Report on the Deliberation Results

November 6, 2020
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Forxiga 5 mg Tablets
	Forxiga 10 mg Tablets
Non-proprietary Name	Dapagliflozin Propylene Glycolate Hydrate (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	January 16, 2020

Results of Deliberation

In its meeting held on October 29, 2020, the First Committee on New Drugs concluded that the partial change application for 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.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

October 12, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Forxiga 5 mg Tablets Forxiga 10 mg Tablets
Non-proprietary Name	Dapagliflozin Propylene Glycolate Hydrate
Applicant	AstraZeneca K.K.
Date of Application	January 16, 2020
Dosage Form/Strength	Each tablet contains Dapagliflozin Propylene Glycolate Hydrate equivalent to 5 or 10 mg of dapagliflozin.
Application Classification	Prescription drug, (4) Drug with a new indication and (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of chronic heart failure, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. However, safety issues requiring further evaluation include the incidences of volume depletion, effects associated with increased ketone levels and ketoacidosis, hypoglycaemia, and renal disorders.

Indications

Type 2 diabetes mellitus
Type 1 diabetes mellitus
Chronic heart failure
(limited to patients who are receiving standard of care for chronic heart failure)

(Underline denotes additions.)

Dosage and Administration

Type 2 diabetes mellitus

The usual adult dosage is 5 mg of dapagliflozin administered orally once daily. The dose may be increased to 10 mg once daily for the patient with an inadequate response to the 5 mg dose if the patient is followed up carefully.

Type 1 diabetes mellitus

The usual adult dosage is 5 mg of dapagliflozin administered orally once daily, in combination with an insulin formulation. The dose may be increased to 10 mg once daily for the patient with an inadequate response to the 5 mg dose if the patient is followed up carefully.

Chronic heart failure

The usual adult dosage is 10 mg of dapagliflozin administered orally once daily.

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

August 21, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Forxiga 5 mg Tablets Forxiga 10 mg Tablets
Non-proprietary Name	Dapagliflozin Propylene Glycolate Hydrate
Applicant	AstraZeneca K.K.
Date of Application	January 16, 2020
Dosage Form/Strength	Each tablet contains Dapagliflozin Propylene Glycolate Hydrate equivalent to 5 or 10 mg of dapagliflozin.

Proposed Indications

Type 2 diabetes mellitus

Type 1 diabetes mellitus

Chronic heart failure

(Underline denotes additions.)

Proposed Dosage and Administration

Type 2 diabetes mellitus

The usual adult dosage is 5 mg of dapagliflozin administered orally once daily. The dose may be increased to 10 mg once daily for the patient with an inadequate response to the 5 mg dose if the patient is followed up carefully.

Type 1 diabetes mellitus

The usual adult dosage is 5 mg of dapagliflozin administered orally once daily, in combination with an insulin formulation. The dose may be increased to 10 mg once daily for the patient with an inadequate response to the 5 mg dose if the patient is followed up carefully.

Chronic heart failure

The usual adult dosage is 10 mg of dapagliflozin administered orally once daily.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Dapagliflozin Propylene Glycolate Hydrate (hereinafter referred to as "dapagliflozin") is a sodium-glucose co-transporter 2 (SGLT2) inhibitor discovered by Bristol-Myers Squibb in the United State (US). Inhibition of SGLT2 by dapagliflozin reduces the reabsorption of glucose in the proximal renal tubule, thereby increasing the urinary excretion of glucose, resulting in lowered blood glucose levels. In Japan, dapagliflozin was approved for the treatment of "type 2 diabetes mellitus" in March 2014, and for the treatment of "type 1 diabetes mellitus" in March 2019.

SGLT2 inhibitors have been shown to reduce the event rates of cardiovascular outcomes in clinical studies in patients with type 2 diabetes mellitus who are at high risk for cardiovascular events (*N Engl J Med.* 2015;373:2117-28, *N Engl J Med.* 2017;377:644-57, and *N Engl J Med.* 2019;380:347-57). Another study has demonstrated that SGLT2 inhibitors may offer cardioprotective benefits for patients with type 2 diabetes mellitus. The mechanism of the cardioprotective benefits appears to be associated with hemodynamic effects resulting from the regulation of fluid volume by SGLT2 inhibition, independent of the hypoglycemic action of these inhibitors (*Diabetologia.* 2018;61:2108-17).

Outside of Japan, dapagliflozin has been approved since 2012 for the treatment of type 2 diabetes mellitus in ≥100 countries/regions including the US and EU, and for the treatment of type 1 diabetes mellitus in ≥30 countries/regions including the EU. For the treatment of chronic heart failure, marketing applications were filed in November 2019 in both the US and EU. Dapagliflozin was approved for the new indication in the US in May 2020, while the application in the EU is still under review as of August 2020.

Based on the results from a global phase III study in patients with heart failure with reduced ejection function (HFrEF) serving as a pivotal study, the applicant has filed a partial change application for dapagliflozin in Japan, to add a new indication and a new dosage for the treatment of chronic heart failure.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for a new indication and a new dosage, no additional data on quality have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Studies in diabetic animal models (CTD 4.2.1.1.1 to 4.2.1.1.2)

Dapagliflozin was administered in drinking water to male 10-week-old ob/ob$^{-/-}$ mice (18 per group) at a dose of 1.5 or 4.0 mg/kg/day for 10 weeks. Animals in the control group received the vehicle (drinking water). Blood sampling, echocardiography, etc. were performed at Weeks 5 and 10. Dose-dependent increases in coronary flow velocity reserve[1)] (CFVR), a measure of microvascular function, were shown in the dapagliflozin groups at Weeks 5 and 10, with a significantly higher value in the dapagliflozin 4.0 mg/kg/day

1) The ratio of the average coronary flow velocity during maximal hyperemia to the average coronary flow velocity at baseline (before maximal hyperemia)

group than in the control group. In addition, left ventricle fractional area change (FAC),[2)] a measure of left ventricle contractile function, was significantly higher in both the dapagliflozin 1.5 and 4.0 mg/kg/day groups than in the control group at Week 10.

Dapagliflozin was administered in a standard diet to male 8-week-old BTBR ob/ob$^{-/-}$ mice (8 per group) or male 8-week-old wild-type C57BL/6J mice (8 per group) at a dose of 1.0 mg/kg/day for 8 weeks. Animals in the control groups received the vehicle (the standard diet). Blood sampling, echocardiography, etc. were performed. In addition, myocardial tissues were harvested at Week 8. The mRNA levels of mouse genes associated with the NLRP3 inflammasome were assessed by RT-PCR, myocardial fibrosis by Masson's trichrome staining, and cell apoptosis by TUNEL staining. An assessment of left ventricular structure and contractile function showed that left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), interventricular septum thickness at end-systole (IVSs), and interventricular septum thickness at end-diastole (IVSd) were significantly higher in the ob/ob$^{-/-}$ control group than in the wild-type control group, and significantly lower in the ob/ob$^{-/-}$ dapagliflozin group than in the ob/ob$^{-/-}$ control group. Fractional shortening (FS) and left ventricular ejection fraction (LVEF) were significantly lower in the ob/ob$^{-/-}$ control group than in the wild-type control group, and significantly higher in the ob/ob$^{-/-}$ dapagliflozin group than in the ob/ob$^{-/-}$ control group. An assessment of myocardial fibrosis showed that the mRNA levels of collagen-I and collagen-II, and the degree of fibrosis detected by tissue staining were significantly higher in the ob/ob$^{-/-}$ control group than in the wild-type control group, and significantly lower in the ob/ob$^{-/-}$ dapagliflozin group than in the ob/ob$^{-/-}$ control group. The percentage of apoptotic myocytes detected by tissue staining was significantly higher in the ob/ob$^{-/-}$ control group than in the wild-type control group, and significantly lower in the ob/ob$^{-/-}$ dapagliflozin group than in the ob/ob$^{-/-}$ control group. An assessment of the expression of genes associated with the NLRP3 inflammasome indicated that the mRNA levels for ASC, NALP3, IL-1β, IL-6, and caspase I were significantly higher in the ob/ob$^{-/-}$ control group than in the wild-type control group, and significantly lower in the ob/ob$^{-/-}$ dapagliflozin group than in the ob/ob$^{-/-}$ control group.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action and pharmacology of dapagliflozin in the treatment of heart failure

PMDA asked the applicant to explain the mechanism of action by which dapagliflozin contributes to the treatment of heart failure, and to explain whether dapagliflozin can be expected to be effective in the treatment of heart failure regardless of the presence of concurrent diabetes, and independently of its blood glucose-lowering effect.

The applicant's explanation:

In the non-clinical pharmacology studies in diabetic animal models, dapagliflozin lowered blood glucose levels and inhibited the progression of structural damage and contractile dysfunction in the cardiac ventricles. Results suggested that dapagliflozin could suppress ventricular remodeling by reducing myocardial fibrosis

2) The percent change in left ventricular cross-sectional area between diastole and systole

and apoptosis in the left ventricle, and that these effects of dapagliflozin may be associated with the attenuation of NLRP3 inflammasome activation. Although the pharmacology of dapagliflozin has not been investigated in non-diabetic heart failure animal models, a publication reported a study in which high-fat diet-induced obese, insulin-resistant rats received by gavage dapagliflozin (1 mg/kg/day) for 28 days and then underwent cardiac ischemia induced by left anterior descending (LAD) coronary artery ligation, followed by reperfusion; and the results showed a reduction in infarct size and the attenuation of cardiac dysfunction after LAD coronary artery ligation and reperfusion (*J endocrinol.* 2018;236:69-84). Furthermore, in a different study using a transverse aortic constriction mouse model in which dapagliflozin (1 mg/kg/day) was administered by gavage for 4 weeks, dapagliflozin reduced hypertension-induced cardiac hypertrophy, inhibited myocardial fibrosis, and improved cardiac systolic function (*Am J Hypertens.* 2019;32:452-9).

The mechanism of the cardioprotective effect of dapagliflozin remains unknown; however, the following actions (a) through (c), which are beyond its blood glucose-lowering effect, may contribute to this cardioprotective effect:

(a) Hemodynamic action through fluid volume control

Heart failure is accompanied by the retention of body fluid in the interstitium, resulting in peripheral edema and pulmonary edema. One of the goals of treatment for heart failure is the attenuation of such congestion. Inhibition of SGLT2 by dapagliflozin reduces the reabsorption of glucose and sodium in the proximal renal tubule, leading to osmotic diuresis and natriuresis, thereby reducing cardiac preload. Dapagliflozin has been shown to increase urinary volume in both diabetic and non-diabetic animal models (*Diabetes.* 2008;57:1723-9, *Am J Physiol Regul Integr Comp Physiol.* 2012;302:R75-83, etc.). In patients with heart failure, the majority of excess blood accumulates in the veins, and relative arterial underfilling due to a decrease in cardiac output may occur. Diuretics, a modality currently used for the treatment of heart failure, reduce not only the interstitial fluid volume but also the arterial circulating volume. In contrast, osmotic diuresis induced by SGLT2 inhibitors accelerates electrolyte-free water excretion, which may lead to a greater clearance of fluid from the interstitial space than from the circulation (*CPT Pharmacometrics Syst Pharmacol.* 2017;6:393-400, *Diabetes Obes Metab.* 2018;20:479-87). In addition, a reduction in plasma volume and a correlated reduction in blood pressure were observed in patients with type 2 diabetes mellitus following the administration of dapagliflozin, suggesting that diuresis induced by dapagliflozin can reduce cardiac afterload, as well (*Diabetes Obes Metab.* 2013;15:853-62). However, the effects of dapagliflozin on indicators for volume depletion have not yet been investigated in non-diabetic patients.

(b) Action on the peripheral vascular system (arterial pressure and vascular endothelial function)

The onset and progression of heart failure are associated with increased peripheral vascular resistance resulting from abnormal vascular endothelial function (*J Am Coll Cardiol.* 2012;16;60:1455-69). Multiple SGLT2 inhibitors have been reported to improve vascular endothelial function and arterial stiffness (*Diabetes Obes Metab.* 2015;17:1180-93, *Circulation.* 2017;136:1167-9). Dapagliflozin treatment has also been shown to result in an increase in flow-mediated dilation, a reduction in pulse wave velocity (*Cardiovasc Diabetol.* 2017;16:138), and an increase in reactive hyperemia index values (*Interm Med.* 2018;57:2147-56) in patients

with type 2 diabetes mellitus. However, the effects of dapagliflozin on vascular endothelial function have not been investigated in non-diabetic patients.

(c) Action on sodium-hydrogen (Na^+/H^+) antiporter 1 or Na^+/H^+ exchanger 1 (NHE-1)

NHE-1 is expressed on the cell membrane in tissues throughout the body, and regulates cellular pH in cardiac myocytes. The excessive activation of NHE-1 is associated with an increase in intracellular pH, which coincidently leads to an increase in intracellular Na^+ concentration. Cellular Na^+ accumulation then results in Ca^{2+} overload via involvement of the Na^+/Ca^{2+} exchanger, thereby inducing cardiomyocyte injury and apoptosis (*Nat Med.* 2004;10:1193-9). Dapagliflozin has been reported to reduce myocyte shortening and the amplitude of the L-type Ca^{2+} current in cardiac myocytes from diabetic and non-diabetic rats at a dose of 1 to 10 μmol/L (*Mol Cell Biochem.* 2015;400:57-68), and intracellular Na^+ concentration and NHE-1 activity were reduced in mouse cardiac myocytes at a dose of 1 μmol/L. Furthermore, SGLT2 inhibitors, including dapagliflozin, display high binding affinity for the extracellular Na^+-binding site of NHE (*Diabetologia.* 2018;61:722-726). In view of these findings, dapagliflozin may reduce NHE-1 activity and improve the viability of cardiac myocytes, thereby inhibiting the hypertrophy and remodeling of the heart, as well as the resultant myocardial fibrosis, all of which contribute to the risk of heart failure. However, all of these findings were obtained from studies in which dapagliflozin was administered to animals at doses producing drug concentrations higher than the steady-state C_{max} (191 ng/mL) achieved by the administration of dapagliflozin to humans once daily at a dose of 10 mg. Whether these actions would also contribute to cardioprotection in humans remains unclear.

As described above, dapagliflozin is assumed to have several mechanisms of action that could serve to improve the clinical conditions of heart failure. Although dapagliflozin may be more beneficial in the treatment of heart failure in diabetic patients, it can be expected to be effective in non-diabetic patients, as well.

PMDA's view:

Although the mechanism of action by which dapagliflozin improves the clinical conditions of heart failure remains unknown, the applicant's explanation has suggested that dapagliflozin may contribute to the improvement of heart failure via mechanisms that are independent of its blood glucose-lowering effect, such as a hemodynamic action through fluid volume control. However, *in vivo* data suggesting the possibility of using dapagliflozin in the treatment of chronic heart failure have only been obtained in diabetic animal models, and no studies with dapagliflozin have been conducted in non-diabetic heart failure animal models. Therefore, the relationship between the efficacy of dapagliflozin in the treatment of heart failure and concurrent diabetes mellitus should be evaluated based on clinical study results [see Section 7.R.4 "Efficacy and safety of dapagliflozin in patients with or without type 2 diabetes mellitus"].

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended for the addition of a new indication and a new dosage, no new data on non-clinical pharmacokinetics have been submitted. The non-clinical pharmacokinetics of dapagliflozin were evaluated during the review of the previous application.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application is intended for the addition of a new indication and a new dosage, and the toxicity of dapagliflozin was evaluated during the review of the previous application. The applicant has submitted the results of a carcinogenicity study as additional toxicological data in support of the present application.

5.1 Carcinogenicity

A 6-month bladder cancer promotion study in rats was conducted to assess the potential effects of dapagliflozin on the incidence and severity of bladder cancer induced by N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN). This study was conducted as a post-approval commitment in agreement with the US Food and Drug Administration (FDA), because the risk of bladder cancer was reported in early clinical studies of dapagliflozin (sourced from the data submitted for the initial application for "Forxiga 5 mg Tablets and Forxiga 10 mg Tablets"). Treatment with BBN resulted in increases in the incidences and severity of urothelial papilloma and hyperplasia, and transitional cell carcinoma. As shown in Table 1, dapagliflozin increased the incidence of urothelial hyperplasia. However, since no effects on the incidence or severity of transitional cell carcinoma were seen in BBN-pretreated animals, the applicant considers that dapagliflozin is neither a promotor nor a progressor of bladder cancer [see Section 5.R.1 "Risk of bladder cancer due to dapagliflozin"].

Table 1. Carcinogenicity study

Test system	Route of administration	Dosing duration	Main lesions	Dose						Tumor-promoting effect	Attached document CTD
				BBN (mg/kg)		100	100	400	400		
				Dapagliflozin (mg/kg)		0[a]	0.5	0[a]	0.5		
				N		50	50	50	50		
Male rats (SD)	Oral	6 weeks of BBN twice weekly, followed by a 2-week washout period, then 26 weeks of dapagliflozin once daily	Hyperplasia and neoplastic lesions							No	4.2.3.4.2.1
			Urothelial papilloma			16	19	42	44		
			Urothelial hyperplasia								
			Slight			30	36	30	31		
			Mild			0	2	19	14		
			Moderate			0	0	1	5		
			Transitional cell carcinoma								
			No invasion			0	0	4	4		
			Slight invasion			0	0	2	2		
			Marked invasion			0	0	1	2		
			Non-neoplastic lesions			None					

a: Aqueous solution of 90% polyethylene glycol 400

5.R Outline of the review conducted by PMDA

Based on the data submitted and the findings described below, PMDA has concluded that the toxicology study produced no findings that would pose concerns about the clinical use of dapagliflozin.

5.R.1 Risk of bladder cancer associated with use of dapagliflozin

The applicant's explanation about the risk of bladder cancer associated with the use of dapagliflozin:

The results of the 6-month bladder cancer promotion study in rats have shown that dapagliflozin is neither a promotor nor a progressor of bladder cancer. In the study, the incidence of urothelial hyperplasia tended to

increase after treatment with dapagliflozin in BBN-pretreated rats. However, urothelial hyperplasia is known to develop in response to urinary tract infection in rodents (*Infect Agents Cancer.* 2012;7:19). The case of urothelial hyperplasia observed in the study is likely to be associated with a response to urinary tract infection resulting from increased urinary glucose concentrations, as in the case of the hyperplasia of transitional epithelium observed in the non-clinical studies submitted for the initial application for dapagliflozin (sourced from the data submitted for the initial application for "Forxiga 5 mg Tablets and Forxiga 10 mg Tablets"). Although the development of bladder cancer was reported in the early clinical studies of dapagliflozin, the incidence of bladder cancer was lower in the dapagliflozin group than in the placebo group in a large-scale clinical study that evaluated the effects of dapagliflozin on cardiovascular events (the DECLARE-TIMI58 study) (*N Engl J Med.* 2019;380:347-57). Further, in view of findings such as data from 2-year carcinogenicity studies in mice and rats showing no development of bladder cancer (sourced from the data submitted for the initial application for "Forxiga 5 mg Tablets and Forxiga 10 mg Tablets"), the risk of bladder cancer associated with the use of dapagliflozin is expected to be low.

PMDA's view:
The results of the non-clinical studies submitted for the initial application for dapagliflozin have demonstrated no risk of bladder cancer associated with the use of dapagliflozin. In addition, in view of the applicant's discussion on the increased incidence of urothelial hyperplasia observed in the 6-month bladder cancer promotion study in rats, the study results submitted for the present application do not affect the conclusion on the risk of bladder cancer made during the review of the initial application for dapagliflozin.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Data on the biopharmaceutic studies and associated analytical methods and clinical pharmacology were evaluated during the review of the previous applications for dapagliflozin. Although the present application is intended for the addition of a new indication and a new dosage, no new clinical data have been submitted.

The bioequivalence of the drug product used in the global phase III study (the DAPA-HF study) versus the drug product marketed in Japan was demonstrated by a dissolution study conducted in accordance with the Guidelines for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms. This result was confirmed during the review of the previous applications.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in the pharmacokinetics of dapagliflozin between Japanese and non-Japanese patients with chronic heart failure

The applicant's explanation about the differences in the pharmacokinetics of dapagliflozin between Japanese and non-Japanese patients with chronic heart failure:

A population pharmacokinetics (PPK) analysis was conducted using plasma dapagliflozin concentration data from clinical studies in patients with HFrEF (the DAPA-HF study), clinical studies in patients with type 2

diabetes mellitus (Studies MB102003, MB102013, D1690C00006, MB102032, and MB102091), and clinical studies in healthy adult volunteers (Study MB102002) (11,571 blood samples from 3192 subjects in total). The final model of the PPK analysis incorporated the estimated glomerular filtration rate (eGFR) and sex as covariates for CL/F, and body weight as a covariate for V2/F.

The median AUC values estimated from the final model in patients with HFrEF receiving repeated oral doses of dapagliflozin 10 mg once daily, were 567 ng·h/mL in Japanese, 534 ng·h/mL in Caucasians, 513 ng·h/mL in Blacks, and 484 ng·h/mL in Asians (other than Japanese), indicating no marked differences among the races. In Studies MB102010 and MB102001 involving healthy adult volunteers, the ratios of C_{max} and AUC in Japanese subjects to those in non-Japanese subjects ranged from 0.871 to 1.209 and from 0.994 to 1.267, respectively. In Studies MB102025 and MB102003 involving patients with type 2 diabetes mellitus, the ratios of dose-adjusted, steady-state C_{max} and AUC in Japanese patients to those in non-Japanese patients ranged from 0.940 to 1.653 and from 0.976 to 1.294, respectively. Thus, no marked differences in the pharmacokinetics of dapagliflozin were observed between Japanese and non-Japanese patients. Furthermore, the median AUC values in patients receiving repeated oral doses of dapagliflozin 10 mg once daily, estimated from the above model did not markedly differ between patients with HFrEF (517 ng·h/mL in patients with concurrent type 2 diabetes mellitus, 539 ng·h/mL in patients without diabetes) and patients with type 2 diabetes mellitus (454 ng·h/mL).

These results have indicated no marked differences in the pharmacokinetics of dapagliflozin between Japanese and non-Japanese patients with chronic heart failure.

PMDA's view:
In view of the data, including the results of comparisons of dapagliflozin exposures in Japanese and non-Japanese subjects, estimated from the PPK model presented above, the applicant's explanation that the pharmacokinetics of dapagliflozin do not markedly differ between Japanese and non-Japanese patients with chronic heart failure is acceptable.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant has submitted efficacy and safety data from the pivotal clinical study presented in Table 2.

Table 2. Summary of the pivotal clinical study evaluating the efficacy and safety of dapagliflozin

Data category	Geographical region	Study identifier	Phase	Study population	Number of randomized patients	Dosage regimen	Primary endpoints
Evaluation data	Global	D1699C00001 (DAPA-HF)	III	Patients with HFrEF	4744	Oral dose of placebo or dapagliflozin 10 mg once daily	Efficacy Safety

7.1 Global phase III study (Study D1699C00001 [the DAPA-HF study], CTD 5.3.5.1-1, February 2017 to July 2019)

A randomized, double-blind, parallel-group study was conducted at 410 sites in multiple countries/regions, including Japan, the US, and the EU, to evaluate the efficacy and safety of dapagliflozin in patients with

HFrEF who were receiving standard of care therapy for heart failure (target sample size, 4500 patients; the number of events required for analysis of the primary composite endpoint [cardiovascular death, hospitalization for heart failure, or urgent heart failure visit (first event)], 844).
Patients received an oral dose of placebo or dapagliflozin 10 mg once daily. Dose reduction (dapagliflozin 5 mg or matching placebo) or drug interruption was allowed in patients experiencing an adverse event suggestive of volume depletion, hypotension, and/or unexpected worsening of kidney function, at the discretion of the investigator. However, in cases where the symptoms stabilized, the study treatment was able to be restarted at the initial dose (dapagliflozin 10 mg). For concomitant medications, all patients were to receive standard of care for heart failure, and were allowed to receive treatments for cardiovascular risk factors and standard of care for diabetes, as needed. However, the concomitant use of other SGLT2 inhibitors was prohibited. In principle, patients had to remain on stable doses of background standard of care for chronic heart failure, except for diuretics. The median duration of exposure (range) to the study drug was 17.6 (0 to 28.3) months in the placebo group and 17.8 (0 to 28.0) months in the dapagliflozin group.

Key inclusion criteria:
Patients aged ≥18 years with a diagnosis of chronic heart failure in the NYHA functional class II to IV. The patient had to have left ventricular ejection fraction (LVEF) ≤40% and N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥600 pg/mL (or ≥400 pg/mL if hospitalized for heart failure within the previous 12 months, or ≥900 pg/mL, irrespective of a history of heart failure hospitalization, if the patient had atrial fibrillation or atrial flutter). In addition, patients had to be on the following therapies at a stable dose for ≥4 weeks before enrollment (unless contraindicated or not tolerated):

(a) an angiotensin-converting-enzyme (ACE) inhibitor, an angiotensin-receptor blocker (ARB), or sacubitril-valsartan sodium hydrate, and
(b) a β-blocker, and
(c) a mineralocorticoid receptor antagonist (MRA) (if considered appropriate by the treating physician).

Patients with type 1 diabetes mellitus, those with symptomatic hypotension or systolic blood pressure <95 mm Hg, and those with an eGFR <30 mL/min/1.73 m^2 were excluded.

Enrolled patients were randomized at a ratio of 1:1 to receive dapagliflozin or placebo; randomization was stratified based on type 2 diabetes mellitus status.[3)] All 4744 randomized patients (2371 in the placebo group and 2373 in the dapagliflozin group, including 179 and 164 Japanese patients, respectively) were included in the full analysis set (FAS) and used for efficacy analyses. Of these 4744 patients, 8 (3 in the placebo group and 5 in the dapagliflozin group, including 0 and 1 Japanese patient, respectively) who did not receive the study drug were excluded from the analysis, and the remaining 4736 (2368 in the placebo group and 2368 in the dapagliflozin group, including 179 and 163 Japanese patients, respectively) were included in the safety analysis set. A total of 516 patients (262 in the placebo group and 254 in the dapagliflozin group, including 23 and 17 Japanese patients, respectively) discontinued the study treatment. The reasons for discontinuation

3) Patients with a diagnosis of type 2 diabetes mellitus as documented in their medical records, or with HbA1c ≥6.5% both at screening and randomization

included the patient's request in 238 patients (123 in the placebo group and 115 in the dapagliflozin group, including 12 and 6 Japanese patients, respectively), adverse events in 221 patients (112 in the placebo group and 109 in the dapagliflozin group, including 8 and 9 Japanese patients, respectively), non-compliance with the protocol in 9 patients (3 in the placebo group and 6 in the dapagliflozin group), consent withdrawal in 9 patients (4 in the placebo group and 5 in the dapagliflozin group, including 2 and 0 Japanese patients, respectively), having met the discontinuation criteria in 2 patients (0 in the placebo group and 2 in the dapagliflozin group), and 'others' in 37 patients (20 in the placebo group and 17 in the dapagliflozin group, including 1 and 2 Japanese patients, respectively).

The primary efficacy endpoint was the time to the first occurrence of any of the following components: cardiovascular death, hospitalization for heart failure, or urgent heart failure visit.[4)] Table 3 shows the results for the primary composite endpoint and its components, as well as the all-cause mortality. The incidence of the primary composite endpoint was significantly lower in the dapagliflozin group than in the placebo group (Cox proportional-hazards model, stratified by type 2 diabetes mellitus status at randomization, with factors for treatment group and history of hospitalization for heart failure; P <0.0001[5)]). The Kaplan-Meier curves for the time to the first occurrence of cardiovascular death, hospitalization for heart failure, or urgent heart failure visit are presented in Figure 1 (the overall population) and Figure 2 (the Japanese subpopulation).

Table 3. Incidences of efficacy events (FAS)

Overall population	Placebo (N = 2371)	Dapagliflozin (N = 2373)	Hazard ratio[a] [95% CI]
Cardiovascular death, hospitalization for heart failure, or urgent heart failure visit (first event)	21.2 (502)	16.3 (386)	0.74 [0.65, 0.85]
Cardiovascular death	11.5 (273)	9.6 (227)	0.82 [0.69, 0.98]
Hospitalization for heart failure (first event)	13.4 (318)	9.7 (231)	0.70 [0.59, 0.83]
Urgent heart failure visit (first event)	1.0 (23)	0.4 (10)	0.43 [0.20, 0.90]
Cardiovascular death or hospitalization for heart failure (first event)	20.9 (495)	16.1 (382)	0.75 [0.65, 0.85]
All-cause mortality	13.9 (329)	11.6 (276)	0.83 [0.71, 0.97]
Japanese subpopulation	**Placebo (N = 179)**	**Dapagliflozin (N = 164)**	**Hazard ratio[a] [95% CI]**
Cardiovascular death, hospitalization for heart failure, or urgent heart failure visit (first event)	21.8 (39)	14.6 (24)	0.63 [0.38, 1.05]
Cardiovascular death	8.4 (15)	7.3 (12)	0.85 [0.40, 1.82]
Hospitalization for heart failure (first event)	16.8 (30)	9.1 (15)	0.52 [0.28, 0.97]
Urgent heart failure visit (first event)	2.2 (4)	0.6 (1)	–
Cardiovascular death or hospitalization for heart failure (first event)	21.8 (39)	14.6 (24)	0.63 [0.38, 1.05]
All-cause mortality	10.6 (19)	7.9 (13)	0.73 [0.36, 1.48]

% (n)
–, not calculated
a: Calculated from a Cox proportional hazards model stratified by type 2 diabetes mellitus status at randomization, with factors for treatment group and history of heart failure hospitalization. Calculation for all-cause mortality used a model in which the history of heart failure hospitalization was removed from the above model.

4) Whether death, hospitalization, or urgent visit for each patient was related to cardiovascular events was adjudicated in a blinded manner by the Clinical Event Adjudication Committee.
5) The final analysis was performed at the 2-sided significance level of 0.04992 to adjust for an interim analysis.

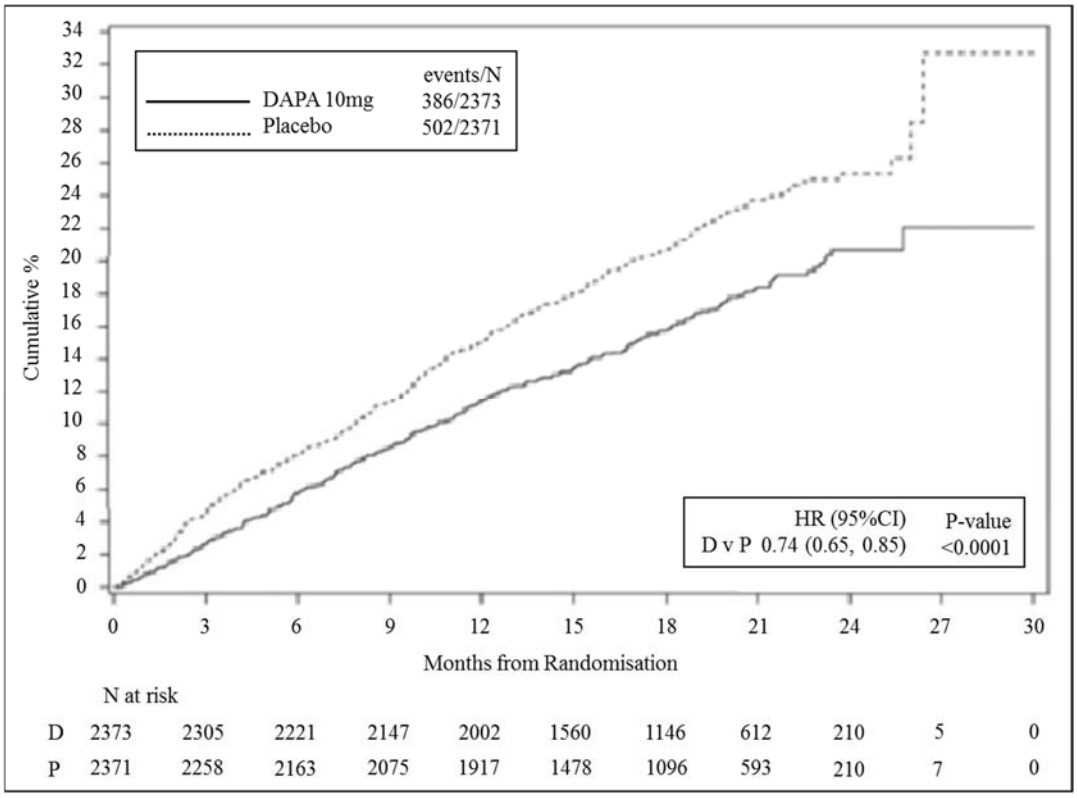

Figure 1. Time to the first occurrence of cardiovascular death, hospitalization for heart failure, or urgent heart failure visit
(Kaplan-Meier curves, FAS [the overall population])

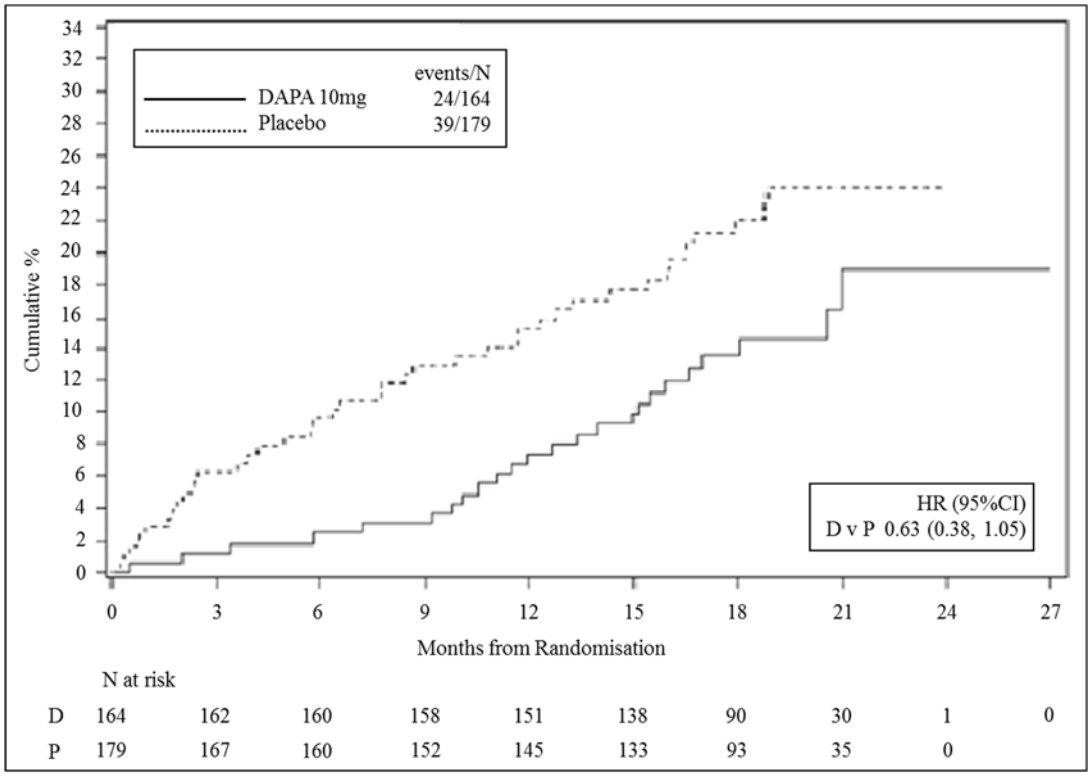

Figure 2. Time to the first occurrence of cardiovascular death, hospitalization for heart failure, or urgent heart failure visit
(Kaplan-Meier curves, FAS [the Japanese subpopulation])

The safety[6] analysis in the overall population revealed that adverse events resulting in death[7] were reported in 14.1% (333 of 2368) of patients in the placebo group and 12.1% (286 of 2368) of patients in the dapagliflozin group. The adverse events resulting in death in ≥1% of patients in either treatment group were cardiac failure (3.2% in the placebo group vs. 2.2% in the dapagliflozin group), death (2.0% vs. 2.0%), and sudden cardiac death (1.1% vs. 0.8%). A causal relationship to the study drug could not be ruled out for events occurring in 0.2% (5 of 2368) of patients in the placebo group (pulmonary embolism, cardiac failure, disseminated tuberculosis, renal neoplasm, and death in 1 patient each) and 0.3% (6 of 2368) of patients in the dapagliflozin group (sudden death in 2 patients, and cardiac failure congestive, sepsis, acute myocardial infarction, and renal failure in 1 patient each). In the Japanese subpopulation, adverse events resulting in death were reported in 11.2% (20 of 179) of patients in the placebo group and 8.0% (13 of 163) of patients in the dapagliflozin group. The adverse events resulting in death in ≥1% of patients in either treatment group were cardiac failure chronic (1.1% in the placebo group vs. 1.8% in the dapagliflozin group), sudden death (0.6% vs. 1.8%), cardiac failure (1.7% vs. 0%), lung neoplasm malignant (1.1% vs. 0%), death (1.1% vs. 1.2%), and sudden cardiac death (1.1% vs. 1.2%). A causal relationship to the study drug could not be ruled out for events occurring in 0.6% (1 of 179) of patients in the placebo group (renal neoplasm in 1 patient) and 1.8% (3 of 163) of patients in the dapagliflozin group (sudden death in 2 patients and acute myocardial infarction in 1 patient).

In the overall population, serious adverse events were reported in 40.2% (951 of 2368) of patients in the placebo group and 35.7% (846 of 2368) patients in the dapagliflozin group. The serious adverse events reported in ≥1% of patients in either treatment group were cardiac failure (13.7% in the placebo group vs. 10.1% in the dapagliflozin group), pneumonia (3.1% vs. 3.0%), cardiac failure congestive (2.7% vs. 2.4%), cardiac failure acute (2.2% vs. 1.5%), death (1.6% vs. 1.4%), acute myocardial infarction (1.4% vs. 1.4%), ventricular tachycardia (2.2% vs. 1.4%), cardiac failure chronic (1.1% vs. 1.0%), ischaemic stroke (1.0% vs. 1.0%), atrial fibrillation (1.6% vs. 1.0%), angina unstable (1.2% vs. 0.9%), acute kidney injury (1.7% vs. 0.8%), and sudden cardiac death (1.1% vs. 0.7%). A causal relationship to the study drug could not be ruled out for events occurring in 2.1% (50 of 2368) of patients in the placebo group and 1.9% (45 of 2368) of patients in the dapagliflozin group. The most common serious adverse events, for which a causal relationship to the study drug could not be ruled out, included cardiac failure (0.3% in the placebo group vs. 0.3% in the dapagliflozin group), urinary tract infection (0.2% vs. 0.3%), cardiac failure congestive (0.2% vs. 0.1%), and acute kidney injury (0.2% vs. 0.1%). In the Japanese subpopulation, serious adverse events were reported in 43.6% (78 of 179) of patients in the placebo group and 36.2% (59 of 163) of patients in the dapagliflozin group. The serious adverse events reported in ≥3% of patients in either treatment group were pneumonia

6) In the DAPA-HF study, adverse event data were collected, focusing primarily on the following events: serious adverse events, adverse events leading to drug discontinuation, adverse events leading to drug interruption, adverse events leading to dose reduction, and adverse events of special interest (adverse events suggestive of volume depletion, renal events, severe hypoglycemic events, bone fractures, diabetic ketoacidosis, adverse events leading to amputation, and adverse events leading to a risk for lower limb amputation ["precursor events"]). Serious adverse events were collected from the time informed consent was obtained to the final visit. Non-serious adverse events were collected from randomization to the final visit. In the Japanese subpopulation, all adverse events were collected throughout the study.

7) Analyses for adverse events resulting in death, bone fractures, adverse events leading to amputation, and adverse events leading to a risk for lower limb amputation included adverse events occurring on or after the day of the first dose of the randomly assigned study drug, regardless of whether the patient was on or off the study treatment at the time of onset of the event (the on- and off-treatment period). Analyses for other adverse events included events occurring on or after the day of the first dose of the randomly assigned study drug, and on or before 30 days after the last dose of the study drug (the on-treatment period).

(5.6% in the placebo group vs. 3.1% in the dapagliflozin group), cardiac failure (11.2% vs. 6.1%), cardiac failure chronic (5.0% vs. 3.1%), and cardiac failure acute (3.4% vs. 1.2%). A causal relationship to the study drug could not be ruled out for events occurring in 3.4% (6 of 179) of patients in the placebo group (cardiac failure acute, ventricular tachycardia, cerebral infarction, cardiac failure, drug-induced liver injury, and renal neoplasm in 1 patient each) and 3.1% (5 of 163) of patients in the dapagliflozin group (cerebral infarction and sudden death in 2 patients each, and acute myocardial infarction in 1 patient).

Adverse events led to drug discontinuation in 4.9% (116 of 2368) of patients in the placebo group and 4.7% (111 of 2368) of patients in the dapagliflozin group. Adverse events leading to drug discontinuation reported in ≥0.2% of patients in either treatment group were cardiac failure (0.6% in the placebo group vs. 0.7% in the dapagliflozin group), dizziness (0.2% vs. 0.2%), hypotension (0.2% vs. 0.2%), urinary tract infection (0.1% vs. 0.2%), renal impairment (0.2% vs. 0.1%), and cardiac failure congestive (0.3% vs. 0%). A causal relationship to the study drug could not be ruled out for events occurring in 1.6% (39 of 2368) of patients in the placebo group and 1.7% (40 of 2368) of patients in the dapagliflozin group. The most common adverse events leading to drug discontinuation, for which a causal relationship to the study drug could not be ruled out, included hypotension (0.2% vs. 0.1%), urinary tract infection (0% vs. 0.2%), and pruritus (0% vs. 0.2%). In the Japanese subpopulation, adverse events led to drug discontinuation in 5.6% (10 of 179) of patients in the placebo group and 6.1% (10 of 163) of patients in the dapagliflozin group. The adverse event leading to drug discontinuation reported in ≥1% of patients in either treatment group was cardiac failure (1.1% vs. 0%). A causal relationship to the study drug could not be ruled out for events occurring in 1.7% (3 of 179) of patients in the placebo group (defaecation urgency, palpitations, and drug-induced liver injury in 1 patient each) and 1.2% (2 of 163) of patients in the placebo group (pruritus, rash, and blood pressure decreased in 1 patient each).

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation about the clinical positioning of dapagliflozin in the treatment of chronic heart failure in Japan:

In Japan, the "Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (2017)" recommends that pharmacotherapy for HFrEF classified as symptomatic heart failure (NYHA functional class II to IV) should start with an ACE inhibitor (or an ARB, if ACE inhibitors are contraindicated or not tolerated), of which the dose is increased to the maximum dose, where appropriate. The use of a β-blocker is also recommended unless the patient has any contraindication. In this case, a selected β-blocker should be started at a low dose and then carefully uptitrated, while the patient is monitored for tolerance. In addition, the guidelines recommends the use of MRAs, unless contraindicated, for patients with symptomatic HFrEF who are already on treatment with loop diuretics and ACE inhibitors. All of these treatment regimens are Class I[8)] and Level of Evidence A.[9)] However, uptitration of β-blockers, ACE inhibitors, and ARBs is often difficult in some patients. Only a small number of patients are actually treated with these drugs at the

8) There is evidence and/or general agreement that a given procedure or treatment is effective and beneficial.
9) Supported by data derived from multiple randomized clinical trials or meta-analyses.

guideline-recommended doses (*Lancet* 2018;6:e1008-18). Thus, highly desired is the development of a new and more beneficial drug that has a safety profile allowing long-term treatment at a recommended clinical dose, and which can be used as an add-on to the current standard of care optimized for each patient.

Dapagliflozin, a selective and reversible SGLT2 inhibitor, is expected to exert its efficacy, regardless of concomitant medications, through its mechanism of action which differs from that of any existing drug for the treatment of chronic heart failure [see Section "3.R.1 Mechanism of action and pharmacology of dapagliflozin in the treatment of heart failure"]. The efficacy and safety of dapagliflozin were demonstrated by the DAPA-HF study in patients with chronic heart failure with LVEF <40% in NYHA functional class II to IV, with or without type 2 diabetes mellitus, whose conditions were stable on the current best standard of care. During the study, the doses of medications used for the standard of care were to be kept stable, in principle, and the proportion of patients using each concomitant medication for chronic heart failure remained nearly constant throughout the study period. The results showed that the efficacy and safety of dapagliflozin in the Japanese subpopulation were consistent with those in the overall population. In view of these findings, dapagliflozin will offer a new treatment option added to the current best standard of care for patients with stable HFrEF, with or without type 2 diabetes mellitus.

PMDA's view:
The results of the DAPA-HF study in patients with HFrEF who were on the standard of care for chronic heart failure demonstrated the superiority of dapagliflozin to placebo in reducing the incidence of the primary efficacy endpoint (i.e., the primary composite endpoint of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit [first event]), as well as the clinically acceptable safety of dapagliflozin [see Section 7.R.2 "Efficacy" and Section 7.R.3 "Safety"]. The efficacy and safety of dapagliflozin in the treatment of chronic heart failure were comparable between patients with type 2 diabetes mellitus and those without diabetes, and consistent between the overall population and the Japanese subpopulation [see Section 7.R.2.2 "Efficacy in the Japanese subpopulation of the DAPA-HF study," Section 7.R.3 "Safety," and Section 7.R.4 "Efficacy and safety of dapagliflozin in patients with or without type 2 diabetes mellitus"]. These study results have suggested that dapagliflozin has meaningful efficacy and acceptable safety in Japanese patients with HFrEF who are on the standard of care for chronic heart failure, regardless of type 2 diabetes mellitus status. It is therefore of significance to offer dapagliflozin to clinical practice in Japan as a new treatment option added to the current standard of care for such patient population.

7.R.2 Efficacy

7.R.2.1 Efficacy evaluation results

The applicant's explanation about the efficacy of dapagliflozin:
The DAPA-HF study revealed that the hazard ratio [95% CI] of the primary composite endpoint of "cardiovascular death, hospitalization for heart failure, and urgent heart failure visit (first event)" for the dapagliflozin group versus the placebo group was 0.74 [0.65, 0.85], demonstrating the superiority of dapagliflozin to placebo in reducing the incidence of the primary composite endpoint. The hazard ratios [95% CIs] of the individual components of the primary composite endpoint for the dapagliflozin group versus the

placebo group were 0.82 [0.69, 0.98] for cardiovascular death, 0.70 [0.59, 0.83] for hospitalization for heart failure, and 0.43 [0.20, 0.90] for urgent heart failure visit. The hazard ratio [95% CI] of all-cause mortality, a secondary endpoint, for the dapagliflozin group versus the placebo group was 0.83 [0.71, 0.97]. All of the hazard ratios of the efficacy endpoints were <1, which supports the consistent efficacy of dapagliflozin (Table 3). The above results support the efficacy of dapagliflozin in patients with HFrEF.

PMDA asked the applicant to explain the appropriateness of including "urgent heart failure visit" in the primary composite endpoint, taking into account the clinical significance of the event and the difference in the incidence of the event between Japanese and non-Japanese patients.

The applicant's explanation:
In the DAPA-HF study, given the recent healthcare situation in the US, in which patients with heart failure are treated at emergency units rather than under hospitalization, urgent heart failure visit was included in the primary composite endpoint. "Urgent heart failure visit" has been used as a component of the primary endpoint in multiple global clinical studies (*N Engl J Med.* 2013;368:1585-93, *N Engl J Med.* 2001;345:1667-75, etc.). Urgent heart failure visit was reported to produce a risk of subsequent death similar to that associated with hospitalization for heart failure (*Eur J Heart Fail.* 2014;16:560-5). Therefore, reducing the incidence of urgent heart failure visits is clinically significant.

For objective assessment of urgent heart failure visits, an urgent heart failure visit was defined using the definition by the Clinical Data Interchange Standards Consortium (CDISC) at the time of study planning, and the adequacy of each potential urgent heart failure visit event was adjudicated by an independent adjudication committee in a blinded manner. Specifically, an urgent heart failure visit was defined as an event that met all the following: (a) The patient had an urgent, unscheduled hospital or emergency department visit for a primary diagnosis of heart failure, but which did not meet the criteria for a heart failure hospitalization (a hospital stay of ≥24 hours [or a change in calendar date if the hospital admission and discharge times were unavailable]); (b) all of the signs and symptoms for heart failure hospitalization (the patient exhibits documented new or worsening symptoms [dyspnea, decreased exercise tolerance, or fatigue] due to heart failure, on presentation), and objective evidence of new or worsening heart failure [physical examination or laboratory findings]) were met; and, (c) the patient received initiation or intensification of treatment (an intravenous diuretic or vasoactive agent, or mechanical or surgical intervention) specifically for heart failure. The criteria for urgent heart failure visits were thus clear and based on objective measures, producing no marked differences in urgent heart failure visits adjudicated in the study between Japanese and non-Japanese patients. When the results of the DAPA-HF study were analyzed by geographical region (Asia, Europe, North America, and South America), the incidences of hospitalization for heart failure and urgent heart failure visit, which were components of the primary composite endpoint, in the placebo group, as well as the hazard ratios for the dapagliflozin group versus the placebo group, in each region were consistent with those in the overall population, indicating no marked differences across the geographical regions (Table 4).

Table 4. Incidences of hospitalization for heart failure and urgent heart failure visit, by geographical region (FAS)

Geographical region	Placebo	Dapagliflozin	Hazard ratio[a] [95% CI]
Hospitalization for heart failure (first event)			
Across all regions	13.4 (318/2371)	9.7 (231/2373)	0.70 [0.59, 0.83]
Japan	16.8 (30/179)	9.1 (15/164)	0.52 [0.28, 0.97]
Asia (including Japan)	13.4 (74/553)	7.6 (41/543)	0.54 [0.37, 0.79]
Europe	12.8 (136/1060)	10.7 (117/1094)	0.81 [0.63, 1.04]
North America	16.7 (57/342)	11.6 (39/335)	0.67 [0.45, 1.01]
South America	12.3 (51/416)	8.5 (34/401)	0.67 [0.43, 1.03]
Urgent heart failure visit (first event)			
Across all regions	1.0 (23/2371)	0.4 (10/2373)	0.43 [0.20, 0.90]
Japan	2.2 (4/179)	0.6 (1/164)	–
Asia (including Japan)	1.4 (8/553)	0.6 (3/543)	–
Europe	0.7 (7/1060)	0.2 (2/1094)	–
North America	1.2 (4/342)	1.2 (4/335)	–
South America	1.0 (4/416)	0.2 (1/401)	–

% (number of patients with the event/number of patients analyzed)
–: not calculated
a: Calculated from a Cox proportional hazards model, stratified by type 2 diabetes mellitus status at randomization, with factors for history of heart failure hospitalization, treatment group, the relevant subgroup variable, and the interaction between the treatment group and the subgroup variable

Based on the above, evaluating the efficacy of dapagliflozin using the primary composite endpoint including urgent heart failure visit, which was appropriately defined and adjudicated, was justifiable. Given the small number of urgent heart failure visits reported in the DAPA-HF study, the impact of this component on the results of the primary endpoint was likely to be modest.

PMDA's view:

The superiority of dapagliflozin to placebo in reducing the incidence of the primary composite endpoint was demonstrated in the overall population of the DAPA-HF study. Urgent heart failure visit, selected as a component of the primary composite endpoint, might have resulted in the collection of events that were clinically less important than hospitalization for heart failure, and the clinical significance of this component may differ between in and outside of Japan depending on the healthcare environment. In the DAPA-HF study, however, urgent heart failure visits were adjudicated by the Clinical Event Adjudication Committee according to the prespecified definition to minimize variations in the nature and clinical significance of urgent heart failure visits subjected to adjudication of the primary composite endpoint. In addition, the incidences of urgent heart failure visit were similar across the geographical regions in the study. Furthermore, the results obtained for the secondary endpoints, cardiovascular death and hospitalization for heart failure (first event) (Table 3), and for each component of the primary composite endpoint supported the efficacy of dapagliflozin, as demonstrated in terms of the primary endpoint. Taking all of these together, evaluating the efficacy of dapagliflozin based on the primary endpoint was appropriate, and the results of the DAPA-HF study successfully demonstrated the efficacy of dapagliflozin in the treatment of HFrEF.

7.R.2.2 Efficacy in the Japanese subpopulation of the DAPA-HF study

PMDA asked the applicant to explain the appropriateness of the participation of Japanese patients in the DAPA-HF study, based on the analyses of intrinsic and extrinsic ethnic factors.

The applicant's explanation:

According to the analyses of intrinsic ethnic factors using patient characteristics identified in large-scale observational studies in Japanese and non-Japanese patients with chronic heart failure, Japanese patients were more often male, had lower BMI values, and were less likely to have ischemic etiology, as compared with non-Japanese patients (*Circ J.* 2011;75:823-33, *Circ J.* 2009;73:2365). However, these differences in patient characteristics were unlikely to produce clinically significant differences in the efficacy or safety of dapagliflozin. The pharmacokinetics of dapagliflozin in patients with chronic heart failure did not differ markedly between Japanese and non-Japanese patients [see Section 6.R.1 "Differences in pharmacokinetics in Japanese and non-Japanese patients with chronic heart failure"]. Comparisons of patient characteristics between the overall population and the Japanese subpopulation in the DAPA-HF study showed the differences in the patient characteristics presented in Table 5; however, other patient characteristic were similar in the populations (LVEF [median], 32% in the overall population versus 31% in the Japanese subpopulation; proportion of patients with type 2 diabetes mellitus, 41.8% versus 43.4%; and, eGFR [median], 64.0 mL/min/1.73 m^2 versus 65.0 mL/min/1.73 m^2).

Table 5. Differences in patient characteristics between the overall population and the Japanese subpopulation in the DAPA-HF study (FAS)

		Overall population (N = 4744)	Japanese subpopulation (N = 343)
Years of age		66.3 ± 10.9	70.0 ± 9.6
>65 years		57.2 (2714)	75.5 (259)
>75 years		21.1 (1003)	29.7 (102)
Sex	Male	76.6 (3635)	84.8 (291)
	Female	23.4 (1109)	15.2 (52)
BMI (kg/m^2)		28.2 ± 6.0	23.8 ± 4.2
Heart failure duration >5 years		39.1 (1855)	51.6 (177)
History of heart failure hospitalization		47.4 (2251)	66.8 (229)
Ischemic etiology		56.4 (2674)	46.6 (160)
NYHA functional class	II	67.5 (3203)	86.9 (298)
	III	31.6 (1498)	12.5 (43)
	IV	0.9 (43)	0.6 (2)

Mean ± standard deviation, % (n)

Although the proportion of patients with ischemic etiology and NYHA function status differed between the overall population and the Japanese subpopulation, the differences in those factors did not substantially affect the efficacy of dapagliflozin [see Section 7.R.2.3 "Efficacy by the severity of heart failure" and Section 7.R.2.4 "Efficacy by the etiology of heart failure"]. In addition, subgroup analyses were performed for patient characteristics that differed between the populations. No clear differences in the incidence of the primary composite endpoint between the dapagliflozin group and the placebo group were observed in any subgroup, suggesting that none of the patient characteristics that differed between the overall population and the Japanese subpopulation were likely to have substantially affected the efficacy evaluation of dapagliflozin. Furthermore, the efficacy of dapagliflozin in the Japanese subpopulation of the DAPA-HF study was consistent with that in the overall population. Thus, while some characteristics of patients with chronic heart failure differed between Japanese and non-Japanese patients, none of these patient characteristics substantially affected the efficacy evaluation of dapagliflozin. Therefore, evaluating the efficacy of

dapagliflozin in Japanese patients with chronic heart failure based on the results of the DAPA-HF study is appropriate.

Extrinsic ethnic factors include guidelines used. Relevant guidelines available in and outside of Japan share similar definitions and diagnoses of chronic heart failure. In view of the Japanese and foreign guidelines, guideline-recommended treatment algorithms for chronic heart failure, including decision regarding the necessity of hospitalization, do not considerably differ across advanced countries, although the approval status varies for some drugs. Table 6 shows the proportions of patients using medications and devices for treatment of chronic heart failure in the overall population and the Japanese subpopulation of the DAPA-HF study. The use of medications and devices for treatment of chronic heart failure did not differ substantially between the populations, except that sacubitril-valsartan sodium hydrate and ivabradine hydrochloride were not approved in Japan during the period in which the DAPA-HF study was conducted, and that a smaller proportion of Japanese patients used an MRA or implantable cardioverter defibrillator (ICD).

Table 6. Use of medications and devices for treatment of chronic heart failure (FAS)

	Overall population			Japanese subpopulation		
	Placebo (N = 2371)	Dapagliflozin (N = 2373)	Total (N = 4744)	Placebo (N = 179)	Dapagliflozin (N = 164)	Total (N = 343)
ACE inhibitors	56.1 (1329)	56.1 (1332)	56.1 (2661)	43.0 (77)	50.6 (83)	46.6 (160)
ARBs	26.7 (632)	28.4 (675)	27.6 (1307)	41.9 (75)	38.4 (63)	40.2 (138)
Sacubitril-valsartan	10.9 (258)	10.5 (250)	10.7 (508)	0 (0)	0 (0)	0 (0)
ACE inhibitors, ARBs, or sacubitril-valsartan	93.1 (2207)	94.2 (2235)	93.6 (4442)	83.8 (150)	88.4 (145)	86.0 (295)
β-Blockers	96.2 (2280)	96.0 (2278)	96.1 (4558)	96.1 (172)	93.3 (153)	94.8 (325)
MRAs	70.6 (1674)	71.5 (1696)	71.0 (3370)	51.4 (92)	54.3 (89)	52.8 (181)
Diuretics	93.5 (2217)	93.4 (2216)	93.4 (4433)	89.4 (160)	84.1 (138)	86.9 (298)
Digitalis preparations	18.6 (442)	18.8 (445)	18.7 (887)	7.3 (13)	9.1 (15)	8.2 (28)
Vasodilators	15.3 (362)	17.0 (404)	16.1 (766)	12.8 (23)	11.6 (19)	12.2 (42)
Ivabradine	4.6 (109)	5.0 (119)	4.8 (228)	0 (0)	0 (0)	0 (0)
ICD	20.5 (486)	19.7 (467)	20.1 (953)	5.6 (10)	7.9 (13)	6.7 (23)
CRT-D or CRT-P	6.9 (164)	8.0 (190)	7.5 (354)	7.3 (13)	12.2 (20)	9.6 (33)

% (n)

Analyses were performed to assess the effects of the extrinsic ethic factors that differed between the overall population and the Japanese subpopulation on the efficacy evaluation. According to subgroup analyses by the use of sacubitril-valsartan sodium hydrate, ivabradine hydrochloride, MRA, or ICD, no clear differences in the incidence of the primary composite endpoint between the dapagliflozin group and the placebo group were observed in any subgroup. Therefore, none of the patient characteristics that differed between the overall population and the Japanese subpopulation are likely to have substantially affected the efficacy evaluation of dapagliflozin.

As described above, there are no major problems with the participation of Japanese patients in the DAPA-HF study, from the viewpoint of either intrinsic or extrinsic ethnic factors.

In the Japanese subpopulation, fewer events of the primary composite endpoint were reported in the dapagliflozin group than in the placebo group, with a hazard ratio [95% CI] of 0.63 [0.38, 1.05] (Table 3).

The events of each component of the primary composite endpoint were reported less frequently in the dapagliflozin than in the placebo group, with hazard ratios [95% CIs] of 0.85 [0.40, 1.82] for cardiovascular death and 0.52 [0.28, 0.97] for hospitalization for heart failure, as well as incidences of urgent heart failure visit of 0.6% (1 of 164 patients) in the dapagliflozin group and 2.2% (4 of 179 patients) in the placebo group. The incidence of all-cause mortality was lower in the dapagliflozin group than in the placebo group, with a hazard ratio [95% CI] of 0.73 [0.36, 1.48]. These results indicated that the efficacy of dapagliflozin in the Japanese subpopulation was consistent with that in the overall population.

PMDA's view:

As the applicant has explained, the preliminary investigation of the intrinsic and extrinsic ethnic factors of patients to be enrolled in the DAPA-HF study showed no marked differences in the factors that might affect the efficacy of dapagliflozin between Japanese and non-Japanese patients. The participation of Japanese patients in the DAPA-HF study, a global clinical study, was thus appropriate. In the DAPA-HF study, some patient characteristics, including the use of medications for chronic heart failure, differed between the overall population and the Japanese subpopulation. However, the results of subgroup analyses by patient characteristics indicated that differences in the patient characteristics between the populations had no substantial impact on the efficacy evaluation of dapagliflozin. In addition, (a) according to the results for the overall population of the DAPA-HF-study, dapagliflozin was shown to be superior to placebo in reducing the incidence of the primary composite endpoint, and the results for each component of the primary composite endpoint and all-cause mortality consistently supported the efficacy of dapagliflozin; and, (b) efficacy results in the Japanese subpopulation were consistent with those in the overall population, as evidenced by, for example, the fact that the point estimates of the hazard ratios of the primary composite endpoint and its components, and the all-cause mortality for the dapagliflozin group versus the placebo group were <1. In view of the above (a) and (b), as with the efficacy of dapagliflozin demonstrated in the overall population of the DAPA-HF study, dapagliflozin can be expected to be effective in Japanese patients with HFrEF, as well.

7.R.2.3 Efficacy by the severity of heart failure

The applicant explained the impact of the severity of chronic heart failure on the efficacy of dapagliflozin. Table 7 shows the results of the primary composite endpoint and its components, and all-cause mortality by NYHA functional class in the DAPA-HF study.

Table 7. Incidences of efficacy events by NYHA functional class (FAS)

NYHA functional class	Endpoints	Placebo	Dapagliflozin	Hazard ratio[a] [95% CI]
Overall population				
II	Primary composite endpoint	18.1 (289/1597)	11.8 (190/1606)	0.63 [0.52, 0.75]
	Cardiovascular death	9.7 (155/1597)	6.2 (100/1606)	0.63 [0.49, 0.81]
	Hospitalization for heart failure/urgent heart failure visit (first event)	11.5 (184/1597)	7.3 (117/1606)	0.61 [0.48, 0.77]
	All-cause mortality	12.0 (192/1597)	7.8 (125/1606)	0.64 [0.51, 0.80]
III	Primary composite endpoint	26.6 (200/751)	25.6 (191/747)	0.93 [0.76, 1.14]
	Cardiovascular death	14.8 (111/751)	16.3 (122/747)	1.11 [0.86, 1.44]
	Hospitalization for heart failure/urgent heart failure visit (first event)	18.0 (135/751)	15.5 (116/747)	0.83 [0.65, 1.07]
	All-cause mortality	17.3 (130/751)	19.5 (146/747)	1.14 [0.90, 1.45]
IV	Primary composite endpoint	56.5 (13/23)	25.0 (5/20)	0.41 [0.14, 1.21]
	Cardiovascular death	30.4 (7/23)	25.0 (5/20)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	30.4 (7/23)	20.0 (4/20)	–
	All-cause mortality	30.4 (7/23)	25.0 (5/20)	–
Japanese subpopulation				
II	Primary composite endpoint	19.2 (30/156)	13.4 (19/142)	0.66 [0.37, 1.18]
	Cardiovascular death	7.7 (12/156)	5.6 (8/142)	0.69 [0.28, 1.70]
	Hospitalization for heart failure/urgent heart failure visit (first event)	14.7 (23/156)	9.2 (13/142)	0.61 [0.31, 1.20]
	All-cause mortality	9.6 (15/156)	6.3 (9/142)	0.63 [0.27, 1.45]
III	Primary composite endpoint	36.4 (8/22)	23.8 (5/21)	–
	Cardiovascular death	9.1 (2/22)	19.0 (4/21)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	31.8 (7/22)	9.5 (2/21)	–
	All-cause mortality	13.6 (3/22)	19.0 (4/21)	–
IV	Primary composite endpoint	100 (1/1)	0 (0/1)	–
	Cardiovascular death	100 (1/1)	0 (0/1)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	0 (0/1)	0 (0/1)	–
	All-cause mortality	100 (1/1)	0 (0/1)	–

% (number of patients with the event/number of patients analyzed)
–: not calculated
a: Calculated from a Cox proportional hazards model stratified by type 2 diabetes mellitus status at randomization, with factors for history of heart failure hospitalization, treatment group, the relevant subgroup variable, and the interaction between the treatment group and the subgroup variable. Calculation for all-cause mortality used a model in which the history of heart failure hospitalization was removed from the above model.

Although the difference between the dapagliflozin group and the placebo group with regards to the incidences of the primary composite endpoint tended to be decreased in the NYHA III subgroup, compared with the NYHA II subgroup, the point estimate of the hazard ratio was <1. The applicant considered that dapagliflozin would also be effective in patients with NYHA III. The point estimate of the hazard ratio of all-cause mortality for the dapagliflozin group versus the placebo group was >1 in the NYHA III subgroup. However, the difference in the incidence of all-cause mortality between the treatment groups was small. In addition, the incidences of the primary composite endpoint and all-cause mortality were lower in the dapagliflozin group than in the placebo group in the NYHA IV subgroup. Thus, no consistent trends have been noted regarding the incidences of efficacy endpoints by the severity of heart failure. Furthermore, subgroup analyses by baseline NT-proBNP (not higher versus higher than the median) or baseline LVEF (not higher versus higher than the median) revealed that the upper limit of the 95% confidence interval of the hazard ratio of the primary composite endpoint for the dapagliflozin group versus the placebo group was <1

for all subgroups. This result, together with the results obtained for the other efficacy endpoints indicates that the therapeutic effect of dapagliflozin is not affected by the severity of heart failure.

The safety analyses showed no marked differences in the incidence of serious adverse events among the subgroups by NYHA functional class in the DAPA-HF study.

Based on the above, dapagliflozin is expected to have efficacy in patients with HFrEF in NYHA class III or IV, as well, and no specific safety concerns have been identified. Therefore, no particular alert regarding NYHA functional class is necessary. However, because the number of Japanese patients in NYHA classe III or IV who received dapagliflozin in the DAPA-HF study was as small as 22 patients, the applicant will collect as much information as possible from this patient population in the post-marketing setting.

PMDA's view:
In the overall population of the DAPA-HF study, the point estimate of the hazard ratio of the primary composite endpoint for the dapagliflozin group versus the placebo group was <1 in the NYHA class III subgroup, whereas the difference between the dapagliflozin group and the placebo group with regards to the incidences of the primary composite endpoint tended to be decreased in the NYHA class III subgroup, compared with the NYHA class II subgroup. In addition, the hazard ratios for cardiovascular death and all-cause mortality for the dapagliflozin group versus the placebo group were >1 in the NYHA class III group. In contrast, in the NYHA class IV subgroup consisting of patients with more severe heart failure, the incidences of the primary composite endpoint and all-cause mortality were lower in the dapagliflozin group than in the placebo group, albeit the results in a small number of patients. Thus, the efficacy of dapagliflozin did not tend to decline with an increase in the severity of heart failure. Furthermore, subgroup analyses by other indicators of heart failure severity, such as baseline NT-proBNP and LVEF, suggested that the severity of heart failure had no impact on the efficacy of dapagliflozin. In view of these results, PMDA has concluded that dapagliflozin can be expected to be effective in patients with chronic heart failure regardless of the severity of heart failure as classified by NYHA functional class. The Japanese subpopulation included few patients in NYHA class III or IV, which preclude a precise evaluation. However, according to the available data, the efficacy of dapagliflozin did not tend to clearly decline with an increase in the severity of heart failure in the Japanese subpopulation, as with the case of the overall population. Based on these results, dapagliflozin can be expected to be effective in in Japanese patients with HFrEF regardless of the severity of heart failure. However, because experience with the use of dapagliflozin in Japanese patients with HFrEF in NYHA class III or IV has been limited, the applicant should collect information regarding the use of dapagliflozin in Japanese patients with HFrEF in NYHA class III or IV in the post-marketing setting.

7.R.2.4 Efficacy by etiology of heart failure

The applicant's explanation about the effects of the etiology of heart failure on the efficacy of dapagliflozin:
Table 8 shows the results for the primary composite endpoint and its components and all-cause mortality by the etiology of chronic heart failure in the DAPA-HF study.

Table 8. Incidences of efficacy events by etiology of chronic heart failure (FAS)

Etiology	Endpoints	Placebo	Dapagliflozin	Hazard ratio[a] [95% CI]
Overall population				
Ischemic	Primary composite endpoint	21.3 (289/1358)	16.9 (223/1316)	0.77 [0.65, 0.92]
	Cardiovascular death	12.5 (170/1358)	11.6 (152/1316)	0.92 [0.74, 1.14]
	Hospitalization for heart failure/urgent heart failure visit (first event)	13.2 (179/1358)	9.2 (121/1316)	0.67 [0.53, 0.85]
	All-cause mortality	15.2 (206/1358)	14.1 (185/1316)	0.92 [0.76, 1.12]
Non-ischemic	Primary composite endpoint	21.0 (213/1013)	15.4 (163/1057)	0.71 [0.58, 0.87]
	Cardiovascular death	10.2 (103/1013)	7.1 (75/1057)	0.69 [0.51, 0.93]
	Hospitalization for heart failure/urgent heart failure visit (first event)	14.5 (147/1013)	11.0 (116/1057)	0.73 [0.57, 0.93]
	All-cause mortality	12.1 (123/1013)	8.6 (91/1057)	0.70 [0.53, 0.92]
Japanese subpopulation				
Ischemic	Primary composite endpoint	21.4 (18/84)	14.5 (11/76)	0.62 [0.29, 1.32]
	Cardiovascular death	9.5 (8/84)	11.8 (9/76)	1.17 [0.45, 3.08]
	Hospitalization for heart failure/urgent heart failure visit (first event)	14.3 (12/84)	6.6 (5/76)	0.41 [0.15, 1.18]
	All-cause mortality	11.9 (10/84)	13.2 (10/76)	1.04 [0.43, 2.52]
Non-ischemic	Primary composite endpoint	22.1 (21/95)	14.8 (13/88)	0.65 [0.32, 1.30]
	Cardiovascular death	7.4 (7/95)	3.4 (3/88)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	18.9 (18/95)	11.4 (10/88)	0.61 [0.28, 1.32]
	All-cause mortality	9.5 (9/95)	3.4 (3/88)	–

% (number of patients with the event/number of patients analyzed)
–: not calculated
a: Calculated from a Cox proportional hazards model stratified by type 2 diabetes mellitus status at randomization, with factors for history of heart failure hospitalization, treatment group, the relevant subgroup variable, and the interaction between the treatment group and the subgroup variable. Calculation for all-cause mortality used a model in which the history of heart failure hospitalization was removed from the above model.

In both of the subgroups by the etiology of heart failure, the incidences of the primary composite endpoint and all-cause mortality were lower in the dapagliflozin group than in the placebo group, with no differences according to the etiology of heart failure. A similar tendency was observed in the Japanese subpopulation. These results suggest that dapagliflozin can be expected to be effective in Japanese patients regardless of the etiology of heart failure.

The safety analyses showed no marked differences in the incidence of serious adverse events between the dapagliflozin group and the placebo group, in either of the subgroups by the etiology of heart failure in the DAPA-HF study.

PMDA's view:
In the overall population of the DAPA-HF study, subgroup analyses by the etiology of heart failure showed that the efficacy of dapagliflozin did not tend to differ according to etiology. In the Japanese subpopulation, the point estimates of the hazard ratios of cardiovascular death and all-cause mortality for the dapagliflozin group versus the placebo group were >1 in the ischemic etiology subgroup. However, the small numbers of patients and events analyzed preclude the precise interpretation of this outcome. The results of subgroup analyses of other efficacy endpoints, including the primary composite endpoint, in the Japanese subpopulation analyzed did not tend to clearly differ from those in the overall population. Based on the above findings, dapagliflozin can be expected to be effective in Japanese patients with HFrEF, regardless of the etiology of heart failure.

7.R.2.5 Effects of LVEF on the efficacy of dapagliflozin

The applicant's explanation about the effects of LVEF on the efficacy of dapagliflozin:

Table 9 shows the results for the primary composite endpoint and its components and all-cause mortality by LVEF in the DAPA-HF study involving patients with HFrEF.

Table 9. Incidences of efficacy events by LVEF (FAS)

LVEF	Endpoint	Placebo	Dapagliflozin	Hazard ratio[a] [95% CI]
Overall population				
≤30%	Primary composite endpoint	25.0 (275/1099)	19.2 (204/1062)	0.74 [0.62, 0.89]
	Cardiovascular death	14.0 (154/1099)	11.9 (126/1062)	0.85 [0.67, 1.07]
	Hospitalization for heart failure/urgent heart failure visit (first event)	16.7 (184/1099)	11.4 (121/1062)	0.65 [0.52, 0.82]
	All-cause mortality	15.7 (172/1099)	13.7 (145/1062)	0.87 [0.70, 1.09]
>30% and ≤35%	Primary composite endpoint	19.4 (113/581)	13.9 (84/606)	0.67 [0.51, 0.89]
	Cardiovascular death	10.2 (59/581)	8.1 (49/606)	0.77 [0.53, 1.13]
	Hospitalization for heart failure/urgent heart failure visit (first event)	13.1 (76/581)	8.4 (51/606)	0.61 [0.43, 0.87]
	All-cause mortality	12.9 (75/581)	9.7 (59/606)	0.73 [0.52, 1.03]
>35% and ≤40%	Primary composite endpoint	16.5 (114/691)	13.9 (98/704)	0.83 [0.63, 1.09]
	Cardiovascular death	8.7 (60/691)	7.4 (52/704)	0.85 [0.59, 1.24]
	Hospitalization for heart failure/urgent heart failure visit (first event)	9.6 (66/691)	9.2 (65/704)	0.95 [0.67, 1.34]
	All-cause mortality	11.9 (82/691)	10.2 (72/704)	0.86 [0.62, 1.18]
Japanese subpopulation				
≤30%	Primary composite endpoint	29.1 (23/79)	21.5 (17/79)	0.71 [0.38, 1.33]
	Cardiovascular death	11.4 (9/79)	12.7 (10/79)	1.07 [0.43, 2.65]
	Hospitalization for heart failure/urgent heart failure visit (first event)	22.8 (18/79)	12.7 (10/79)	0.54 [0.25, 1.18]
	All-cause mortality	12.7 (10/79)	12.7 (10/79)	0.99 [0.41, 2.40]
>30% and ≤35%	Primary composite endpoint	15.9 (7/44)	2.5 (1/40)	–
	Cardiovascular death	6.8 (3/44)	2.5 (1/40)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	11.4 (5/44)	0 (0/40)	–
	All-cause mortality	9.1 (4/44)	2.5 (1/40)	–
>35% and ≤40%	Primary composite endpoint	16.1 (9/56)	13.3 (6/45)	–
	Cardiovascular death	5.4 (3/56)	2.2 (1/45)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	12.5 (7/56)	11.1 (5/45)	–
	All-cause mortality	8.9 (5/56)	4.4 (2/45)	–

% (number of patients with the event/number of patients analyzed)

–: Not calculated

a: Calculated from a Cox proportional hazards model stratified by type 2 diabetes mellitus status at randomization, with factors for history of heart failure hospitalization, treatment group, the relevant subgroup variable, and the interaction between the treatment group and the subgroup variable. Calculation for all-cause mortality used a model in which the history of heart failure hospitalization was removed from the above model.

The incidences of the primary composite endpoint and all-cause mortality in all of the subgroups by LVEF were lower in the dapagliflozin group than in the placebo group. An almost similar tendency was observed in the Japanese subpopulation. Although the hazard ratio of all-cause mortality for the dapagliflozin group versus the placebo group was >1 for the subgroup of Japanese patients with LVEF ≤30%, the small numbers of patients and events analyzed preclude the precise interpretation of this outcome. Based on these results, dapagliflozin can be expected to be effective in Japanese patients, regardless of LVEF.

The safety analyses showed no marked differences in the incidence of serious adverse events between the dapagliflozin group and the placebo group, for any of the subgroups by LVEF in the DAPA-HF study.

PMDA's view:
In the overall population of the DAPA-HF study, subgroup analyses by LVEF showed the promising efficacy of dapagliflozin in all of the subgroups. In the Japanese subpopulation, the point estimate of the hazard ratio of cardiovascular death, a component of the primary composite endpoint, for the dapagliflozin group versus the placebo group was >1 for the LVEF ≤30% subgroup. However, the results of subgroup analyses of other efficacy endpoints, including the primary composite endpoint, in the Japanese subpopulation did not clearly differ from those in the overall population. Based on the above results, dapagliflozin can be expected to be effective in Japanese patients with HFrEF, regardless of the degree of LVEF.

7.R.3 Safety

PMDA's view:
Except for the issuance of a post-market warning about Fournier's gangrene for the approved indications, safety information collected in the post-marketing setting in and outside of Japan has raised no new concerns. In addition, based on the incidence of adverse events in the DAPA-HF study and the following analyses, the safety of dapagliflozin in patients with chronic heart failure is clinically acceptable, in view of its efficacy, as described in Section "7.R.2 Efficacy."

7.R.3.1 Adverse events of special interest

The applicant's explanation:
Table 10 shows the summary of adverse events in the DAPA-HF study. In the DAPA-HF study, adverse events suggestive of volume depletion,[10)] renal events,[11)] diabetic ketoacidosis,[12)] severe hypoglycaemic events,[13)] bone fractures,[14)] adverse events leading to amputation,[15)] and adverse events leading to a risk for lower limb amputation[16)] were collected as adverse events of special interest based on the pharmacological action of dapagliflozin and the data submitted in support of the approved applications, in addition to serious adverse events, adverse events leading to drug discontinuation, adverse events leading to drug interruption, and adverse events leading to dose reduction.

10) Adverse events coded to the following MedDRA preferred terms (PTs): "hypotension," "hypovolaemia," "dehydration," "syncope," "orthostatic hypotension," "blood pressure decreased," "circulatory collapse," "hypovolaemic shock," etc.
11) Adverse events coded to the Standardized MedDRA Query (SMQ), "acute renal failure"
12) Events adjudicated by an independent Diabetic Ketoacidosis Adjudication Committee as "definite" or "probable" diabetic ketoacidosis
13) Adverse events categorized by the investigator as hypoglycaemic events meeting any of the following criteria: (a) symptoms of severe impairment in consciousness or behavior, (b) need of external assistance, (c) need of intervention to treat hypoglycaemia, and (d) prompt recovery of acute symptoms following such intervention.
14) Adverse events coded to the following MedDRA PTs: "ankle fracture," "hip fracture," "femoral neck fracture," "upper limb fracture," "rib fracture," "foot fracture," "fibula fracture," etc.
15) Adverse events that led to surgical or spontaneous/non-surgical amputation, except for amputation due to accidents
16) Adverse events coded to the following MedDRA PTs: "cellulitis," "diabetic foot," "skin ulcer," "osteomyelitis," "gangrene," "peripheral arterial occlusive disease," "peripheral ischaemia," "hypovolaemia," "dehydration," "wound infection," etc.

Table 10. Summary of adverse events in the DAPA-HF study (safety analysis set)

	Overall population		Japanese subpopulation	
	Placebo (N = 2368)	Dapagliflozin (N = 2368)	Placebo (N = 179)	Dapagliflozin (N = 163)
Adverse events resulting in death[a)]	14.1 (333)	12.1 (286)	11.2 (20)	8.0 (13)
Serious adverse events	40.2 (951)	35.7 (846)	43.6 (78)	36.2 (59)
Adverse events leading to drug discontinuation	4.9 (116)	4.7 (111)	5.6 (10)	6.1 (10)
Adverse events leading to drug interruption	14.7 (349)	12.0 (284)	10.1 (18)	8.0 (13)
Adverse events leading to dose reduction	1.1 (25)	1.8 (43)	0.6 (1)	0 (0)
Adverse events suggestive of volume depletion	6.5 (153)	7.2 (170)	8.9 (16)	13.5 (22)
Renal events	6.7 (158)	6.0 (141)	10.1 (18)	1.8 (3)
Diabetic ketoacidosis	0 (0)	0.1 (3)	0 (0)	0 (0)
Severe hypoglycaemic events	0.2 (4)	0.2 (4)	0.6 (1)	0 (0)
Bone fractures[a)]	2.1 (50)	2.1 (49)	5.6 (10)	3.7 (6)
Adverse events leading to amputation[a)]	0.5 (12)	0.5 (13)	0 (0)	0 (0)
Adverse events leading to a risk of lower limb amputation[a)]	5.1 (120)	6.5 (155)	10.6 (19)	12.9 (21)

% (n)

a) Adverse events collected during the "on and off treatment period" (on or after the day of the first dose of the randomly assigned study drug, regardless of whether patients were on or off the study treatment at the time of onset of the event). Adverse events without this note were collected during the "on treatment period" (from the day of the first dose of the randomly assigned study drug, and on or before 30 days after the last dose of the study drug).

7 R.3.1.1 Adverse events suggestive of volume depletion

Table 11 shows the incidences of adverse events suggestive of volume depletion. In the overall population, the incidence of adverse events suggestive of volume depletion was similar in the dapagliflozin group and the placebo group. The incidence of serious adverse events was lower in the dapagliflozin group (1.0% [23 of 2368 patients]) than in the placebo group (1.6% [38 of 2368 patients]). No patients died from adverse events suggestive of volume depletion. The incidences of adverse events leading to drug discontinuation were 0.3% (8 of 2368 patients) in the placebo group and 0.4% (9 of 2368 patients) in the dapagliflozin group, with no large difference. The incidence of adverse events leading to dose reduction was higher in the dapagliflozin group (1.1% [25 of 2368 patients]) than in the placebo group (0.7% [17 of 2368 patients]).

Table 11. Incidences of adverse events suggestive of volume depletion in the DAPA-HF study (safety analysis set)

	Overall population		Japanese subpopulation	
	Placebo (N = 2368)	Dapagliflozin (N = 2368)	Placebo (N = 179)	Dapagliflozin (N = 163)
Hypotension	3.4 (80)	3.9 (92)	1.1 (2)	4.3 (7)
Hypovolaemia	0.9 (21)	1.4 (34)	1.1 (2)	1.8 (3)
Dehydration	1.2 (28)	1.3 (30)	5.6 (10)	6.1 (10)
Syncope	0.9 (21)	0.5 (12)	0.6 (1)	0 (0)
Orthostatic hypotension	0.3 (8)	0.5 (11)	1.1 (2)	1.2 (2)
Decreased blood pressure	0.0 (1)	0.2 (4)	0 (0)	1.8 (3)
Circulatory collapse	0.2 (4)	0.0 (1)	0 (0)	0 (0)
Hypovolaemic shock	0.2 (4)	0 (0)	0 (0)	0 (0)

% (n)

In addition, an analysis was performed to assess the use of concomitant diuretics, which is considered to be an important factor responsible for adverse events suggestive of volume depletion. Among patients receiving diuretics, the incidences of adverse events suggestive of volume depletion were 6.2% (138 of 2214 patients) in the placebo group and 7.5% (167 of 2213 patients) in the dapagliflozin group, with no marked difference between the groups. Among patients receiving no diuretics, the incidences were 9.7% (15 of 154 patients) in

the placebo group and 1.9% (3 of 155 patients) in the dapagliflozin group. In the DAPA-HF study, the doses of concomitant diuretics were to be adjusted prior to the first dose of the study drug, through an assessment of the fluid volume status of each patient based on clinical findings, body weight, etc. to minimize the risk of volume depletion which may be aggravated by the diuretic effect of dapagliflozin. However, specific dose reductions made for the concomitant diuretics were not documented. The doses of concomitant diuretics were to remain stable from the start of the study treatment through the end of the study period, and if dehydration or blood pressure decreased was observed, the dose reduction of concomitant diuretics or antihypertensive agents was recommended prior to the dose adjustment of the study drug. The proportion of patients who received concomitant diuretics at stable doses from baseline through the end of the follow-up period remained almost constant. The study results indicated no clear increase in the risk of volume depletion associated with the concomitant use of diuretics. The package insert for dapagliflozin already includes a precautionary statement regarding the concomitant use of diuretics; accordingly, no additional precaution is necessary.

In the overall population, the incidence of serious thromboembolic events[17)] was similar in the placebo group (5.6% [133 of 2368 patients]) and the dapagliflozin group (5.0% [118 of 2368 patients]). The common thromboembolic events were acute myocardial infarction (1.4% in the placebo group versus 1.4% in the dapagliflozin group) and ischaemic stroke (1.0% versus 1.0%). The incidence of adverse events resulting in death was similar in the placebo group (1.1% [27 of 2368 patients]) and the dapagliflozin group (1.2% [29 of 2368 patients]). The proportions of patients experiencing both adverse events suggestive of volume depletion and thromboembolic events were 0.8% (18 of 2368 patients) in the placebo group and 0.6% (14 of 2368 patients) in the dapagliflozin group. Thus, dapagliflozin did not tend to increase the risk of thromboembolic events associated with adverse events suggestive of volume depletion in patients with chronic heart failure.

Since some patients treated with dapagliflozin for any of the approved indications experience volume depletion induced by polyuria/pollakiuria resulting from osmotic diuresis in the hyperglycemic state associated with diabetes, the package insert warns that patients receiving dapagliflozin for the control of hyperglycaemia should have adequate fluid intake to prevent dehydration. While close monitoring of volume status is also needed in patients with chronic heart failure, some patients who are in a chronic fluid overload state may require strict fluid restriction. Hydration status and diuretics dose adjustment should be assessed, depending on the optimal fluid balance for individual patients. Therefore, the use of a precautionary statement in the package insert similar to that for patients receiving dapagliflozin for the approved indications is not appropriate for patients with chronic heart failure. When dapagliflozin is administered to patients with chronic heart failure, the fluid volume of each patient should be carefully monitored, and the patient should follow the physician’s instructions regarding fluid intake. These precautions will be properly informed to patients with chronic heart failure, through the materials for patients.

17) Adverse events coded to MedDRA SMQ (narrow) "embolic and thrombotic events"

As described above, there is no need for the package insert to include an additional precautionary statement regarding the risk of volume depletion associated with the use of dapagliflozin in patients with chronic heart failure.

PMDA's view:
Dapagliflozin, which has a diuretic action, may more substantially increase the risk of volume depletion when administered to patients with chronic heart failure, than when administered for the approved indications, due to the following differences in patient characteristics between patients with chronic heart failure and those with diabetes.

- A majority of patients with chronic heart failure use diuretics.
- Diabetic patients are advised to have adequate fluid intake to protect against the risk of volume depletion associated with dapagliflozin therapy, whereas patients with chronic heart failure may be placed on strict fluid restriction; thus, fluid intake is not always recommended for patients with chronic heart failure.
- Dapagliflozin can also be used for the treatment of chronic heart failure in diabetic patients with renal impairment with eGFR <45 mL/min/1.73m^2, who are not recommended to use dapagliflozin for the approved indications, and may experience increased exposure to dapagliflozin [see Section "7.R.5 Efficacy and safety of dapagliflozin in patients with renal impairment"].
- Patients with chronic heart failure are prone to thrombus formation resulting from blood stagnation due to decreased cardiac function.

However, the "Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure (2017)" available in Japan recommends daily body weight control, and in some cases, fluid intake control to prevent heart failure. The risks related to fluid balance are assumed to be adequately controlled in clinical practice. In addition, in the DAPA-HF study involving the standard of care for chronic heart failure employed in clinical practice, the incidence of adverse events suggestive of volume depletion did not differ markedly between the dapagliflozin group and the placebo group. In view of this result and other findings, PMDA considers that the risk of volume depletion associated with the use of dapagliflozin in patients with chronic heart failure is also manageable to a certain degree in clinical practice. Furthermore, considering the fact that the package insert for dapagliflozin already includes a precautionary statement regarding dehydration associated with dapagliflozin therapy, the applicant's claim that the addition of a precautionary statement about the risk of volume depletion to the package insert is unnecessary is acceptable. PMDA's decision will be finalized after taking into account the comments from the Expert Discussion.

7.R.3.1.2 Other adverse events of special interest

The incidence of renal events was similar in the dapagliflozin group and the placebo group. The incidence of serious adverse events was lower in the dapagliflozin group (1.4% [34 of 2368 patients]) than in the placebo group (2.4% [58 of 2368 patients]). Death occurred in 1 patient (acute kidney injury) in the placebo group and 4 patients (acute kidney injury and renal failure in 2 patients each). A causal relationship to the study drug was ruled out for events occurring in all but 1 patient (renal failure). The incidence of adverse events

leading to drug discontinuation was similar in the placebo group (0.4% [9 of 2368 patients]) and the dapagliflozin group (0.3% [8 of 2368 patients]).

Diabetic ketoacidosis was reported in 3 patients in the dapagliflozin group. All of these 3 patients had type 2 diabetes mellitus and received antidiabetic medications during the study period (1 patient was on insulin therapy). These patients had contributing factors, such as infection, illness, poor intake of food/drink, and dehydration. One event of diabetic ketoacidosis resulted in death in 1 patient (a 7[redacted]-year-old woman). This patient, who was on treatment with metformin and gliclazide, was found unconscious at home and hospitalized on Day 399. Eight days after admission, the patient died due to a diabetic ketoacidotic hyperglycaemic coma. There were no adverse events leading to drug discontinuation.

The incidence of severe hypoglycaemic events was similar in the placebo group (0.2% [4 of 2368 patients]) and the dapagliflozin group (0.2% [4 of 2368 patients]). All patients with hypoglycaemic events had diabetes mellitus at baseline, and were using sulphonylureas or insulin, alone or in combination, at the time the event occurred, with the exception of 1 patient in the placebo group.

The incidences of bone fractures and adverse events leading to amputation were similar in the placebo group and the dapagliflozin group. The incidence of adverse events leading to a risk for lower limb amputation was 6.5% (155 of 2368 patients) in the dapagliflozin group and 5.1% (120 of 2368 patients) in the placebo group. Among these patients, 8 in the dapagliflozin group and 3 in the placebo group underwent subsequent amputations.

The incidences of the important identified risks for dapagliflozin, including urinary tract infection,[18)] genital infection,[19)] and polyuria/pollakuria,[20)] were also assessed for the DAPA-HF study.

The incidence of serious adverse events of urinary tract infection was similar in the placebo group (0.7% [17 of 2368 patients]) and the dapagliflozin group (0.6% [14 of 2368 patients]). One event of urinary tract infection resulted in death in only 1 patient in the placebo group. The incidence of adverse events leading to drug discontinuation was similar in the placebo group (0.2% [5 of 2368 patients]) and the dapagliflozin group (0.2% [5 of 2368 patients]). Serious adverse events of genital infection were reported in only 1 patient in the placebo group, with no adverse events resulting in death. Adverse events led to drug discontinuation in 7 patients in the dapagliflozin group. All of the events were non-serious, and the events were resolving or resolved in 5 of these 7 patients. None of the adverse events were considered to be Fournier's gangrene.[21)]

No serious adverse events of polyuria/pollakiuria were reported.

---

18) Events coded to MedDRA PTs "urinary tract infection," "pyelonephritis acute," pyelocystitis," "pyelonephritis," cystitis," "renal abscess," "renal cyst infection," etc.
19) Events coded to MedDRA PTs "bacterial vaginosis," "penile infection," "genital abscess," etc.
20) Events coded to MedDRA PTs "polyuria" and "pollakiuria"
21) Events identified as genital infections (Note 19) were assessed by AstraZeneca in a blinded manner, based on the diagnosis made by the investigator, symptoms suggestive of Fournier's gangrene, documented surgical intervention, etc. confirming necrotizing fasciitis, documented intravenous antibiotics, anatomical records of suspected Fournier's gangrene, and other findings.

The incidences of serious adverse events of liver disorder[22)] and malignant tumours[23)] (including bone malignancy, bladder cancer, and breast cancer), which are important potential risks associated with the use of dapagliflozin, were similar in the dapagliflozin group and the placebo group.

In addition to the above events assessed, all adverse events were collected from the Japanese subpopulation, regardless of the nature or severity of the event. Table 12 shows adverse events reported by ≥5% of patients in the dapagliflozin group in the Japanese subpopulation. The proportion of patients with any adverse event was 89.9% (161 of 179 patients) in the placebo group and 85.9% (140 of 163 patients) in the dapagliflozin group. The incidence of adverse events for which a causal relationship to the study drug could not be ruled out was 12.3% (22 of 179 patients) in the placebo group and 14.7% (24 of 163 patients) in the dapagliflozin group. No new safety concerns were identified in the dapagliflozin group.

Table 12. Adverse events reported by ≥5% of patients in the dapagliflozin group in the Japanese subpopulation (safety analysis set)

	Placebo (N = 179)	Dapagliflozin (N = 163)
Nasopharyngitis	30.7 (55)	27.6 (45)
Cardiac failure	20.1 (36)	11.7 (19)
Pneumonia	10.1 (18)	6.7 (11)
Dehydration	5.6 (10)	6.1 (10)
Dizziness	0.6 (1)	5.5 (9)

% (n)

Patients with HFrEF are more likely to be elderly, have a history of coronary artery diseases, and have comorbidities which are causes of heart failure, such as hypertension, diabetes, or atherosclerotic diseases. A high proportion of such patients would receive medications for these illnesses. The patients would often concomitantly use diuretics or other medications to alleviate edema or other symptoms of HFrEF. In addition, many of them have decreased renal function resulting from organ malperfusion induced by heart failure, aging, and concurrent atherosclerotic diseases (*Eur J Heart Fail.* 2019;21:1402-11). In general, these patients are prone to develop volume depletion or renal adverse drug reactions. Adverse events were generally more common in the DAPA-HF study than in clinical studies targeting diabetic patients, although a similar trend was also noted in the placebo group. The incidences of the known risks associated with the use of dapagliflozin in the dapagliflozin group did not tend to differ from those in the placebo group. No unknown risks were identified in the dapagliflozin group.

PMDA's view:

In the DAPA-HF study, the assessments of serious adverse events, adverse events leading to drug discontinuation, and other adverse events identified no new safety concerns about the use of dapagliflozin in the treatment of chronic heart failure, compared with the approved indications. There was no clear increases in the risks of the prespecified adverse events of special interest in the dapagliflozin group, compared with

22) Events coded to MedDRA SOC "hepatobiliary disorders"
23) Events coded to MedDRA SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)"

the placebo group. Based on the above results, PMDA considers that there is no need for the package insert to include an additional precautionary statement regarding the adverse events of special interest, except for volume depletion. This PMDA's decision will be finalized after taking into account the comments from the Expert Discussion.

7.R.3.2 Safety in the elderly

Table 13 shows the summary of adverse events by age in the DAPA-HF study.

Table 13. Summary of adverse events by age (safety analysis set)

Overall population				
Age	≤65 years		>65 years	
Adverse events	Placebo (N = 997)	Dapagliflozin (N = 1029)	Placebo (N = 1371)	Dapagliflozin (N = 1339)
Adverse events resulting in death[a)]	12.2 (122)	10.9 (112)	15.4 (211)	13.0 (174)
Serious adverse events	36.7 (366)	33.2 (342)	42.7 (585)	37.6 (504)
Adverse events leading to drug discontinuation	3.7 (37)	3.5 (36)	5.8 (79)	5.6 (75)
Adverse events leading to drug interruption	11.5 (115)	10.9 (112)	17.1 (234)	12.8 (172)
Adverse events leading to dose reduction	1.1 (11)	1.6 (16)	1.0 (14)	2.0 (27)
Adverse events suggestive of volume depletion	5.1 (51)	5.8 (60)	7.4 (102)	8.2 (110)
Renal events	4.4 (44)	5.7 (59)	8.3 (114)	6.1 (82)
Diabetic ketoacidosis	0 (0)	0.2 (2)	0 (0)	0.1 (1)
Severe hypoglycaemic events	0 (0)	0.1 (1)	0.3 (4)	0.2 (3)
Bone fractures[a)]	1.2 (12)	1.3 (13)	2.8 (38)	2.7 (36)
Adverse events leading to amputation[a)]	0.3 (3)	0.6 (6)	0.7 (9)	0.5 (7)
Adverse events leading to a risk for lower limb amputation[a)]	4.2 (42)	4.8 (49)	5.7 (78)	7.9 (106)
Japanese subpopulation				
Age	≤65 years		>65 years	
Adverse events	Placebo (N = 48)	Dapagliflozin (N = 36)	Placebo (N = 131)	Dapagliflozin (N = 127)
Adverse events resulting in death[a)]	12.5 (6)	2.8 (1)	4.6 (6)	5.5 (7)
Serious adverse events	43.8 (21)	22.2 (8)	43.5 (57)	40.2 (51)
Adverse events leading to drug discontinuation	4.2 (2)	0 (0)	6.1 (8)	7.9 (10)
Adverse events leading to drug interruption	6.3 (3)	11.1 (4)	11.5 (15)	7.1 (9)
Adverse events leading to dose reduction	0 (0)	0 (0)	0.8 (1)	0 (0)
Adverse events suggestive of volume depletion	6.3 (3)	19.4 (7)	9.9 (13)	11.8 (15)
Renal events	6.3 (3)	0 (0)	11.5 (15)	2.4 (3)
Diabetic ketoacidosis	0 (0)	0 (0)	0 (0)	0 (0)
Severe hypoglycaemic events	0 (0)	0 (0)	0.8 (1)	0 (0)
Bone fractures[a)]	4.2 (2)	5.6 (2)	6.1 (8)	3.1 (4)
Adverse events leading to amputation[a)]	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to a risk for lower limb amputation[a)]	12.5 (6)	16.7 (6)	9.9 (13)	11.8 (15)

% (n)

a) Adverse events collected during the "on and off treatment period" (on or after the day of the first dose of the randomly assigned study drug, regardless of whether the patient was on or off the study treatment at the time of onset of the event). Adverse events without this note were collected during the "on treatment period" (on or after the day of the first dose of the randomly assigned study drug, and on or before 30 days after the last dose of the study drug).

In the overall population, adverse events leading to dose reduction, adverse events suggestive of volume depletion, and adverse events leading to a risk for lower limb amputation tended to occur more frequently in

patients aged >65 years than in those aged ≤65 years; however, these tendencies were also found in the placebo group. Although a small number of Japanese patents aged ≤65 years precluded precise comparisons, no marked differences were observed in the incidences of adverse events between the age groups in the Japanese population.

Thus, the study results identified no events that were more frequently reported in patients aged >65 years than in those aged ≤65 years in the dapagliflozin group, indicating no major concerns about the safety of dapagliflozin treatment in elderly patients.

PMDA's view:
The summary of adverse events by age group in the overall population of the DAPA-HF study have raised no new safety concerns about the use of dapagliflozin in elderly patients with chronic heart failure, compared with the approved indications. Nevertheless, in view of the mechanism of action of dapagliflozin, precautions should be provided regarding the use of dapagliflozin in elderly patients with chronic heart failure, as with the case of the approved indications.

7.R.4 Efficacy and safety of dapagliflozin in patients with or without type 2 diabetes mellitus

The applicant's explanation:
To evaluate the efficacy of dapagliflozin in the treatment of chronic heart failure by type 2 diabetes mellitus status, patients with concurrent type 2 diabetes mellitus were defined as those with a documented diagnosis of type 2 diabetes mellitus in their medical records, or those with HbA1c ≥6.5% at both screening and randomization. The DAPA-HF study excluded patients with type 1 diabetes mellitus. Table 14 shows the incidences of the primary composite endpoint and its components, and all-cause mortality by type 2 diabetes mellitus status in the DAPA-HF study.

Table 14. Incidences of efficacy endpoints by type 2 diabetes mellitus status (FAS)

Type 2 diabetes mellitus status	Endpoints	Placebo	Dapagliflozin	Hazard ratio[a] [95% CI]
Overall population				
With	Primary composite endpoint	25.5 (271/1064)	20.0 (215/1075)	0.75 [0.63, 0.90]
	Cardiovascular death	13.9 (148/1064)	11.3 (121/1075)	0.79 [0.63, 1.01]
	Hospitalization for heart failure/urgent heart failure visit (first event)	16.5 (176/1064)	13.2 (142/1075)	0.77 [0.61, 0.95]
	All-cause mortality	16.7 (178/1064)	13.3 (143/1075)	0.78 [0.63, 0.97]
Without	Primary composite endpoint	17.7 (231/1307)	13.2 (171/1298)	0.73 [0.60, 0.88]
	Cardiovascular death	9.6 (125/1307)	8.2 (106/1298)	0.85 [0.66, 1.10]
	Hospitalization for heart failure/urgent heart failure visit (first event)	11.5 (150/1307)	7.3 (95/1298)	0.62 [0.48, 0.80]
	All-cause mortality	11.6 (151/1307)	10.2 (133/1298)	0.88 [0.70, 1.12]
Japanese subpopulation				
With	Primary composite endpoint	23.4 (18/77)	15.1 (11/73)	0.60 [0.28, 1.29]
	Cardiovascular death	7.8 (6/77)	6.8 (5/73)	－
	Hospitalization for heart failure/urgent heart failure visit (first event)	18.2 (14/77)	12.3 (9/73)	0.63 [0.27, 1.47]
	All-cause mortality	10.4 (8/77)	6.8 (5/73)	－
Without	Primary composite endpoint	20.6 (21/102)	14.3 (13/91)	0.64 [0.32, 1.28]
	Cardiovascular death	8.8 (9/102)	7.7 (7/91)	0.90 [0.33, 2.42]
	Hospitalization for heart failure/urgent heart failure visit (first event)	15.7 (16/102)	6.6 (6/91)	0.38 [0.15, 0.98]
	All-cause mortality	10.8 (11/102)	8.8 (8/91)	0.85 [0.34, 2.10]

% (number of patients with the event/number of patients analyzed)
－: Not calculated
a: Calculated from a Cox proportional-hazards model with factors for history of heart failure hospitalization, treatment group, the relevant subgroup variable, and the interaction between the treatment group and the subgroup variable. Calculation for all-cause mortality used a model in which the history of hospitalization for heart failure was removed from the above model.

In the overall population, the incidences of the primary composite endpoint and all-cause mortality were lower in the dapagliflozin group than in the placebo group, both in patients with and without type 2 diabetes mellitus, indicating that dapagliflozin can be expected to be effective in patients with chronic heart failure, regardless of type 2 diabetes mellitus status. A similar tendency was observed in the Japanese subpopulation. In addition, patients without type 2 diabetes mellitus were divided into “patients with borderline blood glucose” (patients who were outside the category of those with type 2 diabetes mellitus, and had HbA1c ≥5.7% at both screening and randomization) and “patients with normal blood glucose” (patients who were neither those with type 2 diabetes mellitus or those with borderline blood glucose), to compare the incidences of the efficacy endpoints between patients with diabetes and patients with normal blood glucose. The resulting comparisons yielded tendencies similar to the above results for comparisons between patients with type 2 diabetes mellitus and those without diabetes.

Figure 3 shows the hazard ratios of the primary endpoint by baseline HbA1c level.

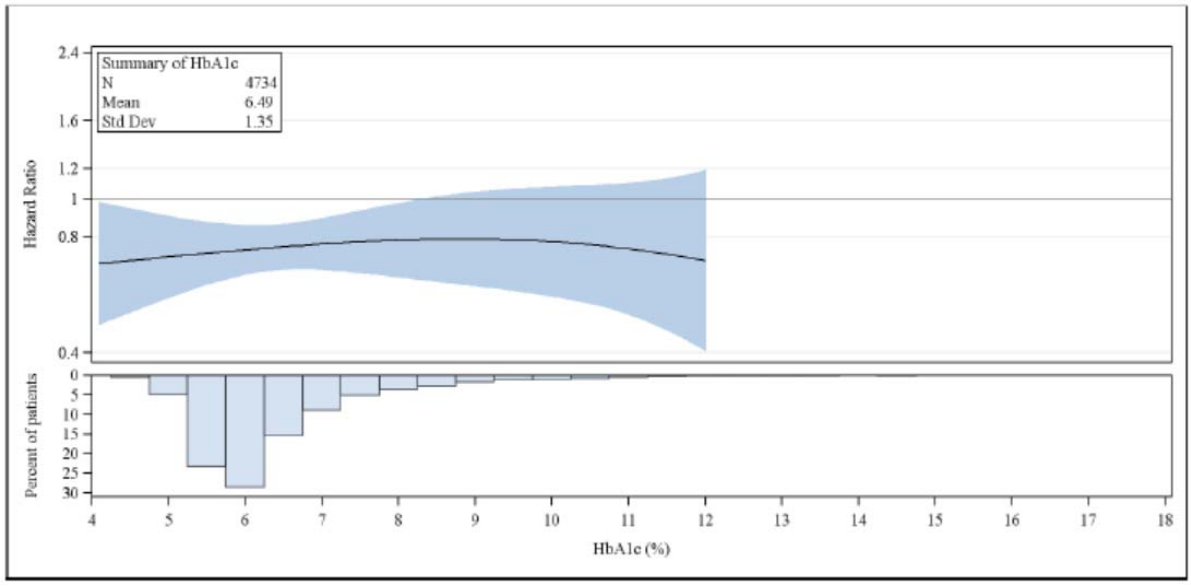

Figure 3. Hazard ratios[a)] of the primary endpoint by baseline HbA1c (FAS)

a) A hazard ratio and its 95% confidence interval, estimated from a Cox proportional-hazards model incorporating a restricted cubic spline with 3 knots placed at the 5th, 50th, and 95th percentiles of the range of HcA1c at baseline

Table 15 shows the use of antidiabetic medications in patients with type 2 diabetes mellitus in the DAPA-HF study. The proportions of patients receiving antidiabetic medications remained generally constant throughout the study period, with no marked differences between the dapagliflozin group and the placebo group. Table 16 shows the changes from baseline in HbA1c by type 2 diabetes mellitus status. In patients with type 2 diabetes mellitus, the HbA1c level declined in the dapagliflozin group compared with the placebo group, whereas the HbA1c level remained unchanged in both the dapagliflozin group and the placebo group in patients without type 2 diabetes mellitus.

Table 15. Use of antidiabetic medications in patients with type 2 diabetes mellitus (FAS)

	Overall population		Japanese subpopulation	
	Placebo (N = 1064)	Dapagliflozin (N = 1075)	Placebo (N = 77)	Dapagliflozin (N = 73)
Insulin	25.0 (266)	25.5 (274)	15.6 (12)	11.0 (8)
Biguanide	48.4 (515)	47.0 (505)	18.2 (14)	19.2 (14)
Sulfonylureas	19.8 (211)	21.3 (229)	7.8 (6)	12.3 (9)
α-Glucosidase inhibitors	4.5 (48)	4.0 (43)	11.7 (9)	11.0 (8)
Thiazolidine	0.5 (5)	0.7 (7)	3.9 (3)	2.7 (2)
DPP-4 inhibitors	14.0 (149)	15.0 (161)	55.8 (43)	58.9 (43)
GLP-1	0.9 (10)	1.0 (11)	1.3 (1)	1.4 (1)
Others	1.6 (17)	1.3 (14)	6.5 (5)	2.7 (2)

% (n)

Table 16. Change from baseline in HbA1c (%) by type 2 diabetes mellitus status (FAS)

Type 2 diabetes mellitus status	With			Without		
	Placebo	Dapagliflozin	Placebo - dapagliflozin	Placebo	Dapagliflozin	Placebo - dapagliflozin
Baseline	7.38 ± 1.56 N = 1061	7.41 ± 1.51 N = 1074	–	5.77 ± 0.39 N = 1305	5.74 ± 0.40 N = 1294	–
Day 14	−0.01 ± 0.35 N = 1027	−0.08 ± 0.40 N = 1044	−0.08±0.016	0.01 ± 0.21 N = 1281	0.01 ± 0.19 N = 1252	−0.00±0.008
Month 2	−0.03 ± 0.85 N = 1015	−0.32 ± 0.85 N = 1004	−0.30±0.036	0.02 ± 0.37 N = 1242	−0.03 ± 0.33 N = 1225	−0.06±0.013
Month 4	−0.02 ± 1.17 N = 987	−0.29 ± 1.05 N = 1007	−0.26±.047	−0.01 ± 0.35 N = 1211	0.00 ± 0.32 N = 1208	0.00±0.013
Month 8	0.04 ± 1.29 N = 942	−0.21 ± 1.14 N = 971	−0.24±0.053	0.01 ± 0.44 N = 1165	−0.02 ± 0.34 N = 1158	−0.04±0.016
Month 12	0.15 ± 1.35 N = 868	−0.19 ± 1.16 N = 918	−0.32±0.056	0.02 ± 0.38 N = 1120	−0.01 ± 0.34 N = 1130	−0.03±0.014
Month 16	0.15 ± 1.39 N = 724	−0.17 ± 1.23 N = 758	−0.30±0.062	0.05 ± 0.53 N = 942	0.02 ± 0.35 N = 937	−0.03±0.020
Month 20	0.20 ± 1.52 N = 487	−0.08 ± 1.23 N = 519	−0.26±0.079	0.04 ± 0.36 N = 652	0.04 ± 0.37 N = 648	−0.01±0.018
Month 24	0.14 ± 1.47 N = 224	−0.09 ± 1.39 N = 226	−0.22±0.103	0.08 ± 0.40 N = 289	0.05 ± 0.37 N = 284	−0.05±0.027

Mean ± standard deviation, except for between-treatment differences expressed as least squares mean ± standard error
–: Not applicable

These results indicate that dapagliflozin reduces the risks of cardiovascular death and heart failure events in patients with or without type 2 diabetes mellitus, in a manner that does not depend solely on glycaemic control.

Table 17 shows the summary of adverse events by type 2 diabetes mellitus status.

Table 17. Summary of adverse events by type 2 diabetes mellitus status (safety analysis set)

Overall population				
Type 2 diabetes mellitus status	With		Without	
Adverse events	Placebo (N = 1063)	Dapagliflozin (N = 1073)	Placebo (N = 1305)	Dapagliflozin (N = 1295)
Adverse events resulting in death[a)]	16.8 (179)	13.7 (147)	11.8 (154)	10.7 (139)
Serious adverse events	46.7 (496)	39.7 (426)	34.9 (455)	32.4 (420)
Adverse events leading to drug discontinuation	5.4 (57)	4.0 (43)	4.5 (59)	5.3 (68)
Adverse events leading to drug interruption	16.1 (171)	13.0 (139)	13.6 (178)	11.2 (145)
Adverse events leading to dose reduction	0.9 (10)	1.7 (18)	1.1 (15)	1.9 (25)
Adverse events suggestive of volume depletion	7.5 (80)	7.4 (79)	5.6 (73)	7.0 (91)
Renal events	8.2 (87)	7.8 (84)	5.4 (71)	4.4 (57)
Diabetic ketoacidosis	0 (0)	0.3 (3)	0 (0)	0 (0)
Severe hypoglycaemic events	0.4 (4)	0.4 (4)	0 (0)	0 (0)
Bone fractures[a)]	2.4 (25)	2.1 (22)	1.9 (25)	2.1 (27)
Adverse events leading to amputation[a)]	0.8 (9)	1.1 (12)	0.2 (3)	0.1 (1)
Adverse events leading to a risk for lower limb amputation[a)]	6.0 (64)	8.1 (87)	4.3 (56)	5.3 (68)
Japanese subpopulation				
Type 2 diabetes mellitus	With		Without	
Adverse events	Placebo (N = 77)	Dapagliflozin (N = 72)	Placebo (N = 102)	Dapagliflozin (N = 91)
Adverse events resulting in death[a)]	10.4 (8)	6.9 (5)	11.8 (12)	8.8 (8)
Serious adverse events	51.9 (40)	38.9 (28)	37.3 (38)	34.1 (31)
Adverse events leading to drug discontinuation	5.2 (4)	8.3 (6)	5.9 (6)	4.4 (4)
Adverse events leading to drug interruption	7.8 (6)	6.9 (5)	11.8 (12)	8.8 (8)
Adverse events leading to dose reduction	0 (0)	0 (0)	1.0 (1)	0 (0)
Adverse events suggestive of volume depletion	9.1 (7)	13.9 (10)	8.8 (9)	13.2 (12)
Renal events	11.7 (9)	2.8 (2)	8.8 (9)	1.1 (1)
Diabetic ketoacidosis	0 (0)	0 (0)	0 (0)	0 (0)
Severe hypoglycaemic events	1.3 (1)	0 (0)	0 (0)	0 (0)
Bone fractures[a)]	9.1 (7)	4.2 (3)	2.9 (3)	3.3 (3)
Adverse events leading to amputation[a)]	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to a risk for lower limb amputation[a)]	10.4 (8)	13.9 (10)	10.8 (11)	12.1 (11)

% (n)

a) Adverse events collected during the "on and off treatment period" (on or after the day of the first dose of the randomly assigned study drug, regardless of whether the patient was on or off the study treatment at the time of onset of the event). Adverse events without this note were collected during the "on treatment period" (on or after the day of the first dose of the randomly assigned study drug, and on or before 30 days after the last dose of the study drug).

In the overall population, the incidences of adverse events leading to drug discontinuation and adverse events suggestive of volume depletion tended to be slightly higher in the dapagliflozin group than in the placebo group in patients without type 2 diabetes mellitus.

The incidence of adverse events leading to drug discontinuation, for which a causal relationship to the study drug could not be ruled out was similar in the placebo group (1.8% [23 of 1305 patients]) and the dapagliflozin group (2.1% [27 of 1295 patients]). The incidence of serious adverse events was lower in the dapagliflozin group (2.1% [27 of 1295 patients]) than in the placebo group (2.7% [35 of 1305 patients]). The dapagliflozin group also produced lower mortality (2 patients) than the placebo group (4 patients).

The incidence of adverse events suggestive of volume depletion, for which a causal relationship to the study drug could not be ruled out was slightly higher in the dapagliflozin group (3.0% [39 of 1295 patients]) than in the placebo group (2.4% [31 of 1305 patients]). The incidence of serious adverse events did not markedly differ between the placebo group (0.9% [12 of 1305 patients]) and the dapagliflozin group (1.1% [14 of 1295 patients]). No deaths were reported in either of the treatment groups. Adverse events leading to dose reduction occurred more frequently in the dapagliflozin group (1.2% [15 of 1295 patients]) than in the placebo group (0.8% [10 of 1305 patients]), whereas the incidences of adverse events leading to drug discontinuation and adverse events leading to drug interruption did not differ markedly between the treatment groups. These results indicated that dapagliflozin treatment is unlikely to increase the risk of adverse events suggestive of volume depletion in patients without type 2 diabetes mellitus. The incidence of serious thromboembolic events in patients with type 2 diabetes mellitus was 7.1% (76 of 1063 patients) in the placebo group and 5.7% (61 of 1073 patients) in the dapagliflozin group, while that in patients without diabetes was 4.4% (57 of 1305 patients) and 4.4% (57 of 1295 patients), respectively, indicating no marked differences between the treatment groups, regardless of type 2 diabetes mellitus status.

All adverse events collected in the Japanese subpopulation was analyzed. The proportions of patients with type 2 diabetes mellitus experiencing at least 1 adverse event were 89.6% (69 of 77 patients) in the placebo group and 87.5% (63 of 72 patients) in the dapagliflozin group, while the proportions of patients without diabetes experiencing at least 1 adverse event were 90.2% (92 of 102 patients) and 84.6% (77 of 91 patients), respectively. There were no adverse events of clinical concern reported more frequently in patients without diabetes than in those with type 2 diabetes mellitus.

As describe above, the study results showed no increases in the risks of adverse events specific to the use of dapagliflozin in patients without type 2 diabetes mellitus; therefore, no additional precautionary statement regarding the use of dapagliflozin in patients without type 2 diabetes mellitus is necessary.

In contrast, severe hypoglycaemic events and diabetic ketoacidosis were reported only in patients with type 2 diabetes mellitus. The findings, combined with the following points, have indicated that the risks of hypoglycaemia and diabetic ketoacidosis associated with the use of dapagliflozin are unlikely to increase in patients without diabetes. Precautions regarding the risks of hypoglycaemia and diabetic ketoacidosis in patients without diabetes are therefore unnecessary.

Hypoglycaemia

- In view of the mechanism of action of dapagliflozin (lowering the threshold of renal glucose excretion, and thereby enhancing urinary glucose excretion in a blood glucose-dependent manner) and the clinical study results submitted in support of the approved applications, the risk of hypoglycaemia associated with the use of dapagliflozin is expected to increase when blood glucose levels are higher than normal or dapagliflozin is administered in combination with other blood glucose-lowering agents. Dapagliflozin is unlikely to have an excessive blood glucose-lowering effect in patients without diabetes who have no such contributing factors.

- In Japanese and foreign clinical studies, in which dapagliflozin was administered to a total of 515 healthy volunteers as a single dose of 0.001 to 500 mg or repeated doses of 2.5 to 100 mg, only 2 patients (one who received a single dose of 20 mg and the other who received repeated doses of 10 mg) experienced hypoglycaemia.

Diabetic ketoacidosis

- In patients with type 1 or 2 diabetes mellitus, dapagliflozin treatment has been reported to increase the frequency of diabetic ketoacidosis and acidosis with normal blood glucose and no obvious hyperglycemia (*Diabetes Care.* 2015;38:1638-42, *N Engl J Med.* 2019;380:347-57, etc). Dapagliflozin induces a mild increase in blood ketone bodies by accelerating urinary glucose excretion. This state of ketosis does not necessarily progress immediately to metabolic ketoacidosis, but a lack of insulin action as well as the presence of factors contributing to metabolic acidosis (sick days, dehydration, excessive exercise, pre- and post-operative periods, and excessive alcohol consumption) are also essential for disease progression. Dapagliflozin-induced urinary glucose excretion is lower in non-diabetic patients with normal endogenous insulin secretion than in diabetic patients, suggesting a lower risk of blood ketone body production.
- Urinary ketone body concentration was measured in clinical pharmacology studies in healthy volunteers (Studies MB102001 and MB102002), and the results suggested no signs of ketosis.

PMDA's view:

In the overall population of the DAPA-HF study, the efficacy of dapagliflozin in the treatment of chronic heart failure did not differ between patients with type 2 diabetes mellitus and those without diabetes, and a similar trend was noted in the Japanese subpopulation. These results have indicated that dapagliflozin can be expected to be effective in Japanese patients with chronic heart failure, regardless of diabetes status. The adverse events of special interest identified for the approved indications did not tend to increase substantially in patients with chronic heart failure who had no type 2 diabetes mellitus, compared with patients with chronic heart failure who had type 2 diabetes mellitus. In the Japanese subpopulation, from which all adverse events were collected unlike the overall population, none of the adverse events reported in the dapagliflozin group were specific to patients without type 2 diabetes mellitus. Based on these results, PMDA has agreed with the applicant's claim that the use of dapagliflozin in patients with chronic heart failure, regardless of type 2 diabetes mellitus status, requires no new precautionary statement, in addition to those for the approved indications. Meanwhile, the applicant's explanation that the risks of hypoglycaemia and ketoacidosis associated with the use of dapagliflozin may be higher in patients with diabetes is reasonable to a certain degree. Nevertheless, the same precaution as that provided for diabetic patients is needed for non-diabetic patients with chronic heart failure, in view of the fact that the risks of hypoglycaemia and ketoacidosis are attributable to the mechanism of action of dapagliflozin, regardless of diabetes status, in addition to the following points:

- Patients with chronic heart failure, regardless of diabetes status, are assumed to have factors contributing to hypoglycaemia and ketoacidosis, including malnutrition, irregular eating habits, excessive alcohol consumption, and excessive exercise.

- Patients with chronic heart failure may have contributing factors to ketoacidosis, for example, they may develop dehydration due to osmotic diuresis induced by dapagliflozin, and many of such patients are likely to use concomitant diuretics. In addition, these patients may be on fluid intake restriction.

PMDA's decision will be finalized after taking into account the comments from the Expert Discussion.

7.R.5 Efficacy and safety of dapagliflozin in patients with renal impairment

The applicant's explanation about the efficacy of dapagliflozin in patients with renal impairment:

Table 18 shows the results for the primary composite endpoint and its components, and all-cause mortality by renal function in the DAPA-HF study. In the study, patients who had eGFR <30 mL/min/1.73 m^2 at the time of enrollment were excluded.

Table 18. Incidences of efficacy endpoints by renal function (FAS)

eGFR at enrollment (mL/min/1.73 m^2)	Endpoints	Placebo	Dapagliflozin	Hazard ratio[a] [95% CI]
Overall population				
<45	Primary composite endpoint	32.8 (117/357)	20.7 (75/362)	0.59 [0.44, 0.78]
	Cardiovascular death	17.4 (62/357)	14.4 (52/362)	0.81 [0.56, 1.18]
	Hospitalization for heart failure/urgent heart failure visit (first event)	22.4 (80/357)	12.4 (45/362)	0.51 [0.36, 0.74]
	All-cause mortality	21.0 (75/357)	16.9 (61/362)	0.80 [0.57, 1.12]
≥45 and <60	Primary composite endpoint	22.6 (137/607)	19.3 (116/600)	0.83 [0.65, 1.06]
	Cardiovascular death	11.9 (72/607)	11.2 (67/600)	0.94 [0.67, 1.31]
	Hospitalization for heart failure/urgent heart failure visit (first event)	15.3 (93/607)	12.5 (75/600)	0.78 [0.58, 1.06]
	All-cause mortality	15.3 (93/607)	13.7 (82/600)	0.89 [0.66, 1.20]
≥60	Primary composite endpoint	17.6 (248/1406)	13.8 (195/1410)	0.76 [0.63, 0.92]
	Cardiovascular death	9.9 (139/1406)	7.7 (108/1410)	0.76 [0.59, 0.98]
	Hospitalization for heart failure/urgent heart failure visit (first event)	10.9 (153/1406)	8.3 (117/1410)	0.75 [0.59, 0.95]
	All-cause mortality	11.5 (161/1406)	9.4 (133/1410)	0.81 [0.64, 1.02]
Japanese subpopulation				
<45	Primary composite endpoint	30.0 (9/30)	15.4 (4/26)	–
	Cardiovascular death	10.0 (3/30)	11.5 (3/26)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	30.0 (9/30)	3.8 (1/26)	–
	All-cause mortality	10.0 (3/30)	11.5 (3/26)	–
≥45 and <60	Primary composite endpoint	17.1 (7/41)	35.9 (14/39)	2.20 [0.87, 5.52]
	Cardiovascular death	0 (0/41)	15.4 (6/39)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	17.1 (7/41)	25.6 (10/39)	1.49 [0.55, 4.00]
	All-cause mortality	2.4 (1/41)	15.4 (6/39)	–
≥60	Primary composite endpoint	21.3 (23/108)	6.1 (6/99)	0.26 [0.10, 0.63]
	Cardiovascular death	11.1 (12/108)	3.0 (3/99)	–
	Hospitalization for heart failure/urgent heart failure visit (first event)	13.0 (14/108)	4.0 (4/99)	0.28 [0.09, 0.85]
	All-cause mortality	13.9 (15/108)	4.0 (4/99)	0.27 [0.09, 0.83]

% (number of patients with the event/number of patients analyzed)
–: Not calculated
a: Calculated from a Cox proportional hazards model stratified by type 2 diabetes mellitus status at randomization, with factors for history of heart failure hospitalization, treatment group, the relevant subgroup variable, and the interaction between the treatment group and the subgroup variable. Calculation for all-cause mortality used a model in which the history of hospitalization for heart failure was removed from the above model.

In the overall population, the incidences of the primary composite endpoint and all-cause mortality were lower in the dapagliflozin group than in the placebo group, in all subgroups by renal impairment, suggesting that dapagliflozin can be expected to be effective in patients with chronic heart failure, regardless of baseline eGFR. In the Japanese subpopulation, the hazard ratio [95% CI] of the primary composite endpoint for the dapagliflozin group versus the placebo group was 2.20 [0.87, 5.52] in the subgroup of eGFR ≥45 and <60 mL/min/1.73 m^2, which was not consistent with the result obtained in the overall population. However, the inconsistency between the populations was likely to be accidental, for the following reasons: (a) the small number of patients in the subgroup precluded a precise interpretation of the results, and (b) there was no consistent trend in the relationship between the severity of renal impairment and the magnitude of efficacy, as evidenced by the lower incidence of the primary composite endpoint in the dapagliflozin group than in the placebo group in the subgroup of eGFR <45 mL/min/1.73 m^2.

Figure 4 shows the hazard ratios of the primary endpoint by eGFR at enrollment.

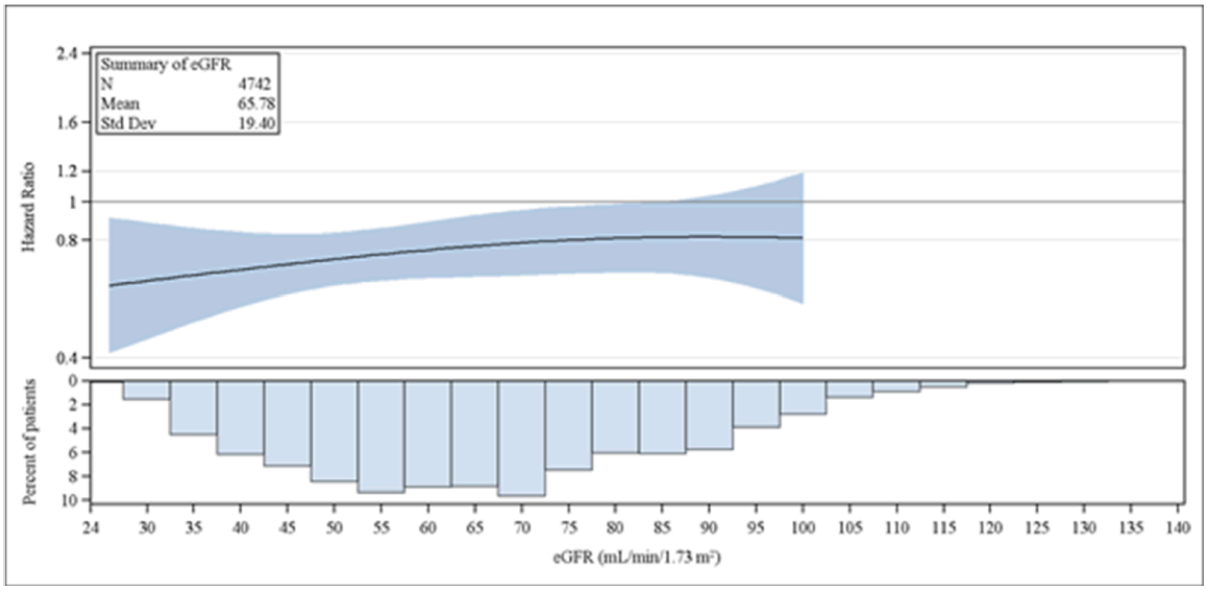

Figure 4. Hazard ratios[a)] of the primary endpoint by eGFR at enrollment (FAS)
a) A hazard ratio and its 95% confidence interval, estimated from a Cox proportional-hazards model incorporating a restricted cubic spline with 3 knots placed at the 5th, 50th, and 95th percentiles of the range of eGFR at enrollment

These results indicate that dapagliflozin reduces the risks of cardiovascular death and cardiovascular events in patients with HFrEF, regardless of renal function status.

Table 19 shows the summary of adverse events by renal function. To evaluate the pharmacokinetics of dapagliflozin in patients with renal impairment, a PPK analysis was conducted based on the pharmacokinetic data from the DAPA-HF study, clinical studies in patients with type 2 diabetes mellitus, and clinical studies in other subjects. The results revealed that the estimated AUC values of dapagliflozin in patients with moderate (eGFR 45 to 59 mL/min/1.73 m^2 or 30 to 44 mL/min/1.73 m^2) and severe (eGFR <30 mL/min/1.73 m^2) renal impairment were 1.50, 1.79, and 1.86-fold higher, respectively, than that in patients with normal renal function (eGFR >90 mL/min/1.73 m^2).

Table 19. Summary of adverse events by renal function (safety analysis set)

Overall population						
eGFR at enrollment (mL/min/1.73 m^2)	<45		≥45 and <60		≥60	
	Placebo (N = 357)	Dapagliflozin (N = 362)	Placebo (N = 605)	Dapagliflozin N = 598	Placebo (N = 1405)	Dapagliflozin (N = 1407)
Adverse events resulting in death[a)]	21.3 (76)	17.7 (64)	15.9 (96)	13.9 (83)	11.5 (161)	9.9 (139)
Serious adverse events	52.9 (189)	42.3 (153)	44.6 (270)	39.5 (236)	35.0 (492)	32.5 (457)
Adverse events leading to drug discontinuation	6.7 (24)	5.0 (18)	5.8 (35)	6.4 (38)	4.1 (57)	3.9 (55)
Adverse events leading to drug interruption	22.4 (80)	13.8 (50)	15.9 (96)	14.7 (88)	12.3 (173)	10.4 (146)
Adverse events leading to dose reduction	1.4 (5)	2.8 (10)	0.8 (5)	1.8 (11)	1.1 (15)	1.6 (22)
Adverse events suggestive of volume depletion	10.4 (37)	10.8 (39)	7.1 (43)	8.4 (50)	5.2 (73)	5.8 (81)
Renal events	16.2 (58)	12.7 (46)	8.9 (54)	7.0 (42)	3.3 (46)	3.8 (53)
Diabetic ketoacidosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (3)
Severe hypoglycaemic events	0 (0)	0.3 (1)	0 (0)	0.3 (2)	0.3 (4)	0.1 (1)
Bone fractures[a)]	2.8 (10)	4.1 (15)	2.5 (15)	2.2 (13)	1.8 (25)	1.5 (21)
Adverse events leading to amputation[a)]	1.4 (5)	0.8 (3)	0.7 (4)	0.8 (5)	0.2 (3)	0.4 (5)
Adverse events leading to a risk for lower limb amputation[a)]	9.5 (34)	9.7 (35)	5.5 (33)	8.2 (49)	3.8 (53)	5.0 (71)
Japanese subpopulation						
eGFR at baseline (mL/min/1.73 m^2)	<45		≥45 and <60		≥60	
	Placebo (N = 30)	Dapagliflozin (N = 26)	Placebo (N = 41)	Dapagliflozin (N = 38)	Placebo (N = 108)	Dapagliflozin (N = 99)
Adverse events resulting in death[a)]	10.0 (3)	11.5 (3)	4.9 (2)	15.8 (6)	13.9 (15)	4.0 (4)
Serious adverse events	43.3 (13)	38.5 (10)	46.3 (19)	50.0 (19)	42.6 (46)	30.3 (30)
Adverse events leading to drug discontinuation	0 (0)	3.8 (1)	4.9 (2)	10.5 (4)	7.4 (8)	5.1 (5)
Adverse events leading to drug interruption	10.0 (3)	11.5 (3)	12.2 (5)	7.9 (3)	9.3 (10)	7.1 (7)
Adverse events leading to dose reduction	3.3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events suggestive of volume depletion	16.7 (5)	19.2 (5)	9.8 (4)	15.8 (6)	6.5 (7)	11.1 (11)
Renal events	13.3 (4)	3.8 (1)	12.2 (5)	2.6 (1)	8.3 (9)	1.0 (1)
Diabetic ketoacidosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe hypoglycaemic events	0 (0)	0 (0)	0 (0)	0 (0)	0.9 (1)	0 (0)
Bone fractures[a)]	6.7 (2)	3.8 (1)	2.4 (1)	2.6 (1)	6.5 (7)	4.0 (4)
Adverse events leading to amputation[a)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to a risk for lower limb amputation[a)]	16.7 (5)	11.5 (3)	14.6 (6)	15.8 (6)	7.4 (8)	12.1 (12)

% (n)

a) Adverse events collected during the "on and off treatment period" (on or after the day of the first dose of the randomly assigned study drug, regardless of whether patients were on or off the study treatment at the time of onset of the event). Adverse events without this note were collected during the "on treatment period" (on or after the day of the first dose of the randomly assigned study drug, and on or before 30 days after the last dose of the study drug).

In both the overall population and the Japanese subpopulation, the incidences of adverse events did not differ markedly regardless of renal function, between the dapagliflozin group and the placebo group.

Eleven patients in the placebo group and 13 patients in the dapagliflozin group had baseline eGFR <30 mL/min/1.73 m^2 (mean of the values obtained at enrollment and randomization). The efficacy and safety of dapagliflozin were evaluated in these patients. The efficacy analyses revealed that the incidences of the primary composite endpoint in the placebo group and dapagliflozin group were 54.5% (6 of 11 patients) and 38.5% (5 of 13 patients), respectively, while the incidences of cardiovascular death were 36.4% (4 of 11 patients) and 23.1% (3 of 13 patients), respectively; the incidences of hospitalization for heart failure/urgent heart failure visit (first event) were 36.4% (4 of 11 patients) and 23.1% (3 of 13 patients), respectively; and the incidences of all-cause mortality were 36.4% (4 of 11 patients) and 30.8% (4 of 13 patients), respectively. Thus, the incidences of all of the efficacy endpoints were lower in the dapagliflozin group than in the placebo group. The safety analyses showed incidences of adverse events resulting in death of 36.4% (4 of 11 patients) in the placebo group and 30.8% (4 of 13 patients) in the dapagliflozin group, and incidences of serious adverse events of 81.8% (9 of 11 patients) and 69.2% (9 of 13 patients), respectively, with no marked differences between the treatment groups. Adverse events leading to drug discontinuation (9.1% [1 of 11 patients] in the placebo group, 23.1% [3 of 13 patients] in the dapagliflozin group), adverse events suggestive of volume depletion (18.2% [2 of 11 patients], 30.8% [4 of 13 patients]), renal events (18.2% [2 of 11 patients], 30.8% [4 of 13 patients]), and adverse events leading to a risk for lower limb amputation (9.1% [1 of 11 patients], 30.8% [4 of 13 patients]) were more frequently reported in the dapagliflozin group than in the placebo group. The serious adverse events for which a causal relationship to the study drug could not be ruled out were hypovolaemia in 1 patient in the placebo group and renal disorder in 1 patient in the dapagliflozin group. The latter event resolved without a change in the dose of the study drug. No severe cases of hypoglycaemic events, diabetic ketoacidosis, bone fractures, or adverse events leading to amputation were reported.

In light of the above findings, dapagliflozin has promising efficacy and acceptable safety in the treatment of chronic heart failure in patients with moderate renal impairment, although the package insert warns that this patient population may fail to achieve an adequate response (a blood glucose-lowering effect) to dapagliflozin for the approved indications. It is thus unnecessary to provide a precautionary statement regarding the use of dapagliflozin in patients with moderate renal impairment who have chronic heart failure. The use of dapagliflozin is not recommended in patients with severe renal impairment for the approved indications because the patient population is unlikely to achieve an adequate response (a blood glucose-lowering effect) to dapagliflozin. Although a precise assessment is difficult due to limited clinical experience, some patients with severe renal impairment were assessed in the study. The DAPA-HF study showed that the safety of dapagliflozin in patients with severe renal impairment did not tend to differ markedly from that in other renal function subgroups. Therefore, dapagliflozin can be used in patients with severe renal impairment for the treatment of heart failure. However, the package insert will include a precautionary statement to the effect that clinical experience with the use of dapagliflozin in patients with severe renal impairment is limited, and information about the use of dapagliflozin in patients with renal impairment with eGFR <45 mL/min/1.73 m^2 will be collected through the post-marketing surveillance.

PMDA's view on the use of dapagliflozin in the treatment of chronic heart failure in patients with renal impairment:

Efficacy

The mechanism of action by which dapagliflozin contributes to the treatment of chronic heart failure remains unclear, and the relationship between renal function and the efficacy of dapagliflozin cannot be assessed from the viewpoint of the mechanism of action. However, a subgroup analysis by eGFR at enrollment in the overall population of the DAPA-HF study showed that the efficacy of dapagliflozin did not tend to differ markedly according to the severity of renal impairment. This result suggests that dapagliflozin can be expected to be effective in all of the subgroups analyzed.

Safety

In the overall population of the DAPA-HF study, the incidences of a majority of the adverse events tended to be higher with an increase in the severity of renal impairment in the dapagliflozin group; however, the incidences in the dapagliflozin group did not differ markedly from those in the placebo group. The safety of dapagliflozin is thus clinically acceptable. The safety of dapagliflozin in the Japanese subpopulation did not tend to clearly differ from that in the overall population, although the small number of Japanese patients with moderate or severe renal impairment precluded a precise interpretation of the study results.

Based on the above, the results of the DAPA-HF study have shown that dapagliflozin has promising efficacy and acceptable safety in the treatment of chronic heart failure in patients with moderate renal impairment including those with eGFR <45 mL/min/1.73 m^2. Therefore, the applicant's claim is acceptable; namely, patients with moderate renal impairment are eligible for dapagliflozin treatment, and an additional precautionary statement regarding the use of dapagliflozin in such patient population is unnecessary.

In addition, the results of the DAPA-HF study have identified no clinically unacceptable risks associated with the use of dapagliflozin in patients with severe renal impairment. However, the package insert should include a precautionary statement to the effect that the use of dapagliflozin in patients with renal impairment with eGFR <30 mL/min/1.73 m^2 should be carefully considered, in view of the following: (a) Clinical experience with the use of dapagliflozin in patients with renal impairment with eGFR <30 mL/min/1.73 m^2 is extremely limited; (b) the AUC of dapagliflozin in such patient population is expected to increase to 1.86 times that in patients with normal renal function; (c) renal impairment can be a risk factor for volume depletion and ketoacidosis, which are known risks associated with the use of dapagliflozin; and, (d) the incidences of adverse events suggestive of volume depletion and renal events tended to be higher in patients with eGFR <30 mL/min/1.73 m^2 on dapagliflozin than in those on placebo in the DAPA-HF study. In addition, information about the use of dapagliflozin in patients with renal impairment with eGFR <45 mL/min/1.73 m^2 should be collected in the post-marketing setting. The appropriateness of including precautionary statements regarding the use of dapagliflozin in patients with renal impairment in the package insert will be determined after taking into account the comments from the Expert Discussion.

7.R.6 Indication and target patient population

The applicant's explanation about the indication and target patient population of dapagliflozin:

The eligible population for enrollment in the DAPA-HF study, which served as the pivotal study demonstrating the efficacy and safety of dapagliflozin in the treatment of chronic heart failure, was patients with HFrEF who were treated with the standard of care for chronic heart failure. The efficacy and safety of dapagliflozin in the treatment of chronic heart failure were demonstrated in the DAPA-HF study, and the results were similar in patients with type 2 diabetes mellitus and those without diabetes [see Section "7.R.4 Efficacy and safety of dapagliflozin in patients with or without type 2 diabetes mellitus"]. Since the present application has included no data regarding the efficacy or safety of dapagliflozin in patients with heart failure with preserved LVEF, dapagliflozin should be indicated for patients with chronic heart failure who were eligible for enrollment in the DAPA-HF study. Accordingly, the proposed indication is the treatment of "chronic heart failure." To clarify the recommended patient population for dapagliflozin therapy, the proposed "Precautions Concerning Indications" section will include a precautionary statement that eligible patients should be identified based on a good understanding of the characteristics (LVEF) of patients enrolled in the clinical study.

PMDA's view:

The DAPA-HF study, which served as the pivotal study demonstrating the efficacy and safety of dapagliflozin in the present application, showed the efficacy of dapagliflozin as an add-on to the standard of care for chronic heart failure in patients with HFrEF, regardless of type 2 diabetes mellitus, and the results raised no new safety concerns in the treatment of chronic heart failure, as compared with the approved indications [see Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4 Efficacy and safety of dapagliflozin in patients with or without type 2 diabetes mellitus"]. The efficacy of dapagliflozin in the Japanese subpopulation was consistent with that in the overall population. In addition, safety analyses identified no clinically significant differences in the incidences of adverse events analyzed between Japanese and non-Japanese patients, although not all adverse events were collected in the overall population [see Sections "7.R.2.2 Efficacy in the Japanese subpopulation of the DAPA-HF study" and "7.R.3 Safety"]. In principle, the target patient population of dapagliflozin should be the same as the patients eligible for enrollment in the DAPA-HF study, which demonstrated the efficacy and safety of dapagliflozin.

In view of the above considerations, dapagliflozin should be used as a treatment option added to the standard of care for chronic heart failure in patients with HFrEF. To clarify the target patient population of dapagliflozin, the "Indications" section should include the statement presented below, and information about the characteristics (e.g., LVEF) of patients who are currently recommended to receive dapagliflozin should be included in the "Precautions Concerning Indications" section. A clinical study in patients with chronic heart failure with preserved ejection fraction (HFpEF) is still underway, and the efficacy and safety of dapagliflozin have not been established in patients with HFpEF; therefore, information about the use of dapagliflozin in patients with HFpEF should be appropriately provided to healthcare professionals. The target patient population, and statements to be included in the "Indications" and "Precautions Concerning Indications" sections will be finalized after taking into account the comments from the Expert Discussion.

Indications (Underline denotes changes from the proposed indication)
Chronic heart failure
(limited to patients who are receiving standard of care for chronic heart failure)

7.R.7 Dosage and administration

The applicant's explanation about the rationale for the proposed dosage and administration:
In the clinical development program undertaken to obtain the marketing approval of dapagliflozin for the treatment of chronic heart failure, no dose-finding studies were conducted. Dapagliflozin is approved in Japan for the treatments of type 2 and 1 diabetes mellitus, with the following dosage regimen: "The usual adult dosage is 5 mg once daily. The dose may be increased to 10 mg once daily for patients with an inadequate response." The safety of dapagliflozin 10 mg once daily has been demonstrated in clinical studies in patients with type 2 or 1 diabetes mellitus, as well as clinical practice. The results of a dose-finding study in healthy adult volunteers and patients with type 2 diabetes mellitus have indicated that dapagliflozin 10 mg almost maximally inhibits SGLT2 in the kidneys. Chronic heart failure is a progressive disease, and is highly fatal if aggravated. The applicant therefore considered that a dosage regimen with reliable efficacy should be selected for the DAPA-HF study unless safety concerns would be raised. Thus, a dose of 10 mg was selected to maximally inhibit SGLT2 while ensuring safety. The results of the DAPA-HF study demonstrated the promising efficacy and acceptable safety of dapagliflozin. The applicant decided to propose the dosage regimen used in the study. In the DAPA-HF study, the dose reduction of the study drug was allowed in cases where an adverse event suggestive of volume depletion, hypotension, and/or an unexpected worsening of renal function occurred. Among the randomized patients, 1.6% (39 of 2368) of patients in the placebo group and 1.9% (45 of 2368) of patients in the dapagliflozin group had at least 1 dose reduction to dapagliflozin 5 mg (or matching placebo). The majority of the patients with a dose reduction (30 of 39 patients in the placebo group and 37 of 45 patients in the dapagliflozin group) did not return to the dose of 10 mg (or matching placebo). The reasons for dose reductions in the placebo group were "adverse events" in 28 patients, "serious adverse events" in 1 patient, "the patient's decision" in 7 patients, and "unknown" in 3 patients, while those in the dapagliflozin group were "adverse events" in 42 patients and "serious adverse events" in 3 patients. The incidences of adverse events leading to dose reduction were 1.1% (25 of 2368 patients) in the placebo group and 1.8% (43 of 2368 patients) in the dapagliflozin group. The most common adverse events leading to dose reduction included hypotension (0.5% in the placebo group vs. 0.8% in the dapagliflozin group), hypovolaemia (0.1% vs. 0.2%), and renal failure (0.1% vs. 0.2%). In the Japanese subpopulation, 1 patient each in both of the treatment groups had a dose reduction due to adverse events. The patient in the dapagliflozin group did not return to the dose of 10 mg. The adverse event leading to dose reduction in the patient in the placebo group was chronic kidney disease. The efficacy of dapagliflozin at a dose of 5 mg in the treatment of chronic heart failure was not evaluated due to the small number of patients requiring a dose reduction to 5 mg; therefore, no conclusion regarding the benefit-risk balance of dapagliflozin 5 mg can be drawn. Based on the above findings, healthcare professionals will be advised to take appropriate measures, including treatment discontinuation, if treatment with dapagliflozin 10 mg cannot be continued due to a dapagliflozin-related adverse event. There is no need to specify a rule for dose reduction to 5 mg.

PMDA asked the applicant to explain the dosage regimen recommended for the treatment of chronic heart failure in patients with type 1 diabetes mellitus, and the necessity of any precautionary statement specific to this patient population:

The applicant's explanation:
Although patients with type 1 diabetes mellitus were excluded from the DAPA-HF study, the regimen of dapagliflozin 10 mg once daily is within the approved dosage regimens for the treatment of type 1 diabetes mellitus, for which the safety of dapagliflozin has been demonstrated. No new safety concerns are likely to be raised by the use of the once-daily 10 mg regimen for the treatment of chronic heart failure in patients with type 1 diabetes mellitus. In view of the fact that the efficacy of dapagliflozin at a dose of 5 mg in the treatment of chronic heart failure has not been demonstrated, the 10 mg dose is required for patients with chronic heart failure who have type 1 diabetes mellitus. In contrast, the recommended initial dose of dapagliflozin in the treatment of type 1 diabetes mellitus is 5 mg, followed by appropriate insulin dose adjustment. As with the treatment of type 1 diabetes mellitus, dapagliflozin therapy for chronic heart failure in patients with type 1 diabetes mellitus should be initiated at 5 mg to minimize the risks of severe hypoglycaemia and diabetic ketoacidosis. In clinical studies that evaluated the efficacy and safety of dapagliflozin administered as an adjunct to insulin therapy in patients with type 1 diabetes mellitus (Studies MB102229 and MB102230), the daily dose of insulin was kept nearly stable from 2 weeks after the start of dapagliflozin therapy onwards. In view of the results, an increase in the dose of dapagliflozin to 10 mg should be decided to gain adequate clinical benefits, at 2 to 4 weeks after the start of treatment with dapagliflozin 5 mg, after confirming a stable insulin dose achieved and the patient's safety. This decision should be made comprehensively, based on the percent reduction of the insulin dose, the incidences of severe hypoglycaemia and diabetic ketoacidosis, signs of hypoglycaemia and diabetic ketoacidosis, urinary and blood ketone body concentrations, and other relevant data. Based on the above, the package insert will include a precautionary statement that dapagliflozin therapy for patients with chronic heart failure who have type 1 diabetes mellitus should be initiated at 5 mg once daily, and that the insulin dose should be adjusted while carefully monitoring the patient's condition, after which the dose of dapagliflozin should be increased to 10 mg once daily, in close cooperation with a physician who is well-versed in the treatment of diabetes. The use of dapagliflozin has been shown to increase the risk of diabetic ketoacidosis, particularly in patients with type 1 diabetes mellitus, and precautions regarding this risk have been provided in the package insert, and materials for healthcare professionals and patients. These risk minimization activities will be extended to cardiologists, and information about the use of dapagliflozin in patients with chronic heart failure who have type 1 chronic diabetes mellitus will be collected in the post-marketing setting.

PMDA's view:
Although limited information about the recommended dose of dapagliflozin in the treatment of heart failure was available when the DAPA-HF study was planned, the results of the study have shown that the proposed dosage and administration is appropriate for the treatment of chronic heart failure. In the DAPA-HF study, dose reduction of dapagliflozin to 5 mg was allowed per protocol; however, only a few patients actually had

dose reduction. A majority of patients tolerated the 10 mg dose. In view of this fact, combined with the applicant's explanation that limited information is available to support the efficacy of dapagliflozin chronically administered at 5 mg in the treatment of heart failure, the recommended dosage of 10 mg once daily is appropriate, provided that healthcare professionals should be cautioned to take appropriate measures, including treatment discontinuation, if the 10 mg dose is intolerable.

The applicant's explanation about dapagliflozin therapy for patients with chronic heart failure who have type 1 diabetes mellitus is appropriate. Namely, dapagliflozin therapy for such patients should be initiated at 5 mg once daily to reduce the risks of severe hypoglycaemia, ketoacidosis, and other events, and the dose should be increased to 10 mg once daily after confirming a stable insulin dose achieved and the patient's safety, by carefully monitoring the percent reduction of insulin dose, signs of severe hypoglycaemia and diabetic ketoacidosis, clinical laboratory results, etc. When dapagliflozin is administered to patients with chronic heart failure who have type 1 diabetes mellitus, it is crucial to adjust the insulin dose while carefully monitoring the patient's condition, and to then decide whether to continue treatment with dapagliflozin at a dose increased to 10 mg, in cooperation with a physician who is well-versed in the treatment of diabetes. The applicant plans to include a precautionary statement to this effect in the package insert, and materials for healthcare professionals and patients. The applicant's plan is appropriate. PMDA's decision will be finalized after taking into account the comments from the Expert Discussion.

7.R.8 Post-marketing investigations

The applicant's explanation about the post-marketing investigations for dapagliflozin:

The results of the DAPA-HF study have raised no new safety concerns about the use of dapagliflozin in the treatment of chronic heart failure, as compared with the safety profiles observed in patients receiving dapagliflozin for the approved indications. However, patients with chronic heart failure are assumed to more often have risk factors for volume depletion, such as the concomitant use of diuretics, and dapagliflozin therapy for chronic heart failure has not yet been adequately evaluated in patients with type 1 diabetes mellitus, or patients with moderate or severe renal impairment in clinical studies. In view of these and other facts, concerns to be addressed as the safety specifications in the risk management plan (draft) are volume depletion, and effects associated with increased ketone levels and ketoacidosis in diabetic patients with chronic heart failure. Therefore, a general use-results survey will be conducted to investigate the incidences of volume depletion, effect associated with increased ketone levels, and ketoacidosis in patients with chronic heart failure receiving dapagliflozin in clinical practice. This survey will employ a central registry system, with a target sample size of 1000 patients with evaluable safety data, and an observation period of 1 year. The target sample size of 1000 patients will enable an exploration of the risk factors contributing to volume depletion, and an assessment of the risks of diabetic ketoacidosis in individual patients with chronic heart failure who have type 1 diabetes mellitus, who were excluded from the DAPA-HF study. In addition, as much information as possible will be collected from other special populations, including those with NYHA class III or higher and those with renal impairment.

PMDA's view:

The post-marketing surveillance should involve the assessment of events such as hypoglycaemia and renal disorder, which were selected as important identified risks or important potential risks for the approved indications, and which will also warrant attention when dapagliflozin is administered to patients with chronic heart failure, including non-diabetic patients, in addition to events proposed by the applicant. Details of the post-marketing surveillance, including the identification of safety specifications and the appropriateness of risk classification, pharmacovigilance activities, and risk minimization activities, will be finalized according to the Risk Management Guidance (Notification No. 0411-1 of the Safety Division, Pharmaceutical Food and Safety Bureau (PFSB), Ministry of Health, Labour and Welfare (MHLW) and No. 0411-2 of the Evaluation and Licensing Division, PFSB, MHLW, jointly issued on April 11, 2012), after discussed in the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that dapagliflozin (Forxiga) has efficacy in the treatment of chronic heart failure and that dapagliflozin has acceptable safety in view of its benefits. Forxiga, an SGLT2 inhibitor, offers a new treatment option to patients with chronic heart failure, which is of clinical significance. The indication, dosage and administration, precautionary statements to be included in the package insert, post-marketing investigations, etc. should be further discussed.

PMDA has concluded that Forxiga may be approved if Forxiga is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

October 12, 2020

Product Submitted for Approval	
Brand Name	Forxiga 5 mg Tablets, Forxiga 10 mg Tablets
Non-proprietary Name	Dapagliflozin Propylene Glycolate Hydrate
Applicant	AstraZeneca K.K.
Date of Application	January 16, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

1.1 Efficacy

Results from the DAPA-HF study showed the superiority of dapagliflozin to placebo in reducing the incidence of the primary composite endpoint, and the consistency of efficacy results between the Japanese subpopulation and the overall population. Based on the study results and other findings, PMDA has concluded that the efficacy of dapagliflozin had been demonstrated in Japanese patients with heart failure with reduced ejection fraction (HFrEF). The expert advisors supported PMDA's conclusion.

1.2 Safety

According to the results of the DAPA-HF study, no new safety concerns have been raised regarding any of the adverse events requiring attention identified for the approved indications, including adverse events suggestive of volume depletion, which are considered to warrant more attention in the treatment of chronic heart failure than for the approved indications. In addition, the package insert for dapagliflozin already includes appropriate precautionary statements on each of the adverse events requiring attention. Based on these facts, PMDA has concluded that there is currently no need to provide additional precautions. The expert advisors supported PMDA's conclusion.

1.3 Efficacy and safety of dapagliflozin in patients with chronic heart failure who have type 2 or those without diabetes mellitus

In the DAPA-HF study, there were no differences in the efficacy of dapagliflozin in the treatment of chronic heart failure between patients with type 2 diabetes mellitus and those without diabetes, and a similar tendency was observed in the Japanese subpopulation. Based on the study results, PMDA has concluded that dapagliflozin can be expected to be effective in Japanese patients with chronic heart failure, regardless of type 2 diabetes mellitus status. PMDA's conclusion was supported by the expert advisors.

In the DAPA-HF study, the incidence of the adverse events requiring attention identified for the approved indications did not tend to increase substantially in patients without type 2 diabetes mellitus, compared with those with diabetes. All adverse events were collected in the Japanese subpopulation, unlike the overall population. According to an analysis of the adverse events, there were no adverse events specific to patients without type 2 diabetes mellitus. Based on the above study results, PMDA has concluded that no additional precautions are necessary to address safety concerns associated with the use of dapagliflozin in the treatment of chronic heart failure, compared with those specified for the approved indications. PMDA's conclusion was supported by the expert advisors. Both hypoglycaemia and ketoacidosis are risks expected from the mechanism of action of dapagliflozin, regardless of diabetes status, and patients with chronic heart failure with or without diabetes are assumed to have factors contributing to hypoglycaemia or ketoacidosis. Based on these and other findings, PMDA has concluded that the same precautions as that provided to advise diabetic patients are needed for non-diabetic patients with chronic heart failure. This PMDA's conclusion was also supported by the expert advisors.

1.4 Efficacy and safety of dapagliflozin in patients with renal impairment

In the DAPA-HF study, the efficacy or safety of dapagliflozin did not tend to differ depending on eGFR at enrollment in the overall population, and there was also no trend toward a clear difference among the subgroups classified by eGFR in the Japanese subpopulation. Based on these study results, PMDA has concluded that patients with moderate renal impairment are eligible for dapagliflozin therapy for chronic heart failure, and that no additional precautions regarding the use of dapagliflozin in such patients are necessary. PMDA's conclusion was supported by the expert advisors.

The expert advisors' comments on the use of dapagliflozin in patients with severe renal impairment:
The mechanism of action by which dapagliflozin contributes to the treatment of chronic heart failure remains unknown. However, decreased renal function results in a reduction in osmotic diuresis induced by SGLT2 inhibition by dapagliflozin in the proximal renal tubules, possibly lowering the effectiveness of dapagliflozin in the treatment of heart failure. In addition, dapagliflozin exposure is expected to increase in patients with severe renal impairment, and clinical experience with the use of dapagliflozin in this patient population was extremely limited in the DAPA-HF study, In light of the above information, the eligibility of patients with severe renal impairment for dapagliflozin therapy should be carefully assessed.

PMDA's conclusion:

Patients with severe renal impairment should not be excluded from the target patient population of dapagliflozin, provided that physicians are alerted of the need to carefully consider whether to initiate dapagliflozin therapy in such patients; and information about the use of dapagliflozin in patients with renal impairment with eGFR <45 mL/min/1.73 m^2 should be collected in the post-marketing setting, in view of the following: (a) A diuretic action is not necessarily considered to solely responsible for the effectiveness of dapagliflozin in the treatment of heart failure; (b) the results of the DAPA-HF study have shown that the efficacy of dapagliflozin does not differ depending on the severity of renal impairment; and, (c) available (albeit limited) data have identified no clinically unacceptable safety concerns.

PMDA's conclusion was supported by the expert advisors.

1.5 Clinical positioning and indication

The expert advisors supported PMDA's conclusion that offering dapagliflozin to patients in clinical practice in Japan as a new treatment option added to standard of care for chronic heart failure in patients with HFrEF has significance.

At the same time, the expert advisors gave the following comments regarding PMDA's conclusion that dapagliflozin should be indicated for the treatment of "chronic heart failure (limited to patients who are receiving standard of care for chronic heart failure)," and that information about the characteristics (e.g., LVEF) of patients who are currently recommended to receive dapagliflozin should be included in the "Precautions Concerning Indications" section of the package insert, to clarify the target patient population of dapagliflozin:

- The target patient population for dapagliflozin therapy to be stated in the "Indications" and "Precautions Concerning Indications" sections should be more clearly defined based on current scientific knowledge and evidence, because the clinical condition of chronic heart failure is recently classified according to LVEF.
- Many patients with HFpEF have diabetes, and dapagliflozin has been approved for the treatment of diabetes. In view of these facts, dapagliflozin may be chosen by non-cardiologists who are not well-versed in the treatment of chronic heart failure in diabetic patients, with an expectation of a therapeutic effect on chronic heart failure without consideration for LVEF. Since dapagliflozin may be more easily used for patients with HFpEF than existing medications for chronic heart failure, the package insert should further clarify the target patient population of dapagliflozin based on LVEF.
- Little evidence is available to conclude that dapagliflozin has no promising efficacy or that it raises safety concerns in the treatment of HFpEF. The osmotic diuretic action of dapagliflozin may be effective to treat HFpEF. Thus, no evidence suggest that patients with HFpEF are ineligible for dapagliflozin therapy. A statement that the efficacy and safety of dapagliflozin have not been established in the treatment of HFpEF should be included in the "Precautions Concerning Indications" section.

PMDA's conclusion:
PMDA rediscussed the clinical positioning and indication of dapagliflozin, in view of the above comments from the expert advisors, combined with the fact that dapagliflozin is expected to produce a new pharmacological action for treatment of heart failure, as well as the fact that a clinical study of dapagliflozin is currently underway in patients with HFpEF, with no currently available data on the efficacy or safety of dapagliflozin. As a result of the discussion, PMDA has concluded that the following statements should be included in the "Indications" and "Precautions Concerning Indications" sections of the package insert, that a detailed description of the characteristics, including LVEF, of the patients enrolled in the clinical study should be included in the "Clinical Studies" section, and that healthcare professionals should be advised through materials for healthcare professionals to appropriately identify eligible patients for dapagliflozin therapy, in cooperation with a physician who is well-versed in each indication of dapagliflozin, as necessary. Data from the clinical study in patients with HFpEF should be appropriately communicated to healthcare professionals.

In the end, PMDA's conclusions were supported by the expert advisors. PMDA instructed the applicant to take the necessary measures, and confirmed that the applicant had done so.

Indications

Chronic heart failure
(limited to patients who are receiving standard of care for chronic heart failure)

Precautions Concerning Indications

Chronic heart failure

- Since the efficacy and safety of dapagliflozin in the treatment of HFpEF have not been established, dapagliflozin should be administered to patients with HFrEF.
- Eligible patients should be identified after carefully reading the "Clinical Studies" section to understand the characteristics (e.g., prior treatments, LVEF) of patients enrolled in the clinical study.

1.6 Dosage and administration

The expert advisors supported PMDA's conclusion that the dosage and administration of dapagliflozin for the treatment of chronic heart failure should be 10 mg orally once daily.

The expert advisors also supported the following PMDA's conclusions: Although patients with type 1 diabetes mellitus were excluded from the DAPA-HF study, dapagliflozin is allowed to be used in the treatment of chronic heart failure in patients with type 1 diabetes mellitus, provided that it should be administered to such patients according to the starting dosage and advice provided specifically for patients with type 1 diabetes mellitus, in cooperation with a physician who is well-versed in the treatment of diabetes or under his/her supervision, while the patient's condition is carefully monitored to reduce the risks of severe hypoglycaemia, ketoacidosis, and other events; and healthcare professionals and patients should be alerted to this effect through the package insert and other materials.

Based on the above, the following statements should be included in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections.

Dosage and Administration

The usual adult dosage is 10 mg of dapagliflozin administered orally once daily.

Precautions Concerning Dosage and Administration

Chronic heart failure

- Dapagliflozin therapy for patients with type 1 diabetes mellitus should be initiated at 5 mg once daily, under management that enables appropriate measures, in cooperation with a physician who is well-versed in the treatment of diabetes or under his/her supervision, and the dose should be increased to 10 mg once daily after a stable insulin dose has been achieved, while the patient's condition is carefully monitored. The efficacy of dapagliflozin administered at 5 mg once daily in the treatment of chronic heart failure has not been established.

1.7 Risk management plan (draft)

In view of the discussions presented in Section "7.R.8 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the safety specifications itemized in Table 20 should be included in the current draft risk management plan for dapagliflozin, and that the additional pharmacovigilance activities and risk minimization activities listed in Table 21 for the new indication, and the general use-results survey summarized in Table 22 should be conducted.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Genital infection • Urinary tract infection • Hypoglycaemia • Polyuria/pollakiuria • Events related to volume depletion • Impact of increased ketone bodies/ketoacidosis	• Impact of decreased weight on safety • Renal disorder • Liver disorder • Fracture • Malignant tumour • Lower limb amputation	• Safety in elderly patients during treatment • Safety in patients with renal impairment during treatment • Safety in patients with hepatic impairment during treatment
Efficacy specification		
None		

Table 21. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance in patients with chronic heart failure • Post-marketing database investigation in patients with type 1 diabetes mellitus (effect associated with increased ketone levels and ketoacidosis) • General use-results survey in patients with chronic heart failure	• Disseminate data gathered during the early post-marketing phase vigilance in patients with chronic heart failure • Organize and disseminate information for patients (for patients receiving Forxiga Tablets and their families [all indications]) • Organize and disseminate information for patients (for patients with type 1 diabetes mellitus receiving Forxiga Tablets and their families [type 1 diabetes mellitus], guide for patients with type 1 diabetes mellitus [portable patient card] [type 1 diabetes mellitus]) • Organize and disseminate information for healthcare professionals (guide for proper use [all indications]) • Organize and disseminate information for healthcare professionals (guide for healthcare professionals using Forxiga Tablets [type 1 diabetes mellitus])

Underline denotes activities relating to the indication proposed in the present application.

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

Objective	To evaluate the safety and other aspects of dapagliflozin in clinical practice
Survey method	Central registry system
Population	Patients with chronic heart failure who received dapagliflozin for the first time
Observation period	1 year
Planned sample size	1000 patients with evaluable safety data
Main survey items	Hypoglycaemia, events related to volume depletion, effects associated with increased ketone levels and ketoacidosis, incidence of renal disorder, patient characteristics (age, NYHA functional class, renal function, complications, etc.), concomitant medications, heart failure events (all-cause mortality, cardiovascular death, hospitalization for heart failure), etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved with the indications and the dosage and administration as shown below with the following approval condition. The present application is intended for the addition of a new indication and a new dosage; accordingly, the re-examination period is 4 years for the indication and dosage and administration in the present application.

Indications

Type 2 diabetes mellitus

Type 1 diabetes mellitus

Chronic heart failure

(limited to patients who are receiving standard of care for chronic heart failure)

Dosage and Administration

Type 2 diabetes mellitus

The usual adult dosage is 5 mg of dapagliflozin administered orally once daily. The dose may be increased to 10 mg once daily for the patient with an inadequate response to the 5 mg dose if the patient is followed up carefully.

Type 1 diabetes mellitus

The usual adult dosage is 5 mg of dapagliflozin administered orally once daily, in combination with an insulin formulation. The dose may be increased to 10 mg once daily for the patient with an inadequate response to the 5 mg dose if the patient is followed up carefully.

Chronic heart failure

The usual adult dosage is 10 mg of dapagliflozin administered orally once daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ACE	Angiotensin converting enzyme
ARB	Angiotensin II receptor blocker
AUC	Area under the plasma concentration-time curve
ASC	Apoptosis-associated speck-like protein
BBN	N-butyl-N-(4-hydroxybutyl)-nitrosamine
BMI	Body mass index
BTBR	Black and tan brachyury
C_{max}	Maximum plasma concentration
CL/F	Apparent clearance
Ccr	Creatinine clearance
CKD classification	Classification based on the estimated glomerular filtration rate
CRT-D	Cardiac resynchronization therapy defibrillator
CRT-P	Cardiac resynchronization therapy pacemaker
Dapagliflozin	Dapagliflozin Propylene Glycolate Hydrate
DPP-4	Dipeptidyl peptidase-4
D1699C00001 study	DAPA-HF study
EC_{50}	Effective concentration resulting in 50%
eGFR	Estimated glomerular filtration rate
E_{max}	Maximum effect
FAS	Full Analysis Set
FDA	Food and Drug Administration
Forxiga	Forxiga Tablets 5 mg and Forxiga Tablets 10 mg
FS	Fractional shortening
GFR	Glomerular filtration rate
GLP-1	Glucagon-like peptide-1
Guidelines for Bioequivalence Studies	Guidelines for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (Notification No. 67 dated February 14, 2000, by the Evaluation and Licensing Division, PMSB, amended by Notification 0229 No. 10 dated February 29, 2012, by the Evaluation and Licensing Division, PFSB)
HbA1c	Glycosylated haemoglobin Hemoglobin A1c
HFrEF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter defibrillator
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IVSd	Interventricular septum thickness at end-diastole
IVSs	Interventricular septum thickness at end-systole
LAD	Left anterior descending artery
LC-MS/MS	high performance liquid chromatography/tandem mass spectrometry
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
LVEDV	Left ventricular end-diastolic volume
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MRA	Mineralocorticoid receptor antagonist
mRNA	Messenger ribonucleic acid
NHE-1	Sodium-hydrogen antiporter-1
NLRP3	NACHT, LRR and PYD domains-containing protein 3
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association

PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred terms
PPK	Population pharmacokinetics
RT-PCR	Reverse transcription-polymerase chain reaction
SGLT2	Sodium-glucose co-transporter 2
SMQ	Standardised MedDRA queries
SOC	System Organ Class
V2/F	Apparent volume of distribution of the central compartment