Report on the Deliberation Results

September 4, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Zagallo Capsules 0.1 mg
	Zagallo Capsules 0.5 mg
[Non-proprietary name]	Dutasteride (JAN*)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	November 25, 2014

[Results of deliberation]
In its meeting held on August 28, 2015, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years. The drug product is classified as a powerful drug. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

August 12, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Zagallo Capsules 0.1 mg
	(b) Zagallo Capsules 0.5 mg
[Non-proprietary name]	Dutasteride
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	November 25, 2014
[Dosage form/Strength]	Each 0.1 mg capsule contains 0.1 mg of dutasteride.
	Each 0.5 mg capsule contains 0.5 mg of dutasteride.
[Application classification]	(a) Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage, and (8) Drug in an additional dosage form (subjected to re-examination)
	(b) Prescription drug; (4) Drug with a new indication, (6) Drug with a new dosage, and (10) Other drugs (subjected to re-examination)
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

Review Results

August 12, 2015

[Brand name]	Zagallo Capsules 0.1 mg
	Zagallo Capsules 0.5 mg
[Non-proprietary name]	Dutasteride
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	November 25, 2014

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of dutasteride in the treatment of androgenetic alopecia in men has been demonstrated, and its safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]	Androgenetic alopecia in men
[Dosage and administration]	The usual dosage for adult men is 0.1 mg of dutasteride administered orally once daily. The dose may be increased to 0.5 mg orally once daily, as necessary.
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

July 10, 2015

I. Product Submitted for Registration

[Brand name]	Zagallo Capsules 0.1 mg Zagallo Capsules 0.5 mg
[Non-proprietary name]	Dutasteride
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	November 25, 2014
[Dosage form/Strength]	Each 0.1 mg capsule contains 0.1 mg of dutasteride. Each 0.5 mg capsule contains 0.5 mg of dutasteride.
[Proposed indication]	Hair growth, hair restoration, and prevention of the progression of hair loss in men with androgenetic alopecia
[Proposed dosage and administration]	The usual dosage for adult men is 0.1 mg of dutasteride administered orally once daily. If a greater effect is desired, the dose may be increased to 0.5 mg orally once daily.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

The hair growth cycle consists of three phases: anagen, catagen, and telogen. Anagen refers to the phase of active hair growth and catagen is the phase of apoptosis-driven hair regression. Telogen is the resting phase in which the germ cells of the follicles induce follicular regeneration leading to new hair growth.

Androgenetic alopecia is characterized by progression of androgen-induced hair loss primarily on the frontal and vertex areas of the scalp. A progressive miniaturization of hair follicles leads to a decrease in the duration of the anagen phase, which promotes the replacement of thick and long terminal hairs with thinner and shorter vellus hairs. Eventually, there are no hairs present on the scalp surface.[1] The pathogenesis of androgenetic alopecia involves androgens and genetic predisposition. The major androgen that affects scalp hair growth is dihydrotestosterone (DHT), which is converted from testosterone by 5 α-reductase. DHT binds to androgen receptors and shortens the anagen phase of the

[1] *Skin Pharmacol.* 1994;7:84-89; BMJ 1998:317:865-869.

hair growth cycle.[2] It has been reported that DHT inhibits growth of terminal hair on the scalp of men with a genetic predisposition to androgenetic alopecia.[3]

In Japan, a prescription drug finasteride (a 5 α-reductase inhibitor) and an over-the-counter drug minoxidil are strongly recommended as pharmacotherapeutic options for the treatment of androgenetic alopecia by the "Guidelines for the management of androgenetic alopecia (2010)" (edited by the Japanese Dermatological Association).[4] Men whose symptoms of alopecia do not improve with pharmacotherapy often undergo surgical interventions such as hair transplantation and scalp reduction. Although androgenetic alopecia causes psychosocial stress in patients,[5] it is not a life-threatening physical condition. For this reason, medications for androgenetic alopecia are regarded as lifestyle drugs.

The active ingredient of Zagallo Capsules 0.1 mg and Zagallo Capsules 0.5 mg is dutasteride, a 5 α-reductase inhibitor. The drug inhibits 5 α-reductase types 1 and 2, the converter of testosterone into DHT. With this background, the applicant developed a new capsule formulation of dutasteride filled in a capsule shell in a different color from that of Avolve Capsules 0.5 mg, a dutasteride formulation approved for the indication for prostatic hyperplasia, so that these are distinguishable from each other. The applicant conducted a global phase II/III study enrolling male patients with androgenetic alopecia, and has filed a marketing application on the basis of the study data that support the efficacy and safety of dutasteride in the study population.

Dutasteride was approved as a drug for the treatment of prostatic hyperplasia in the United States in November 2001 and in Japan in July 2009. As of June 2015, it is approved in ≥100 countries. Dutasteride is approved for the indication of androgenetic alopecia in South Korea.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

The drug substance is identical to that contained in the approved drug product, Avolve Capsules 0.5 mg.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product, and formulation design

The drug product is a soft capsule containing 0.1 mg or 0.5 mg of dutasteride. The drug product also contains medium-chain mono- and diglycerides, dibutylhydroxytoluene, gelatin, concentrated glycerin, titanium oxide, red ferric oxide (both in the 0.1 mg and 0.5 mg capsules), and yellow ferric oxide (0.1 mg capsules only) as excipients.

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2 *Br J Dermatol.* 1995;133:371-376; *J Invest Dermatol Symp Proc.* 2005;10:209-211.

3 *Mol Cell Endocrinol.* 2002;198:89-95.

4 *The Japanese Journal of Dermatology.* 2010;120:977-986.

5 *Br J Dermatol.* 1999;141:398-405.

2.A.(2).2) Manufacturing process

The drug product is manufactured through the process comprising the following steps: preparation of gelatin solution for capsule shells, preparation of drug content, encapsulation, drying, and packaging. [redacted]

2.A.(2).3) Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (thin layer chromatography), uniformity of dosage units (content uniformity [high-performance liquid chromatography, HPLC]), dissolution (HPLC), content of dibutylhydroxytoluene (HPLC), and assay (HPLC).

2.A.(2).4) Stability of drug product

The stability studies of the drug product are shown in Table 1.

Table 1. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production-scale batches	25°C	60% RH	Blister pack	18 months
Accelerated	3 production-scale batches	40°C	75% RH		6 months

[redacted] The long-term stability study will be continued for up to [redacted] months.

2.B Outline of the review by PMDA

Based on the submitted data and the findings presented below, PMDA considers that the quality of the drug substance and the drug product is adequately controlled.

New Excipients

[redacted]

1) Specifications and stability

Based on the submitted data, PMDA considers that there are no particular problems with the proposed specifications for and stability of medium-chain mono- and diglycerides.

2) Safety

Based on the submitted data, PMDA considered that there are no safety concerns about the maximum daily exposure to medium-chain mono- and diglycerides in the proposed commercial formulation.

3. Non-clinical data

The results of the non-clinical pharmacokinetic studies and toxicity studies of dutasteride were submitted and reviewed in the initial application for Avolve Capsules 0.5 mg. Therefore, no new non-clinical pharmacokinetic or toxicity data have been submitted for the present application. In addition, no new pharmacological data have been submitted because there are currently no animal models available to adequately evaluate the efficacy of dutasteride in the treatment of androgenetic alopecia. The pharmacological action of dutasteride (inhibition of 5 α-reductase types 1 and 2) was evaluated based on the primary pharmacodynamic data submitted in the initial application for Avolve Capsules 0.5 mg.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

[redacted]

The serum concentrations of unchanged dutasteride were measured by liquid chromatography/tandem mass spectrometry (LC/MS/MS) with lower limits of quantification of 0.1 ng/mL for both the foreign phase II study (ARIA2004) and global phase II/III study (ARI114263) and 25.0 pg/mL for the bioequivalence study (ARI117342).

Bioequivalence study (5.3.1.2, Study ARI117342 [September 2013 to January 2014])

An open-label, randomized, two-way crossover study was conducted at 1 foreign site to evaluate the bioequivalence of 2 different capsule formulations of dutasteride (0.1 mg and 0.5 mg strengths) in healthy adult men aged 18 to 65 years (target sample size, 36 subjects).

In this study, subjects received a single oral dose of one 0.5 mg capsule or five 0.1 mg capsules of dutasteride. There was a washout period of ≥ 28 days before the crossover.

All the 36 subjects who received study treatment were included in the pharmacokinetic analysis and safety analysis populations. Three subjects[6] discontinued study treatment after completion of Period I.

Table 2 shows the pharmacokinetic parameters of unchanged dutasteride in serum following a single dose of dutasteride capsules, and the 90% confidence intervals (CI) of the geometric least squares mean ratios of C_{max} and AUC_{0-t} between the two formulations. Both 90% CI values met the criteria for bioequivalence defined in the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated February 29, 2012). The results demonstrated the bioequivalence of the two formulations.

Table 2. Pharmacokinetic parameters of serum unchanged dutasteride following single administration

	N	C_{max} (ng/mL)	AUC_{0-t} (h·ng/mL)	t_{max} (h)	Geometric least squares mean ratio[a)] [90% CI]	
					C_{max}	AUC_{0-t}
1 × 0.5 mg capsule	33	3.29 ± 1.16	52.32 ± 20.53	1.6 ± 1.0	0.91 [0.84, 1.00]	1.01 [0.97, 1.05]
5 × 0.1 mg capsules	36	2.89 ± 0.74	53.02 ± 21.28	2.1 ± 1.5		

Mean ± standard deviation
a) (Treatment with 5 × 0.1 mg capsules)/(treatment with 1 × 0.5 mg capsule)

Safety results included adverse events in 58.3% (21 of 36) of subjects. Adverse events occurring in ≥2 subjects were headache (10 of 36 subjects, 27.8%), dermatitis contact (3 of 36 subjects, 8.3%), and nausea and haematoma (2 of 36 subjects each, 5.6%). Adverse events for which a causal relationship to the study drug could not be ruled out (i.e., adverse drug reactions) occurred in 22.2% (8 of 36) of subjects. Adverse drug reactions occurring in ≥2 subjects were headache (5 of 36 subjects, 13.9%) and nausea (2 of 36 subjects, 5.6%). There were no serious adverse events or deaths. There was 1 adverse event leading to discontinuation of treatment (upper-airway cough syndrome in 1 subject).

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

4.(ii).A.(1) *In vitro* studies using human samples (5.3.2.2, Study RR2008/00019/01 [March 2005 to July 2006])

4.(ii).A.(1).1) Inhibition of cytochrome P450 isoenzymes

The inhibitory effect of dutasteride on human cytochrome P450 (CYP) isoenzymes was studied using *Escherichia coli* cells expressing CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Dutasteride inhibited the activity of CYP2C19 and CYP3A4, with an IC_{50} of 50 μmol/L while it showed almost no inhibition of other CYPs studied.

[6] One subject each due to "lost to follow-up," "adverse event (upper-airway cough syndrome)," and "withdrawal of consent."

4.(ii).A.(1).2) Induction of CYPs

The ability of dutasteride to induce CYP3A4 through activation of pregnane X receptor (PXR) was studied using HepG2 cells transfected with reporter gene expression vectors containing human PXR and CYP3A4 promoter sequences. Dutasteride did not induce CYP3A4.

4.(ii).A.(1).3) Inhibition of transporters

The inhibitory effect of dutasteride on various transporters was investigated using Sf-9 cells expressing human multidrug resistance-related protein (MRP) 2, U2-OS cells expressing human organic anion transporter 1 (OAT1) or 3 (OAT3), or organic anion transporting polypeptide (OATP) 1B3, and CHO cells expressing human OATP1B1.[7] Dutasteride inhibited OAT3, OATP1B1, and OATP1B3, showing the lowest IC_{50} of 0.5, 0.8, and 20 μmol/L, respectively.

4.(ii).A.(2) Foreign phase II study (5.3.5.1, Study ARIA2004 [December 1997 to February 2000])

The outline of the study is presented in "4.(iii).A.(1) Foreign phase II study."

Non-Japanese male patients with androgenetic alopecia received multiple oral doses of dutasteride 0.05 mg, 0.1 mg, 0.5 mg, or 2.5 mg once daily for 24 weeks. Table 3 shows serum dutasteride concentrations measured.

Table 3. Serum concentrations of unchanged dutasteride (ng/mL)

Time point	0.05 mg	0.1 mg	0.5 mg	2.5 mg
Week 6	0.30 ± 0.26 (47)	1.38 ± 0.89 (43)	22.14 ± 9.60 (43)	132.40 ± 41.99 (46)
Week 12	0.29 ± 0.24 (45)	1.56 ± 1.14 (41)	27.56 ± 11.71 (42)	182.53 ± 58.02 (46)
Week 24	0.21 ± 0.24 (40)	1.51 ± 0.96 (36)	30.69 ± 13.90 (42)	209.88 ± 78.60 (44)

Mean± standard deviation (number of subjects); pre-dose (trough) concentrations

Non-Japanese male patients with androgenetic alopecia received multiple oral doses of dutasteride 0.05 mg, 0.1 mg, 0.5 mg, or 2.5 mg, finasteride 5.0 mg, or placebo once daily for 24 weeks. Table 4 shows the percent change from baseline in serum DHT levels.

[7] The following substrates were used:
Fluo3 for MRP2, 6-carboxyfluorescein for OAT1 and OAT3, and fluorescein-methotrexate for OATP1B1 and OATP1B3.

Table 4. Percent change from baseline in serum DHT levels (%)

Time point		Placebo	Dutasteride				Finasteride 5.0 mg
			0.05 mg	0.1 mg	0.5 mg	2.5 mg	
Week 6	Adjusted mean	3.7 (54)	−51.3 (60)	−68.9 (65)	−90.3 (55)	−95.9 (63)	−73.5 (60)
	Difference from placebo	—	−55.0	−72.6	−94.1	−99.6	−77.3
	P-value[b)]	—	<0.001	<0.001	<0.001	<0.001	<0.001
Week 12	Adjusted mean	3.0 (56)	−51.4 (61)	−68.1 (65)	−91.9 (56)	−95.5 (64)	−71.0 (62)
	Difference from placebo	—	−54.5	−71.2	−94.9	−98.5	−74.1
	P-value[b)]	—	<0.001	<0.001	<0.001	<0.001	<0.001
Week 24	Adjusted mean	4.2 (56)	−47.9 (62)	−64.9 (65)	−90.2 (56)	−95.3 (64)	−71.4 (62)
	Difference from placebo	—	−52.1	−69.1	−94.4	−99.5	−75.5
	P-value[b)]	—	<0.001	<0.001	<0.001	<0.001	<0.001
Week 36[a)]	Adjusted mean	−2.6 (50)	−1.5 (50)	6.9 (54)	−22.6 (55)	−85.2 (58)	0.7 (59)
	Difference from placebo	—	1.1	9.5	−19.9	−82.6	3.3
	P-value[b)]	—	0.92	0.41	0.040	<0.001	0.76

Percent change from baseline in serum DHT levels (%) = (serum DHT measured at each time point – baseline serum DHT)/(baseline serum DHT) × 100
a) At 12 weeks after the end of treatment
b) Two-sample t-test with a two-sided significance level of 5%

4.(ii).A.(3) Global phase II/III study (5.3.5.1, Study ARI114263 [October 2010 to February 2012])

The outline of the study is presented in "4.(iii).A.(2) Global phase II/III study."

Japanese and non-Japanese male patients with androgenetic alopecia received multiple oral doses of dutasteride 0.02 mg, 0.1 mg, or 0.5 mg once daily for 24 weeks. Table 5 shows the serum concentrations of unchanged dutasteride.

Table 5. Serum concentrations of unchanged dutasteride (ng/mL)

Time point		0.02 mg	0.1 mg	0.5 mg
Week 12	Japanese	0.0 ± 0.1 (39)	3.2 ± 1.5 (40)	48.6 ± 17.9 (37)
	Non-Japanese	0.2 ± 2.2 (133)	1.8 ± 1.6 (132)	28.7 ± 18.5 (128)
Week 24	Japanese	0.1 ± 0.2 (36)	3.2 ± 2.0 (37)	52.9 ± 22.2 (34)
	Non-Japanese	0.0 ± 0.1 (122)	1.6 ± 1.7 (121)	31.3 ± 21.2 (119)
Week 26[a)]	Japanese	0.0 ± 0.0 (36)	0.7 ± 1.0 (36)	33.6 ± 19.8 (35)
	Non-Japanese	0.1 ± 1.0 (120)	0.3 ± 0.5 (118)	17.4 ± 15.2 (117)

Mean± standard deviation (number of subjects); pre-dose (trough) concentrations
a) At 2 weeks after the end of treatment

Japanese and non-Japanese male patients with androgenetic alopecia received multiple oral doses of dutasteride 0.02 mg, 0.1 mg, or 0.5 mg, finasteride 1.0 mg, or placebo once daily for 24 weeks. Table 6 shows the percent change from baseline in serum DHT levels.

Table 6. Percent change from baseline in serum DHT levels (%)

Time point			Placebo	Dutasteride			Finasteride 1.0 mg
				0.02 mg	0.1 mg	0.5 mg	
Week 12	Japanese	Adjusted mean	−2.6 (40)	−27.5 (39)	−85.8 (40)	−91.2 (39)	−74.6 (39)
		Difference from placebo	—	−24.9	−83.2	−88.6	−72.0
		P-value[b)]	—	0.017	<0.001	<0.001	<0.001
	Non-Japanese	Adjusted mean	4.0 (131)	−30.3 (133)	−71.6 (131)	−84.0 (131)	−71.3 (121)
		Difference from placebo	—	−34.3	−75.5	−88.0	−75.2
		P-value[b)]	—	<0.001	<0.001	<0.001	<0.001
Week 24	Japanese	Adjusted mean	−6.2 (40)	−28.8 (40)	−83.6 (40)	−90.9 (39)	−78.5 (40)
		Difference from placebo	—	−22.6	−77.4	−84.7	−72.3
		P-value[b)]	—	0.033	<0.001	<0.001	<0.001
	Non-Japanese	Adjusted mean	7.4 (132)	−8.5 (135)	−64.9 (135)	−84.6 (131)	−66.0 (124)
		Difference from placebo	—	−15.8	−72.3	−92.0	−73.4
		P-value[b)]	—	0.092	<0.001	<0.001	<0.001
Week 26[a)]	Japanese	Adjusted mean	3.0 (40)	−7.7 (40)	−64.7 (40)	−90.9 (39)	−25.7 (40)
		Difference from placebo	—	−10.7	−67.8	−93.9	−28.7
		P-value[b)]	—	0.39	<0.001	<0.001	0.011
	Non-Japanese	Adjusted mean	9.1 (132)	−2.4 (135)	−36.0 (136)	−80.8 (132)	−19.5 (124)
		Difference from placebo	—	−11.5	−45.1	−89.9	−28.6
		P-value[b)]	—	0.21	<0.001	<0.001	<0.001

Percent change from baseline in serum DHT level (%) = (serum DHT measured at each time point – baseline serum DHT)/(baseline serum DHT) × 100
a) At 2 weeks after the end of treatment
b) t-test

4.(ii).A.(4) Japanese long-term study (5.3.5.2, Study ARI114264 [April 2013 to July 2014])

The outline of the study is presented in "4.(iii).A.(3) Japanese long-term study."

Japanese male patients with androgenetic alopecia received multiple oral doses of dutasteride 0.5 mg once daily for 52 weeks. The mean percent change from baseline in serum DHT levels was −84.9% at Week 26 and −85.4% at Week 52.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Comparison of pharmacokinetic and pharmacodynamic actions between Japanese and non-Japanese subjects

The applicant's explanation:

In the global phase II/III study, the Japanese subjects groups showed a trend toward slightly higher serum concentrations of unchanged dutasteride, as compared with non-Japanese subjects in both the dutasteride 0.1 mg and 0.5 mg groups. This may be attributable to the differences in the mean age and mean body weight between the Japanese and non-Japanese subjects (the mean age in the dutasteride 0.1

mg and 0.5 mg groups was approximately 44 years for Japanese and approximately 37 years for non-Japanese, and the mean body weight was approximately 69 kg for Japanese and approximately 78 kg for non-Japanese).

The percent reduction from baseline in serum DHT levels was greater in Japanese subjects than in non-Japanese subjects in the dutasteride 0.1 mg group, while the percent changes were similar between Japanese and non-Japanese subjects in the dutasteride 0.5 mg group (Table 6). Because serum DHT level is related to the serum concentration of dutasteride, the greater percent reduction in serum DHT in Japanese subjects than in non-Japanese subjects in the dutasteride 0.1 mg group was considered to be attributable to increased serum dutasteride concentrations in the Japanese subjects compared with the non-Japanese subjects. Meanwhile, the serum DHT level was below the lower limit of quantification for many of the samples from both Japanese and non-Japanese subjects in the dutasteride 0.5 mg group. This finding suggested that trough serum DHT levels in both subgroups contributed to comparable serum DHT levels between Japanese and non-Japanese subjects in the dutasteride 0.5 mg group. A population PK/PD analysis using an Emax model was performed on the data from the global phase II/III study to describe the relationship between serum DHT concentrations and serum dutasteride concentrations. None of the examined factors including race and ethnicity (Japanese vs. non-Japanese) was identified as a covariate.

Based on the above, the applicant considers that there are no ethnic differences in the dose-response relationship between dutasteride exposure and serum DHT concentrations.

PMDA's view:
In the global phase II/III study in male patients with androgenetic alopecia, the serum concentration of dutasteride was slightly higher in Japanese subjects than in non-Japanese subjects in the dutasteride 0.1 and 0.5 mg groups, but the range of distribution and the degree of variance were generally similar. In addition, there were no clinically relevant differences in the percent change from baseline in serum DHT levels between the Japanese and non-Japanese subjects.

Based on the above, the pharmacokinetic and pharmacodynamic actions of dutasteride are unlikely to differ significantly between Japanese and non-Japanese male patients with androgenetic alopecia.

4.(ii).B.(2) Drug interactions

The inhibitory effect of dutasteride on CYP2C19, CYP3A4, OAT3, OATP1B1, and OATP1B3 was observed in the *in vitro* study. The applicant provided the following explanation about whether precautionary advice regarding this finding should be included in the package insert.

The IC_{50} values of dutasteride against CYP2C19, OAT3, OATP1B1, and OATP1B3 in the *in vitro* study (50, 0.5, 0.8, and 20 μmol/L, respectively) were 714-, 7.1-, 11.4-, and 286-fold, respectively, the serum

dutasteride concentration (approximately 0.07 μmol/L) in the patients with androgenetic alopecia, including Japanese male patients, who received multiple oral doses of dutasteride 0.5 mg for 24 weeks in the global phase II/III study. Therefore, dutasteride is unlikely to inhibit CYP2C19-mediated drug metabolism or OAT3-, OATP1B1-, or OATP1B3-mediated drug transport in routine clinical use. In the 3 clinical studies (the foreign phase II study, global phase II/III study, and Japanese long-term study), some subjects received dutasteride concomitantly with drugs serving as major substrates of CYP2C19, OAT3, OATP1B1, or OATP1B3 (excluding those who received concomitant medication for the treatment of adverse events or those who had an adverse event temporally unrelated to concomitant medication). Causality was assessed for adverse events experienced by the subjects. Subjects receiving concomitant diazepam (CYP2C19 is responsible for its metabolism) reported seborrhoeic dermatitis, leg injury, fatigue, and phantom taste perception; those receiving concomitant lansoprazole (CYP2C19 is responsible for its metabolism) reported influenza; and those receiving concomitant atorvastatin, fexofenadine, or famotidine (substrates of OATP1B1 or OATP1B3) reported influenza, pharyngodynia, and insomnia. None of these events was serious or causally related to dutasteride. The events resolved without specific treatment. Further, published literature was searched for reports of possible drug-drug interaction between dutasteride and major substrates of CYP2C19, OAT3, OATP1B1, or OATP1B3, but no such report was found.

Based on the above, it is not necessary at this point to provide precautionary advice in the package insert regarding possible interaction between dutasteride and the drugs that undergo CYP2C19-mediated metabolism or OAT3-, OATP1B1-, or OATP1B3-mediated transport/elimination. However, precautionary advice about the possible interaction with CYP3A4 inhibitors will be included in the package insert, as in the case of Avolve Capsules 0.5 mg.

PMDA accepted the applicant's explanation.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted the efficacy and safety evaluation data, containing the results from 3 Japanese and foreign clinical studies (the foreign phase II study, global phase II/III study, and Japanese long-term study). These studies enrolled patients who were assessed for the progression of hair loss based on the Norwood-Hamilton classification (Figure 1) and who then had a clinical diagnosis of androgenetic alopecia.

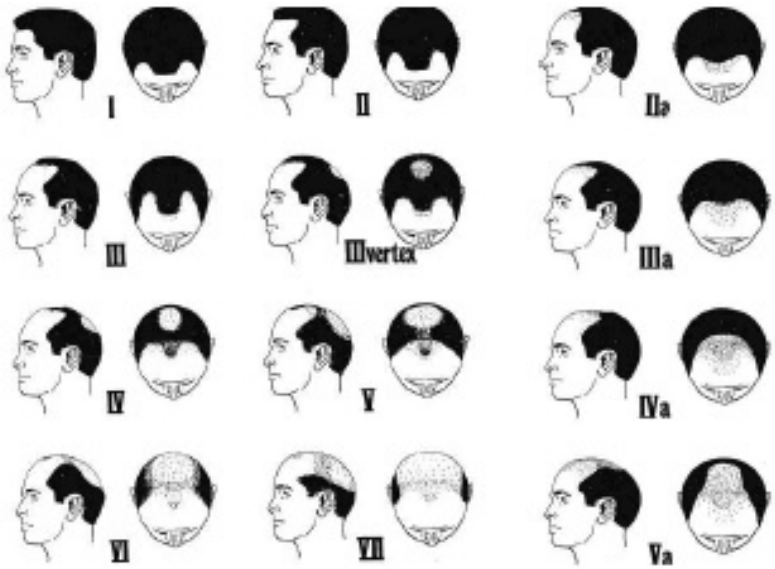

Figure 1. Norwood-Hamilton classification

4.(iii).A.(1) Foreign phase II study (5.3.5.1, Study ARIA2004 [December 1997 to February 2000])

A multi-center, randomized, double-blind, parallel-group comparison study was conducted at 21 centers overseas to investigate the dose-response relationship and safety of dutasteride in non-Japanese male patients aged 21 to 45 years who had a clinical diagnosis of androgenetic alopecia classified as types III vertex, IV, or V of the Norwood-Hamilton scale (target sample size, 360 subjects).

In this study, subjects received oral doses of dutasteride 0.05 mg, 0.1 mg, 0.5mg, or 2.5 mg, finasteride 5 mg,[8] or placebo once daily for 24 weeks.

A total of 378 subjects[9] received study treatment (58 subjects in the placebo group, 65 in the dutasteride 0.05 mg group, 66 in the dutasteride 0.1 mg group, 61 in the dutasteride 0.5 mg group, 64 in the dutasteride 2.5 mg group, and 64 in the finasteride 5 mg group). All the subjects treated were included in the intention-to-treat (ITT) population and safety analysis population, and the ITT was the population for the primary efficacy analysis. A total of 70 subjects discontinued the study (10 in the placebo group, 19 in the dutasteride 0.05 mg group, 15 in the dutasteride 0.1 mg group, 6 in the dutasteride 0.5 mg group, 15 in the dutasteride 2.5 mg group, and 5 in the finasteride 5 mg group). Reasons for discontinuation were "withdrawal of consent" for 29 subjects (5 in the placebo group, 10 in the dutasteride 0.05 mg group, 4 in the dutasteride 0.1 mg group, 3 in the dutasteride 0.5 mg group, 6 in the dutasteride 2.5 mg group, and 1 in the finasteride 5 mg group), "lost to follow-up" for 16 subjects (2 in the placebo group; 4 in the dutasteride 0.05 mg group, 4 in the dutasteride 0.1 mg group, 1 in the dutasteride 0.5 mg group, 3 in the dutasteride 2.5 mg group, and 2 in the finasteride 5 mg group),

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[8] The dosage of finasteride approved for the treatment of prostatic hyperplasia was used as control, because finasteride 1 mg was not approved for the treatment of androgenetic alopecia in men in and outside Japan when the foreign phase II study was conducted.

[9] The data of the 38 subjects handled by an investigator who was listed in the Debarment List (list of persons and firms that have been convicted for a conduct relating to development or approval of new drug products) by the US Food and Drug Administration (FDA) were excluded from the analysis. The efficacy and safety results did not differ significantly before and after exclusion of the data.

"protocol deviation" for 13 subjects (3 in the dutasteride 0.05 mg group, 1 in the dutasteride 0.1 mg group, 1 in the dutasteride 0.5 mg group, 6 in the dutasteride 2.5 mg group, and 2 in the finasteride 5 mg group), and "adverse events" for 10 subjects (3 in the placebo group, 6 in the dutasteride 0.1 mg group, and 1 in the dutasteride 0.5 mg group), and "other" for 2 subjects (2 in the dutasteride 0.05 mg group).

The primary endpoint for efficacy was the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Weeks 12, 24, and 36." The results are shown in Table 7.

Table 7. Change from baseline in hair count within a of 2.54-cm diameter circle at the vertex at Weeks 12, 24, and 36 (ITT)

	Treatment	N[b)]	Change from baseline hair count	Difference from placebo[c)] [95% CI]
Week 12 (LOCF)	Placebo	52	−21.8 ± 11.2	—
	Dutasteride 0.05 mg	55	5.5 ± 10.9	27.2 [−3.5, 58.0]
	Dutasteride 0.1 mg	60	58.6 ± 10.4	80.4 [50.4, 110.4]
	Dutasteride 0.5 mg	52	64.8 ± 11.2	86.6 [55.5, 117.6]
	Dutasteride 2.5 mg	57	100.0 ± 10.7	121.8 [91.4, 152.1]
	Finasteride 5 mg	62	51.2 ± 10.3	72.9 [43.2, 102.7]
Week 24 (LOCF)	Placebo	53	−26.2 ± 10.6	—
	Dutasteride 0.05 mg	56	22.6 ± 10.3	48.8 [19.8, 77.8]
	Dutasteride 0.1 mg	61	72.4 ± 9.9	98.6 [70.3, 127.0]
	Dutasteride 0.5 mg	56	94.5 ± 10.3	120.7 [91.7, 149.6]
	Dutasteride 2.5 mg	60	107.4 ± 10.0	133.5 [105.1, 162.0]
	Finasteride 5 mg	63	65.7 ± 9.7	91.9 [63.7, 120.1]
Week 36 [a)]	Placebo	41	−36.2 ± 14.2	—
	Dutasteride 0.05 mg	42	−11.2 ± 14.0	25.0 [−14.1, 64.2]
	Dutasteride 0.1 mg	47	21.6 ± 13.3	57.8 [19.8, 95.8]
	Dutasteride 0.5 mg	45	80.6 ± 13.5	116.8 [78.4, 155.3]
	Dutasteride 2.5 mg	48	115.9 ± 13.1	152.2 [114.3, 190.0]
	Finasteride 5 mg	56	7.2 ± 12.2	43.4 [6.9, 80.0]

Least squares mean ± standard error; missing data at Weeks 12 and 24 were imputed using the last observation carried forward (LOCF) approach.
a) At 12 weeks after the end of treatment
b) Subjects without vertex hair count at each time point were excluded from the analysis.
c) Estimated based on a general linear model with treatment group, region, and baseline hair count as explanatory variables.

Safety results were summarized. The incidence of adverse events was 79.3% (46 of 58 subjects) in the placebo group, 56.9% (37 of 65 subjects) in the dutasteride 0.05 mg group, 65.2% (43 of 66 subjects) in the dutasteride 0.1 mg group, 65.6% (40 of 61 subjects) in the dutasteride 0.5 mg group, 67.2% (43 of 64 subjects) in the dutasteride 2.5 mg group, and 70.3% (45 of 64 subjects) in the finasteride 5 mg group. Table 8 shows the adverse events observed in ≥5.0% of subjects in any treatment group. The incidence of adverse drug reactions was 24.1% (14 of 58 subjects) in the placebo group, 15.4% (10 of 65 subjects) in the dutasteride 0.05 mg group, 28.8% (19 of 66 subjects) in the dutasteride 0.1 mg group, 14.8% (9 of 61 subjects) in the dutasteride 0.5 mg group, 28.1% (18 of 64 subjects) in the dutasteride 2.5 mg group, and 23.4% (15 of 64 subjects) in the finasteride 5 mg group. Table 9 shows the adverse drug reactions observed in ≥2.0% of subjects in any treatment group.

Table 8. Adverse events observed in ≥5.0% of subjects in any treatment group

	Placebo (N = 58)		Dutasteride 0.05 mg (N = 65)		Dutasteride 0.1 mg (N = 66)		Dutasteride 0.5 mg (N = 61)		Dutasteride 2.5 mg (N = 64)		Finasteride 5 mg (N = 64)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	79.3%	46	56.9%	37	65.2%	43	65.6%	40	67.2%	43	70.3%	45
Libido decreased	3.4%	2	3.1%	2	3.0%	2	1.6%	1	12.5%	8	4.7%	3
Headache	3.4%	2	3.1%	2	16.7%	11	13.1%	8	10.9%	7	7.8%	5
Malaise/fatigue	3.4%	2	3.1%	2	3.0%	2	1.6%	1	7.8%	5	3.1%	2
Musculoskeletal pain	0%	0	6.2%	4	1.5%	1	3.3%	2	6.3%	4	0%	0
Viral upper respiratory tract infection	15.5%	9	13.8%	9	4.5%	3	8.2%	5	4.7%	3	9.4%	6
Nasal disorder	3.4%	2	6.2%	4	1.5%	1	3.3%	2	4.7%	3	1.6%	1
Upper respiratory tract infection	10.3%	6	6.2%	4	3.0%	2	14.8%	9	3.1%	2	7.8%	5
Respiratory tract infection viral	3.4%	2	4.6%	3	3.0%	2	9.8%	6	1.6%	1	10.9%	7
Seborrhoeic dermatitis	5.2%	3	3.1%	2	3.0%	2	1.6%	1	1.6%	1	0%	0
Nausea/ vomiting	5.2%	3	1.5%	1	0%	0	3.3%	2	1.6%	1	3.1%	2
Diarrhoea	6.9%	4	1.5%	1	3.0%	2	4.9%	3	0%	0	0%	0
Erectile dysfunction	5.2%	3	3.1%	2	0%	0	0%	0	0%	0	1.6%	1

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Table 9. Adverse drug reactions observed in ≥2.0% of subjects in any treatment group

	Placebo (N = 58)		Dutasteride 0.05 mg (N = 65)		Dutasteride 0.1 mg (N = 66)		Dutasteride 0.5 mg (N = 61)		Dutasteride 2.5 mg (N = 64)		Finasteride 5 mg (N = 64)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	24.1%	14	15.4%	10	28.8%	19	14.8%	9	28.1%	18	23.4%	15
Libido decreased	3.4%	2	3.1%	2	3.0%	2	0%	0	12.5%	8	4.7%	3
Malaise/fatigue	3.4%	2	0%	0	1.5%	1	1.6%	1	7.8%	5	3.1%	2
Headache	1.7%	1	0%	0	9.1%	6	4.9%	3	6.3%	4	3.1%	2
Nausea/ vomiting	5.2%	3	0%	0	0%	0	1.6%	1	1.6%	1	0%	0
Abdominal discomfort/ gastrointestinal pain	0%	0	0%	0	1.5%	1	3.3%	2	1.6%	1	0%	0
Ejaculation disorder	0%	0	0%	0	3.0%	2	0%	0	1.6%	1	3.1%	2
Erectile dysfunction	5.2%	3	1.5%	1	0%	0	0%	0	0%	0	1.6%	1
Liver function test abnormal	3.4%	2	1.5%	1	1.5%	1	0%	0	0%	0	0%	0
Aptyalism	0%	0	0%	0	0%	0	0%	0	0%	0	3.1%	2
Hypertrichosis	3.4%	2	1.5%	1	0%	0	0%	0	0%	0	0%	0
Somnolence	0%	0	0%	0	0%	0	0%	0	0%	0	3.1%	2

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No deaths occurred. The incidence of serious adverse events was 1.6% (1 of 58 subjects; migraine in 1 subject) in the placebo group, 1.5% (1 of 65 subjects; gastroenteritis in 1 subject) in the dutasteride 0.05 mg group, 3.0% (2 of 66 subjects; hepatobiliary infection/pancreas infection, and calculus urinary

in 1 subject each) in the dutasteride 0.1 mg group, 1.6% (1 of 64 subjects; bone disorder/chondropathy in 1 subject) in the dutasteride 2.5 mg group, and 1.6% (1 of 64 subjects; embolism/peripheral ischaemia in 1 subject) in the finasteride 5 mg group. A causal relationship to the study drug was ruled out for all of these events. The incidence of adverse events leading to discontinuation of the study drug was 5.2% (3 of 58 subjects) in the placebo group, 9.1% (6 of 66 subjects) in the dutasteride 0.1 mg group, and 1.6% (1 of 61 subjects) in the dutasteride 0.5 mg group.[10]

4.(iii).A.(2) Global phase II/III study (5.3.5.1, Study ARI114263 [October 2010 to February 2012])

A multi-center, randomized, double-blind, parallel-group study was conducted at 39 centers in 9 countries and regions (5 in Japan, 6 in Mexico, 5 in the Philippines, 5 in Russia, 5 in Taiwan, 4 in Argentina, 4 in Thailand, 3 in Peru, and 2 in Chile) to investigate the dose response, efficacy, and safety of dutasteride in Japanese and non-Japanese male subjects aged 20 to 50 years who had a clinical diagnosis of androgenetic alopecia classified as the Norwood-Hamilton type III vertex, IV, or V (excluding types IVa and Va) (target sample size, 900 subjects).

In this study, subjects received oral doses of dutasteride 0.02 mg, 0.1 mg, or 0.5 mg, finasteride 1 mg, or placebo once daily for 24 weeks.

A total of 917 subjects received study treatment (181 subjects [including 40 Japanese] in the placebo group, 185 [including 40 Japanese] in the dutasteride 0.02 mg group, 188 [including 40 Japanese] in the dutasteride 0.1 mg group, 184 [including 40 Japanese] in the dutasteride 0.5 mg group, and 179 [including 40 Japanese] in the finasteride 1 mg group). All the subjects treated were included in the ITT population and safety analysis population, and the ITT was the population for primary efficacy analysis. A total of 156 subjects discontinued the study (24 in the placebo group, 29 in the dutasteride 0.02 mg group, 34 in the dutasteride 0.1 mg group, 31 in the dutasteride 0.5 mg group, and 38 in the finasteride 1 mg group). Reasons for discontinuation were “withdrawal of consent” for 58 subjects (9 in the placebo group, 9 in the dutasteride 0.02 mg group, 9 in the dutasteride 0.1 mg group, 14 in the dutasteride 0.5 mg group, and 17 in the finasteride 1 mg group), “lost to follow-up” for 48 subjects (4 in the placebo group, 13 in the dutasteride 0.02 mg group, 11 in the dutasteride 0.1 mg group, 10 in the dutasteride 0.5 mg group, and 10 in the finasteride 1 mg group); “adverse events” for 21 subjects (5 in the placebo group, 8 in the dutasteride 0.1 mg group, 4 in the dutasteride 0.5 mg group, and 4 in the finasteride 1 mg group), “investigator’s discretion” for 20 subjects (4 in the placebo group, 4 in the dutasteride 0.02 mg group, 3 in the dutasteride 0.5 mg group, and 5 in the finasteride 1 mg group), “protocol deviation” for 9 subjects (2 in the placebo group, 3 in the dutasteride 0.02 mg group, 2 in the dutasteride 0.1 mg group, and 2 in the finasteride 1 mg group).

[10] The following events were observed: erectile dysfunction (2 subjects) and irritable bowel syndrome (1 subject) in the placebo group; headache, rash, abdominal discomfort/abdominal pain, affective disorder/malaise/fatigue, malaise/fatigue/memory impairment/affective disorder, and abdominal discomfort/gastrointestinal pain/diarrhoea/headache/libido decreased/acne/folliculitis (1 subject each) in the dutasteride 0.1 mg group; and abdominal discomfort/gastrointestinal pain (1 subject) in the dutasteride 0.5 mg group.

The primary endpoint for efficacy was the "change from baseline in hair count within a circle of 2.54 cm diameter at the vertex at Week 24." The results are shown in Table 10. A statistically significant difference from placebo was observed in the dutasteride 0.1 and 0.5 mg groups (t-test using a general linear model with a two-sided significance level of 1.67%, with Bonferroni adjustment for multiplicity). The dutasteride 0.1 and 0.5 groups demonstrating a statistically significant difference from the placebo group were then compared with the finasteride 1 mg group. The lower limits of the 98.33% CI for the differences between the dutasteride 0.1 or 0.5 mg group and the finasteride 1 mg group were greater than the pre-specified non-inferiority margin of −35 hairs, thus the non-inferiority of dutasteride 0.1 and 0.5 mg to finasteride 1 mg was demonstrated. Table 11 shows the "change from baseline in hair count within 2.54-cm diameter circle at the vertex at Week 24" in the subgroup of Japanese subjects.

Table 10. Change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24 in the overall study population (ITT)

Treatment group	Baseline hair count	Change from baseline hair count[a)]	Difference from placebo [98.33% CI][b)]	*P*-value for the difference from placebo[c)]	Least squares mean difference from finasteride 1 mg[d)] [98.33% CI]
Placebo	760.9 ± 226.9 (N = 151)	−4.9 ± 7.9 (n = 148)	—	—	—
Dutasteride 0.02 mg	774.4 ± 226.5 (N = 157)	17.1 ± 7.7 (n = 155)	22.0 [−4.4, 48.4]	0.046	−39.4 [−66.1, −12.7]
Dutasteride 0.1 mg	721.3 ± 220.2 (N = 160)	63.0 ± 7.7 (n = 158)	67.9 [41.6, 94.2]	<0.001	6.5 [−20.1, 33.1]
Dutasteride 0.5 mg	767.5 ± 218.0 (N = 151)	89.6 ± 7.9 (n = 150)	94.4 [67.8, 121.0]	<0.001	33.0 [6.1, 60.0]
Finasteride 1 mg	763.8 ± 180.6 (N = 142)	56.5 ± 8.1 (n = 141)	61.4 [34.4, 88.4]	—	—

Least squares mean ± standard error (number of subjects); missing data were imputed using LOCF.
a) Subjects without hair count in the vertex area at this time point were excluded from the analysis.
b) Estimated based on a general linear model with treatment group, region, and baseline hair count as explanatory variables.
c) T-test using a general linear model with a two-sided significance level of 1.67%, with Bonferroni adjustment for multiplicity
d) Any dutasteride group demonstrating a statistically significant difference from the placebo group was to be compared with the finasteride 1 mg group. The non-inferiority margin was set at −35 hairs. The non-inferiority of dutasteride to finasteride was demonstrated if the lower limit of the 98.33% CI for the difference was greater than the non-inferiority margin (−35 hairs).

Table 11. Change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24 in the Japanese population (ITT)

Treatment group	Baseline hair count	Change from baseline hair count[a)]	Difference from placebo [98.33% CI][b)]	Least squares mean difference from finasteride 1 mg [98.33% CI]
Placebo	751.1 ± 188.9 (N = 37)	−17.3 ± 15.7 (n = 37)	—	—
Dutasteride 0.02 mg	826.8 ± 192.6 (N = 37)	0.4 ± 15.9 (n = 37)	17.8 [−36.3, 71.8]	−20.9 [−75.1, 33.4]
Dutasteride 0.1 mg	710.5 ± 178.2 (N = 40)	39.4 ± 15.2 (n = 40)	56.7 [4.1, 109.4]	18.1 [−35.0, 71.2]
Dutasteride 0.5 mg	756.2 ± 153.4 (N = 36)	68.5 ± 16.1 (n = 35)	85.8 [31.5, 140.1]	47.2 [−7.5, 101.9]
Finasteride 1 mg	762.3 ± 162.5 (N = 36)	21.3 ± 15.9 (n = 36)	38.6 [−15.3, 92.5]	—

Least squares mean ± standard error; missing data were imputed using LOCF.
a) Subjects without hair count in the vertex area at this time point were excluded from the analysis.
b) Estimated based on a general linear model with treatment group, region, and baseline hair count as explanatory variables.

Safety results were summarized. The incidence of adverse events was 51.9% (94 of 181 subjects) in the placebo group, 49.2% (91 of 185 subjects) in the dutasteride 0.02 mg group, 50.5% (95 of 188 subjects) in the dutasteride 0.1 mg group, 54.3% (100 of 184 subjects) in the dutasteride 0.5 mg group, and 52.5% (94 of 179 subjects) in the finasteride 1 mg group. Table 12 shows the adverse events observed in ≥2.0% of subjects in any treatment group. The incidence of adverse drug reactions was 14.9% (27 of 181 subjects) in the placebo group, 14.1% (26 of 185 subjects) in the dutasteride 0.02 mg group, 20.7% (39 of 188 subjects) in the dutasteride 0.1 mg group, 16.3% (30 of 184 subjects) in the dutasteride 0.5 mg group, and 19.6% (35 of 179 subjects) in the finasteride 1 mg group. Table 13 shows the adverse drug reactions observed in ≥2 subjects in any treatment group.

Table 12. Adverse events observed in ≥2.0% of subjects in any treatment group

	Placebo (N = 181)		Dutasteride 0.02 mg (N = 185)		Dutasteride 0.1 mg (N = 188)		Dutasteride 0.5 mg (N = 184)		Finasteride 1 mg (N = 179)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	51.9%	94	49.2%	91	50.5%	95	54.3%	100	52.5%	94
Nasopharyngitis	8.8%	16	10.3%	19	8.0%	15	12.5%	23	7.8%	14
Headache	8.8%	16	4.3%	8	4.3%	8	6.0%	11	2.8%	5
Erectile dysfunction	3.9%	7	4.3%	8	3.7%	7	5.4%	10	5.6%	10
Libido decreased	1.1%	2	5.4%	10	4.8%	9	3.3%	6	5.0%	9
Upper respiratory tract infection	5.0%	9	2.7%	5	1.1%	2	3.3%	6	0.6%	1
Rhinitis allergic	0.6%	1	1.1%	2	0.5%	1	2.2%	4	3.4%	6
Dizziness	0.6%	1	1.6%	3	1.1%	2	2.2%	4	1.1%	2
Acne	0.6%	1	0.5%	1	0%	0	2.2%	4	0.6%	1
Back pain	2.2%	4	2.7%	5	1.6%	3	1.6%	3	2.2%	4
Pharyngitis	3.9%	7	0.5%	1	1.1%	2	1.6%	3	2.8%	5
Abdominal pain	1.1%	2	3.2%	6	3.7%	7	1.1%	2	1.1%	2
Abdominal pain upper	0.6%	1	2.2%	4	0.5%	1	1.1%	2	2.8%	5
Diarrhoea	1.7%	3	1.1%	2	3.7%	7	1.1%	2	0%	0
Bronchitis	1.1%	2	2.2%	4	0%	0	1.1%	2	1.1%	2
Influenza	2.8%	5	1.6%	3	2.1%	4	0.5%	1	1.1%	2
Ejaculation failure	1.1%	2	0.5%	1	1.1%	2	0.5%	1	2.2%	4
Toothache	0%	0	2.2%	4	0.5%	1	0.5%	1	1.7%	3
Hypertension	0.6%	1	0%	0	2.7%	5	0.5%	1	1.1%	2

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Table 13. Adverse drug reactions observed in ≥2 subjects in any treatment group

	Placebo (N = 181)		Dutasteride 0.02 mg (N = 185)		Dutasteride 0.1 mg (N = 188)		Dutasteride 0.5 mg (N = 184)		Finasteride 1 mg (N = 179)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	14.9%	27	14.1%	26	20.7%	39	16.3%	30	19.6%	35
Erectile dysfunction	3.3%	6	4.3%	8	3.2%	6	5.4%	10	5.6%	10
Libido decreased	1.1%	2	4.9%	9	4.8%	9	2.2%	4	3.9%	7
Nasopharyngitis	0%	0	0.5%	1	0%	0	1.6%	3	0.6%	1
Ejaculation disorder	0.6%	1	0%	0	1.6%	3	1.1%	2	1.1%	2
Semen volume decreased	0%	0	1.1%	2	1.6%	3	1.1%	2	0%	0
Transaminases increased	0.6%	1	0%	0	1.1%	2	1.1%	2	0.6%	1
Ejaculation failure	1.1%	2	0.5%	1	1.1%	2	0.5%	1	1.7%	3
Sexual dysfunction	0%	0	1.1%	2	0.5%	1	0.5%	1	1.1%	2
Abdominal pain upper	0%	0	1.1%	2	0%	0	0.5%	1	1.1%	2
Abdominal pain	1.1%	2	1.1%	2	2.1%	4	0%	0	0%	0
Loss of libido	0%	0	1.1%	2	1.1%	2	0%	0	0.6%	1

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No deaths occurred. The incidence of serious adverse events was 1.1% (2 of 181 subjects) in the placebo group (syncope and nephrolithiasis in 1 subject each), 1.6% (3 of 188 subjects) in the dutasteride 0.1 mg group (blood pressure increased, cartilage injury, and hepatic cancer metastatic/rectal cancer in 1 subject each), 0.5% (1 of 184 subjects) in the dutasteride 0.5 mg group (infection parasitic/salmonellosis/gastric

ulcer in 1 subject), and 1.1% (2 of 179 subjects) in the finasteride 1 mg group (laryngitis/pharyngeal abscess and fractured sacrum/lower limb fracture in 1 subject each). A causal relationship to the study drug could not be ruled out for the 1 event of syncope in the placebo group. The incidence of adverse events leading to discontinuation of the study drug was 2.8% (5 of 181 subjects) in the placebo group, 4.3% (8 of 188 subjects) in the dutasteride 0.1 mg group, 2.7% (5 of 184 subjects) in the dutasteride 0.5 mg group, and 2.2% (4 of 179 subjects) in the finasteride 1 mg group.[11]

4.(iii).A.(3) Japanese long-term study (5.3.5.2, Study ARI114264 [April 2013 to November 2014])

A multi-center, open-label, uncontrolled study was conducted at 5 centers in Japan to investigate the long-term safety and efficacy of dutasteride in Japanese male patients aged 20 to 50 years who had a clinical diagnosis of androgenetic alopecia classified as the Norwood-Hamilton type III vertex, IV, or V (excluding types IVa and Va) (target sample size, 140 subjects).

In this study, subjects received oral doses of dutasteride 0.5 mg once daily for 52 weeks.

A total of 120 subjects received study treatment. All the subjects treated were included in the ITT population and safety analysis population, and the ITT was the population for the primary efficacy analysis. Ten subjects discontinued the study due to "withdrawal of consent."

As a measure of efficacy, the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Weeks 26 and 52" (mean ± standard deviation) was determined, and the results were 87.3 ± 81.1 hairs and 68.1 ± 82.1 hairs, respectively.

Safety results were summarized. The incidence of adverse events was 53.3% (64 of 120 subjects). Adverse events observed in ≥2.0% of subjects were nasopharyngitis (15.0%, 18 of 120 subjects), erectile dysfunction (11.7%, 14 of 120 subjects), libido decreased (8.3%, 10 of 120 subjects), influenza and ejaculation disorder (4.2%, 5 of 120 subjects each), sexual dysfunction (3.3%, 4 of 120 subjects), gingivitis, upper respiratory tract infection, headache, and prostatic specific antigen (PSA) increased (2.5%, 3 of 120 subjects each). The incidence of adverse drug reactions was 16.7% (20 of 120 subjects). Observed adverse drug reactions were erectile dysfunction (10.8%, 13 of 120 subjects), libido decreased (8.3%, 10 of 120 subjects), ejaculation disorder (4.2%, 5 of 120 subjects), sexual dysfunction (3.3%, 4 of 120 subjects), retrograde ejaculation, depressed mood, suicidal ideation, headache, sensory disturbance, fatigue, rash, and hypertension (0.8%, 1 of 120 subjects each).

[11] The following events were observed: erectile dysfunction, abdominal distension, urticaria, syncope, and abdominal pain/abdominal rigidity/dyspnoea/ejaculation delayed/erectile dysfunction/libido decreased (1 subject each) in the placebo group; libido decreased and hypertension (2 subjects each), depression, lower limb fracture, erectile dysfunction/loss of libido, and rectal cancer/hepatic cancer metastatic (1 subject each) in the dutasteride 0.1 mg group; sexual dysfunction, dermatitis atopic, seborrhoeic dermatitis, tachycardia, and gastric ulcer/infection parasitic/salmonellosis (1 subject each) in the dutasteride 0.5 mg group; erectile dysfunction, abdominal distension, dermatitis atopic, and erectile dysfunction/ejaculation disorder (1 subject each) in the finasteride 1 mg group.

No deaths occurred. Serious adverse events occurred in 1.7% (2 of 120) of subjects (stress fracture and post-traumatic neck syndrome in 1 subject each), and a causal relationship to the study drug was ruled out for both events. No adverse events leading to discontinuation of study drug were observed.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Evaluation in the global study

The phase II/III study (ARI114263) was a global clinical study. PMDA asked the applicant to explain the impact of extrinsic and intrinsic ethnic factors on the efficacy and safety of dutasteride in light of the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007).

The applicant's explanation:
Finasteride and minoxidil topical solution are commonly used for the treatment of androgenetic alopecia in all the participating countries including Japan and Asian, Latin American, and other nations. For this reason, there are no major differences in extrinsic ethnic factors.

The primary pathogenic mechanism of androgenetic alopecia is thought to be 5 α-reductase-mediated conversion of testosterone into DHT in the dermal papilla cells in the frontal and vertex regions of the scalp, which results in DHT-induced activation of androgen receptor.[2] There have been no reports of intrinsic ethnic difference in this pathogenic mechanism.

In the global phase II/III study where male patients with androgenetic alopecia received dutasteride 0.1 mg or 0.5 mg, the serum concentration of dutasteride was slightly higher in Japanese than in non-Japanese subjects, but the range of distribution and the degree of variance were generally similar in the 2 subgroups. Dutasteride is a 5 α-reductase inhibitor and has been confirmed to produce similar serum DHT reduction in Japanese and Caucasian subjects in the Japanese and foreign clinical studies conducted in healthy adult men and male patients with prostatic hyperplasia. In the global phase II/III study, Japanese subjects receiving dutasteride 0.1 mg exhibited greater percent reduction in serum DHT compared with non-Japanese subjects receiving dutasteride 0.1 mg, but the percent reduction was similar between Japanese and non-Japanese subjects in the dutasteride 0.5 mg group. There were no ethnic differences that may cause concern. Based on the above findings, the applicant considers that there are no obvious ethnic differences that affect the serum concentration of dutasteride or DHT [see "4.(ii).B.(1) Comparison of pharmacokinetic and pharmacodynamic actions between Japanese and non-Japanese subjects"]. In conclusion, there were no major intrinsic ethnic differences between Japanese and non-Japanese subjects from the perspectives of the pathogenic mechanism of androgenetic alopecia, mechanism of action of dutasteride, and the pharmacokinetics and pharmacodynamics of dutasteride.

PMDA's view:

Given that no significant differences were found between Japan and other countries participating in the global phase II/III study in terms of extrinsic factors including therapeutic environments or intrinsic factors including the primary pathogenic mechanism of androgenetic alopecia, there were no particular concerns about the participation of Japanese subjects in this study. The efficacy and safety of dutasteride in the overall study population and in the Japanese subgroup in the global phase II/III study will be discussed in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety."

4.(iii).B.(2) Efficacy

PMDA's view:

The efficacy of dutasteride in male patients with androgenetic alopecia has been demonstrated by the review and findings presented in 4.(iii).B.(2).1) to 4.(iii).B.(2).3) below. However, the long-term efficacy of dutasteride should continue to be investigated via post-marketing surveillance etc.

PMDA will make a final decision on the efficacy of dutasteride, taking account of comments raised in the Expert Discussion.

4.(iii).B.(2).1) Efficacy in the overall study population

The primary endpoint of the global phase II/III study (ARI114263) was the "change from baseline in hair counts within a 2.54-cm diameter circle at the vertex at Week 24." The results are shown in Table 10. The dutasteride 0.1 mg and 0.5 mg groups showed a statistically significant increase in hair counts compared to the placebo group ($P < 0.001$, t-test using a general linear model with a two-sided significance level of 1.67%). The non-inferiority of dutasteride 0.1 mg and 0.5 mg to finasteride 1 mg was also demonstrated.

In the global phase II/III study, in addition to the primary assessment of hair counts, the following secondary endpoints were assessed as measures of change in hair growth and appearance: hair width,[12] terminal hair count,[13] and photographic assessment by the expert panel (hereinafter "panel photographic assessment").[14] Secondary endpoints also included patient satisfaction with hair growth, as assessed by the total scores of the Hair Growth Index (HGI)[15] and Hair Growth Satisfaction Scale (HGSS).[16] As in

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[12] The total width of nonvellus hairs (≥30 μm in width) was obtained and used as a parameter.

[13] Terminal hairs (≥60 μm in width) were counted.

[14] An expert panel consisting of 3 dermatologists assessed the change from baseline in hair growth in the vertex and frontal regions using a 7-point scale.

[15] The HGI (questionnaire developed by the applicant) was used to allow patients to assess their hair growth using 3 questions scored on a 7-point scale. Patients assessed their global photographs of vertex view and frontal view to answer the following questions: "Since the start of treatment, when I look at my thinning area, I can see... *(i.e., how the balding scalp has changed)*," "Since the start of treatment, my hair now covers… *(i.e., how the thinning area has changed)*," and "Since the start of treatment, the appearance (thickness/quality/amount) of the thinning area on my head is… *(i.e., how the overall appearance of the thinning area has changed).*"

[16] The HGSS (questionnaire developed by the applicant) was used to allow patients to assess their satisfaction with the hair appearance and growth using 5 questions on a 7-point scale. Patients provided their ratings for the following points: "the overall appearance of hair (thickness, hair quality, amount)," "the appearance of the thinning area(s)," "the amount of scalp that can be seen in the thinning area(s)," "the amount of hair in the thinning area(s)," and "the growth of hair in the thinning area(s)."

the case of the primary endpoint, the secondary endpoints showed a trend toward an improvement in the assessment scores in both the dutasteride 0.1 mg and 0.5 mg groups as compared with the placebo group.

PMDA's view:

The efficacy of dutasteride in patients with androgenetic alopecia has been demonstrated, on the basis of the following findings of the global phase II/III study: (1) the dutasteride 0.1 mg and 0.5 mg groups showed a statistically significant increase in hair count compared with the placebo group and the non-inferiority of the dutasteride doses to finasteride 1 mg was demonstrated; and (2) a trend toward improvement in some of the secondary endpoints was found in the dutasteride 0.1 mg and 0.5 mg groups, as with the primary endpoint.

4.(iii).B.(2).2) Efficacy by country or region

Table 11 shows the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24" in the global phase II/III study. The change in hair count was smaller in the Japanese subgroup than in the overall study population. PMDA asked the applicant to explain the reason for the difference.

The applicant's explanation:

Table 14 shows the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24" in the global phase II/III study for the overall study population and for the subgroups of Japanese, non-Japanese Asian, Hispanic/Latino, and Caucasian subjects. Among the dutasteride-treated subjects, the change in hair count tended to be greater in the Hispanic/Latino subgroup and smaller in the Japanese and non-Japanese Asian subgroups than other ethnic subgroups.

Table 14. Change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24 by subgroup (ITT)

Treatment group	Overall study population		Japanese		Non-Japanese Asian		Hispanic/Latino		Caucasian	
	N	Change from baseline hair count[a)]	N	Change from baseline hair count[a)]	N	Change from baseline hair count[a)]	N	Change from baseline hair count[a)]	N	Change from baseline hair count[a)]
Placebo	148	−4.9 ± 7.9	37	−17.3 ± 15.7	45	−16.7 ± 10.2	60	6.2 ± 15.0	6	−22.6 ± 49.8
Dutasteride 0.02 mg	155	17.1 ± 7.7	37	0.4 ± 15.9	54	2.5 ± 9.3	57	29.4 ± 15.4	7	31.2 ± 44.2
Dutasteride 0.1 mg	158	63.0 ± 7.7	40	39.4 ± 15.2	53	43.3 ± 9.4	60	85.9 ± 15.0	5	51.4 ± 53.0
Dutasteride 0.5 mg	150	89.6 ± 7.9	35	68.5 ± 16.1	54	64.9 ± 9.3	55	116.7 ± 15.7	6	78.6 ± 55.0
Finasteride 1 mg	141	56.5 ± 8.1	36	21.3 ± 15.9	50	42.4 ± 9.6	51	79.1 ± 16.2	4	92.3 ± 64.9

Least squares mean ± standard error; missing data were imputed using LOCF.
a) Subjects without vertex hair count were excluded from the analysis.

There have been no reports so far about ethnic differences in the effect of DHT on hair cycle or response mechanisms including miniaturization of hair follicles. However, the follicle and hair density on the

scalp is lower in Asians than in Caucasians[17]; therefore, the possibility cannot be ruled out that the ethnic difference in the change from baseline in hair count observed in the global phase II/III study was due to the ethnic difference in the follicle and hair density as well as due to multiple factors such as individual data variability and inter-patient differences in hair loss progression.

Nevertheless, in the global phase II/III study, a trend toward a dose-dependent increase in hair count at the vertex was observed in the subgroup of Japanese subjects receiving dutasteride as well as in the overall study population. The applicant therefore consider that there are no obvious ethnic differences in the efficacy of dutasteride.

PMDA's view on the efficacy in Japanese patients:
The applicant explained the reason why the Japanese subgroup showed a trend toward a smaller change compared with the overall study population in terms of the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24" (the primary endpoint of the global phase II/III study). The applicant's explanation is acceptable.

The differences observed between the dutasteride groups and the placebo group or the finasteride 1 mg group in the global phase II/III study (Tables 10 and 11) were examined to assess the efficacy of dutasteride relative to placebo or finasteride 1 mg. As a result, no clinically significant differences were noted in the results of the endpoint between the overall study population and the Japanese subgroup. On the basis of these findings, PMDA concluded that the efficacy results in the overall study population were consistent with those in the Japanese subgroup, and that the efficacy of dutasteride in the Japanese population may be discussed based on the data from the global phase II/III study.

4.(iii).B.(2).3) Long-term efficacy

In order to evaluate the long-term efficacy of dutasteride, the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex" (mean ± standard deviation) was assessed in the Japanese long-term study (ARI114264). The results were 87.3 ± 81.1 at Week 26 and 68.1 ± 82.1 at Week 52, showing a trend toward a decrease in the hair count change at Week 52 compared with that at Week 26. PMDA asked the applicant to explain the possibility of reduced therapeutic response resulting from the long-term use of dutasteride.

The applicant's explanation:
The reason why the change in hair count from baseline at Week 52 was decreased compared with that at Week 26 is not clear, but the long-term use of dutasteride is unlikely to markedly reduce its efficacy because the panel photographic assessment of improvement in hair growth from baseline showed a higher proportion of subjects with any improvement (slight, moderate, or great) in panel assessment scores at Week 52 than that at Week 26. More specifically, the proportion of subjects with improved hair

[17] *J Am Acad Dermatol*. 2002;46:218-221; *Skin Pharmacol Physiol.* 2006;19:159-167.

growth at Week 26 was 81.2% (95 of 117 subjects) for the vertex view and 76.1% (89 of 117 subjects) for the frontal view, whereas the proportion of such subjects at Week 52 was 85.5% (100 of 117 subjects) for the vertex view and 78.6% (92 of 117) for the frontal view.

PMDA considers that the applicant should continue to collect information via post-marketing surveillance etc., to investigate whether the long-term use of dutasteride reduce its efficacy.

4.(iii).B.(3) Safety

PMDA's view:

Based on the review and findings presented in 4.(iii).B.(3).1) to 4.(iii).B.(3).4) below, the safety of dutasteride in male patients with androgenetic alopecia is acceptable. Patients with androgenetic alopecia are younger than those with prostatic hyperplasia[18]; therefore, decreased male fertility is considered to pose a more significant risk to this patient population. Because at present there is only limited information about the long-term safety of dutasteride in Japanese male patients with androgenetic alopecia, information on adverse events related to sexual function should continue to be collected via post-marketing surveillance etc. In addition, dutasteride (for the proposed additional indication) is a lifestyle drug and androgenetic alopecia is a condition that does not necessarily require pharmacotherapy. Therefore, physicians should fully inform patients of the risk of adverse events related to sexual function and breast disorders through patient education materials.

PMDA will make a final decision on the safety of dutasteride, taking account of comments raised at the Expert Discussion.

4.(iii).B.(3).1) Adverse events in the global phase II/III study

An analysis was made on adverse events reported in the global phase II/III study (Table 12). No specific adverse events or trends in the incidence of adverse events were noted in the dutasteride groups compared with the placebo group or the finasteride 1 mg group. There were no clinically relevant differences in the incidence of serious adverse events between the dutasteride groups and the finasteride 1 mg group. A causal relationship to the study drug was ruled out for all the serious adverse events.

PMDA confirmed that no specific clinically relevant adverse events or trends in adverse events were noted in the dutasteride groups compared the placebo group or the finasteride group. Adverse events related to sexual function (e.g., erectile dysfunction and libido decreased) will be discussed in "4.(iii).B.(3).3) Adverse events of special interest."

[18] The mean age was 44 years for Japanese male patients with androgenetic alopecia subjects the global phase II/III study, which was submitted in the present application. The mean age was 65 years for patients with prostatic hyperplasia enrolled in the Japanese phase III study (Study ARI105326).

4.(iii).B.(3).2) Incidence of adverse events by country or region

Adverse events and adverse drug reactions reported in the overall study population in the global phase II/III study are shown in Tables 12 and 13, respectively [see "4.(iii).A.(2) Global phase II/III study"]. Adverse events and adverse drug reactions occurring in ≥2 subjects in any treatment group within the Japanese subgroup are shown in Tables 15 and 16, respectively.

Table 15. Adverse events occurring in ≥2 subjects in any treatment group within the Japanese subgroup (global phase II/III study)

	Placebo (N = 40)		Dutasteride 0.02 mg (N = 40)		Dutasteride 0.1 mg (N = 40)		Dutasteride 0.5 mg (N = 40)		Finasteride 1 mg (N = 40)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	42.5%	17	45.0%	18	37.5%	15	57.5%	23	37.5%	15
Nasopharyngitis	10.0%	4	17.5%	7	10.0%	4	12.5%	5	15.0%	6
Erectile dysfunction	5.0%	2	2.5%	1	2.5%	1	10.0%	4	5.0%	2
Libido decreased	0%	0	5.0%	2	7.5%	3	5.0%	2	2.5%	1
Seborrhoeic dermatitis	0%	0	0%	0	0%	0	5.0%	2	0%	0
Dental caries	5.0%	2	5.0%	2	0%	0	2.5%	1	0%	0
Abdominal discomfort	2.5%	1	5.0%	2	0%	0	2.5%	1	0%	0
Anaemia	2.5%	1	5.0%	2	0%	0	2.5%	1	0%	0
Ligament sprain	0%	0	0%	0	5.0%	2	0%	0	0%	0
Back pain	0%	0	5%	2	2.5%	1	0%	0	0%	0
Headache	5.0%	2	2.5%	1	2.5%	1	0%	0	0%	0

MedDRA/J ver14.1

Table 16. Adverse drug reactions occurring in ≥2 subjects in any treatment group within the Japanese subgroup (global phase II/III study)

	Placebo (N = 40)		Dutasteride 0.02 mg (N = 40)		Dutasteride 0.1 mg (N = 40)		Dutasteride 0.5 mg (N = 40)		Finasteride 1 mg (N = 40)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	15.0%	6	7.5%	3	12.5%	5	15.0%	6	10.0%	4
Erectile dysfunction	5.0%	2	2.5%	1	2.5%	1	10.0%	4	5.0%	2
Libido decreased	0%	0	5.0%	2	7.5%	3	5.0%	2	2.5%	1

MedDRA/J ver14.1

PMDA confirmed that no clinically significant differences were found in the incidence or pattern of adverse events between the overall study population and the Japanese subgroup in the global phase II/III study.

4.(iii).B.(3).3) Adverse events of special interest

(a) Adverse events related to sexual function

The applicant's explanation:

Adverse events related to sexual function, including erectile dysfunction and libido decreased, are known as relatively common adverse reactions to dutasteride (see "Review Report of Avolve Capsules 0.5 mg," dated April 13, 2009 [in Japanese only]). The use-results survey of Avolve Capsules 0.5 mg conducted in Japan revealed adverse events related to sexual function (e.g., libido decreased, erectile

dysfunction, and ejaculation disorder) experienced by 9 of 1169 patients (0.8%); however, all the events were non-serious and the outcome was reported either as resolved or resolving (except for events with unknown outcome). As such, there are no concerns about the occurrence of these events in routine clinical practice.

Adverse events related to sexual function reported in the studies submitted in the present application (a foreign phase II study, a global phase II/III study, and a long-term study) were classified according to the definition shown in Tables 17 and 18 for evaluation.

Table 17. Definition of adverse events related to sexual function in the foreign phase II study

Definition	Preferred term (MedDRA/J ver16.1)
Libido decreased	Libido decreased, loss of libido, sexual dysfunction
Ejaculation disorder	Semen volume decreased, orgasm abnormal, and premature ejaculation
Erectile dysfunction	Erectile dysfunction, and organic erectile dysfunction
Sexual dysfunction	Sexual dysfunction

Table 18. Definition of adverse events related to sexual function in the global phase II/III study and long-term study

Definition	Preferred term (common for MedDRA/J ver14.1 and 17.0)
Libido decreased	Sexual dysfunction, male sexual dysfunction, libido decreased, loss of libido, and libido disorder
Ejaculation disorder	Ejaculation delayed, ejaculation disorder, ejaculation failure, retrograde ejaculation, anorgasmia, orgasm abnormal, premature ejaculation, male orgasmic disorder, orgasmic sensation decreased, and semen volume decreased
Erectile dysfunction	Erectile dysfunction, organic erectile dysfunction, disturbance in sexual arousal, and psychogenic erectile dysfunction

Tables 19 and 20 show adverse events related to sexual function reported in the foreign phase II study and the global phase II/III study, respectively. The majority of the adverse events were mild in severity, and no serious adverse events were observed. Adverse events led to discontinuation of the study drug in 1 subject (libido decreased) in the dutasteride 0.1 mg group in the foreign phase II study, and in 3 subjects (libido decreased [2] and erectile dysfunction [1]) in the dutasteride 0.1 mg group in the global phase II/III study. All events resolved following discontinuation of dutasteride.

Table 19. Incidence of adverse events related to sexual function (foreign phase II study)

	Placebo (N = 58)		Dutasteride 0.05 mg (N = 65)		Dutasteride 0.1 mg (N = 66)		Dutasteride 0.5 mg (N = 61)		Dutasteride 2.5 mg (N = 64)		Finasteride 5 mg (N = 64)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Libido decreased	3.4%	2	3.1%	2	3.0%	2	1.6%	1	12.5%	8	4.7%	3
Ejaculation disorder	0%	0	0%	0	3.0%	2	0%	0	1.6%	1	3.1%	2
Sexual dysfunction	0%	0	0%	0	1.5%	1	0%	0	0%	0	0%	0
Erectile dysfunction	5.2%	3	3.1%	2	0%	0	0%	0	0%	0	1.6%	1

MedDRA/J ver16.1

Table 20. Incidence of adverse events related to sexual function (global phase II/III study)

	Placebo (N = 181)		Dutasteride 0.02 mg (N = 185)		Dutasteride 0.1 mg (N = 188)		Dutasteride 0.5 mg (N = 184)		Finasteride 1 mg (N = 179)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Erectile dysfunction	3.9%	7	4.3%	8	3.7%	7	5.4%	10	6.1%	11
Libido decreased	1.7%	3	8.1%	15	6.9%	13	4.9%	9	6.7%	12
Ejaculation disorder	3.3%	6	2.2%	4	4.8%	9	3.3%	6	3.9%	7

MedDRA/J ver14.1

PMDA's view:

Adverse events related to sexual function are unlikely to cause clinically significant problems, on the grounds that: (1) in the foreign phase II study and the global phase II/III study, the incidence of adverse events related to sexual function was similar between the dutasteride groups and the placebo group, and all events were non-serious; (2) the adverse events related to sexual function leading to discontinuation in the dutasteride groups resolved after interventions including treatment interruption; and (3) no specific concerns are identified with the post-marketing safety information from patients with prostatic hyperplasia (approved indication) treated with dutasteride. That said, physicians should fully inform patients of the risk of adverse events related to sexual function associated with the use of dutasteride through patient education materials, prior to the start of treatment with dutasteride. Information on adverse events related to sexual function should continue to be collected via post-marketing surveillance etc., because (i) clinical study data from Japanese male patients with androgenetic alopecia are limited and (ii) patients with androgenetic alopecia are relatively younger than those with prostatic hyperplasia and therefore decreased male fertility is considered a more significant risk for the former patient population.

(b) Breast disorders

The applicant's explanation:

Dutasteride inhibits metabolism of testosterone to DHT, thereby altering the androgen to estrogen ratio in patients treated with the drug. This may result in the risk of breast disorders including gynaecomastia as adverse events associated with the use of dutasteride. In a Japanese clinical study in patients with prostatic hyperplasia, adverse events related to breast disorders including breast induration, gynaecomastia, and nipple pain were reported (see "Review Report of Avolve Capsules 0.5 mg," dated April 13, 2009 [in Japanese only]). The use-results survey of Avolve Capsules 0.5 mg conducted in Japan revealed adverse events related to breast disorders experienced by 9 of 1169 patients (0.8%); however, all these breast disorders were non-serious. The outcomes of the events were reported either as resolved or resolving.

In the clinical studies in male patients with androgenetic alopecia submitted in the present application, breast disorders occurred in 1 subject (gynaecomastia) in the placebo group in the foreign phase II study. In the global phase II/III study, breast disorders occurred in 1 subject (nipple pain) in the dutasteride

0.02 mg group, 2 subjects (breast enlargement and breast tenderness in 1 subject each) in the dutasteride 0.1 mg group, 1 subject (gynaecomastia) in the dutasteride 0.5 mg group, and 1 subject (breast enlargement) in the finasteride 1 mg group. These breast disorders were all mild or moderate in severity, and non-serious. All the events resolved without discontinuation of treatment.

Breast cancer male was reported in patients with prostatic hyperplasia receiving dutasteride. In a foreign phase III study in which dutasteride was administered to patients with prostatic hyperplasia for 4 years, breast cancer was reported in 3 of 4325 subjects (2 subjects receiving dutasteride and 1 subject receiving placebo) (see "Review Report of Avolve Capsules 0.5 mg," dated April 13, 2009 [available in Japanese only]). No breast cancer occurred in male patients with androgenetic alopecia participating in the clinical studies submitted in the present application.

PMDA's view:
The clinical studies in male patients with androgenetic alopecia showed no risk of breast disorders requiring new measures. On the basis of the results of the studies and the post-marketing safety information from patients with prostatic hyperplasia (approved indication) treated with dutasteride, there appears to be no particular concern about breast disorders at present. However, physicians should inform patients of the risk of breast disorders through patient education materials, prior to the start of treatment with dutasteride. The incidence, severity, and outcome of breast disorders should be monitored (if any) through post-marketing surveillance etc.

4.(iii).B.(3).4) Incidence of adverse events by treatment duration

Table 21 shows adverse events occurring in ≥2.0% of subjects in the long-term study by time to onset.

Table 21. Adverse events occurring in ≥2.0% of subjects in the long-term study by time to onset

Time to onset (days)	1-91 days (N = 120)		92-182 days (N = 119)		183-273 days (N = 114)		274-364 days (N = 112)		≥365 days (N = 72)		Overall (N = 120)	
	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n
Overall	25.0%	30	16.8%	20	24.6%	28	10.7%	12	1.4%	1	53.3%	64
Nasopharyngitis	5.0%	6	0.8%	1	7.0%	8	3.6%	4	1.4%	1	15.0%	18
Erectile dysfunction	7.5%	9	3.4%	4	0.9%	1	0.9%	1	0%	0	11.7%	14
Libido decreased	6.7%	8	0.8%	1	0%	0	0.9%	1	0%	0	8.3%	10
Influenza	0%	0	0%	0	2.6%	3	1.8%	2	0%	0	4.2%	5
Ejaculation disorder	2.5%	3	1.7%	2	0%	0	0%	0	0%	0	4.2%	5
Sexual dysfunction	1.7%	2	0.8%	1	0%	0	0.9%	1	0%	0	3.3%	4
Gingivitis	1.7%	2	0%	0	0.9%	1	0%	0	0%	0	2.5%	3
Upper respiratory tract infection	0.8%	1	0%	0	1.8%	2	0%	0	0%	0	2.5%	3
Headache	1.7%	2	0.8%	1	0%	0	0%	0	0%	0	2.5%	3
PSA increased	0%	0	0%	0	2.6%	3	0%	0	0%	0	2.5%	3

MedDRA/J ver17.0

PMDA confirmed that no increased incidence of adverse events was seen in patients treated with dutasteride for prolonged periods.

4.(iii).B.(4) Clinical positioning

The applicant's explanation of the clinical positioning of dutasteride:

The treatment algorithm of the guidelines for the management of androgenetic alopecia strongly recommends a prescription drug finasteride and an over-the-counter drug minoxidil as pharmacotherapeutic options for the treatment of androgenetic alopecia. In Japan, finasteride, a 5 α-reductase inhibitor, is currently the only medication that can be prescribed by physicians in healthcare facilities based on the pathophysiology of androgenetic alopecia.

Dutasteride is another 5 α-reductase inhibitor and therefore considered to fall under the same category as finasteride in the treatment algorithm. In the global phase II/III study, the non-inferiority of dutasteride 0.1 and 0.5 mg to finasteride 1 mg was demonstrated for the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24" [see "4.(iii).B.(2) Efficacy"]. The safety profiles of the 2 dutasteride doses were shown to be similar to that of finasteride 1 mg [see "4.(iii).B.(3) Safety"].

Based on the above, dutasteride is considered beneficial for the treatment of androgenetic alopecia in men.

PMDA's view:

In light of the fact that dutasteride is a 5 α-reductase inhibitor like finasteride and on the basis of the results of the clinical studies submitted in the present application, the clinical positioning of dutasteride is similar to that of finasteride. Therefore, dutasteride can be a therapeutic option for androgenetic alopecia in men.

4.(iii).B.(5) Indications

The initially proposed indication of dutasteride was "hair growth, hair restoration, and prevention of the progression of hair loss in men with androgenetic alopecia." The applicant proposed the indication on the basis of the results of the global phase II/III study where subjects in the dutasteride groups achieved increases in hair counts and hair width and improvement in the global assessment of hair growth, in contrast to a decrease in hair counts experienced by subjects in the placebo group [see "4.(iii).B.(2) Efficacy"]. The applicant also explained that male patients with types of alopecia other than androgenetic alopecia would not be included in the indication, because the efficacy and safety of dutasteride in such patient population have not been confirmed in clinical study results and other data.

The applicant's explanation of the efficacy and safety data analyzed by Norwood-Hamilton type:
The global phase II/III study enrolled subjects with a clinical diagnosis of androgenetic alopecia classified as the Norwood-Hamilton type III vertex, IV, or V (excluding types IVa and Va).[19] The "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24" showed a trend toward a dose-dependent increase for all Norwood-Hamilton types in the dutasteride groups, and the change was greater in the dutasteride 0.1 and 0.5 mg groups than in the placebo group. No major difference was observed in the safety profile among the Norwood-Hamilton types.

PMDA asked the applicant to explain the appropriateness of an indication including male patients with androgenic alopecia classified as the Norwood-Hamilton types other than III vertex, IV, and V, who were excluded from the global phase II/III study.

The applicant's response:
In the global phase II/III study, increases in hair count were observed across patients with different type of hair loss (types III vertex, IV, and V of the Norwood-Hamilton scale) in the dutasteride groups. In light of the pathogenic mechanism of hair loss and mechanism of action of dutasteride, the drug is expected to be effective regardless of the stage of androgenetic alopecia, namely, in male patients with androgenetic alopecia classified not only as types III vertex, IV, and V but also as other types according to the Norwood-Hamilton classification. Finasteride, a drug with a mechanism of action similar to that of dutasteride, is indicated for androgenetic alopecia irrespective of the Norwood-Hamilton classification. However, the applicant considers that physicians and patients should be informed of the Norwood-Hamilton classification employed in the efficacy endpoint of the global phase II/III study, and thus plans to include a description of the classification in the package insert.

PMDA asked the applicant to explain whether patients aged <20 years (excluding children) are expected to be included in the patient population in whom the use of dutasteride is indicated, as male patients with androgenetic alopecia aged 20 to 50 years were eligible for enrollment in the global phase II/III study.

The applicant's response:
Androgenetic alopecia develops at any age after puberty in individuals with a genetic predisposition. The prevalence of androgenetic alopecia in Japanese men is estimated to be approximately 30%. When the data were broken down by age group, 12.5% of men in their 20s, 20.5% of men in their 30s, 32.5% of men in their 40s, 39.9% of men in their 50s, and 43.4% of men in their 60s were found to perceive hair loss or thinning hair. As early as in the 20s, 12.5% of men are already aware of hair loss or thinning hair, and the proportion of such men increases with age.[20] The earliest age of onset of androgenetic

[19] The applicant explains that men with hair loss in the vertex area were eligible and men with severe alopecia (types VI and VII) or mild alopecia (type II), in which assessment of treatment response were difficult, were ineligible.

[20] *Japan Medical Journal.* 2004;4209:27-29.

alopecia reported in the medical interview with patients enrolled in the foreign phase II study, the global phase II/III study, and the Japanese long-term study was 12, 12, and 14 years, respectively, and the median age of onset was 25, 29, and 33 years, respectively. This suggests that many patients notice hair loss or thinning hair in their 20s to 40s, and some do as early as in their teens. Considering that hair loss is irreversible and progresses with age, a relatively broad range of age groups would be treated with dutasteride.

While men aged <20 years (excluding children) have not been included in the past clinical studies in patients with androgenetic alopecia, a post-marketing clinical study conducted in South Korea reported experience with the use of dutasteride in 23 subjects aged 18 and 19 years. From the perspective of physical growth, testis maturation and androgen levels as well as body height and other morphological dimensions in male adolescents aged approximately 18 years are usually comparable to those in male adults.[21] In the physiological aspect, therefore, the efficacy and safety of dutasteride are unlikely to differ significantly between patients aged ≥18 and <20 years and patients aged ≥20 years.

Based on the above, the applicant considers that male adolescents aged ≥18 and <20 years can be included in the patient population in whom dutasteride is indicated.

PMDA's view:
On the basis of the efficacy of dutasteride demonstrated in the global phase II/III study [see "4.(iii).B.(2) Efficacy"] and the acceptable safety profile of dutasteride [see "4.(iii).B.(3) Safety"], there are no particular problems with defining the target patient population as men with androgenetic alopecia. The initially proposed indication of dutasteride was "hair growth, hair restoration, and prevention of the progression of hair loss in men with androgenetic alopecia." However, the indication should be changed to "androgenetic alopecia in men" because (1) the global phase II/III study did not evaluate the ability of dutasteride to prevent hair loss, (2) increases in hair count were observed during treatment with dutasteride, and (3) dutasteride is an ethical drug that must be prescribed by a physician for patients with a clinical diagnosis of androgenetic alopecia. A final decision will be made taking account of comments raised at the Expert Discussion. The package insert should include a precautionary statement that the efficacy and safety of dutasteride in the treatment of types of alopecia other than androgenetic alopecia in men have not been established.

For the purpose of efficacy assessment, the global phase II/III study enrolled only patients with androgenetic alopecia classified as types III vertex, IV, and V according to the Norwood-Hamilton scale. However, there is not much need to limit the use of dutasteride to patients with androgenetic alopecia of types III vertex, IV, and V, because (1) the Norwood-Hamilton classification is based only on the appearance of patients; (2) the pharmacological action of dutasteride is also expected in patients with androgenetic alopecia classified as types other than types III vertex, IV, and V; and (3) the safety profile

[21] *JCE&M*. 1974;39:664-672.

is unlikely to differ among patients with androgenetic alopecia classified into different Norwood-Hamilton types. However, as proposed by the applicant, information on the Norwood-Hamilton classification employed in the efficacy endpoint of the global phase II/III study should be provided in the package insert.

Since dutasteride is an inhibitor of the enzyme that converts testosterone into DHT, a decision on whether dutasteride is indicated for the use in adolescent patients aged <20 years (i.e., excluding children) should be made after assessment of the risks and benefits of the therapy in the younger patient population. Currently, the overseas data are not sufficient and the safety and efficacy of dutasteride have been confirmed only in male patients aged ≥20 years in the global phase II/III study and the long-term study. In light of these facts, the package insert should include a precautionary statement that the efficacy and safety of dutasteride in adolescent patients aged <20 years have not been established.

PMDA will make a final decision on the indication of dutasteride and the appropriate patient population, taking account of comments raised at the Expert Discussion.

4.(iii).B.(6) Dosage and administration

The applicant explained the rationale for the doses of dutasteride in the global phase II/III study and the proposed dosage and administration. Details are presented in the following sections.

4.(iii).B.(6).1) Rationale for the selection of dutasteride 0.02 mg, 0.1 mg, and 0.5 mg once daily as dose levels in the global phase II/III study

When the clinical development of dutasteride for the indication of androgenetic alopecia in men was initiated in Japan, the dosing regimen for the global phase II/III study were selected based on the results of the foreign phase II study.

The primary endpoint of the foreign phase II study conducted in male patients with androgenetic alopecia was the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Weeks 12, 24, and 36." As shown in Table 7, hair count increased at Weeks 12 and 24 in a dose-dependent manner. The safety profile was similar among the dutasteride groups.

Based on these results, three dose levels of dutasteride (0.5 mg, 0.1 mg, and 0.02 mg) were selected for the global phase II/III study. The 0.5 mg dose is approved for the treatment of prostatic hyperplasia in Japan and for the treatment of androgenetic alopecia in men in South Korea; the 0.1 mg dose was predicted to have efficacy comparable to that of finasteride 1 mg; and the 0.02 mg dose was expected to demonstrate a certain level of low-dose efficacy.

4.(iii).B.(6).2) Rationale for the dosage and administration proposed based on the results of the global phase II/III study

The primary endpoint of the global phase II/III study was the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24." As shown in Table 10, the superiority of dutasteride 0.1 and 0.5 mg over placebo and the non-inferiority of dutasteride 0.1 and 0.5 mg to finasteride 1 mg were demonstrated in the study. The safety profile of dutasteride in the clinical studies conducted in male patients with androgenetic alopecia suggested no trend toward a dose-dependent increase in the incidence of adverse events [see "4.(iii).B.(3) Safety"]. However, a dose-dependent reduction in the prostate volume was seen in patients with prostatic hyperplasia receiving dutasteride at doses ranging from 0.05 to 0.5 mg. Androgenetic alopecia is a type of hair loss with no other abnormal physical findings and does not necessarily require pharmacotherapy. On the basis of the above findings and discussions, the recommended dose of 0.1 mg is appropriate, as this dose level is considered to be the minimum effective dose. Meanwhile, assessment of therapeutic response in male patients with androgenetic alopecia is largely affected by individual patients' satisfaction; therefore, the use of the 0.5 mg dose in patients who desire a higher therapeutic goal can be decided based on the physician's overall assessment of the risks and benefits.

PMDA asked the applicant to explain the criteria for determining whether dutasteride treatment is continued, because there is a possibility that dutasteride treatment is continued in a patient, at the physician's discretion, if the patient wishes to receive treatment for a prolonged period.

The applicant's response:

In the global phase II/III study, serum DHT levels were reduced in the dutasteride 0.1 and 0.5 mg groups at Week 12 and remained at the reduced levels at Week 24 (Table 6). Examination of the changes from baseline in hair count, hair width, and terminal hair count revealed some improvements as early as at Week 12 and further improvements at Week 24. The panel photographic assessment revealed an improvement in appearance at Week 24. Based on these results, generally, a treatment period of approximately 6 months is necessary to assess the therapeutic response.

Assessment of therapeutic response in male patients with androgenetic alopecia is largely affected by individual patients' satisfaction. Patients will hope to continue treatment if there are no safety concerns that require treatment discontinuation and patient satisfaction with hair growth is high. To prevent the unnecessary prolonged use of dutasteride, physicians are required to assess therapeutic response and safety as well as patient satisfaction with hair growth through regular examinations and interviews, thereby making a comprehensive decision on the need for continued treatment.

PMDA's view:

The dose levels of dutasteride (0.02 mg, 0.1 mg, and 0.5 mg) selected for the global phase II/III study are acceptable. The study demonstrated the superiority of dutasteride 0.1 and 0.5 mg over placebo and

the non-inferiority of dutasteride 0.1 and 0.5 mg to finasteride 1 mg. In the global phase II/III study, the change in hair count was greater in the dutasteride 0.5 mg group than in the dutasteride 0.1 mg group. Safety results showed no clinically significant differences between the dutasteride 0.1 and 0.5 mg groups. In the clinical studies conducted in male patients with androgenetic alopecia, there was no trend toward a dose-dependent increase in the incidence of adverse events or adverse drug reactions [see "4.(iii).B.(3) Safety"]. However, dutasteride (for the proposed additional indication) is a lifestyle drug and arogenetic alopecia is a condition that does not necessarily require pharmacotherapy. Although the clinical significance of reduced prostate volume is not clear, unnecessary exposure to dutasteride is not desirable. Therefore, the recommended dose of dutasteride should be 0.1 mg for the treatment of patients with androgenetic alopecia, and if a patient desires, the dose may be increased to 0.5 mg, based on the physician's assessment of the risks and benefits. Nevertheless, as the unnecessary prolonged use of dutasteride is not desirable, physicians should assess therapeutic response on a regular basis to determine the need for continued treatment.

PMDA will make a final decision on the dosage and administration of dutasteride, taking account of comments raised at the Expert Discussion.

4.(iii).B.(7) Co-administration of dutasteride with conventional medications

Dutasteride is expected to be co-administered with therapeutic drugs recommended by the guidelines for the management of androgenetic alopecia. PMDA asked the applicant to explain the drugs possibly co-administered with dutasteride and the efficacy and safety of dutasteride in combination with these drugs.

The applicant's response:

Among the drugs recommended by the guidelines for the management of androgenetic alopecia, finasteride is unlikely to be prescribed concomitantly with dutasteride, because both drugs are 5 α-reductase inhibitors. Further, the safety information of Avolve Capsules 0.5 mg from Japan and overseas indicate no notable trend in the incidence of adverse drug reactions attributable to co-administration with finasteride, nor does it include any fatal adverse drug reactions reported. Topical preparations intended for the treatment of androgenetic alopecia (e.g., minoxidil and carpronium chloride hydrate) are expected to be co-administered with dutasteride, but the use of the topical preparations recommended by the guidelines for the management of androgenetic alopecia was prohibited in the global phase II/III study and the long-term study. Therefore, there is no data on the safety and efficacy of dutasteride in combination with these topical preparations.

PMDA accepted the applicant's explanation about the co-administration of dutasteride with finasteride. Information on co-administration of dutasteride with the topical preparations recommended by the guidelines for the management of androgenetic alopecia, as well as information on the impact of co-administration with these conventional medications on the safety and efficacy of dutasteride, should be

continuously collected via post-marketing surveillance etc., for the following reasons: (1) minoxidil was detected in the blood from patients with premature alopecia receiving minoxidil for prolonged periods,[22] and (2) the percutaneous absorption of carpronium chloride hydrate was determined in healthy adults treated with a single application of the topical drug.[23]

4.(iii).B.(8) Post-marketing investigations

4.(iii).B.(8).1) Post-marketing surveillance

The applicant plans to conduct a use-results survey. The proposed plan is summarized in Table 22.

Table 22. Outline of use-results survey (draft)

Objective	**To investigate the safety and efficacy of dutasteride in male patients with androgenetic alopecia in routine clinical practice**
Survey method	**Central registration system**
Population	**Male patients with androgenetic alopecia**
Planned sample size	**4000 patients (planned number of patients for registration)**
Survey period	**2 years and 9 months (registration period, 1 year and 6 months)**
Observation period	**1 year**
Main survey items	• **Patient characteristics (sex [male], age, reasons for use, Norwood-Hamilton classification, complications, etc.)** • **Status of administration of dutasteride (daily dose, frequency per day, treatment duration, reason for treatment discontinuation, reason for the change of dose or regimen)** • **Status of administration of concomitant drugs (co-administration or monotherapy, name of drug, purpose of co-administration)** • **Efficacy (comprehensive assessment of hair count, hair width, hair loss count, and change in Norwood-Hamilton classification)** • **Adverse events (onset date, serious or non-serious, outcome, causal relationship to dutasteride, measures taken for dutasteride, etc.)** • **Key survey items: sexual dysfunctions including persistent sexual dysfunctions (change of libido, erectile dysfunction, and ejaculation disorder)**

PMDA considers that the post-marketing surveillance should be performed focusing especially on the following issues. PMDA will make a final decision on the details of the post-marketing surveillance plan, taking account of comments raised at the Expert Discussion.

- Long-term safety and efficacy
- Incidence of adverse events related to sexual function
- Safety and efficacy of dutasteride in combination with other medications for androgenetic alopecia

4.(iii).B.(8).2) Proper use

The applicant's explanation:

In light of the facts that androgenetic alopecia is a type of hair loss with no other abnormal physical findings and that dutasteride (for the proposed additional indication) is a lifestyle drug, the applicant recognized the need to ensure that physicians inform patients of the risks associated with the use of dutasteride, prior to the start of treatment. Therefore, the applicant plans to develop patient education

[22] Review Report for RiUP 5 and RiUP X5 (August 7, 2008, in Japanese only)

[23] Interview Form for Furozin solution 5%, 7th edition (September 2012, in Japanese only)

materials regarding the risk of the adverse events related to sexual function and breast disorders with an aim to promote the proper use of dutasteride.

PMDA considers that the following issues should be taken into consideration when patient education materials are developed:

- In addition to providing information on the risk of adverse events related to sexual function, the applicant should ensure that patients is advised to consult healthcare professionals if they notice any abnormality.
- Dutasteride is not indicated for types of alopecia other than androgenetic alopecia in men
- Women should be advised to avoid exposure to dutasteride that has a high potential to cause teratogenicity in male fetuses exposed to the drug. The teratogenic risk is associated with the mechanism of action by which dutasteride inhibits the production of DHT involved in the development of the fetal male genitalia (see "Review Report of Avolve Capsules 0.5 mg," dated April 13, 2009 [in Japanese only]).

PMDA will make a final decision on the above measures to promote the proper use of dutasteride, taking account of comments raised at the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspections are currently underway, and the results and PMDA's conclusion will be presented in Review Report (2).

2. PMDA's conclusion concerning the results of GCP on-site inspection

The inspection is currently underway, and the results and PMDA's conclusion will be presented in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of dutasteride in the treatment of androgenetic alopecia in men has been demonstrated and its safety is acceptable in view of its observed benefits. The efficacy and safety of dutasteride, and the proposed indications, dosage and administration, and post-marketing investigation plan require further discussion.

This application may be approved if dutasteride is not considered to have any particular problems based on comments raised at the Expert Discussion.

Review Report (2)

August 12, 2015

I. Product Submitted for Registration

[Brand name]	Zagallo Capsules 0.1 mg
	Zagallo Capsules 0.5 mg
[Non-proprietary name]	Dutasteride
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	November 25, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

PMDA's view:

The primary endpoint of the global phase II/III study was the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex at Week 24" (Table 10). Dutasteride 0.1 and 0.5 mg groups showed a statistically significant increase in hair count as compared with the placebo group. The study also demonstrated the non-inferiority of dutasteride 0.1 and 0.5 mg to finasteride 1 mg. Besides hair count, the global phase II/III study assessed hair width, terminal hair count, panel photographic assessment, and patient satisfaction with hair growth as the secondary endpoints. As in the case of the primary endpoint, all the secondary endpoints showed a trend toward a greater improvement in the dutasteride 0.1 and 0.5 mg groups as compared with the placebo group. The above findings suggest the efficacy of dutasteride in men with androgenetic alopecia.

Between Japan and other countries participating in the global phase II/III study, there are no significant differences in extrinsic factors including treatment environments or intrinsic factors including the primary pathogenic mechanism of androgenetic alopecia. Additionally, there are no obvious ethnic differences in serum concentrations of dutasteride or dihydrotestosterone (DHT). Therefore, there were no particular concerns about the participation of Japanese subjects in the study. An analysis was performed to assess the treatment differences between the dutasteride groups and the placebo group or the finasteride 1 mg group in the global phase II/III study (Tables 10 and 11). The results showed no clinically significant differences in the efficacy of dutasteride relative to placebo or finasteride 1 mg between the overall study population and the Japanese subgroup. Therefore, PMDA concluded that the

results of the overall study population were consistent with that of the Japanese subgroup, and that the efficacy of dutasteride in the Japanese population may be discussed based on the data from the global phase II/III study.

The long-term efficacy of dutasteride was assessed by the "change from baseline in hair count within a 2.54-cm diameter circle at the vertex" as an outcome measure in the long-term study, and the results revealed a trend toward a decrease in hair count at Week 52 as compared with Week 26. The applicant should continuously collect information via post-marketing surveillance, so as to investigate whether the prolonged use of dutasteride reduce its efficacy.

The above conclusion by PMDA was supported by the expert advisors.

(2) Safety

PMDA's view:

In the global phase II/III study, no clinically relevant adverse events or trends in the incidence of adverse events were noted in the dutasteride group as compared with the placebo or finasteride 1 mg group. Further, no clinically significant differences in the pattern or incidence of adverse events were found between the overall study population and the Japanese subgroup (Tables 12 and 13). In the long-term study, there was no trend toward an increased incidence of adverse events in patients treated with dutasteride for prolonged periods.

Based on the above, the safety of dutasteride in men with androgenetic alopecia is acceptable. However, information on adverse events related to sexual function in Japanese male patients with androgenetic alopecia should continue to be collected via post-marketing surveillance etc., on the grounds that: (1) adverse events related to sexual function such as erectile dysfunction and libido decreased are known as relatively common adverse reactions to dutasteride and were reported in the global phase II/III study; (2) male patients with androgenetic alopecia is younger than those with prostatic hyperplasia, and therefore the risk of decreased male fertility is considered more relevant for the former patient population; and (3) at present, there is only limited information on the long-term safety of dutasteride in Japanese male patients with androgenetic alopecia. Moreover, physicians should fully inform patients of the risk of adverse events related to sexual function and breast disorders through patient education materials, for the following reasons: (i) dutasteride inhibits metabolism of testosterone to DHT, thereby altering the androgen to estrogen ratio in patients, and this may result in the risk of breast disorders including gynaecomastia; and (ii) dutasteride (for the proposed additional indication) is a lifestyle drug and androgenetic alopecia is a condition that does not necessarily require pharmacotherapy.

The above conclusion by PMDA was supported by the expert advisors.

(3) Indications

PMDA's view:

The global phase II/III study did not evaluate the ability of dutasteride to prevent hair loss but demonstrated an increase in in hair count in subjects on treatment with the drug. Dutasteride is an ethical drug that must be prescribed by physicians for patients with a clinical diagnosis of androgenetic alopecia. On the basis of these facts and the results of the efficacy and safety evaluation, the indication should be "androgenetic alopecia in men." In addition, the package insert should include a precautionary statement that the efficacy and safety of dutasteride in the treatment of types of alopecia other than androgenetic alopecia in men have not been established.

The global phase II/III study enrolled only patients with androgenetic alopecia classified as types III vertex, IV, and V according to the Norwood-Hamilton scale for the purpose of efficacy assessment. However, there is not much need to limit the use of dutasteride to patients with androgenetic alopecia of types III vertex, IV, and V, because (1) the Norwood-Hamilton classification is based only on the appearance of patients; (2) the pharmacological action of dutasteride is also expected in patients with androgenetic alopecia classified as types other than types III vertex, IV, and V; and (3) the safety profile is unlikely to differ among patients with androgenetic alopecia classified into different Norwood-Hamilton types. However, information on the Norwood-Hamilton classification employed in the efficacy endpoint of the global phase II/III study should be provided in the package insert.

Since dutasteride is an inhibitor of the enzyme that converts testosterone into DHT, its use in adolescent patients aged <20 years (i.e., excluding children) should be decided at the physician's discretion after assessment of the risks and benefits of the therapy. Currently, the overseas data is not sufficient and the safety and efficacy of dutasteride have been confirmed only in male patients aged ≥20 years in the global phase II/III study and the long-term study. In light of these facts, the package insert should include a precautionary statement that the efficacy and safety of dutasteride in adolescent patients aged <20 years have not been established.

The above conclusion by PMDA was supported by the expert advisors. Consequently, PMDA instructed the applicant to modify the wording in the "Indication" and the "Precautions for Indication" sections as shown below. The applicant's adequate response was accepted by PMDA.

[Indication]

Androgenetic alopecia in men

[Precautions for indication]

- Dutasteride is indicated only for androgenetic alopecia in men, and not indicated for other types of alopecia.
- The efficacy and safety of dutasteride in adolescent patients aged <20 years have not been established.

(4) Dosage and administration

PMDA's view:

The applicant selected 3 dose levels of dutasteride (0.02 mg, 0.1 mg, and 0.5 mg) for the global phase II/III study, based on the results of the foreign phase II study. The dose levels selected for the study are reasonable. The global phase II/III study demonstrated the superiority of dutasteride 0.1 and 0.5 mg over placebo and the inferiority of dutasteride 0.1 and 0.5 mg to finasteride 1 mg. Also, the change in hair count was greater in the dutasteride 0.5 mg group than in the dutasteride 0.1 mg group. Safety results showed no clinically significant differences between the dutasteride 0.1 and 0.5 mg groups. The clinical studies in male patients with androgenetic alopecia reported no trend toward a dose-dependent increase in the incidence of adverse events or adverse drug reactions. However, dutasteride (for the proposed additional indication) is a lifestyle drug and androgenetic alopecia is a condition that does not necessarily require pharmacotherapy. Unnecessary exposure to dutasteride is not desirable. Therefore, the recommended dose of dutasteride should be 0.1 mg for the treatment of patients with androgenetic alopecia, and if a patient desires, the dose may be increased to 0.5 mg, based on the physician's assessment of the risks and benefits. Nevertheless, as the unnecessary prolonged use of dutasteride is not desirable, physicians should assess therapeutic response on a regular basis in order to determine the need for continued treatment.

The above conclusion by PMDA was supported by the expert advisors. Consequently, PMDA instructed the applicant to modify the wording in the "Dosage and administration" and "Precautions for dosage and administration" sections as shown below. The applicant's adequate response was accepted by PMDA.

[Dosage and administration]

The usual dosage for adult men is 0.1 mg of dutasteride administered orally once daily. The dose may be increased to 0.5 mg orally once daily, as necessary.

[Precautions for dosage and administration]

- The capsules should not be chewed or opened because the capsule contents may induce oropharyngeal irritation.
- Although clinical improvement may be observed in some men after 12 weeks of treatment, a treatment period of 6 months is usually necessary to assess whether a therapeutic response has been achieved.
- Dutasteride should be discontinued if no improvement is seen after ≥6 months of treatment. If dutasteride treatment is continued for ≥6 months, patients should be regularly checked for efficacy and assessed for the need for continued treatment.

(5) Risk management plan (draft)

1) Post-marketing surveillance

PMDA considers that the draft use-results survey plan proposed by the applicant should especially focus on the following items:

- Long-term safety and efficacy
- Incidence of adverse events related to sexual function and breast disorders
- Safety and efficacy of dutasteride in combination with other medications for androgenetic alopecia

The above conclusion by PMDA was supported by the expert advisors.

2) Proper use

In light of the facts that androgenetic alopecia is a type of hair loss with no other abnormal physical findings and that dutasteride (for the proposed additional indication) is a lifestyle drug, the applicant has recognized the need to ensure that physicians inform patients of the risks associated with the use of dutasteride, prior to the start of treatment. Therefore, the applicant plans to develop patient education materials regarding the risk of adverse events related to sexual function and breast disorders with an aim to promote the proper use of dutasteride.

PMDA considers that the following issues should be taken into consideration when patient education materials are developed:

- In addition to providing information on the risk of adverse events related to sexual function, the applicant should ensure that patients are advised to consult healthcare professionals if they notice any abnormality.
- Dutasteride is not indicated for types of alopecia other than androgenetic alopecia in men.
- Women should be advised to avoid exposure to dutasteride that has a potential to cause teratogenicity in male fetuses exposed to the drug. The teratogenic risk is associated with the mechanism of action by which dutasteride inhibits the production of DHT involved in the development of the fetal male genitalia (see "Review Report of Avolve Capsules 0.5 mg," dated April 13, 2009 [in Japanese only]).

The above conclusion by PMDA was supported by the expert advisors with the following comments:

- "Breast disorders" should be included in the list of possible adverse reactions to dutasteride in order to ensure that this information is communicated to patients.
- Patients should be thoroughly instructed to follow the physician's advice as to continuation of treatment and not to make a decision on their own.

PMDA advised the applicant to develop patient education materials considering the above points. The applicant responded that it would duly follow the advice. PMDA accepted the applicant's response.

PMDA asked the applicant to draft a risk management plan based on the above discussion. The applicant submitted the safety and efficacy specifications in the risk management plan (Table 23), the draft summary of additional pharmacovigilance activities and risk minimization activities (Table 24), and the draft outline of the use-results survey (Table 25). PMDA accepted the proposed RMP.

Table 23. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
• Sexual dysfunctions including persistent sexual dysfunctions (change of libido, impotence, and ejaculation disorder) • Tenderness and enlargement of breast	• Depressed mood • Breast cancer male • Prostate cancer • Teratogenicity (impaired development of male external genitalia) • Decreased male fertility due to influence on sperm/semen characteristics	• None
Efficacy specification		
• Efficacy in men with androgenetic alopecia in routine clinical practice		

Table 24. Summary of additional pharmacovigilance activities and risk minimization activities included in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey	• Dissemination of information obtained through early post-marketing phase vigilance • Production and distribution of patient education materials

Table 25. Outline of use-results survey (draft)

Objective	To investigate the safety and efficacy of dutasteride in male patients with androgenetic alopecia in routine clinical practice
Survey method	Central registration system
Population	Male patients with androgenetic alopecia
Planned sample size	4000 patients (planned number of patients for registration)
Survey period	2 years and 9 months (registration period, 1 year and 6 months)
Observation period	1 year
Main survey items	• Patient characteristics (sex [male], age, reasons for use, Norwood-Hamilton type, complications, etc.) • Status of administration of dutasteride (daily dose, frequency per day, treatment duration, reason for treatment discontinuation, reason for the change of dose or regimen) • Status of administration of concomitant drugs (co-administration or monotherapy, name of drug, purpose of co-administration) • Efficacy (comprehensive assessment of hair count, hair width, hair loss count, and change in Norwood-Hamilton classification) • Adverse events (onset date, serious or non-serious, outcome, causal relationship to dutasteride, measures taken for dutasteride, etc.) • Key survey items: sexual dysfunctions including persistent sexual dysfunctions (change of libido, erectile dysfunction, and ejaculation disorder)

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection[24] and data integrity assessment were conducted for the data submitted in the new drug application, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that no problem was identified that may preclude the conduct of regulatory review based on the submitted application documents.

2. PMDA's conclusion concerning the results of on-site GCP inspection

On-site GCP inspection was conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application (5.3.5.1, Study ARI114263; 5.3.5.2, Study ARI114264). PMDA concluded that no problem was identified that may preclude the conduct of regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that dutasteride may be approved with the following conditions after the indication and dosage and administration are modified as shown below. The application for a new indication and new dosage form has been filed to expand the indication of dutasteride so as to include androgenetic alopecia, which represents a different therapeutic area from the approved one. Therefore, the re-examination period should be 4 years. The drug product is classified as a powerful drug, and not classified as a biological product or a specified biological product.

[Indication]	Androgenetic alopecia in men
[Dosage and administration]	The usual dosage for adult men is 0.1 mg of dutasteride administered orally once daily. The dose may be increased to 0.5 mg orally once daily, as necessary.
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.

[24] A physician listed in the FDA Debarment List was involved in Study ARIA2004 as an investigator. PMDA checked the process in which the physician and other investigators were chosen, and confirmed that the study data were reanalyzed after the exclusion of the data from the subjects handled by the physician, and that this was not the case for other studies submitted in the present application.