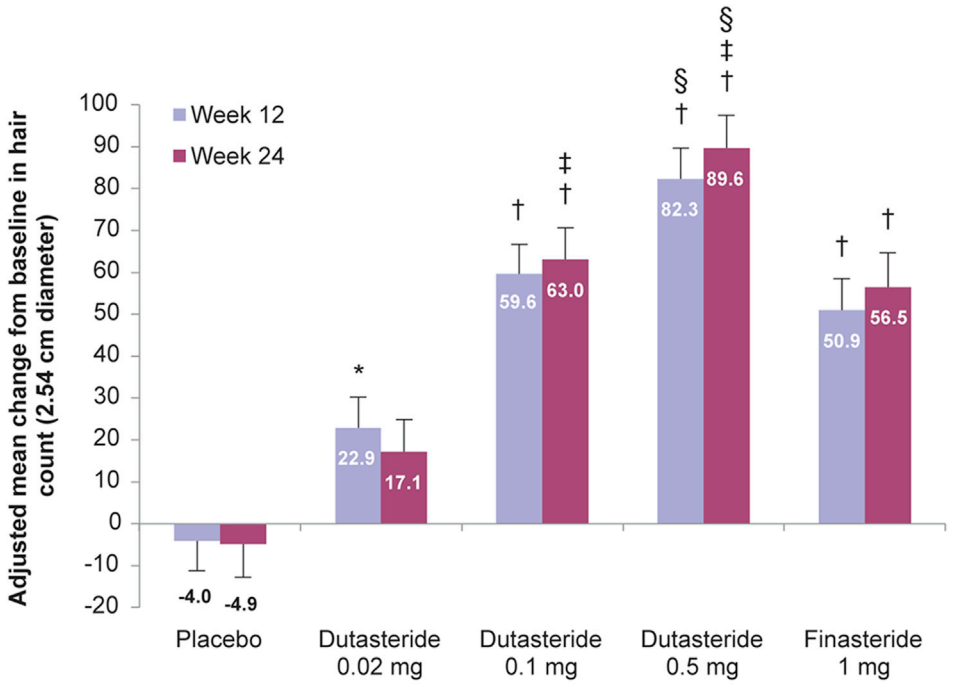
Table I. Baseline characteristics and demographics

	Placebo	Dutasteride			Finasteride
	N = 181	0.02 mg N = 185	0.1 mg N = 188	0.5 mg N = 184	1 mg N = 179
Age, y					
Mean (SD)	38.7 (8.43)	38.5 (7.72)	38.7 (7.44)	38.6 (7.66)	38.0 (7.81)
Minimum–maximum	20-50	21-50	22-50	20-50	21-50
Race, n (%)					
Asian	100 (55)	103 (56)	103 (55)	101 (55)	100 (56)
Hispanic/Latino	72 (40)	71 (38)	75 (40)	73 (40)	70 (39)
White, not Hispanic	9 (5)	11 (6)	10 (5)	10 (5)	9 (5)
BMI, kg/m^2					
Mean (SD)	25.4 (3.61)	25.6 (3.47)	25.8 (4.28)	25.1 (3.46)	25.7 (4.01)
Minimum–maximum	17.8-37.4	14.1-35.6	17.9-42.2	17.3-38.9	17.3-38.9
Current smokers, n (%)	55 (30)	70 (38)	70 (37)	50 (27)	59 (33)
Former smokers, n (%)	26 (14)	25 (14)	29 (15)	33 (18)	24 (13)
Consume alcohol, n (%)	120 (67)	118 (64)	119 (63)	121 (66)	117 (65)
Age hair loss first noticed, y					
Mean (SD)	29.0 (7.84)	29.9 (8.06)	28.4 (6.79)	29.6 (7.73)	29.8 (7.45)
Minimum–maximum	17-49	12-49	15-45	13-47	16-45
Currently experiencing hair loss, n (%)	151 (83)	152 (82)	161 (86)	160 (87)	154 (86)
Baseline Norwood–Hamilton stage, n (%)					
III Vertex	82 (45)	77 (42)	76 (40)	83 (45)	79 (44)
IV	56 (31)	61 (33)	65 (35)	58 (32)	59 (33)
V	43 (24)	47 (25)	47 (25)	43 (23)	41 (23)
Baseline hair count (2.54-cm diameter)					
Mean (SD)	761 (227)	774 (226)	721 (220)	768 (218)	764 (181)
Baseline hair count (1.13-cm diameter)					
Mean (SD)	148 (45.1)	149 (45.7)	140 (44.6)	149 (44.1)	148 (37.7)

BMI, Body mass index.

finasteride at week 24 (1-sided 99.165% confidence interval: −20.1 to 33.1 and 6.1 to 60.0, respectively); however, only dutasteride 0.5 mg was superior to finasteride at weeks 12 and 24 (both $P = .003$).

Hair count (1.13-cm diameter). All active treatment groups except dutasteride 0.02 mg were superior to placebo in increasing hair count at week 24 (all $P < .001$) (Fig 2, *B*). Dutasteride 0.5 mg



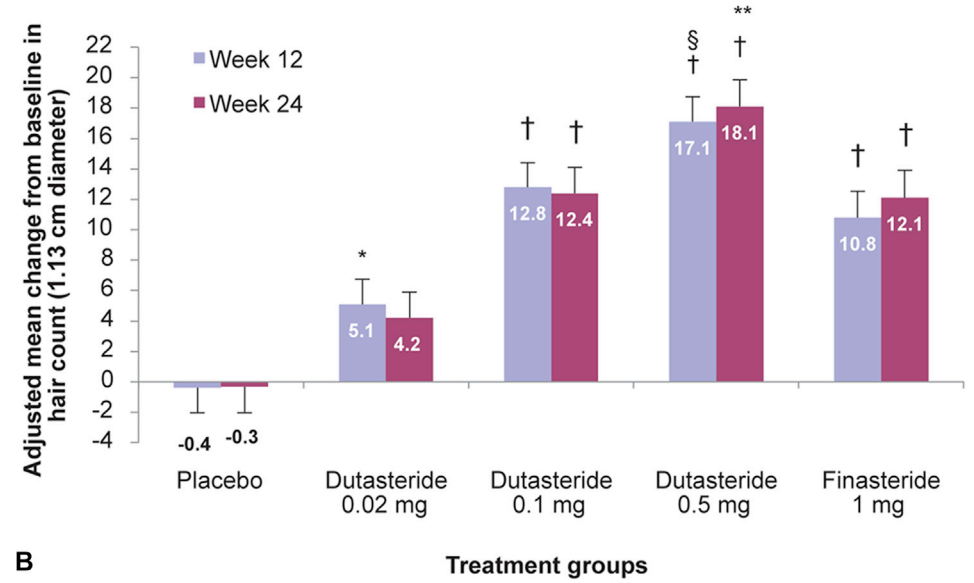


Fig 2. **A**, Adjusted mean change from baseline in target area hair count (2.54 cm) at weeks 12 and 24 for placebo, dutasteride 0.02 to 0.5 mg, and finasteride 1 mg. *P = .009, †P < .001 vs placebo; ‡noninferior to finasteride; §P = .003 vs finasteride (superiority). **B**, Adjusted mean change from baseline in target area hair count (1.13 cm) at weeks 12 and 24 for placebo, dutasteride 0.02 to 0.5 mg, and finasteride 1 mg. *P = .015, †P < .001 vs placebo; §P = .008, **P = .016 vs finasteride (superiority).

significantly increased hair count versus finasteride at week 24 (P = .016).

Hair restoration

Hair width. Dutasteride 0.1, dutasteride 0.5 mg, and finasteride were superior to placebo at increasing hair width (2.54-cm diameter) versus placebo at week 24 (all P < .001) (Fig 3); only dutasteride 0.5 mg significantly increased hair width versus finasteride at week 24 (P = .004).

Terminal hair count. Adjusted mean change from baseline in terminal hair count (2.54-cm

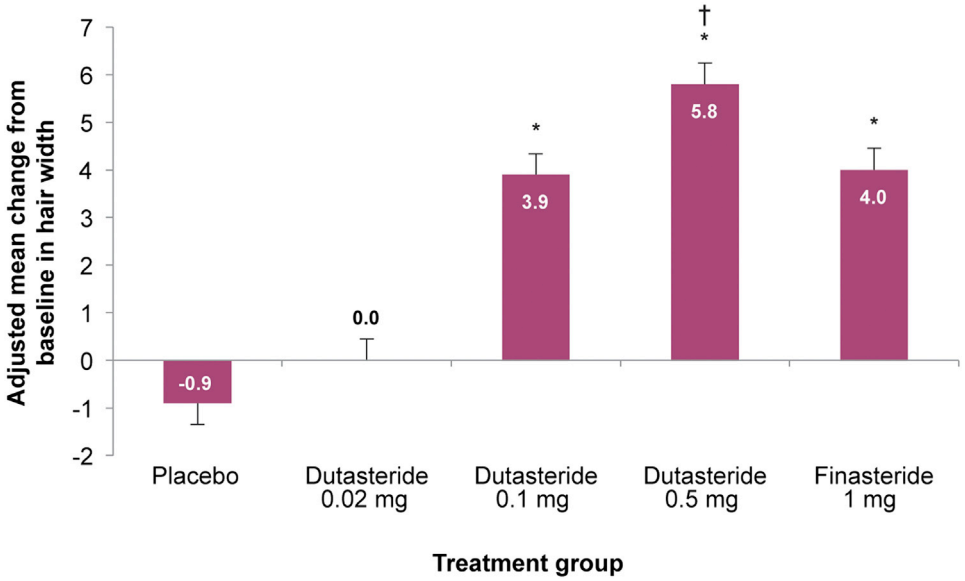


Fig 3. Adjusted mean change from baseline in target area (2.54-cm diameter) hair width (μm × 1e-3) at week 24 for placebo, dutasteride 0.02 to 0.5 mg, and finasteride 1 mg. *$P < .001$ vs placebo; †$P = .004$ vs finasteride (superiority).

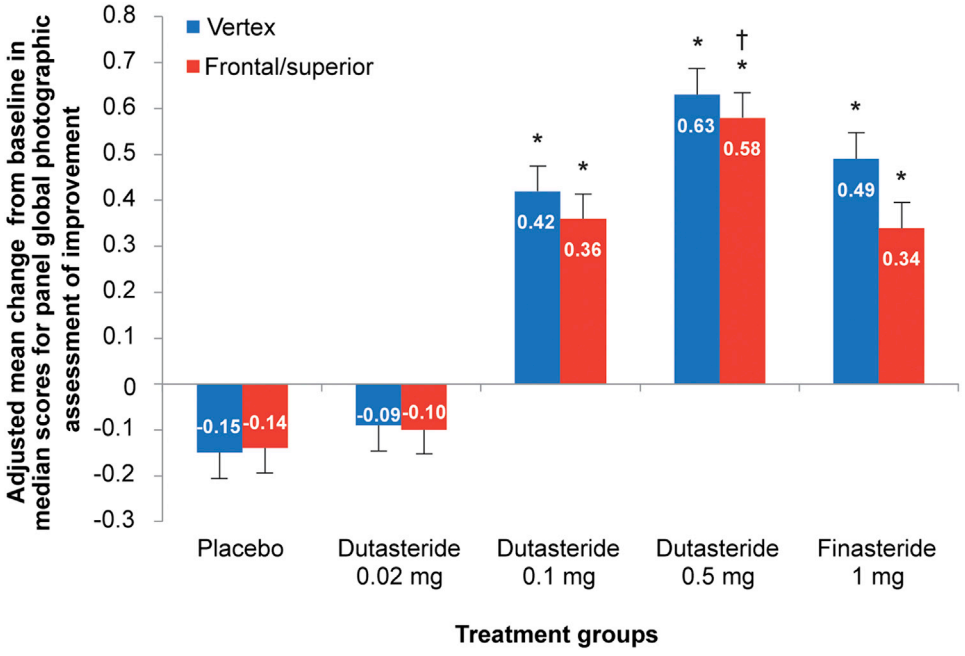


Fig 4. Median scores for panel global photographic assessment of improvement of hair growth at the vertex and frontal/superior views at week 24. *$P < .001$ vs placebo; †$P = .002$ vs finasteride (superiority).

diameter) at week 24 was superior in the dutasteride 0.1 and 0.5 mg (29.4 and 46.0 hairs) and finasteride (36.3 hairs) groups versus placebo (−17.5 hairs; all $P < .001$); dutasteride 0.02 mg was not superior to placebo (−15.7 hairs, $P = .81$). Dutasteride 0.1 and 0.5 mg were not superior to finasteride at increasing terminal hair count at week 24 ($P = .34$ and $P = .19$).

Panel global photographic assessment

There was fair to moderate agreement on individual scores assigned by 3 dermatologists for global photographic assessment of improvement in hair growth at week 24 (kappa coefficients 0.28-0.43). According to this assessment, dutasteride 0.1, dutasteride 0.5 mg, and finasteride were superior to placebo at promoting hair growth in the vertex and

Table II. Median panel global assessment in hair growth at week 24

	Placebo	Dutasteride			Finasteride
	N = 181 n (%)	0.02 mg N = 185 n (%)	0.1 mg N = 188 n (%)	0.5 mg N = 184 n (%)	1 mg N = 179 n (%)
Vertex					
n	172	174	176	167	164
Greatly decreased	0	0	0	0	0
Moderately decreased	7 (4)	7 (4)	0	1 (<1)	0
Slightly decreased	27 (16)	25 (14)	6 (3)	5 (3)	3 (2)
No change	126 (73)	123 (71)	112 (64)	82 (49)	103 (63)
Slightly increased	11 (6)	17 (10)	39 (22)	52 (31)	38 (23)
Moderately increased	1 (<1)	2 (1)	18 (10)	23 (14)	19 (12)
Greatly increased	0	0	1 (<1)	4 (2)	1 (<1)
Frontal/superior					
n	171	174	176	167	165
Greatly decreased	0	0	0	0	0
Moderately decreased	6 (4)	4 (3)	0	1 (<1)	0
Slightly decreased	29 (18)	27 (17)	4 (3)	3 (2)	7 (5)
No change	111 (70)	112 (71)	105 (68)	87 (56)	92 (64)
Slightly increased	9 (5)	12 (7)	39 (22)	37 (22)	40 (24)
Moderately increased	3 (2)	3 (2)	11 (6)	21 (13)	9 (5)
Greatly increased	0	0	1 (<1)	7 (4)	0

Table V. Adverse events, including common adverse events reported postrandomization by treatment group

		Dutasteride			Finasteride
	Placebo	0.02 mg	0.1 mg	0.5 mg	1 mg
	N = 181	N = 185	N = 188	N = 184	N = 179
	n (%) [events]	n (%) [events]	n (%) [events]	n (%) [events]	n (%) [events]
Any AE	94 (52) [185]	91 (49) [192]	95 (51) [201]	100 (54) [217]	94 (53) [189]
Any drug-related AE	27 (15) [40]	26 (14) [48]	39 (21) [52]	30 (16) [41]	35 (20) [48]
Any SAE*	2 (1) [2]	0	3 (2) [4]	1 (<1) [3]	2 (1) [4]
Death	0	0	0	0	0
Common AEs (≥3% in any group)					
Nasopharyngitis	16 (9)	19 (10)	15 (8)	23 (13)	14 (8)
Decreased libido	2 (1)	10 (5)	9 (5)	6 (3)	9 (5)
Headache	16 (9)	8 (4)	8 (4)	11 (6)	5 (3)
Erectile dysfunction	7 (4)	8 (4)	7 (4)	10 (5)	10 (6)
Abdominal pain	2 (1)	6 (3)	7 (4)	2 (1)	2 (1)
Upper respiratory tract infection	9 (5)	5 (3)	2 (1)	6 (3)	1 (<1)
Back pain	4 (2)	5 (3)	3 (2)	3 (2)	4 (2)
Upper abdominal pain	1 (<1)	4 (2)	1 (<1)	2 (1)	5 (3)
Influenza	5 (3)	3 (2)	4 (2)	1 (<1)	2 (1)
Diarrhea	3 (2)	2 (1)	7 (4)	2 (1)	0
Allergic rhinitis	1 (<1)	2 (1)	1 (<1)	4 (2)	6 (3)
Pharyngitis	7 (4)	1 (<1)	2 (1)	3 (2)	5 (3)

AE, Adverse event; *SAE*, serious adverse event.

*SAEs reported postrandomization were: syncope and nephrolithiasis in the placebo group; cartilage injury, rectal cancer, increased blood pressure, and metastatic hepatic cancer in the dutasteride 0.1 mg group; parasitic infection, salmonellosis, and gastric ulcer in the dutasteride 0.5 mg group; and laryngitis, pharyngeal abscess, fractured sacrum, and lower limb fracture in the finasteride group.

frontal/superior views at week 24 (all $P < .001$) (Fig 4). Dutasteride 0.5 mg was superior to finasteride at promoting hair growth in the frontal/superior view but not the vertex at week 24 ($P = .002$).

The proportion of subjects with any improvement in median panel assessment scores at week 24 in both the vertex and frontal/superior views (Fig 5; available at http://www.jaad.org) was higher in the dutasteride 0.1, dutasteride 0.5 mg, and finasteride groups versus placebo and dutasteride 0.02 mg (Table II). The proportion of subjects with great improvement was highest with dutasteride 0.5 mg.

Table VI. Adverse events leading to drug/study withdrawal reported postrandomization by treatment group

	Placebo	Dutasteride			Finasteride
	N = 181 n (%)	0.02 mg N = 185 n (%)	0.1 mg N = 188 n (%)	0.5 mg N = 184 n (%)	1 mg N = 179 n (%)
AE drug withdrawals	5 (3)	0	8 (4)	5 (3)	4 (2)
AE study withdrawals	5 (3)	0	8 (4)	4 (2)	4 (2)
AEs leading to study withdrawal (≥2 subjects in any group)					
Erectile dysfunction	2 (1)	0	1 (<1)	0	2 (1)
Decreased libido	1 (<1)	0	2 (1)	0	0
Hypertension	0	0	2 (1)	0	0

AE, Adverse event.

Investigator assessment

IPAQ scores at week 24 are shown in Table III (available at http://www.jaad.org). Compared with placebo, dutasteride 0.1, dutasteride 0.5 mg, and finasteride significantly improved hair growth (assessed by adjusted mean IPAQ scores) in the vertex (1.03, 1.30, and 1.07 vs 0.36, respectively) and frontal/superior views (0.78, 1.11, and 0.88 vs 0.30, respectively) at week 24 (all $P < .001$). Dutasteride was not superior to finasteride at improving hair growth in the vertex and frontal/superior views (assessed by mean IPAQ scores) at week 24.

Androgenetic alopecia stage

Few subjects (n = 17) had a worsening of stage over the 24-week treatment period (Table IV; available at http://www.jaad.org). In subjects with stage IV at baseline, a greater proportion remained stage IV at week 24 in the placebo group (85%) versus the active treatment groups (dutasteride 0.02 mg [78%], 0.1 mg [66%], and 0.5 mg [66%]; and finasteride [67%]). More subjects with stage V at baseline had an improvement in stage at week 24 with dutasteride 0.5 mg (39%) versus the other treatments (placebo [29%], dutasteride 0.02 mg [28%], dutasteride 0.1 mg [28%], and finasteride [31%]).

Health outcomes

Adjusted mean HGI total scores at week 24 were significantly higher in the dutasteride 0.1 mg (2.8), dutasteride 0.5 mg (3.2), and finasteride (2.5) groups versus placebo (1.1; all $P < .001$); there was no significant difference between adjusted mean HGI total scores in the dutasteride 0.02 mg (1.1) and placebo (1.1; $P = .80$) groups.

At week 24, adjusted mean change from baseline in total HGSS scores was higher with dutasteride 0.1 (11.4) and 0.5 mg (12.0) versus placebo (9.1; $P = .002$ and $P < .001$, respectively); adjusted mean total HGSS scores for dutasteride 0.02 mg (8.5) and finasteride (10.4) were not significantly different from placebo ($P = .37$ and $P = .084$, respectively).

Adjusted mean total Problem Assessment Scale of the Sexual Function Inventory scores decreased from baseline to week 24 in all treatment groups (range −0.3 to −0.9 points); the decrease was not significantly different from placebo in any treatment group (dutasteride 0.02 mg, $P = .041$; dutasteride 0.1 mg, $P = .19$; dutasteride 0.5 mg, $P = .11$; finasteride, $P = .024$).

Safety

Most AEs reported postrandomization (Table V) were mild or moderate; few were severe (placebo, n = 4; dutasteride 0.02 mg, n = 0; dutasteride 0.1 mg, n = 5; dutasteride 0.5 mg, n = 5; finasteride, n = 6).

The overall incidence of AEs was similar between treatment groups with no evidence of a dutasteride dose response (placebo, n = 94; dutasteride 0.02 mg, n = 91; dutasteride 0.1 mg, n = 95; dutasteride 0.5 mg, n = 100; finasteride, n = 94). There were no statistically significant differences between active treatment groups and placebo in the incidence of AEs, drug-related AEs, SAEs, or AE withdrawals from the study or study drug. Of the SAEs reported during the study (Table V), only syncope (placebo group) was considered drug-related. AEs leading to study withdrawal in 2 or more subjects in any group are shown in Table VI.

The incidence of AEs of special interest related to sexual functioning and breast disorders was similar in the active treatment groups and lower with placebo (Table VII), with the composite AE "altered libido" being the main cause for the difference between placebo and active treatments. There was no evidence of a dutasteride dose response in AEs related to sexual functioning (placebo, n = 12; dutasteride 0.02 mg, n = 21; dutasteride 0.1 mg, n = 24; dutasteride 0.5 mg, n = 19; finasteride, n = 24). There were no reports of prostate cancer, breast cancer, or cardiovascular AEs of special interest.

The number of subjects with postbaseline laboratory and vital signs outside threshold values were similar across treatment groups (range: 2-6 subjects [placebo—dutasteride 0.1 mg] and 3-7 subjects

Table VII. Adverse events of special interest

Preferred term	Placebo N = 181 n (%)	Dutasteride 0.02 mg N = 185 n (%)	Dutasteride 0.1 mg N = 188 n (%)	Dutasteride 0.5 mg N = 184 n (%)	Finasteride 1 mg N = 179 n (%)
Any special interest AE	12 (6.6)	21 (11.4)	24 (12.8)	19 (10.3)	24 (13.4)
Altered libido	3 (1.7)	15 (8.1)	13 (6.9)	9 (4.9)	12 (6.7)
Decreased libido	2 (1.1)	10 (5.4)	9 (4.8)	6 (3.3)	9 (5.0)
Sexual dysfunction	1 (0.6)	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.1)
Loss of libido	0	2 (1.1)	2 (1.1)	0	1 (0.6)
Libido disorder	0	0	0	1 (0.5)	0
Impotence	7 (3.9)	8 (4.3)	7 (3.7)	10 (5.4)	11 (6.1)
Erectile dysfunction	7 (3.9)	8 (4.3)	7 (3.7)	10 (5.4)	10 (5.6)
Organic erectile dysfunction	0	0	0	0	1 (0.6)
Ejaculation disorders	6 (3.3)	4 (2.2)	9 (4.8)	6 (3.3)	7 (3.9)
Ejaculation failure	2 (1.1)	1 (0.5)	2 (1.1)	1 (0.5)	4 (2.2)
Ejaculation disorder	2 (1.1)	0	3 (1.6)	2 (1.1)	2 (1.1)
Semen volume decrease	0	2 (1.1)	3 (1.6)	2 (1.1)	0
Premature ejaculation	1 (0.6)	1 (0.5)	0	1 (0.5)	1 (0.6)
Ejaculation delayed	1 (0.6)	1 (0.5)	1 (0.5)	0	0
Breast enlargement	0	0	1 (0.5)	1 (0.5)	1 (0.6)
Breast enlargement	0	0	1 (0.5)	0	1 (0.6)
Gynecomastia	0	0	0	1 (0.5)	0
Breast tenderness	0	1 (0.5)	1 (0.5)	0	0
Breast tenderness	0	0	1 (0.5)	0	0
Nipple pain	0	1 (0.5)	0	0	0

AE, Adverse event.

[placebo—dutasteride 0.02 mg and finasteride], respectively).

DISCUSSION

In this study, dutasteride 0.5 mg was statistically superior to finasteride 1 mg and placebo, whereas finasteride was superior to placebo, at increasing hair count and width after 24 weeks of treatment in men with androgenetic alopecia. These results are consistent with another phase III trial, in which dutasteride 0.5 mg significantly increased hair count at week 24 versus placebo.[24] Although dutasteride 0.5 mg significantly increased hair count versus placebo at 12 and 24 weeks in a phase II dose-finding study, the 0.5 mg dose was not significantly different versus finasteride 5 mg. However, in the same study, dutasteride 2.5 mg was superior to finasteride 5 mg at increasing hair count at 12 and 24 weeks.[25]

Consistent with previously reported data,[25] dutasteride and finasteride were relatively well tolerated with similar tolerability data reported here for both active treatments. The incidence of sexual AEs was similar in the active treatment groups but lower in the placebo group, with no evidence of a dose—response relationship with increasing dutasteride dose. This finding has been reported in patients with androgenetic alopecia receiving finasteride (1 mg)[28] and in patients with benign prostatic hyperplasia receiving dutasteride (0.5 mg) in a 4-year follow-up study; however, the incidence of sexual AEs decreased over time in the latter study.[29]

Published data indicate that 5ARIs may cause an increased incidence of Gleason score 8 to 10 prostate cancer.[30] No cases of prostate cancer were reported during this study; however, long-term data are required to support this finding. Recent meta-analyses of phase III benign prostatic hyperplasia studies of dutasteride alone or in combination with tamsulosin showed no increased risk of Gleason score 7 to 10 and 8 to 10 cancer in patients at increased risk of the disease, supporting the use of dutasteride.[31] No new safety signals concerning dutasteride emerged in this phase III study.

Some baseline macrophotographs were taken on treatment, potentially influencing the hair growth and restoration results; however, these were required for analysis. Because of short treatment duration in this study, long-term data may be required to establish the full effects of dutasteride versus finasteride on hair growth and restoration.

To our knowledge, this phase III study is the first to compare dutasteride 0.5 mg with finasteride 1 mg for the treatment of male androgenetic alopecia.

We would like to thank all study investigators (Appendix; available at http://www.jaad.org) for their contribution to the initiation and conduct of this study.

REFERENCES

1. Rhodes T, Girman CJ, Savin RC, Kaufman KD, Guo S, Lilly FR, et al. Prevalence of male pattern hair loss in 18-49 year old men. Dermatol Surg 1998;24:1330-2.
2. Paik JH, Yoon JB, Sim WY, Kim BS, Kim NI. The prevalence and types of androgenetic alopecia in Korean men and women. Br J Dermatol 2001;145:95-9.
3. Wang TL, Zhou C, Shen YW, Wang XY, Ding XL, Tian S, et al. Prevalence of androgenetic alopecia in China: a community-based study in six cities. Br J Dermatol 2010;162:843-7.
4. Su LH, Chen TH. Association of androgenetic alopecia with smoking and its prevalence among Asian men: a community-based survey. Arch Dermatol 2007;143:1401-6.
5. Pathomvanich D, Pongratananukul S, Thienthaworn P, Manoshai S. A random study of Asian male androgenetic alopecia in Bangkok, Thailand. Dermatol Surg 2002;28:804-7.
6. Tang PH, Chia HP, Cheong LL, Koh D. A community study of male androgenetic alopecia in Bishan, Singapore. Singapore Med J 2000;41:202-5.
7. Goh CL. A retrospective study on the characteristics of androgenetic alopecia among Asian races in the National Skin Center, a tertiary dermatological referral center in Singapore. Ann Acad Med Singapore 2002;31:751-5.
8. Cash TF. The psychological effects of androgenetic alopecia in men. J Am Acad Dermatol 1992;26:926-31.
9. Han SH, Byun JW, Lee WS, Kang H, Kye YC, Kim KH, et al. Quality of life assessment in male patients with androgenetic alopecia: result of a prospective, multicenter study. Ann Dermatol 2012;24:311-8.
10. Sawant N, Chikhalkar S, Mehta V, Ravi M, Madke B, Khopkar U. Androgenetic alopecia: quality-of-life and associated lifestyle patterns. Int J Trichology 2010;2:81-5.
11. Stough D, Stenn K, Haber R, Parsley WM, Vogel JE, Whiting DA, et al. Psychological effect, pathophysiology, and management of androgenetic alopecia in men. Mayo Clin Proc 2005;80:1316-22.
12. Sato A, Takeda A. Evaluation of efficacy and safety of finasteride 1 mg in 3177 Japanese men with androgenetic alopecia. J Dermatol 2012;39:27-32.
13. Kawashima M, Hayashi N, Igarashi A, Kitahara H, Maeguchi M, Mizuno A, et al. Finasteride in the treatment of Japanese men with male pattern hair loss. Eur J Dermatol 2004;14:247-54.
14. Lin JH, Chen WC. Finasteride in the treatment of Taiwanese men with androgenetic alopecia: a 12-month open-label study. Kaohsiung J Med Sci 2002;18:379-85.
15. Finasteride Male Pattern Hair Loss Study Group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. Eur J Dermatol 2002;12:38-49.
16. McElwee KJ, Shapiro JS. Promising therapies for treating and/or preventing androgenic alopecia. Skin Therapy Lett 2012;17:1-4.
17. Chen W, Zouboulis CC, Orfanos CE. The 5 alpha-reductase system and its inhibitors: recent development and its perspective in treating androgen-dependent skin disorders. Dermatology 1996;193:177-84.
18. Messenger A. Male androgenetic alopecia. In: Blume-Peytavi U, Tosti A, Whiting DA, Trueb R, editors. Hair growth and disorders. Berlin: Springer; 2008. pp. 159-70.
19. Kaufman KD. Androgen metabolism as it affects hair growth in androgenetic alopecia. Dermatol Clin 1996;14:697-711.
20. Olsen EA. Androgenetic alopecia. In: Olsen EA, editor. Disorders of hair growth: diagnosis and treatment. New York: McGraw-Hill; 1994. pp. 257-83.
21. Godoy A, Kawinski E, Li Y, Oka D, Alexiev B, Azzouni F, et al. 5Alpha-reductase type 3 expression in human benign and malignant tissues: a comparative analysis during prostate cancer progression. Prostate 2011;71:1033-46.
22. Sato T, Sonoda T, Itami S, Takayasu S. Predominance of type I 5alpha-reductase in apocrine sweat glands of patients with excessive or abnormal odor derived from apocrine sweat (osmidrosis). Br J Dermatol 1998;139:806-10.
23. Thiboutot D, Harris G, Iles V, Cimis G, Gilliland K, Hagari S. Activity of the type 1 5 alpha-reductase exhibits regional differences in isolated sebaceous glands and whole skin. J Invest Dermatol 1995;105:209-14.
24. Eun HC, Kwon OS, Yeon JH, Shin HS, Kim BY, Ro BI, et al. Efficacy, safety, and tolerability of dutasteride 0.5 mg once daily in male patients with male pattern hair loss: a randomized, double-blind, placebo-controlled, phase III study. J Am Acad Dermatol 2010;63:252-8.
25. Olsen EA, Hordinsky M, Whiting D, Stough D, Hobbs S, Ellis ML, et al. The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. J Am Acad Dermatol 2006;55:1014-23.
26. Norwood OT. Male pattern baldness: classification and incidence. South Med J 1975;68:1359-65.
27. Canfield D. Photographic documentation of hair growth in androgenetic alopecia. Dermatol Clin 1996;14:713-21.
28. McClellan KJ, Markham A. Finasteride: a review of its use in male pattern hair loss. Drugs 1999;57:111-26.
29. Debruyne F, Barkin J, van Erps P, Reis M, Tammela TL, Roehrborn C. Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. Eur Urol 2004;46:488-95.
30. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med 2010;362:1192-202.
31. Monga N, Sayani A, Rubinger DA, Wilson TH, Su Z. The effect of dutasteride on the detection of prostate cancer: a set of meta-analyses. Can Urol Assoc J 2013;7:E161-7.

APPENDIX
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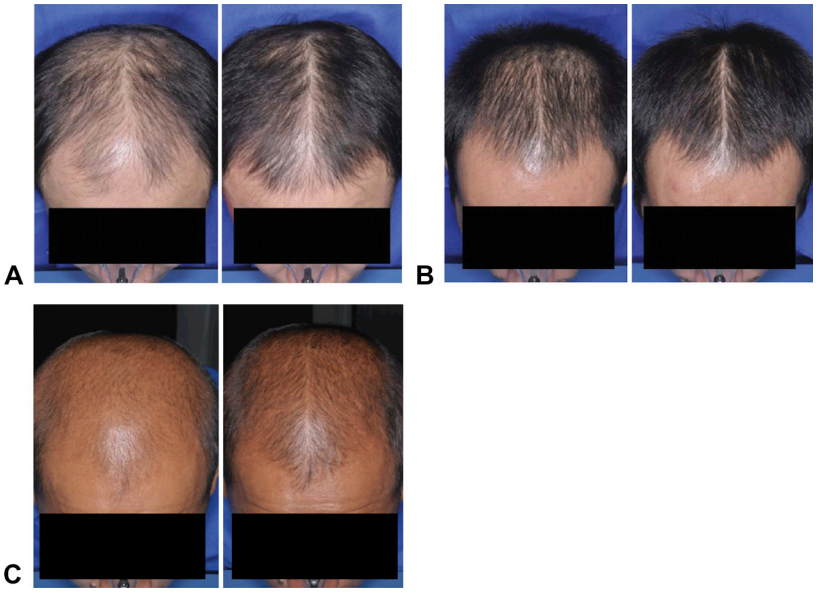

Fig 5. Androgenetic alopecia. Global photograph of greatly (**A**), moderately (**B**), and slightly (**C**) improved median panel scores for androgenetic alopecia in the frontal/superior region at week 24.

Table III. Investigator Photographic Assessment Questionnaire scores for the vertex and frontal/superior views at week 24

	Placebo	Dutasteride			Finasteride
	N = 181 n (%)	0.02 mg N = 185 n (%)	0.1 mg N = 188 n (%)	0.5 mg N = 184 n (%)	1 mg N = 179 n (%)
Vertex					
n	173	174	177	167	165
Greatly decreased	1 (<1)	2 (1)	0	0	1 (<1)
Moderately decreased	8 (5)	7 (4)	2 (1)	1 (<1)	1 (<1)
Slightly decreased	25 (14)	24 (14)	4 (2)	3 (2)	4 (2)
No change	60 (35)	70 (40)	49 (28)	34 (20)	40 (24)
Slightly increased	60 (35)	44 (25)	69 (39)	60 (36)	72 (44)
Moderately increased	16 (9)	22 (13)	43 (24)	51 (31)	34 (21)
Greatly increased	3 (2)	5 (3)	10 (6)	18 (11)	13 (8)
Frontal/superior					
n	173	174	177	167	165
Greatly decreased	2 (1)	3 (2)	0	0	1 (<1)
Moderately decreased	4 (2)	5 (3)	1 (<1)	1 (<1)	1 (<1)
Slightly decreased	26 (15)	24 (14)	10 (6)	2 (1)	5 (3)
No change	73 (42)	78 (45)	70 (40)	45 (27)	55 (33)
Slightly increased	52 (30)	42 (24)	54 (31)	65 (39)	62 (38)
Moderately increased	14 (8)	22 (13)	35 (20)	43 (26)	37 (22)
Greatly increased	2 (1)	0	7 (4)	11 (7)	4 (2)

Table IV. Change from baseline in AGA stage at week 24

	Placebo	Dutasteride			Finasteride
AGA stage	**N = 181 n (%)**	**0.02 mg N = 185 n (%)**	**0.1 mg N = 188 n (%)**	**0.5 mg N = 184 n (%)**	**1 mg N = 179 n (%)**
Baseline stage IIIv					
N at wk 24	80	72	72	72	76
Worsening in stage	4 (5)	1 (1)	1 (1)	1 (1)	1 (1)
Stage unchanged	67 (84)	61 (85)	58 (81)	54 (75)	59 (78)
Improvement in stage	9 (11)	10 (14)	13 (18)	17 (24)	16 (21)
Baseline stage IV					
N at wk 24	52	59	59	56	54
Worsening in stage	2 (4)	2 (3)	4 (7)	0	1 (2)
Stage unchanged	44 (85)	46 (78)	39 (66)	37 (66)	36 (67)
Improvement in stage	6 (12)	11 (19)	16 (27)	19 (34)	17 (31)
Baseline stage V					
N at wk 24	41	46	46	41	35
Worsening in stage	0	0	0	0	0
Stage unchanged	29 (71)	33 (72)	33 (72)	25 (61)	24 (69)
Improvement in stage	12 (29)	13 (28)	13 (28)	16 (39)	11 (31)

AGA, Androgenetic alopecia.