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ORIGINAL ARTICLE

Long-term safety and efficacy of dutasteride in the treatment of male patients with androgenetic alopecia

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ABSTRACT

Androgenetic alopecia is an androgen-induced pattern of progressive hair loss, which occurs in genetically predisposed people. This study aimed to determine long-term safety, tolerability and efficacy of dutasteride 0.5 mg, an inhibitor of 5-α-reductase, in Japanese male patients with androgenetic alopecia. This was a multicenter, open-label, prospective outpatient study (clinicaltrials.gov NCT01831791, GSK identifier ARI114264) in which patients took dutasteride 0.5 mg p.o. once daily for 52 weeks. Primary end-points included adverse event assessment, incidence of drug-related adverse event and premature discontinuations. Secondary end-points included hair growth, hair restoration and global improvement in hair. A total of 120 patients were enrolled, of whom 110 completed 52 weeks of treatment. Nasopharyngitis, erectile dysfunction and decreased libido were the most frequently reported adverse events and most adverse events were mild. Drug-related adverse events were reported with an incidence of 17%, none of which led to study withdrawal. Hair growth (mean target area hair count at week 52), hair restoration (mean target area hair width at week 52) and global appearance of hair (mean of the median score at week 52) improved from baseline during the study. As a potential future treatment option for male androgenetic alopecia, dutasteride 0.5 mg exhibited long-term safety, tolerability and efficacy within this study population.

Key words: 5-alpha-reductase inhibitor, dihydrotestosterone, dutasteride, male androgenetic alopecia, safety.

INTRODUCTION

Androgenetic alopecia is a common androgen-induced pattern of progressive loss of scalp hair with onset at any age after puberty in genetically predisposed people.[1] The characteristics of androgenetic alopecia in the Asian population, including the Japanese population, are generally distinct from those of other populations, with a lower incidence and later onset (predominantly occurring after the age of 40 years) compared with European populations.[2] Nevertheless, a survey of hair loss and thinning in Japanese adult men revealed that 12.6 million men were aware of hair thinning, 8 million were concerned about hair thinning, 6.5 million had taken some actions against it and 5 million were taking some action to improve it at the time of the survey.[3] In a separate sample, it was found that of men who reported moderate to extensive hair loss, at approximately 60% were concerned about the present and future condition of their hair, and this percentage was higher in men in their 20s and 30s, compared with older men.[4]

The pathological mechanism underlying androgenetic alopecia involves the local and systemic conversion of testosterone to dihydrotestosterone (DHT), a more potent androgen, by the enzyme 5-α-reductase (5αR); 5αR exists as two isozymes: type 1 and type 2.[5,6] Type 1 is distributed throughout the body including hair follicle epithelial cells and dermal papilla cells, and it predominantly acts in the apocrine sweat glands and sebaceous glands in the skin;[7,8] type 2 is primarily expressed in male genitalia, as well as dermal papilla cells of the anterior and parietal scalp areas.[9] Both isozymes have been isolated in scalp skin of patients with alopecia.[9] A number of pharmacological treatments for androgenetic alopecia target the underlying hormonal changes associated with this disease. Two medical treatments approved by the US Food and Drug Administration for androgenetic alopecia are topical minoxidil (a potassium channel modulator) and oral finasteride (a selective type 2 5αR inhibitor).[1]

Dutasteride is an oral inhibitor of both type 1 and type 2 5αR. It was first approved worldwide for the treatment of

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benign prostatic hyperplasia (BPH) and was approved in Korea in 2009 for the treatment of androgenetic alopecia in men.[10] Analysis of data collected during a global phase II/III study of dutasteride (NCT01231607; GSK study identifier ARI114263) showed a significant increase in target area hair count for two dutasteride groups (0.1 and 0.5 mg) compared with the placebo arm over 24 weeks of treatment. Both the dutasteride 0.1 and 0.5 mg treatment arms also demonstrated non-inferiority compared with the finasteride 1 mg arm.[11] Furthermore, treatment with dutasteride 0.5 mg demonstrated a significant increase in target area hair count compared with finasteride 1 mg,[11] and in patients who did not respond to finasteride treatment, there is evidence for efficacy of dutasteride in terms of hair density and hair thickness.[12]

The aim of this study, conducted after the global phase II/III study (ARI114263), was to assess the safety, tolerability and efficacy of dutasteride 0.5 mg administrated once daily for 52 weeks, over a longer treatment period, in Japanese male patients with androgenetic alopecia.

METHODS

Study design

This was an open-label, prospective, single-arm outpatient study conducted at five centers in Japan, registered with clinicaltrials.gov (NCT01831791; ARI114264). It consisted of a screening phase (3 weeks prior to baseline) and a treatment phase (52 weeks), during which there were a total of seven scheduled clinic visits (weeks 0, 6, 13, 26, 39 and 52) and three contacts by telephone (weeks 19, 32 and 45). Safety evaluations were conducted at all visits and contacts; efficacy evaluations were conducted at weeks 26 and 52.

The study protocol and all amendments were approved by the institutional review boards of the participating institutions (Table S1); no amendments were made after enrollment began. The study was conducted in accordance with the Declaration of Helsinki (2008) and monitored in accordance with Good Clinical Practice. Written informed consent was obtained from each patient prior to study participation.

Patients

Adults were eligible for inclusion if they were: male outpatients aged 20–50 years; had androgenetic alopecia classified as type III vertex, IV or V (excluding type IV anterior and V anterior) utilizing the Norwood–Hamilton classification;[13] were fluent and literate in Japanese; had aspartate aminotransferase and alanine aminotransferase of less than 2-times the upper limit of normal (ULN), and alkaline phosphatase and bilirubin of 1.5-times ULN or less; willing to comply with the study requirements to retain the same hairstyle and color throughout the study duration and keep hair in non-balding areas of 2 cm or more in length; and able to swallow and retain oral medication.

The exclusion criteria are provided in full in the supporting information (Table S2). The main medical exclusion criteria were: evidence of hypogonadism; unstable liver disease; history of malignancy within the past 5 years; history of prostate cancer before 50 years of age in a first-degree relative; and the presence of any unstable, co-existing medical condition (as detailed in Table S2). The main hair and scalp exclusions were: global scalp hair thinning; scarring of the scalp; evidence of other hair loss; and use of other hair-related treatments. There were also medication exclusions consisting of hypersensitivity to 5αR inhibitors, use of dutasteride within 18 months or of finasteride within 12 months prior to screening, use of systemic cytotoxic agents and use of glucocorticoids within 3 months prior to screening.

Treatment

During the treatment period, all patients were to take one soft gelatin capsule of dutasteride 0.5 mg p.o. once daily for 52 weeks. Dutasteride was to be taken either with or without food, at approximately the same time every day.

End-points and assessments

Safety. The primary end-points were safety related and included the following: the assessment of adverse events (AE), including sexual dysfunction AE (SDAE) of special interest; the incidence of drug-related AE, premature discontinuations, serious AE (SAE) and abnormal laboratory tests; changes from baseline in vital signs and laboratory values; changes from baseline in breast examination findings; and suicidality assessment using the Columbia Suicide Severity Rating Scale.[14,15] The investigators at each site were responsible for detecting, documenting and reporting AE or SAE. The duration, severity (mild, moderate, severe), causality, actions taken and outcomes for each AE were recorded.

Adverse events were collected from baseline to the end of the study, while SAE related to study participation were collected from screening to study end. Breast examinations, suicidality and all clinical laboratory analyses were conducted at the same three time points (screening and weeks 26 and 52).

Efficacy. The efficacy end-points were secondary to the safety end-points and included hair growth, hair restoration, global improvement in hair and change in androgenetic alopecia stage.

Hair growth was assessed by change from baseline in target area hair count at weeks 26 and 52. Hair restoration was assessed by change from baseline in target area hair width and in terminal hair count at weeks 26 and 52. These two efficacy end-points were assessed using macrophotographic techniques to determine the number and width of hairs within a 2.54-cm diameter circle at the vertex.

A panel assessed the global improvement from baseline to the same time points, assessed separately for the vertex and frontal views using global photographic images. The panel comprised three dermatologists who independently assessed the change in hair growth from baseline to weeks 26 and 52, according to a 7-point scale ranging from “greatly decreased” (score −3) to “greatly increased” (score 3).

The study-site investigators assessed the change in stage of androgenetic alopecia according to the Norwood–Hamilton scale at weeks 26 and 52 by direct visual examination of the

patient. Every effort was made to keep the same investigator for each patient.

Other end-points. Serum concentrations of DHT were measured at screening and weeks 26 and 52.

Health outcomes end-points included change from baseline in sexual problems including sex drive, erections and ejaculation, as assessed at weeks 13, 26, 39 and 52 using the Problem Assessment Scale of Sexual Function Inventory (PAS SFI).[16] The questions posed in the PAS SFI asked patients to grade on a 5-point scale the extent of the problem caused by a lack of sex drive, ability to get and keep erections, and issues with ejaculation during the preceding 30 days. Change from baseline in quality of life (QoL) was also assessed at the same time points using the Dermatology Life Quality Index (DLQI).[17]

Sample size determination

A sample size of 100 patients was determined to provide 95% power to detect more than one AE with an incidence rate of approximately 3%. Assuming a post-enrollment dropout rate of approximately 15%, 120 patients were enrolled to receive study treatment. A further 14% initial screen failure rate was assumed based on a previous study,[10] therefore, 140 patients were to be screened to obtain 100 patients who would complete the study.

Statistical analysis and populations analyzed

No statistical hypotheses were tested in this study. Data were summarized using descriptive statistics with the SAS System version 9.3 software (SAS Institute, Cary, NC, USA). The primary analysis approach used was last observation carried forward (LOCF), wherein the last non-missing post-baseline assessment for patients was brought (carried) forward for any patients with missing visit data and/or who had discontinued from the study.

The safety population (SP) consisted of all patients who were enrolled and received at least one dose of dutasteride. The intention-to-treat (ITT) population consisted of all those who were enrolled, regardless of whether or not treatment was administrated. The per protocol (PP) population was comprised of all ITT patients who complied closely with the study protocol; PP population analysis was scheduled only if it comprised less than 80% of the ITT population.

RESULTS

Patients and treatment exposure

Of a total of 144 patients screened, 120 patients from five centers in Japan were enrolled in this study, 10 of whom withdrew prematurely from the study due to withdrawal of consent. One patient was excluded from the PP population because he used a medication prohibited according to the study protocol. As all enrolled patients received at least one dose of the study medication, the SP and ITT populations were identical and also the PP population comprised more than 99% of the ITT population (Fig. 1). For all reported analyses, therefore, the ITT population was used. The majority of patients were older than 41 years of age and were experiencing hair loss at the time of enrollment; demographics and baseline characteristics are shown in Table 1.

A total of 112 (94%) patients received dutasteride 0.5 mg for more than 273 days (range, 44–378), with a mean exposure of 350.9 days (standard deviation [SD], 52.90). Overall subject exposure was 114 years. The mean compliance with the study treatment regimen was 97.9% (SD, 2.92%).

Outcomes

Safety. The incidence of any on-treatment AE was 53%. Most AE were mild and no severe events were reported. Nasopharyngitis was the most frequently reported AE (Table 2). The incidence of most AE was higher during the first 6-month study period compared with the second 6-month period.

The overall incidence of drug-related AE was 17%. SDAE were the most common drug-related AE, specifically erectile dysfunction and decreased libido (Table 2). At week 52, three patients reported events that were considered to be possible suicidality-related AE: suicidal ideation in one patient and depressed mood in two patients. No AE resulted in study withdrawal.

Sexual dysfunction AE of special interest were reported in 19 (15.8%) patients (Table 3); there were no reports of breast disorders. All of the reported SDAE of special interest were drug-related except one case of impotence, and none led to withdrawal from the study or was considered severe. The onset of SDAE and time until recovery are presented in Table 4. SDAE reported in six patients had resolved during the 52-week treatment period; the 13 patients with SDAE that persisted at the end of the treatment period were all resolved within the 6-month follow-up period of treatment cessation. There were no reports of cardiovascular AE other than

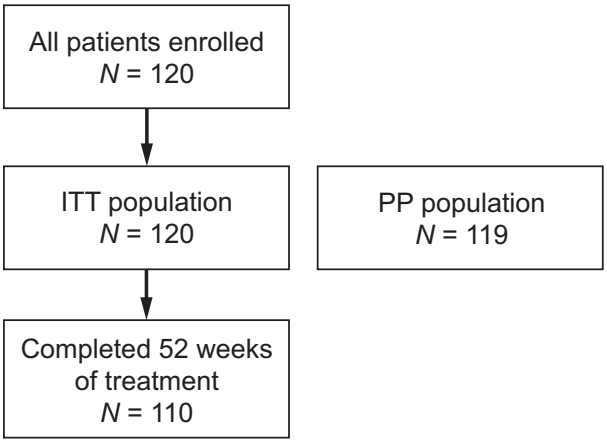

Figure 1. Patient flow diagram. ITT, intention-to-treat (all patients who enrolled, whether or not they received any study treatment); PP, per protocol (all patients in the ITT population who complied with the study protocol).

Table 1. Patient characteristics and baseline demographics (ITT population)

	Dutasteride 0.5 mg (n = 120)
Age, years	
Mean (SD)	42.2 (5.66)
Range	26–50
Age category, *n* (%)	
≤41 years	49 (41)
>41 years	71 (59)
Race category, *n* (%)	
Asian–Japanese heritage	120 (100)
Body mass index, kg/m^2	
Mean (SD)	23.64 (3.070)
Range	18.0–33.8
Tobacco use, *n* (%)	
Never	42 (35)
Former	38 (32)
Current	40 (33)
Alcohol use, *n* (%)	
Yes	84 (70)
No	36 (30)
Age at which patient noticed hair loss (years)	
Mean (SD)	33.1 (7.14)
Range	14–48
Currently experiencing hair loss, *n* (%)	
Yes	97 (81)
No	23 (19)
Norwood–Hamilton stage, *n* (%)	
Stage III vertex	55 (46)
Stage IV	46 (38)
Stage V	19 (16)

ITT, intention-to-treat; SD, standard deviation.

Table 2. Number of patients with common on-treatment AE (≥3% in incidence) and all drug-related AE (ITT population)

	Dutasteride 0.5 mg (n = 120)	
AE by preferred term, *n* (%)	Total (n = 120)	Drug-related AE (n = 120)
Any AE	64 (53)	20 (17)
Nasopharyngitis	18 (15)	–
Erectile dysfunction	14 (12)	13 (11)
Libido decreased	10 (8)	10 (8)
Influenza	5 (4)	–
Ejaculation disorder	5 (4)	5 (4)
Sexual dysfunction	4 (3)	4 (3)
Gingivitis	3 (3)	–
Upper respiratory tract infection	3 (3)	–
Headache	3 (3)	–
Prostatic-specific antigen increased	3 (3)	–
Retrograde ejaculation	NA	1 (<1)
Depressed mood	NA	1 (<1)
Suicidal ideation	NA	1 (<1)
Headache	NA	1 (<1)
Sensory disturbance	NA	1 (<1)
Fatigue	NA	1 (<1)
Rash	NA	1 (<1)
Hypertension	NA	1 (<1)

Events coded using Medical Dictionary for Regulatory Activities (version 17.0). AE, adverse event; ITT, intention-to-treat; NA, not applicable (event was reported in <3% patients).

Table 3. Number of patients with on-treatment SDAE of special interest (ITT population)

No. of patients, *n* (%)	Dutasteride 0.5 mg (n = 120)
Any sexual AE of special interest	19 (15.8)
Altered (decreased) libido	14 (11.7)
Libido decreased	10 (8.3)
Sexual dysfunction	4 (3.3)
Impotence	14 (11.7)
Erectile dysfunction	14 (11.7)
Ejaculation disorders	6 (5.0)
Ejaculation disorder	5 (4.2)
Retrograde ejaculation	1 (0.8)

AE, adverse event; ITT, intention-to-treat; SDAE, sexual dysfunction AE.

hypertension, which occurred in one patient and was considered by the investigator to be related to study treatment.

There were no deaths in this study, and neither of the two reported SAE (stress fracture and post-traumatic neck syndrome) were considered related to the study treatment.

A total of 51 out of 118 (43%) patients experienced a change in clinical laboratory values from normal at baseline to abnormal at any time post-baseline. The most frequently reported abnormalities (shift from normal at baseline to abnormal at any time post-baseline) were low red blood cell count, low hemoglobin, low creatinine, high glucose, high total bilirubin and high alanine aminotransferase. Throughout the study, 2% or less of patients experienced changes to their vital signs. Breast examinations found nipple tenderness in one patient at week 52, but no other abnormal findings were reported.

Efficacy. Hair growth increased during the study period as shown by the increase in mean target area hair count (number of hairs of ≥30-μm diameter) from baseline to week 26 LOCF (87.3; SD, 81.14; 95% confidence interval [CI], 72.0–102.6) and to week 52 LOCF (68.1; SD, 82.14; 95% CI, 52.5–83.6; Fig. 2), reflecting improvement from baseline at both 26 and 52 weeks.

Hair restoration also increased during the study period, with increases from baseline in the target area hair width of non-vellus hairs (≥30-μm diameter) (week 26, 6.7 μm × 1e-3 [SD, 4.8; 95% CI, 5.8–7.6]; week 52, 6.5 μm × 1e-3 [SD, 5.29; 95% CI, 5.5–7.5]; Fig. 3a) and in terminal hair count (number of hairs of ≥60-μm diameter) (week 26, 60.8 [SD, 70.22; 95% CI, 47.5–74.1]; week 52, 76.9 [SD, 86.19; 95% CI, 60.7–93.2]; Fig. 3b).

Improvements in hair growth were independently quantified by a central panel of three dermatologists. The assessments of this panel measured the change from baseline in hair growth at the vertex to be 1.34 (mean of the median score on a scale

Table 4. Incidence status of on-treatment SDAE at week 52 (ITT population)

	Dutasteride 0.5 mg (n = 120)			
	No. of patients (%)	Days until incidence, mean (SD)	Days until recovery, mean (SD)	Proportion not resolved[†] (%)
Libido decreased	14 (12)	71.5 (91.7)	221.5 (146.2)	7/14 (50)
Impotence	14 (12)	81.0 (59.4)	193.2 (111.6)	8/14 (57)
Ejaculation disorders	6 (5)	76.3 (43.4)	255.0 (21.2)	4/6 (67)

AE, adverse event; ITT, intention-to-treat; SD, standard deviation; SDAE, sexual dysfunction AE. Number of patients for whom the AE has not resolved at study drug withdrawal or by week 52, divided by the total number of patients who experienced the AE.

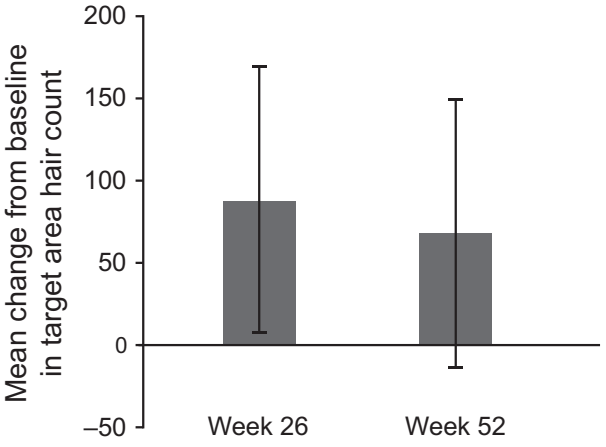

Figure 2. Hair growth as assessed by target area hair count in a 2.54-cm diameter circle (ITT population). Error bars represent the standard deviation. ITT, intention-to-treat.

from −3 [greatly decreased] to 3 [greatly increased]; see also Fig. S1) at week 26 LOCF and 1.50 at week 52 LOCF (Fig. 4). The results at the frontal view were similar (Fig. 4). The proportion of patients with any improvement at both views and at both time points ranged 76–85% (Fig. 5).

When the study-site investigators assessed the androgenetic alopecia Norwood–Hamilton stage by direct visual inspection, the results varied according to patients' stage at baseline. At week 26 LOCF, improvement was observed in six of 53 (11%) patients who were at stage III vertex at baseline, 16 of 46 (35%) patients who were at stage IV at baseline and 14 of 19 (74%) patients who were at stage V at baseline. At week 52 LOCF, the improvements were 21 of 53 (40%) patients, 20 of 46 (43%) patients and 16 of 19 (84%) patients, respectively.

Other end-points. The mean serum level of DHT was 1.55 nmol/L (SD, 0.714) at baseline. This decreased with treatment and the mean percent change from baseline was −84.9% (SD, 33.26) at week 26 LOCF and −85.4% (SD, 31.57) at week 52 LOCF.

There was a mean change from baseline in total PAS SFI score of −0.7 (SD, 2.36) at week 26 LOCF and −0.3 (SD, 1.90) at week 52 LOCF, indicating a minor increase in problems with sexual function.

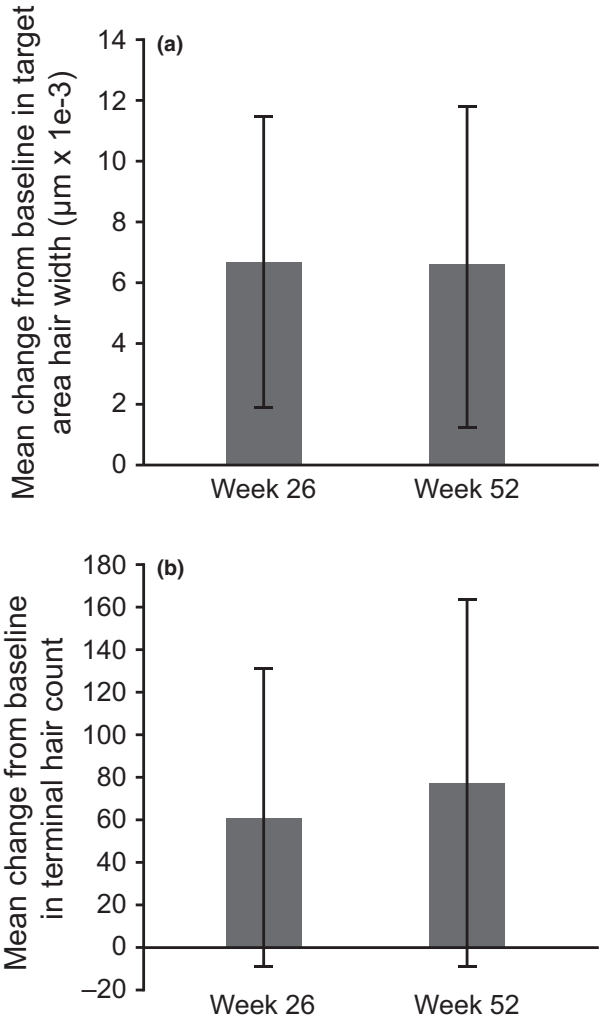

Figure 3. Hair restoration as assessed by (a) hair width and (b) terminal hair count in a 2.54-cm diameter circle (ITT population). Error bars represent the standard deviation. ITT, intention-to-treat.

The mean change from baseline in DLQI total score was −0.25 (SD, 1.367) at week 26 LOCF and −0.23 (SD, 1.393) at week 52 LOCF, which indicated an increase in QoL.

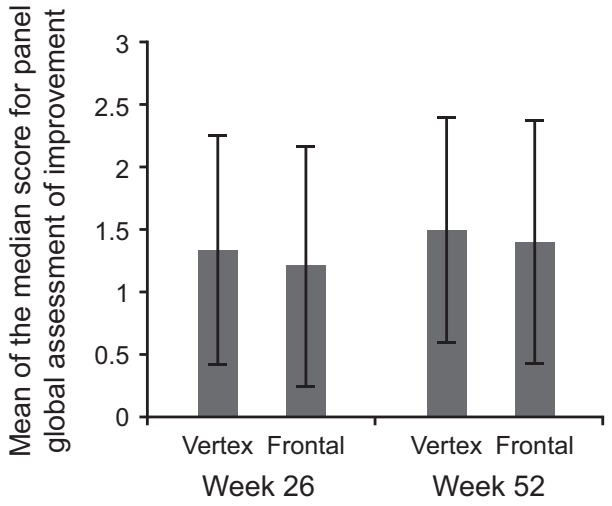

Figure 4. Hair improvement as assessed by an independent panel using global photographs (ITT population). Error bars represent the standard deviation. ITT, intention-to-treat.

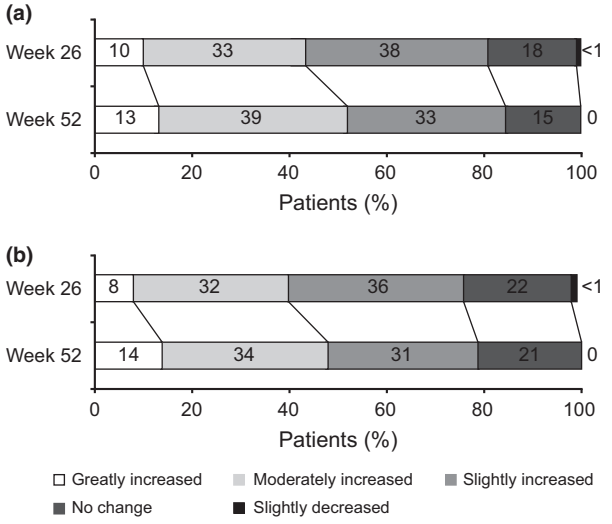

Figure 5. Distribution of the categories assessed by the independent panel for change in hair growth (ITT population). (a) Vertex view. (b) Frontal view. ITT, intention-to-treat.

DISCUSSION

This was a long-term study of the safety of dutasteride in Japanese male patients with androgenetic alopecia, which was conducted following the completion of a global phase II/III study of dutasteride (study ARI114263).[11] The tolerability of dutasteride 0.5 mg taken once daily for 52 weeks was generally good throughout the study population, with the most frequently reported AE being nasopharyngitis, erectile dysfunction, decreased libido, influenza and ejaculation disorder. A total of 19 (15.8%) patients reported any SDAE of special interest, all of which had resolved within 6 months of treatment cessation. No new safety concerns were identified; the safety profile was similar to that in the preceding phase II/III study (ARI114263), where at approximately 10% of patients receiving dutasteride 0.5 mg reported any SDAE of special interest.[11] Furthermore, the safety findings also reflect those of a meta-analysis of studies evaluating dutasteride in the treatment of BPH, where SDAE were reported more frequently with dutasteride, compared with placebo, but that there was no significant increase in study withdrawals due to AE.[18]

Erectile dysfunction (12%) and decreased libido (8%) were observed in this study. In the preceding double-blind ARI114263 study, the reported frequencies of these events were somewhat lower (erectile dysfunction of 3.9% in the placebo group and 5.4% in the dutasteride 0.5 mg group; decreased libido of 1.1% in the placebo group and 3.3% in the dutasteride 0.5 mg group).[11] The frequency of reported SDAE may be in part due to the open-label study design as the patients were fully aware of the active drug they were taking and as such this psychological factor might have affected the reporting of AE related to sexual function. In addition, the reporting of these SDAE might have been influenced by their subjective nature and the fact that, after reading and hearing about the possibility of sexual dysfunction in the informed consent process, the patients were frequently questioned directly about sexual dysfunction during the study. A similar effect was reported by Mondaini *et al.*, who demonstrated that the information supplied by physicians when administrating finasteride under clinical trial conditions has an impact on the frequency of SDAE reported.[19] The most reassuring finding from this study is that all sexual dysfunction resolved within 6 months; there was a previous concern that some patients would experience long-term persistence of this endocrine effect.[20] Apart from one case of hypertension, there were no reports of cardiovascular side-effects in this study, which is in line with the findings of a systematic review reporting meta-analyses where no significant increases in the risk of heart failure, stroke or myocardial infarction in patients receiving dutasteride for BPH were reported.[21]

In male patients with androgenetic alopecia, assessment of the overall appearance may have a considerable influence on patients' self-satisfaction.[11,22] It is, therefore, important that the overall effect of treatment be evaluated in addition to specific numerical measurements, such as hair count. In the efficacy end-points used in this study, both the numerical assessment of hair number and global assessment by the independent reviewers were included and improvements from baseline were observed at week 52 using both assessments. This supports the findings of the previous study that investigated 24 weeks of dutasteride treatment[11] but extends the results to 52 weeks. Here, it was shown that the improvement in target area hair count from baseline persisted at both 26 and 52 weeks. Similarly, improvement from baseline persisted after 26 weeks and at 52 weeks in both total width and terminal hair count. These efficacy results suggest that dutasteride may be appropriate for the treatment of male androgenetic alopecia during a 1-year treatment period in this patient population. This is supported by a recent meta-analysis that examined randomized controlled trials of dutasteride in the treatment of androgenetic

alopecia. Based on pairwise meta-analyses of four studies, including study ARI114263, treatment with dutasteride 0.5 mg conferred a mean increase in hair count of 10.12 (95% CI, 4.54–15.69) versus placebo, as a proportion of baseline hair count. A significant improvement in global photographic assessment versus placebo was also noted.[23] The efficacy of finasteride has been shown to persist for up to 5 years, with 99.4% of patients showing a high level of improvement in global photographic assessment scores.[24] Between weeks 26 and 52 of the present study, the proportion of patients who experienced improvement from baseline in photographic assessment by the external expert panel increased. This implies that the treatment effect may have not yet reached a plateau, therefore, it may be necessary to examine the efficacy of dutasteride over a longer term.

The limitations of this study included the number of patients and the study duration. The study was also limited by its single-arm, open-label design, which cannot distinguish fully between drug-related AE and the perceived side-effects.

In summary, this study revealed a similar safety profile to that of the earlier global phase II/III study (ARI114263) of dutasteride.[11] No new safety signals were identified, the tolerability of 1 years' treatment with dutasteride 0.5 mg once daily was confirmed and there does not appear to be an issue with long-term sexual dysfunction in this patient population. However, sexual dysfunction side-effects did occur during the study and the risk should be communicated appropriately to patients. In terms of efficacy, improvements were evident in hair growth, hair restoration, panel global assessment of hair growth improvement and change in the stage of androgenetic alopecia.

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CONFLICT OF INTEREST: M Manyak and H Ito are employees of GSK and owners of GSK stock; B Brotherton was an employee of GSK at the time of study completion, but is now employed by Parexel; R Tsuboi has served as a speaker and an external medical advisor for GSK; M Kawashima has served as an external medical advisor for GSK; Y Tsunemi, R Irisawa, and H Yoshiie declare no conflict of interest.

REFERENCES

1 Rahnayake D, Sinclair R. Male androgenetic alopecia. In: De Groot LJ, Beck-Peccoz P, Chrousos G, Dungan K *et al.*, eds. *Endotext*. South Dartmouth MA: MDText.com Inc, 2013.
2 Lee WS, Lee HJ. Characteristics of androgenetic alopecia in asian. *Ann Dermatol* 2012; **24**: 243–252.
3 Itami S. Consciousness survey on hair appearance of Japanese male subjects with androgenetic alopecia. *Jpn Med J (Japanese)* 2004; **4209**: 27–29.
4 Girman CJ, Rhodes T, Lilly FR *et al.* Effects of self-perceived hair loss in a community sample of men. *Dermatology* 1998; **197**: 223–229.
5 Kaufman KD. Androgen metabolism as it affects hair growth in androgenetic alopecia. *Dermatol Clin* 1996; **14**: 697–711.
6 Olsen E. Androgenetic alopecia. In: Olsen E, ed. *Disorders of hair growth: diagnosis and treatment*. New York, NY: McGraw-Hill, 1994; 257–283.
7 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**: 177–184.
8 Sato T, Sonoda T, Itami S, Takayasu S. Predominance of type 1 5α-reductase in apocrine sweat glands of patients with excessive or abnormal odour derived from apocrine sweat (osmidrosis). *Br J Dermatol* 1998; **139**: 806–810.
9 Asada Y, Sonoda T, Ojiro M *et al.* 5 alpha-reductase type 2 is constitutively expressed in the dermal papilla and connective tissue sheath of the hair follicle in vivo but not during culture in vitro. *J Clin Endocrinol Metab* 2001; **86**: 2875–2880.
10 Eun HC, Kwon OS, Yeon JH *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**: 252–258.
11 Gubelin Harcha W, Barboza Martinez J, Tsai TF *et al.* 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. *J Am Acad Dermatol* 2014; **70**: 489–498.
12 Jung JY, Yeon JH, Choi JW *et al.* Effect of dutasteride 0.5 mg/d in men with androgenetic alopecia recalcitrant to finasteride. *Int J Dermatol* 2014; **53**: 1351–1357.
13 Norwood OT. Male pattern baldness: classification and incidence. *South Med J* 1975; **68**: 1359–1365.
14 Columbia University Medical Center. Columbia Suicide Severity Rating Scale. Available from: http://www.cssrs.columbia.edu/index.html. Last accessed September 2015.
15 Posner K, Brown GK, Stanley B *et al.* The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011; **168**: 1266–1277.
16 O'Leary MP, Fowler FJ, Lenderking WR *et al.* A brief male sexual function inventory for urology. *Urology* 1995; **46**: 697–706.
17 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–216.
18 Park T, Choi JY. Efficacy and safety of dutasteride for the treatment of symptomatic benign prostatic hyperplasia (BPH): a systematic review and meta-analysis. *World J Urol* 2014; **32**: 1093–1105.
19 Mondaini N, Gontero P, Giubilei G *et al.* Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? *J Sex Med* 2007; **4**: 1708–1712.
20 Irwig MS. Persistent sexual side effects of finasteride: could they be permanent? *J Sex Med* 2012; **9**: 2927–2932.
21 Loke YK, Ho R, Smith M *et al.* Systematic review evaluating cardiovascular events of the 5-alpha reductase inhibitor - Dutasteride. *J Clin Pharm Ther* 2013; **38**: 405–415.
22 Han SH, Byun JW, Lee WS *et al.* Quality of life assessment in male patients with androgenetic alopecia: result of a prospective, multicenter study. *Ann Dermatol* 2012; **24**: 311–318.
23 Gupta AK, Charrette A. The efficacy and safety of 5α-reductase inhibitors in androgenetic alopecia: a network meta-analysis and benefit-risk assessment of finasteride and dutasteride. *J Dermatol Treat* 2014; **25**: 156–161.
24 Yoshitake T, Takeda A, Ohki K *et al.* Five-year efficacy of finasteride in 801 Japanese men with androgenetic alopecia. *J Dermatol* 2015; **42**: 735–738.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Global photograph examples of median panel score. None assessed "slightly decreased" (–1 points), "moderately decreased" (–2 points) or "greatly decreased" (–3 points) at week 52.

Table S1. List of investigators who participated in the study

Table S2. List of exclusion criteria