FORXIGA™

(Dapagliflozin)

1. NAME OF THE MEDICINAL PRODUCT

FORXIGA, tablets, 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

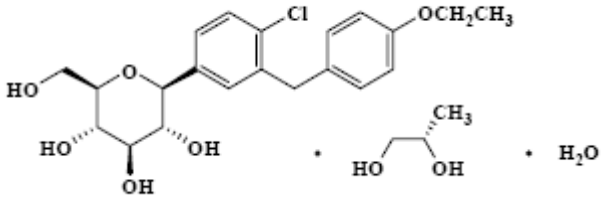
Each film-coated tablet contains 10 mg dapagliflozin as dapagliflozin propanediol

3. PHARMACEUTICAL FORM

Yellow, biconvex, diamond-shaped, film-coated tablets with “10” debossed on one side and “1428” debossed on the other side.

For excipients, see section 6.1

Dapagliflozin propanediol is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ and the molecular weight is 502.98. The structural formula is:



4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Type 2 diabetes mellitus

FORXIGA is indicated in adults with type 2 diabetes mellitus for:

- the treatment of diabetes as an adjunct to diet and exercise. FORXIGA can be given as monotherapy or in combination with other medicinal products indicated for the treatment of type 2 diabetes mellitus (see section 5.1 Pharmacodynamic properties Clinical trial information – type 2 diabetes mellitus).

- reduce the risk of new or worsening heart failure or cardiovascular death (see section 5.1 Pharmacodynamic properties Clinical trial information – type 2 diabetes mellitus).
- reduce the risk of new or worsening nephropathy (see section 5.1 Pharmacodynamic properties Clinical trial information – type 2 diabetes mellitus).

Heart failure

FORXIGA is indicated in adults for the treatment of symptomatic chronic heart failure . (see section 5.1 Pharmacodynamic properties Clinical trial information – heart failure).

Chronic kidney disease

FORXIGA is indicated in adults for the treatment of chronic kidney disease (see section 5.1 Pharmacodynamic properties Clinical trial information – chronic kidney disease).

Limitations of Use

FORXIGA is not indicated for use in patients with type 1 diabetes.

FORXIGA should not be used for the treatment of diabetic ketoacidosis.

4.2. Posology and method of administration

Recommended Dosage

Type 2 diabetes mellitus

The recommended dose of FORXIGA is 10 mg taken orally once daily at any time of the day regardless of meals.

Monotherapy and Add-On Combination Therapy

The recommended dose of FORXIGA is 10 mg once daily as monotherapy or as add-on to combination therapy with metformin (with or without a sulfonylurea), a thiazolidinedione, a sulfonylurea, a DPP4-inhibitor (with or without metformin), or insulin (with or without oral antidiabetic therapy, either metformin plus insulin dual therapy or metformin plus sulfonylurea plus insulin triple therapy).

Initial Combination Therapy

The recommended starting doses of FORXIGA and metformin when used as initial combination therapy are 10 mg FORXIGA plus 500 mg metformin once daily. Patients with inadequate

glycemic control on this dose should further have their metformin dose increased according to approved local label guidelines.

Heart failure

The recommended dose of FORXIGA is 10 mg taken orally once daily at any time of the day regardless of meals.

Chronic kidney disease

The recommended dose of FORXIGA is 10 mg taken orally once daily at any time of the day regardless of meals.

Special Populations

Patients with renal impairment

No dosage adjustment for FORXIGA is required based on renal function.

The glucose lowering efficacy of FORXIGA is reduced in patients with eGFR < 45 mL/min/1.73 m^2 (See section 4.4 Special warnings and special precautions for use and 5.1 Pharmacodynamic properties). Therefore, if eGFR falls below 45 mL/min/1.73m^2, additional glucose lowering treatment should be considered in patients with diabetes mellitus.

Patients with hepatic impairment

No dosage adjustment for FORXIGA is necessary for patients with mild, moderate or severe hepatic impairment (see section 5.2 Pharmacokinetic properties).

Pediatric and adolescent patients

Safety and effectiveness of FORXIGA in pediatric and adolescent patients have not been established.

Geriatric Patients

No dosage adjustment for FORXIGA is required based on age (see section 5.1 Pharmacodynamic properties). Older patients are more likely to have impaired renal function. The renal function

recommendations provided for all patients also apply to elderly patients (see section 4.4 Special warnings and special precautions for use).

4.3. Contraindications

FORXIGA is contraindicated in patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients.

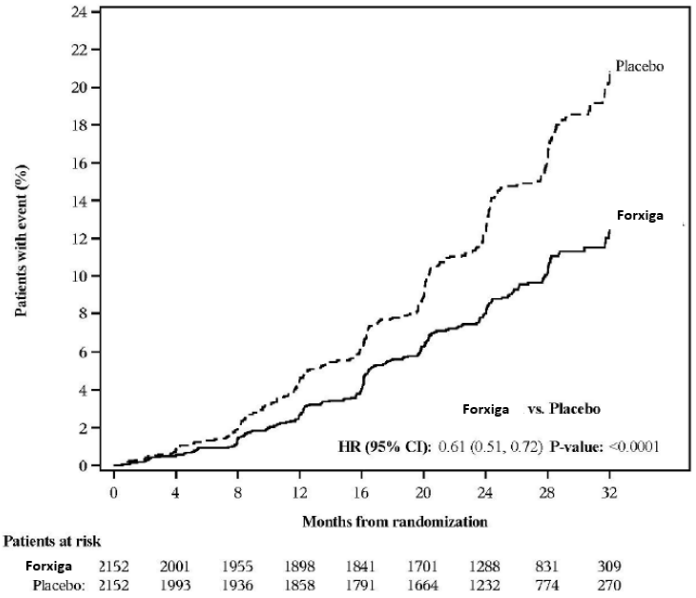
4.4. Special warning and special precautions for use

Use in patients with renal impairment

There is limited experience with FORXIGA in patients with severe renal impairment (eGFR < 25 mL/min/1.73 m^2) or end-stage renal disease (ESRD).

Use in patients

FORXIGA is not r e glycemic control when eGFR is pe of dapagliflozin is dependent on re tiation of FORXIGA and periodically



Use in patients

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1 Pharmacodynamic properties). It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

Ketoacidosis in patients with diabetes mellitus

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery and alcohol abuse. FORXIGA should be used with caution in these patients.

Patients treated with FORXIGA who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/L (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of FORXIGA should be considered and the patient should be promptly evaluated.

There have been reports of ketoacidosis, including diabetic ketoacidosis (DKA), in patients with type 2 diabetes mellitus taking FORXIGA and other SGLT2 inhibitors.

Use with medications known to cause hypoglycemia

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with FORXIGA (see section 5.1 Pharmacodynamic properties).

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to

alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes, and drugs that inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effect of other drugs on dapagliflozin

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of dapagliflozin were not altered by metformin (an hOCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate, and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). Therefore, meaningful interaction of dapagliflozin with other substrates of hOCT-1, hOCT-2, hOAT-3, P-gp, CYP2C8, CYP2C9, CYP3A4, and other α-glucosidase inhibitor would not be expected.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) or mefenamic acid (an inhibitor of UGT1A9), a 22% decrease and a 51% increase, respectively, in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion in either case.

Coadministration of dapagliflozin and bumetanide did not meaningfully change the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy subjects.

Effect of dapagliflozin on other drugs

Concomitant use of dapagliflozin and lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

In interaction studies conducted in healthy subjects, using mainly a single dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin,

glimepiride, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin (a P-gp substrate), or warfarin (S-warfarin is a CYP2C substrate). Therefore, dapagliflozin is not a clinical meaningful inhibitor of hOCT-1, hOCT-2, hOAT-3, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mediated metabolism.

Coadministration of dapagliflozin and bumetanide did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Dapagliflozin did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio [INR]).

Other interactions

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of dapagliflozin have not been specifically studied.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

4.6 Pregnancy and lactation

Pregnancy

FORXIGA must not be used in the second and third trimesters of pregnancy. In the time period corresponding to the second and third trimesters of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny (see section 5.3 Preclinical safety data - Carcinogenesis, mutagenesis, impairment of fertility).

In conventional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the first trimester period of nonrenal organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested (1191× the

maximum recommended human dose [MRHD]). In rats, dapagliflozin was neither embryolethal nor teratogenic (1441× the MRHD) in the absence of maternal toxicity.

There are no adequate and well-controlled studies of FORXIGA in pregnant women. When pregnancy is detected, FORXIGA should be discontinued.

Lactation

FORXIGA must not be used by a nursing woman. Studies in rats have shown excretion of FORXIGA in milk. Direct and indirect exposure of FORXIGA to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny, although the long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, FORXIGA-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body-weight gain associated with lactational exposure in weanling juvenile rats suggest that FORXIGA must be avoided during the first 2 years of life (see section 5.3 Preclinical safety data).

It is not known whether FORXIGA and/or its metabolite are excreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trials

The safety profile of dapagliflozin has been evaluated in clinical development programs for type 2 diabetes mellitus, heart failure, and chronic kidney disease. This includes more than 15000 subjects treated with dapagliflozin for type 2 diabetes and more than 5000 subjects treated with dapagliflozin for heart failure and more than 2000 subjects treated with dapagliflozin for chronic kidney disease. For further information about the clinical studies, see section 5.1 Pharmacodynamic properties.

The incidence of adverse reactions was determined using a pre-specified pool of patients from 13 short-term (mean duration 22 weeks), placebo-controlled studies in type 2 diabetes. Across these 13 studies, 2360 patients were treated once daily with FORXIGA 10 mg and 2295 were treated with placebo (either as monotherapy or in combination with other antidiabetic therapies).

Additionally, FORXIGA 5 mg was evaluated in a 12-study, short-term, placebo-controlled pool of type 2 diabetes patients that included 1145 patients treated with FORXIGA 5 mg (mean exposure = 22 weeks) and 1393 patients treated with placebo (mean exposure = 21 weeks), either as monotherapy or in combination with other antidiabetic therapies.

In the dedicated cardiovascular (CV) outcomes study in patients with type 2 diabetes mellitus (DECLARE), 8574 patients received FORXIGA 10 mg and 8569 received placebo for a median exposure time of 48 months. In total, there were 30623 patient-years of exposure to FORXIGA.

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF), 2368 patients were treated with dapagliflozin 10 mg and 2368 patients with placebo for a median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR $\geq$30 mL/min/1.73m^2. In the dapagliflozin cardiovascular outcome study in patients with heart failure with left ventricular ejection fraction (LVEF) >40% (DELIVER), 3126 patients were treated with dapagliflozin 10 mg and 3127 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥25 mL/min/1.73 m2.

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2149 patients were treated with dapagliflozin 10 mg and 2149 patients with placebo for a median exposure of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥25 and ≤75 mL/min/1.73m^2. Treatment was continued if eGFR fell to levels below 25 mL/min/1.73m^2.
The safety profile of dapagliflozin was overall consistent across the studied indications. DKA was observed only in patients with diabetes mellitus.

Adverse reactions

The adverse reactions in patients treated with FORXIGA 10 mg in clinical trials and post marketing are shown in Table 1.

Table 1: Adverse Drug Reactions by Frequency and System Organ Class (SOC)

System Organ Class	Common	Rare	Unknown
Infections and Infestations	Genital infection[a,b] Urinary tract infection[a,c]		
Metabolism and Nutrition Disorders		Diabetic ketoacidosis[e]	
Skin and subcutaneous tissue disorders			Rash[f,g]
Musculoskeletal and Connective Tissue Disorders	Back pain[a]		
Renal Urinary Disorders	Pollakiuria[a] and polyuria[a,d]		

[a] Identified from 13 placebo-controlled studies with dapagliflozin 10 mg in type 2 diabetes mellitus including 3 monotherapy, 1 initial combination with metformin, 2 add-on to metformin, 2 add-on to insulin, 1 add-on to pioglitazone , 1 add-on to sitagliptin, 1 add-on to glimepiride and 2 studies with combination add-on therapy.

[b] Multiple adverse events terms, including vulvovaginal infections and candidiasis, balanoposthitis, balanitis candida, penile abscess, penile infection, vulval abscess and vaginitis bacterial.

[c] Multiple adverse events terms, including genitourinary tract infection, cystitis, pyelonephritis, trigonitis, urethritis and prostatitis.

[d] Represents multiple adverse events terms, including polyuria, urine output increased.

[e] Identified from the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.

[f] Identified during postmarketed use of FORXIGA. Because these reactions are reported voluntarily from a population of an uncertain size, it is not always possible to reliably estimate their frequency.

[g] Rash includes the following preferred terms, listed in order of frequency in clinical trials: Rash, Rash generalized, Rash pruritic, Rash macular, Rash maculo-papular, Rash pustular, Rash vesicular, Rash erythematous. In active- and placebo-controlled clinical trials (Dapagliflozin, N=5936, All control, N=3403), the frequency of Rash was similar for Dapagliflozin (1.4%) and All control (1.4%), respectively, corresponding to the frequency 'Common'.

Description of selected adverse events observed in studies in type 2 diabetes mellitus

Genital Infections

Events of genital infections were reported in 5.5% and 0.6% of patients who received FORXIGA 10 mg and placebo, respectively, in the 13-study short-term, placebo-controlled pool. The events of genital infections reported in patients treated with FORXIGA 10 mg were all mild to

moderate. Most events of genital infection responded to an initial course of standard treatment and rarely resulted in discontinuation from the study (0.2% FORXIGA 10 mg *versus* 0% in placebo). Infections were reported more frequently in females (8.4% FORXIGA 10 mg *versus* 1.2% placebo) than in males (3.4% FORXIGA 10 mg *versus* 0.2% placebo). The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.

Overall, treatment with FORXIGA 5 mg was similar to treatment with FORXIGA 10 mg.
In the DECLARE study, the number of patients with serious adverse events (SAE) of genital infections were few and balanced: 2 (<0.1%) patients in each of the FORXIGA and placebo groups.

In the DAPA-HF study, no patient reported a SAE of genital infections in the FORXIGA group and one in the placebo group. There were 7 (0.3%) patients with adverse events leading to discontinuations (DAE) due to genital infections in the FORXIGA group and none in the placebo group. In the DELIVER study, one (<0.1%) patient in each treatment group reported a SAE of genital infections. There were 3 (0.1%) patients with DAEs due to genital infection in the FORXIGA group and none in the placebo group

In the DAPA-CKD study, there were 3 (0.1%) patients with SAE of genital infections in the FORXIGA group and none in the placebo group. There were 3 (0.1%) patients with DAEs due to genital infections in the FORXIGA group and none in the placebo group.

Urinary tract infections

Events of urinary tract infections (UTI) were reported in 4.7% and 3.5% of patients who received FORXIGA 10 mg and placebo, respectively, in the 13-study short-term, placebo-controlled pool.

Most events of urinary tract infections reported in patients treated with FORXIGA 10 mg were mild to moderate. Most patients responded to an initial course of standard treatment, and urinary tract infections rarely caused discontinuation from the study (0.2% FORXIGA 10 mg *versus* 0.1% placebo). Infections were more frequently reported in females (8.5% FORXIGA 10 mg *versus* 6.7% placebo) than in males (1.8% FORXIGA 10 mg *versus* 1.3% placebo).

In the DECLARE study there were fewer patients with SAEs of UTI in the FORXIGA group compared with the placebo group: 79 (0.9%) and 109 (1.3%), respectively.

The number of patients with SAEs of UTI were low and balanced in the DAPA-HF and DELIVER studies: in DAPA-HF there were: 14 (0.6%) patients in the FORXIGA group and 17 (0.7%) in the placebo group and in DELIVER there were 41 (1.3%) patients in the FORXIGA group and 37 (1.2%) in the placebo group. In the DAPA-HF study, there were 5 (0.2%) patients with DAEs due to UTI in each of the FORXIGA and placebo groups. In the DELIVER study, there were 13 (0.4%) patients with DAEs due to UTI in the FORXIGA group and 9 (0.3%) in the placebo group.

In the DAPA-CKD study, there were 29 (1.3%) patients with SAEs of UTI in the FORXIGA group and 18 (0.8%) patients in the placebo group. There were 8 (0.4%) patients with DAEs due to UTI in the FORXIGA group and 3 (0.1%) in the placebo group.

Diabetic ketoacidosis (DKA)

Type 2 diabetes mellitus

In the DECLARE study with a median exposure time of 48 months, events of DKA were reported in 27 patients in the FORXIGA 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the FORXIGA group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4 Special warning and precautions for use).

In the DAPA-HF study, events of DKA were reported in 3 patients with type 2 diabetes mellitus in the FORXIGA group and none in the placebo group. In the DELIVER study, events of DKA were reported in 2 patients with type 2 diabetes mellitus in the FORXIGA group and none in the placebo group.

In the DAPA-CKD study, events of DKA were not reported in any patient in the FORXIGA group and in 2 patients with type 2 diabetes mellitus in the placebo group.

4.9 Overdose

Orally administered dapagliflozin has been shown to be safe and well tolerated in healthy subjects at single doses up to 500 mg (50 times the MRHD). These subjects had detectable

glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose) with no reports of dehydration, hypotension, or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycemia for patients treated with dapagliflozin was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) of dapagliflozin were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycemia for subjects administered dapagliflozin was slightly higher than placebo and was not dose related. Rates of adverse events including dehydration or hypotension for patients treated with dapagliflozin were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters including serum electrolytes and biomarkers of renal function.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium-glucose cotransporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus and provides cardio-renal benefits.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduce intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and diastolic function and preserve renal function. Other effects include an increase in hematocrit and, reduction in body weight.

The cardio-renal benefits of dapagliflozin go beyond the blood glucose lowering effect and are not limited to patients with diabetes. In addition to the osmotic diuretic and related hemodynamic actions of SGLT2 inhibition, potential secondary effects on myocardial metabolism, ion channels, fibrosis, adipokines and uric acid may be mechanisms

underlying the cardio-renal beneficial effects of dapagliflozin.

Dapagliflozin improves both fasting and postprandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24- hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose, and/or low GFR, dapagliflozin has a low propensity to cause hypoglycemia, as the amount of filtrated glucose is small and can be reabsorbed by SGLT1 and unblocked SGLT2 transporters. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta-cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

The majority of weight reduction is body-fat loss, including visceral fat, rather than lean tissue, or fluid loss as demonstrated by dual energy x-ray absorptiometry (DXA) and magnetic resonance imaging.

SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is greater than 1400 times more selective for SGLT2 *versus* SGLT1, the major transporter in the gut responsible for glucose absorption.

5.1 Pharmacodynamic properties

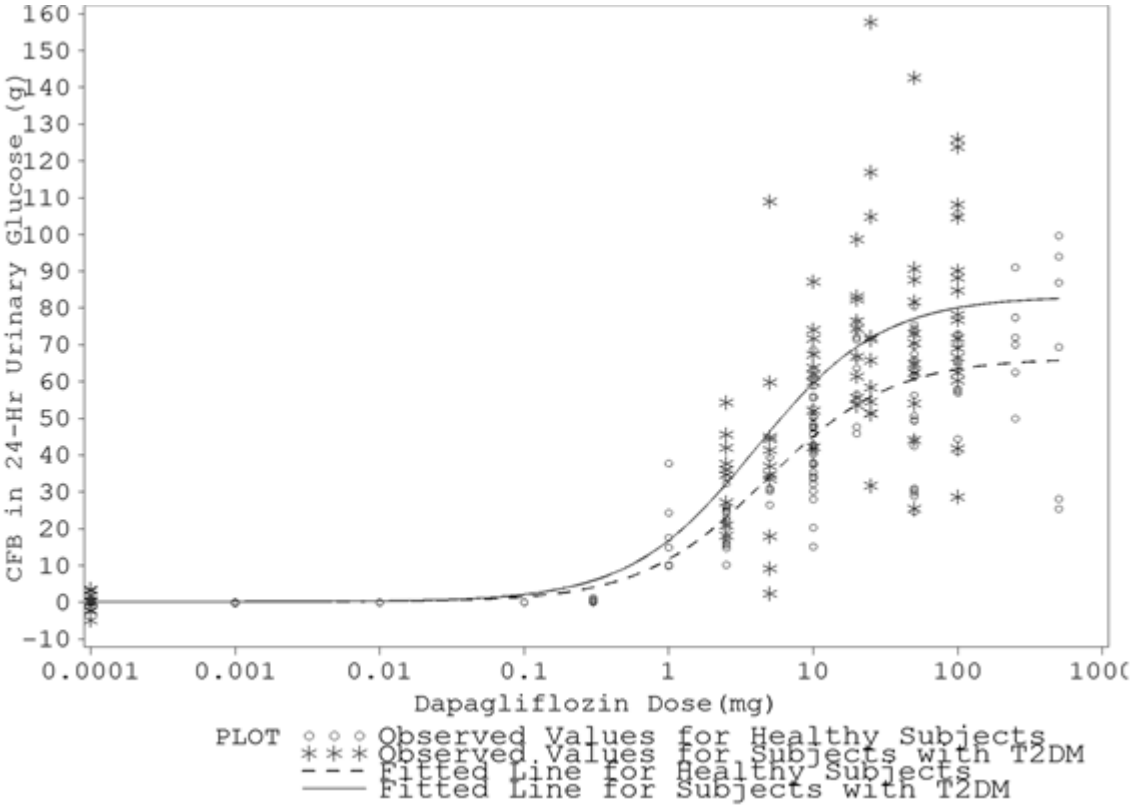
General

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (see Figure 1). Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with FORXIGA 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 0.33 mg/dL to 0.87 mg/dL.

Figure 1: Scatter plot and fitted line of change from baseline in 24-hour urinary glucose amount *versus* dapagliflozin dose in healthy subjects and subjects with T2DM (semi-log plot)



Cardiac electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended dose) in a study of healthy subjects. In

addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended dose) dapagliflozin in healthy subjects.

Clinical trial information – type 2 diabetes mellitus

More than 28000 patients have been included in 22 double-blind, controlled type 2 diabetes mellitus clinical studies conducted to evaluate the safety and efficacy of FORXIGA; more than 15000 patients in these studies were treated with FORXIGA.

FORXIGA has been studied as monotherapy and in combination with metformin with or without a sulfonylurea), sulfonylurea (glimepiride), thiazolidindione (pioglitazone), sitagliptin (with or without metformin), saxagliptin and metformin or insulin (with or without other oral antidiabetic therapy).

Dedicated studies of the glycemic efficacy and safety of FORXIGA were performed in patients with type 2 diabetes and cardiovascular disease (CVD), with type 2 diabetes and hypertension and with type 2 diabetes and moderate renal impairment (see section 5.1 Pharmacodynamic Properties - Clinical trial information -Special populations).

A large CV outcomes trial (DECLARE) assessed the effect of dapagliflozin on CV and renal outcomes in type 2 diabetes mellitus patients with or without established CV disease.

Clinical efficacy

Glycemic efficacy

Treatment with FORXIGA as monotherapy, as add-on combination therapy with metformin (with or without a sulfonylurea), sulfonylurea (glimepiride), thiazolidinedione (pioglitazone), sitagliptin (with or without metformin), saxagliptin and metformin, or insulin (with or without other oral antidiabetic therapy), produced clinically relevant and statistically significant improvements in mean change from baseline at Week 24 in HbA1c, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) (where measured) compared to control. Treatment with FORXIGA in concomitant initiation with saxagliptin as add-on to metformin produced clinically relevant and statistically significant improvements in mean change from baseline at Week 24 in HbA1c compared to control.

These clinically relevant glycemic effects were sustained in all long-term extensions up to 208 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI).

Additionally at Week 24, clinically relevant and statistically significant reductions in mean changes from baseline in body weight were seen with FORXIGA combination treatments compared to control. Body-weight reductions were sustained in long-term extensions up to 208 weeks. In a dedicated clinical study, decrease in weight was mainly attributable to a reduction in body-fat mass as measured by DXA.

In two studies of FORXIGA 10 mg in type 2 diabetes patients with CVD, statistically significant improvements in HbA1c and significant reductions in body weight and seated systolic blood pressure were seen at Week 24 in patients treated with FORXIGA10 mg compared to those treated with placebo, and were sustained through Week 104. In two studies of FORXIGA 10 mg in type 2 diabetes patients with hypertension, statistically significant reductions in mean seated systolic blood pressure were also seen in patients treated with FORXIGA 10 mg combined with other oral antidiabetic and antihypertensive treatments (an angiotensin-converting enzyme inhibitor (ACE) or angiotensin receptor blocker (ARB) in one study and an ACEi or ARB plus one additional antihypertensive treatment in another study) compared to those treated with placebo at Week 12.

FORXIGA was evaluated at 10 mg once daily in 19 of 21 double-blind glycemic efficacy studies. Doses of dapagliflozin 2.5 mg and FORXIGA 5 mg were also evaluated in some of these studies; 2.5 mg was not consistently effective for glycemic control, and 10 mg had numerically better efficacy and comparable safety to FORXIGA 5 mg.

Monotherapy

A total of 840 treatment-naive patients with inadequately controlled type 2 diabetes participated in two placebo-controlled studies to evaluate the efficacy and safety of monotherapy with FORXIGA.

In one monotherapy study, a total of 558 treatment-naive patients with inadequately controlled diabetes participated in a 24-week study with a 78-week controlled, blinded,

extension period. Following a 2-week diet and exercise placebo lead-in period, 485 patients with HbA1c ≥7% and ≤10% were randomized to dapagliflozin 2.5 mg, FORXIGA 5 mg, or 10 mg once daily in either the morning (QAM, main cohort) or evening (QPM), or placebo in the morning only.

At Week 24, treatment with FORXIGA 10 mg QAM provided significant improvements in HbA1c and FPG compared with placebo (Table 2, Figure 2). Overall, the PM administration of FORXIGA had a comparable safety and efficacy profile to FORXIGA administered in the AM. Adjusted mean change from baseline in HbA1c and FPG was −0.61% and −27.0 mg/dL, respectively, at Week 102 in the QAM group for patients treated with FORXIGA 10 mg, and −0.17% and −6.9 mg/dL, respectively, for patients treated with placebo based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients in the main cohort who were rescued or discontinued for lack of glycemic control at Week 24 (adjusted for baseline HbA1c) was higher for placebo (12.0%) than for FORXIGA 10 mg (0.0%). By Week 102 (adjusted for baseline HbA1c), more patients treated with placebo (44.0%) required rescue therapy than patients treated with FORXIGA 10 mg (35.0%).

Table 2: Results at Week 24 (LOCF*) in a Placebo-Controlled Study of FORXIGA Monotherapy in Patients with Type 2 Diabetes (Main Cohort AM Doses)

Efficacy Parameter	**FORXIGA 10 mg N=70†**	**Placebo N=75†**
HbA1c (%)		
Baseline (mean)	8.01	7.79
Change from baseline (adjusted mean‡)	−0.89	−0.23
Difference from placebo (adjusted mean‡) (95% CI)	−0.66§ (−0.96, −0.36)	
Percent of patients achieving HbA1c <7% adjusted for baseline	50.8%¶	31.6%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−2.04¶ (N=14)	0.19 (N=5)
FPG (mg/dL)		

Baseline (mean)	166.6	159.9
Change from baseline (adjusted mean‡)	−28.8	−4.1
Difference from placebo (adjusted mean‡) (95% CI)	−24.7§ (−35.7, −13.6)	
Body Weight (kg)		
Baseline (mean)	94.13	88.77
Change from baseline (adjusted mean‡)	−3.16	−2.19
Difference from placebo (adjusted mean‡) (95% CI)	−0.97 (−2.20, 0.25)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

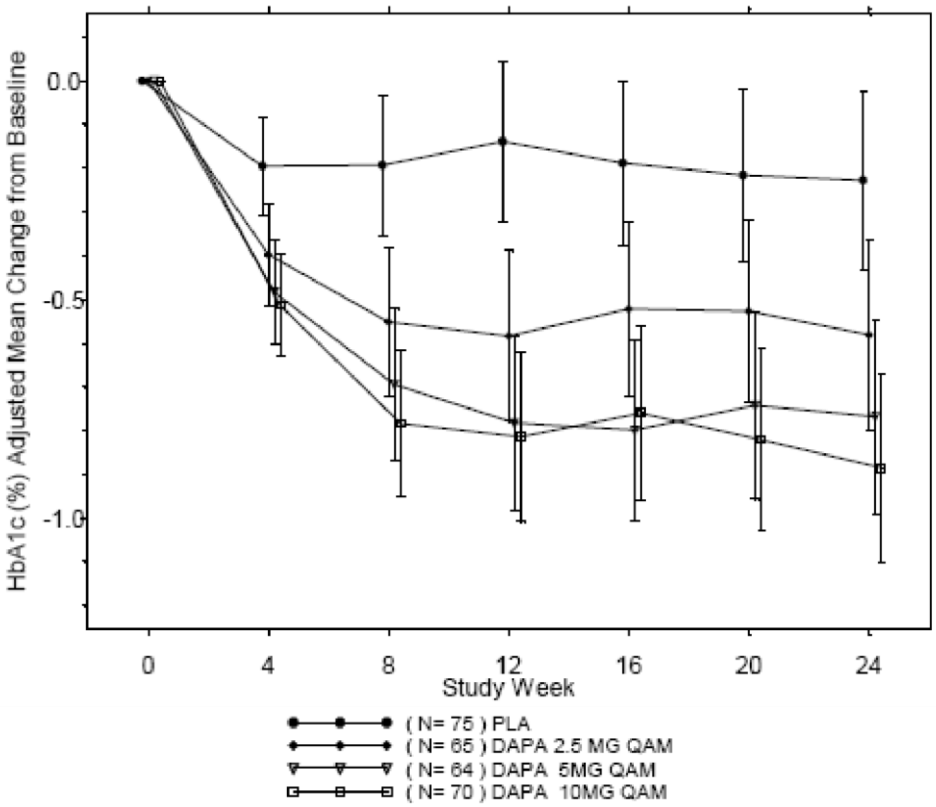
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 *versus* placebo.

¶ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints.

Figure 2: Adjusted mean change from baseline over time (LOCF) in HbA1c (%) in a 24-week placebo-controlled study of FORXIGA monotherapy in patients with type 2 diabetes (Group 1 AM doses)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Another 24-week study conducted evaluating dapagliflozin 1 mg, 2.5 mg and FORXIGA 5 mg monotherapy *versus* placebo also showed clinically relevant and statistically significant improvements in glycemic parameters and body weight.

Combination Therapy

FORXIGA was studied as initial combination with metformin, and as add-on to metformin, sulfonylurea (glimepiride), metformin plus a sulfonylurea, thiazolidinedione (pioglitazone), insulin (with or without other oral antidiabetic therapy), sitagliptin (with or without metformin), or saxagliptin plus metformin, as concomitant initiation therapy with saxagliptin added to metformin.

Combination Therapy with Metformin

Four studies were conducted in combination with metformin therapy. Two studies evaluated FORXIGA added to metformin as initial combination therapy, one study evaluated the effect of FORXIGA added to metformin in patients already on metformin, and one study evaluated the effect of FORXIGA added to metformin *versus* sulfonylurea added to metformin.

Initial Combination Therapy with Metformin

A total of 1236 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c $\geq$7.5% and $\leq$12%) participated in two active-controlled studies of 24-weeks duration to evaluate the efficacy and safety of initial therapy with FORXIGA 5 mg or 10 mg in combination with metformin extended-release formulation (XR).

In one study, 638 patients randomized to one of three treatment arms following a 1-week lead-in period received FORXIGA 10 mg plus metformin XR (up to 2000 mg per day), FORXIGA 10 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of FORXIGA 10 mg plus metformin XR provided significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and significant reductions in body weight compared with metformin XR alone. (Table 3, Figure 3 and 4). FORXIGA 10 mg as monotherapy also provided significant improvements in FPG and

significant reduction in body weight compared with metformin XR alone and was non-inferior to metformin XR monotherapy in lowering HbA1c. The proportion of patients who were rescued or discontinued for lack of glycemic control during the 24-week double-blind treatment period (adjusted for baseline HbA1c) was higher on treatment with metformin XR plus placebo (13.5%) than on FORXIGA 10 mg plus placebo and FORXIGA 10 mg plus metformin XR (7.8% and 1.4%, respectively).

Table 3: Results at Week 24 (LOCF*) in an Active-Controlled Study of FORXIGA Initial Combination Therapy with Metformin XR

Efficacy Parameter	**FORXIGA 10 mg + Metformin XR N=211†**	**FORXIGA 10 mg N=219†**	**Metformin XR N=208†**
HbA1c (%)			
Baseline (mean)	9.10	9.03	9.03
Change from baseline (adjusted mean‡)	−1.98	−1.45	−1.44
Difference from FORXIGA (adjusted mean‡) (95% CI)	−0.53§ (−0.74, −0.32)		
Difference from metformin XR (adjusted mean‡) (95% CI)	−0.54§ (−0.75, −0.33)	−0.01¶ (−0.22, 0.20)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6%#	31.7%	35.2%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−2.59#	−2.14	−2.05
FPG (mg/dL)			
Baseline (mean)	189.6	197.5	189.9
Change from baseline (adjusted mean‡)	−60.4	−46.4	−34.8
Difference from FORXIGA (adjusted mean‡) (95% CI)	−13.9§ (−20.9, −7.0)		
Difference from metformin XR (adjusted mean‡) (95% CI)	−25.5§ (−32.6, −18.5)	−11.6¶ (−18.6, −4.6)	
Body Weight (kg)			
Baseline (mean)	88.56	88.53	87.24
Change from baseline (adjusted mean‡)	−3.33	−2.73	−1.36

Difference from metformin XR (adjusted mean‡) (95% CI)	−1.97§ (−2.64, −1.30)	−1.37§ (−2.03, −0.71)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

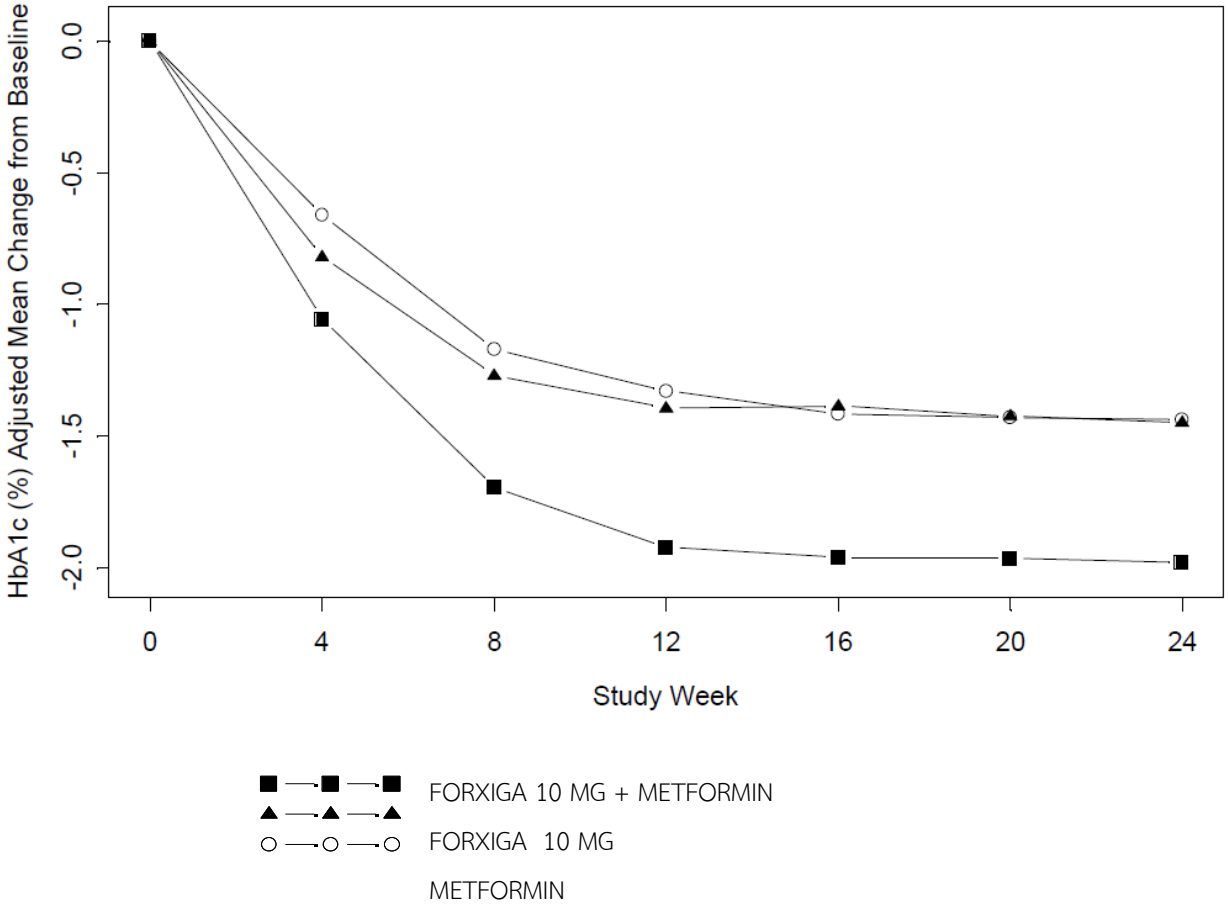
‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ Non-inferior *versus* metformin XR.

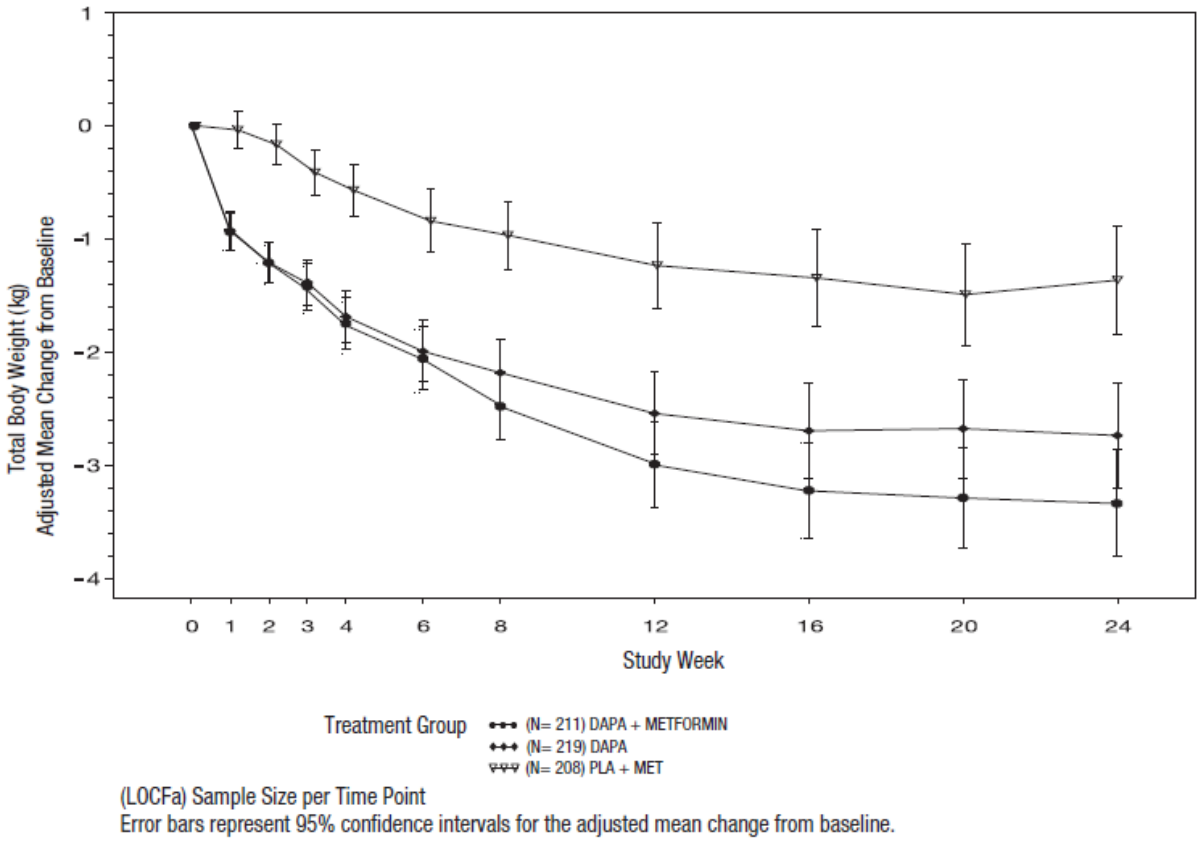
\# p-value <0.05

Figure 3: Adjusted mean change from baseline over time (LOCFa) in HbA1c (%) in a 24-week active-controlled study of FORXIGA initial combination therapy with metformin XR



Values in the plot represent adjusted mean and 95% confidence intervals (for week 24 only) based on the ANCOVA model using LOCF (Last observation (prior to rescue for rescued subjects) carried forward) data

Figure 4: Adjusted mean change from baseline over time (LOCFa) in total body weight (kg) in a 24-week active-controlled study of dapagliflozin initial combination therapy with metformin XR



Another 24-week study evaluating FORXIGA 5 mg plus metformin XR showed clinically relevant and statistically significant improvements in glycemic parameters *versus* FORXIGA 5 mg monotherapy and metformin XR monotherapy.

Add-on to Metformin

A total of 546 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled study with a 78-week controlled, blinded extension period to evaluate FORXIGA in combination with metformin. Patients on metformin at a dose of at least 1500 mg per day were randomized after completing a 2-week, single-blind placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 2.5 mg, FORXIGA 5 mg, or 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, FORXIGA 10 mg provided significant improvements in HbA1c and FPG, and significant reduction in body weight compared with placebo at Week 24 (Table 4). At Week 102, adjusted mean change from baseline in HbA1c (see Figure 5), FPG, and body weight was −0.78%, −24.5 mg/dL, and −2.81 kg, respectively, for patients treated with FORXIGA 10 mg plus metformin and 0.02%, −10.4 mg/dL, and −0.67 kg for patients treated with placebo plus metformin based on the longitudinal repeated measures analysis excluding data after rescue (Figure 5). The proportion of patients who were rescued or discontinued for lack of glycemic control during the 24-week double-blind treatment period (adjusted for baseline HbA1c) was higher in the placebo plus metformin group (15.0%) than in the FORXIGA 10 mg plus metformin group (4.4%). By Week 102 (adjusted for baseline HbA1c), more patients treated with placebo plus metformin (60.1%) required rescue therapy than patients treated with FORXIGA 10 mg plus metformin (44.0%).

Table 4: Results of a 24-Week (LOCF*) Placebo-Controlled Study of FORXIGA in Add-On Combination with Metformin

Efficacy Parameter	**FORXIGA 10 mg + Metformin N=135†**	**Placebo + Metformin N=137†**
HbA1c (%)		
Baseline mean	7.92	8.11
Change from baseline (adjusted mean‡)	−0.84	−0.30
Difference from placebo (adjusted mean‡) (95% CI)	−0.54§ (−0.74, −0.34)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%¶	25.9%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−1.32¶ (N= 18)	−0.53 (N= 22)
FPG (mg/dL)		
Baseline mean	156.0	165.6
Change from baseline at Week 24 (adjusted mean‡)	−23.5	−6.0
Difference from placebo (adjusted mean‡) (95% CI)	−17.5§ (−25.0, −10.0)	

Change from baseline at week 1 (adjusted mean‡)	−16.5§ (N=115)	1.2 (N=126)
Body Weight (kg)		
Baseline mean	86.28	87.74
Change from baseline (adjusted mean‡)	−2.86	−0.89
Difference from placebo (adjusted mean‡) (95% CI)	−1.97§ (−2.63, −1.31)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

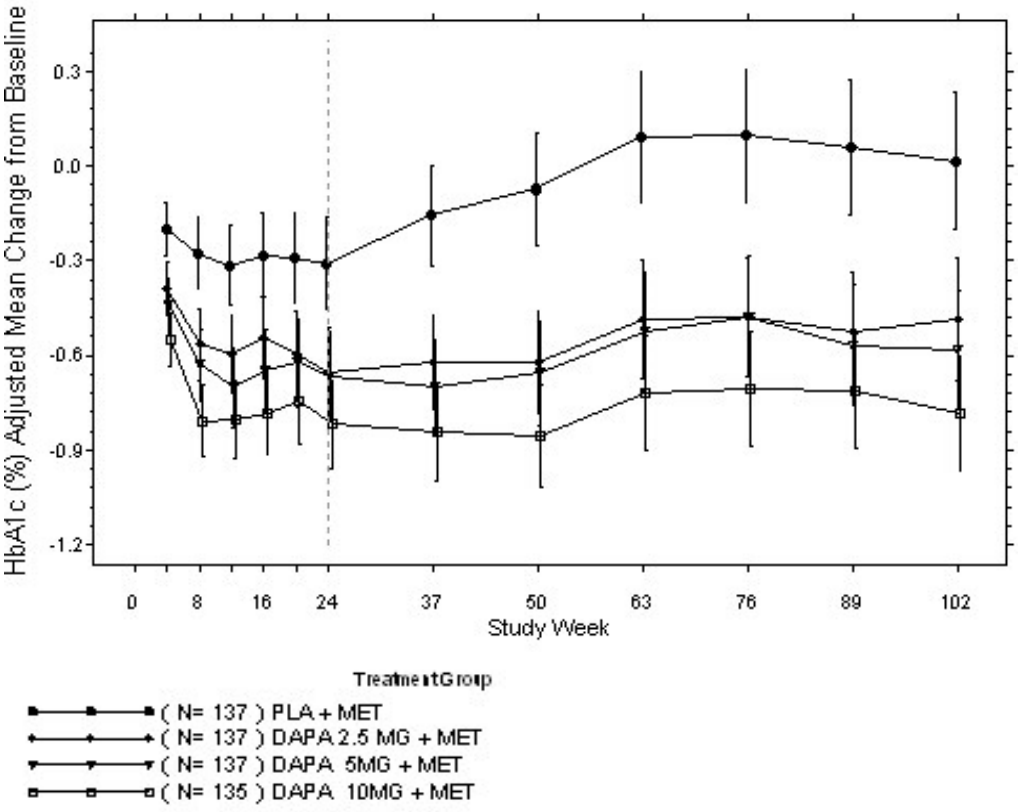
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.00001 *versus* placebo + metformin.

¶ p-value <0.05 *versus* placebo + metformin.

Figure 5: Adjusted mean change from baseline over time in HbA1c (%) in a 102-week placebo-controlled study of FORXIGA in combination with metformin (longitudinal repeated measures analysis, excluding data after rescue)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Active Glipizide Controlled Study Add-on to Metformin

A total of 816 patients with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in this a 52-week, glipizide-controlled, non-inferiority study with a 156-week extension period to evaluate FORXIGA as add-on therapy to metformin. Patients on metformin at a dose of at least 1500 mg per day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 mg or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and FORXIGA 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia. Rescue for lack of glycemic control was not available in this study through Week 104, but was available between Weeks 105 and 208.

At the end of the titration period, 87% of patients treated with FORXIGA had been titrated to the maximum study dose (10 mg) *versus* 73% treated with glipizide (20 mg). FORXIGA led to a similar mean reduction in HbA1c from baseline at Week 52, compared with glipizide, thus demonstrating non-inferiority (Table 5). FORXIGA treatment led to a significant mean reduction in body weight from baseline at Week 52 compared with a mean increase in body weight in the glipizide group.

At Weeks 104 and 208, adjusted mean changes from baseline in HbA1c were −0.32% and -0.1% and changes in body weight were −3.70 kg and -3.95 kg, respectively, for patients treated with FORXIGA; adjusted mean changes from baseline in HbA1c were −0.14% and 0.20%, respectively, and changes in body weight were 1.36 kg and 1.12 kg, respectively, for patients treated with glipizide based on the longitudinal repeated measures analysis (Figures 6 and 7). The percent of patients achieving weight loss of ≥5% (adjusted) at Weeks 104 and 208 were 23.8% and 51.0%, respectively, for patients treated with FORXIGA and 2.8% and 9.9%, respectively, for patients treated with glipizide.

By Weeks 52, 104, and 208, the proportion of patients who discontinued or were rescued for lack of glycemic control (adjusted for baseline HbA1c) were higher for glipizide plus metformin (3.6%, 21.6%, and 44.9%, respectively) than for FORXIGA plus metformin (0.2%, 14.5%, and 39.4%, respectively).

At 52, 104 and 208 weeks, respectively, a significantly lower proportion of patients treated with FORXIGA (3.5%, 4.3% and 5.0%) experienced at least one event of hypoglycemia, compared to glipizide (40.8%, 47.0%, and 50.0%).

Table 5: Results at Week 52 (LOCF*) in an Active-Controlled Study comparing FORXIGA to Glipizide as Add-on to Metformin

Efficacy Parameter	**FORXIGA + Metformin N=400†**	**Glipizide + Metformin N=401†**
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline (adjusted mean‡)	−0.52	−0.52
Difference from Glipizide + Metformin (adjusted mean‡) (95% CI)	0.00§ (−0.11, 0.11)	
Body Weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline (adjusted mean‡)	−3.22	1.44
Difference from Glipizide + Metformin (adjusted mean‡) (95% CI)	−4.65¶ (−5.14, −4.17)	
Percent of patients achieving weight loss >5% (adjusted) (95%CI)	33.3%¶ (28.7, 37.9)	2.5% (1.0, 4.0)

* LOCF: last observation carried forward.

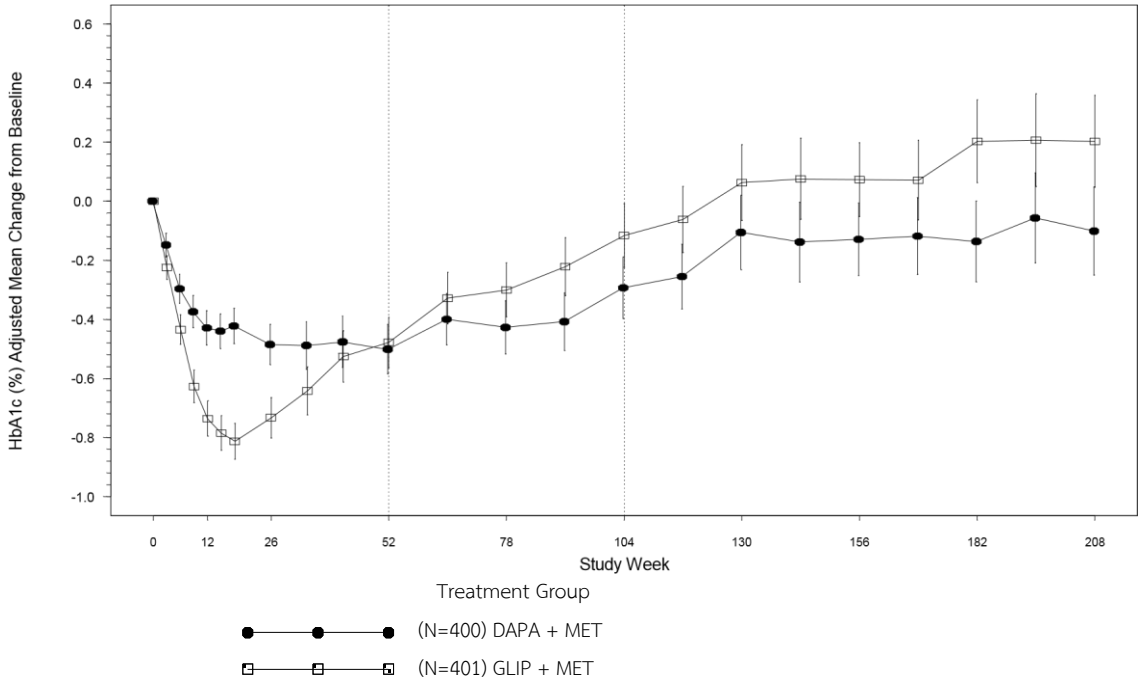
† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ Non-inferior to glipizide + metformin.

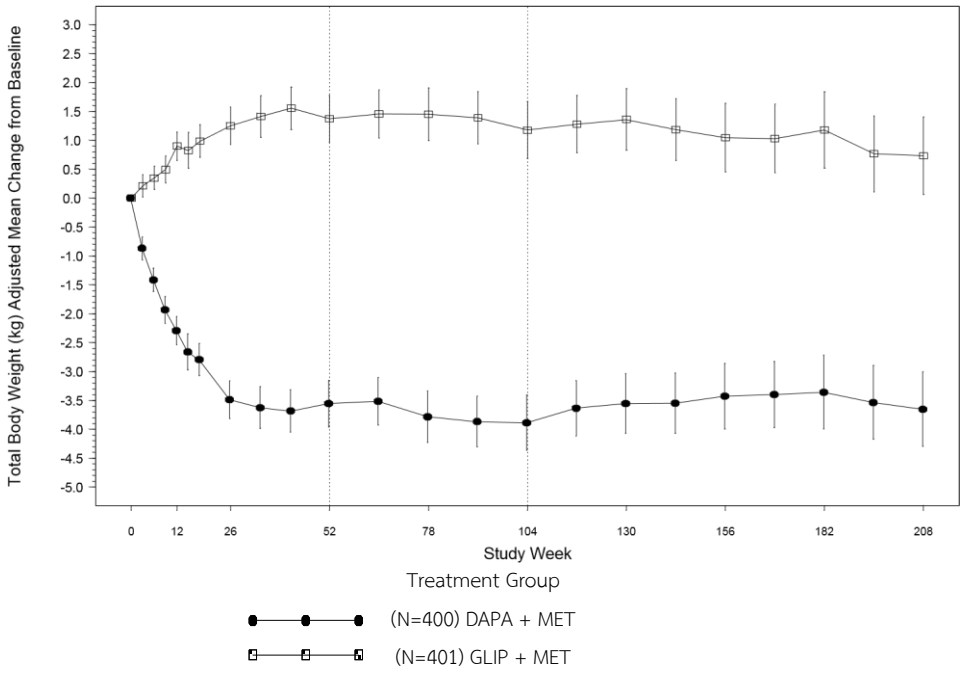
¶ p-value <0.0001.

Figure 6: Adjusted mean change from baseline over time in HbA1c (%) in a 208-week active-controlled study comparing FORXIGA to glipizide as add-on to metformin (longitudinal repeated measures analysis, excluding data after rescue)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Figure 7: Adjusted mean change from baseline over time in body weight (kg) in a 208-week active-controlled study comparing FORXIGA to glipizide as add-on to metformin (longitudinal repeated measures analysis, excluding data after rescue



Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Add-On Combination with Other Antidiabetic Agents

Add-on Combination Therapy with a Sulfonylurea

A total of 597 patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10%) were randomized in this 24-week, placebo-controlled study with a 24-week extension period to evaluate FORXIGA in combination with glimepiride (a sulfonylurea).

Patients on at least half the maximum recommended dose of a glimepiride as monotherapy (4 mg) for at least 8 weeks lead-in were randomized to dapagliflozin 2.5 mg, FORXIGA 5 mg, or 10 mg, or placebo in addition to glimepiride 4 mg per day. Down-titration of glimepiride to 2 mg or 0 mg was allowed for hypoglycemia during the treatment period; no up-titration of glimepiride was allowed.

In combination with glimepiride, treatment with FORXIGA 10 mg provided significant improvement in HbA1c, FPG, 2-hour PPG, and significant reduction in body weight compared with placebo plus glimepiride at Week 24 (Table 6, Figure 8). At Week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight were −0.73%, −28.8 mg/dL, and −2.41 kg, respectively, for patients treated with FORXIGA 10 mg plus glimepiride, and −0.04%, 2.6 mg/dL, and −0.77 kg for patients treated with placebo plus glimepiride at Week 48 based on the longitudinal repeated measures analysis excluding data after rescue.

At week 24, the proportion of patients who were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher for placebo plus glimepiride (16.2%) than for FORXIGA 10 mg plus glimepiride (2.0%). By Week 48 (adjusted for baseline HbA1c), more patients on placebo plus glimepiride (52.1%) required rescue therapy than patients on FORXIGA 10 mg plus glimepiride (18.4%).

Add-on combination therapy with metformin and a sulfonylurea

A total of 218 patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week, placebo-controlled study with a 28-week extension period to evaluate FORXIGA in combination with metformin and a sulfonylurea. Patients on a stable dose of metformin (immediate- or extended-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulfonylurea for at least 8 weeks prior to enrollment were randomized after an 8-week placebo lead-in period to

FORXIGA 10 mg or placebo. Dose-titration of FORXIGA or metformin was not permitted during the 24-week treatment period. Down-titration of sulfonylurea was permitted to prevent hypoglycemia, but no up-titration was permitted.

As add-on treatment to combined metformin and a sulfonylurea, treatment with FORXIGA 10 mg provided significant improvements in HbA1c and FPG and significant reductions in body weight compared with placebo at Week 24 (Table 6). Significant reduction in seated systolic blood pressure at Week 8 was also observed in patients treated with FORXIGA 10 mg compared to placebo. The effects in HbA1C, FPG and body weight observed at Week 24 were sustained at Week 52.

At Week 24, no patients treated with FORXIGA 10 mg combined with metformin and a sulfonylurea and 10 patients (9.3%) treated with placebo combined with metformin and a sulfonylurea were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c). By week 52 (adjusted for baseline HbA1c) more patients on placebo combined with metformin and a sulfonylurea (42.7%) were rescued for lack of glycemic control than patients on FORXIGA (10.1%). No patient was discontinued from study medication due to inadequate glycemic control.

Add-on Combination Therapy with a Thiazolidinedione

A total of 420 patients with type 2 diabetes with inadequate glycemic control (HbA1c $\geq$7% and $\leq$10.5 %) participated in a 24-week, placebo-controlled study with a 24-week extension period to evaluate FORXIGA in combination with pioglitazone (a thiazolidinedione) alone. Patients on a stable dose of pioglitazone of 45 mg/day (or 30 mg/day, if 45 mg/day not tolerated) for 12 weeks were randomized after a 2-week lead-in period to 5 mg or 10 mg of FORXIGA or placebo in addition to their current dose of pioglitazone. Dose titration of FORXIGA or pioglitazone was not permitted during the study.

In combination with pioglitazone, treatment with FORXIGA 10 mg provided significant improvements in HbA1c, 2-hour PPG, FPG, the proportion of patients achieving HbA1c <7% and a significant reduction in body weight compared with the placebo plus pioglitazone treatment groups (Table 6, Figure 9) at Week 24. Treatment with FORXIGA 10 mg plus pioglitazone also led to a significant reduction in waist circumference compared with the placebo plus

pioglitazone group. At Week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight were −1.21%, −33.1 mg/dL, and 0.69 kg, respectively, for patients treated with FORXIGA 10 mg plus pioglitazone, and −0.54%, −13.1 mg/dL, and 2.99 kg for patients treated with placebo based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients who were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher in the placebo plus pioglitazone group (11.6%) than in the FORXIGA 10 mg plus pioglitazone group (3.7%) at Week 24. By Week 48 (adjusted for baseline), more patients treated with placebo plus pioglitazone (33.8%) required rescue therapy than patients treated with FORXIGA 10 mg plus pioglitazone (11.8%).

Add-on Combination Therapy with Insulin

A total of 808 patients with type 2 diabetes who had inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) were randomized in a 24-week, placebo-controlled study with an 80-week extension period to evaluate FORXIGA as add-on therapy to insulin. Patients on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior and on a maximum of two OADs including metformin, were randomized after completing a 2-week enrollment period to receive dapagliflozin 2.5 mg, FORXIGA 5 mg, or 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable. Patients were stratified according to the presence or absence of background OADs. Up- or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycemic goals. Dose modifications of blinded study medication or OADs were not allowed during the treatment phase, with the exception of decreasing OADs where there were concerns over hypoglycemia after cessation of insulin therapy.

In this study, 50% of patients were on insulin monotherapy at baseline, while 50% were on 1 or 2 OADs in addition to insulin. At Week 24, FORXIGA 10 mg dose provided significant improvement in HbA1c, and mean insulin dose, and a significant reduction in body weight compared with placebo in combination with insulin, with or without up to 2 OADs (Table 6); the effect of FORXIGA on HbA1c was similar in patients on insulin alone and patients on insulin plus OADs.

At Weeks 48 and 104, adjusted mean changes from baseline in HbA1c were −0.93% and −0.71%, changes in FPG were −21.5 mg/dL and −18.2 mg/dL, and changes in body weight were −1.79 kg and −1.97 kg, respectively, for patients treated with FORXIGA 10 mg plus insulin; adjusted mean changes from baseline in HbA1c were −0.43% and −0.06%, changes in FPG were −4.4 mg/dL and −11.2 mg/dL, and changes in body weight were −0.18 kg and 0.91 kg, respectively, for patients treated with placebo plus insulin (see Figure 10).

At Week 24, a significantly higher proportion of patients on FORXIGA 10 mg reduce their insulin dose by at least 10% compared to placebo. The proportion of patients who required up-titration of their insulin dose or discontinued due to lack of glycemic control (adjusted for baseline HbA1c) was higher for placebo plus insulin (29.2%) than for FORXIGA 10 mg plus insulin (9.7%). By Weeks 48 and 104, the insulin dose remained stable in patients treated with FORXIGA 10 mg at an average dose of 76 IU/day, but continued to increase (mean increase 10.5 IU and 18.3 IU, respectively, from baseline) in placebo-treated patients. By Weeks 48 and 104 (adjusted for baseline HbA1c), more patients treated with required up-titration with insulin to maintain glycemic levels or discontinued due to lack of glycemic control (42.8% and 50.4%, respectively) compare with patients treated with FORXIGA 10 mg (15.3% and 25.5%, respectively).

Table 6: Results of 24-Week Placebo-Controlled Studies of FORXIGA in Combination with Antidiabetic Agents

Efficacy Parameter	**FORXIGA 10 mg**	**Placebo**
In Combination with Sulfonylurea (Glimepiride)		
Intent-to-Treat Population	N=151[†]	N=145[†]
HbA1c (%)*		
Baseline (mean)	8.07	8.15
Change from baseline (adjusted mean[‡])	−0.82	−0.13
Difference from placebo (adjusted mean[‡]) (95% CI)	−0.68[§] (−0.86, −0.51)	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.7%[§]	13.0%
FPG (mg/dL)		
Baseline (mean)	172.4	172.7

Change from baseline (adjusted mean‡)	−28.5	−2.0
Difference from placebo (adjusted mean‡) (95% CI)	−26.5§ (−33.5, −19.5)	
2-hour PPG¶ (mg/dL)		
Baseline (mean)	329.6	324.1
Change from baseline (adjusted mean‡)	−60.6	−11.5
Difference from placebo (adjusted mean‡) (95% CI)	−49.1§ (−64.1, −34,1)	
Body Weight (kg)		
Baseline (mean)	80.56	80.94
Change from baseline (adjusted mean‡)	−2.26	−0.72
Difference from placebo (adjusted mean‡) (95% CI)	−1.54§ (−2.17, −0.92)	

In combination with metformin and sulfonylurea		
Intent-to-Treat Population	**N=108†**	**N=108†**
HbA1c (%)‡‡		
Baseline mean	8.08	8.24
Change from baseline (adjusted mean‡)	−0.86	−0.17
Difference from placebo (adjusted mean‡) (95% CI)	−0.69§ (−0.89, −0.49)	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.8%§	11.1%
FPG (mg/dL)*		
Baseline mean	167.4	180.3
Change from baseline at Week 24 (adjusted mean‡)	−34.2	−0.8
Difference from placebo (adjusted mean‡) (95% CI)	−33.5§ (−43.1, −23.8)	
Body Weight (kg)*		
Baseline mean	88.57	90.07
Change from baseline (adjusted mean‡)	−2.65	−0.58
Difference from placebo (adjusted mean‡) (95% CI)	−2.07§ (−2.79, −1.35)	
Seated Systolic Blood Pressure at Week 8 (mmHg)		

Baseline mean	134.7	136.3
Change from baseline at Week 8 (adjusted mean‡)	−4.0	−0.3
Difference from placebo (adjusted mean‡) (95% CI)	−3.8** (−7.1, −0.5)	
In Combination with Thiazolidinedione (Pioglitazone)		
Intent-to-Treat Population	N=140#	N=139#
HbA1c (%)*		
Baseline (mean)	8.37	8.34
Change from baseline (adjusted mean‡)	−0.97	−0.42
Difference from placebo (adjusted mean‡) (95% CI)	−0.55§ (−0.78, −0.31)	
Percent of patients achieving HbA1c <7% adjusted for baseline	38.8%**	22.4%
FPG (mg/dL)		
Baseline (mean)	164.9	160.7
Change from baseline (adjusted mean‡)	−29.6	−5.5
Difference from placebo (adjusted mean‡) (95% CI)	−24.1§ (−32.2, −16.1)	
2-hour PPG¶ (mg/dL)		
Baseline (mean)	308.0	293.6
Change from baseline (adjusted mean‡)	−67.5	−14.1
Difference from placebo (adjusted mean‡) (95% CI)	−53.3§ (−71.1, −35.6)	
Body Weight (kg)		
Baseline (mean)	84.82	86.40
Change from baseline (adjusted mean‡)	−0.14	1.64
Difference from placebo (adjusted mean‡) (95% CI)	−1.78§ (−2.55, −1.02)	
Change from baseline in waist circumference (cm) (adjusted mean‡)	−0.17**	1.38
In Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies		
Intent-to-Treat Population	N=194†	N=193†
HbA1c (%)		

Baseline (mean)	8.58	8.46
Change from baseline (adjusted mean‡)	−0.90	−0.30
Difference from placebo (adjusted mean‡) (95% CI)	−0.60§ (−0.74, −0.45)	
Mean Daily Insulin Dose (IU)††		
Baseline (mean)	77.96	73.96
Change from baseline (adjusted mean‡)	−1.16	5.08
Difference from placebo (95% CI)	−6.23§ (−8.84, −3.63)	
Percent of patients with mean daily insulin dose reduction of at least 10% adjusted for baseline	19.7%**	11.0%
FPG (mg/dL)		
Baseline (mean)	173.7	170.0
Change from baseline (adjusted mean‡)	−21.7	3.3
Difference from placebo (adjusted mean‡) (95% CI)	−25.0§ (−34.3, −15.8)	
Body Weight (kg)		
Baseline (mean)	94.63	94.21
Change from baseline (adjusted mean‡)	−1.67	0.02
Difference from placebo (adjusted mean‡) (95% CI)	−1.68§ (−2.19, −1.18)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 *versus* placebo.

¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

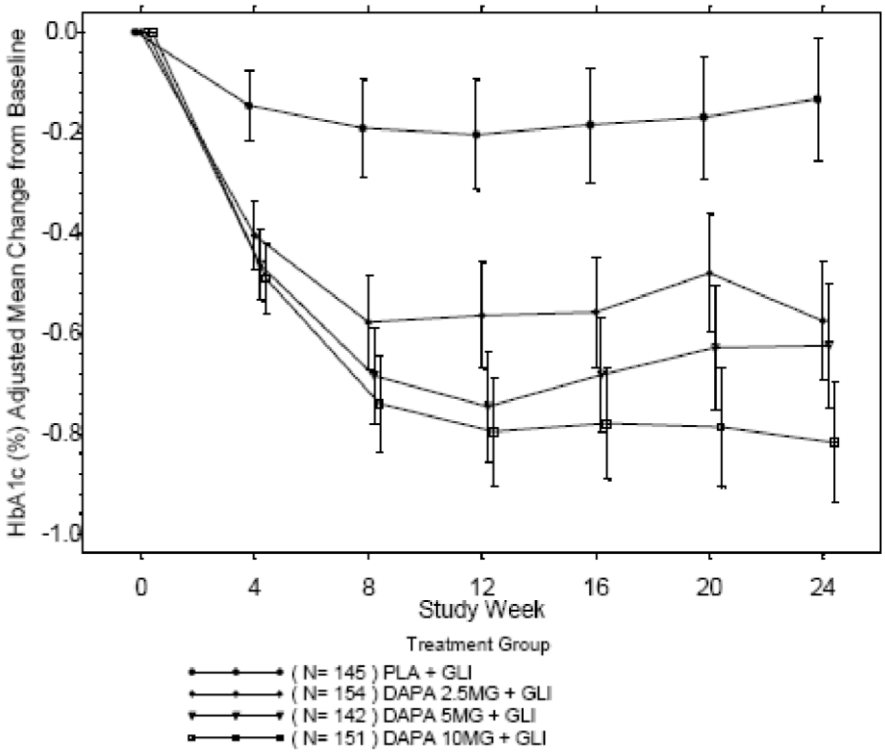
All randomized patients who took at least one dose of double-blind study medication during the short-term, double-blind period.

** p-value <0.05 *versus* placebo.

†† LOCF: last observation (after rescue) carried forward.

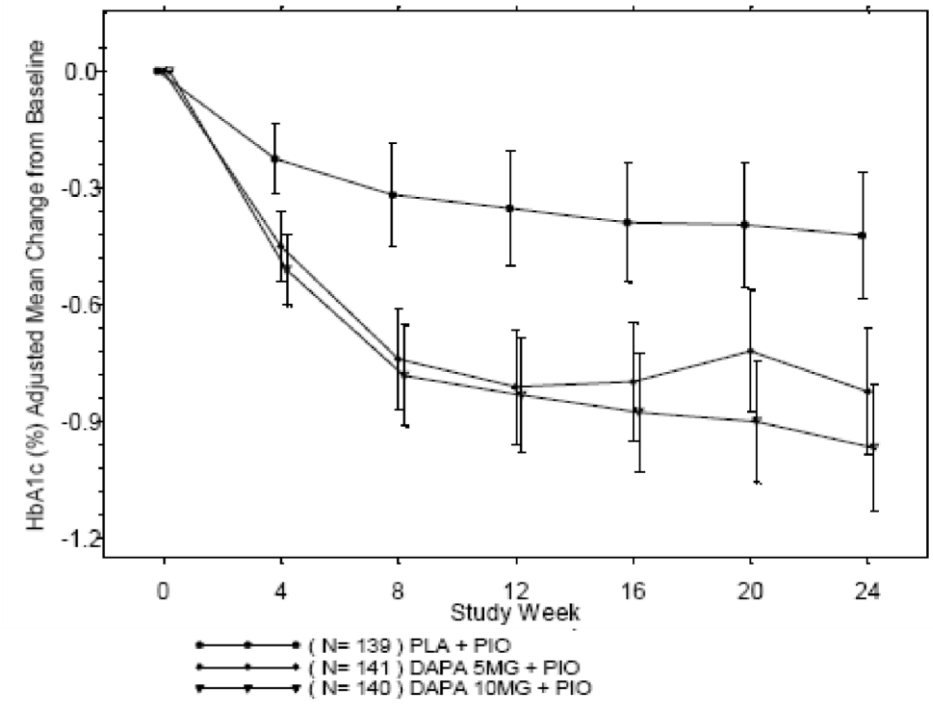
‡‡ LRM: longitudinal repeated measures analysis.

Figure 8: Adjusted mean change from baseline over time (LOCF) in HbA1c (%) in a 24-week, placebo-controlled study of FORXIGA in combination with sulfonylurea (Glimepiride)



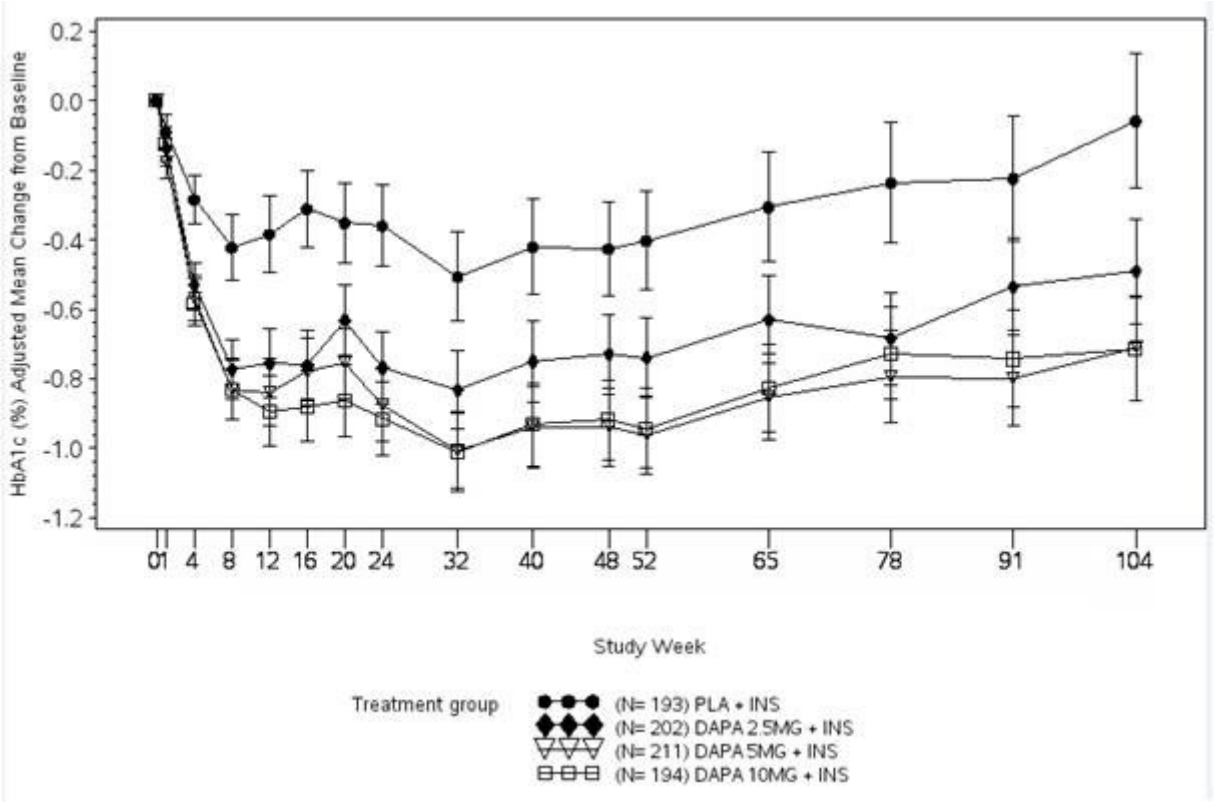
Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 9: Adjusted mean change from baseline over time (LOCF) in HbA1c (%) in a 24-week placebo-controlled study of FORXIGA in combination with a thiazolidinedione (pioglitazone)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 10: Adjusted mean change from baseline over time in HbA1c (%) in a 104-week placebo-controlled study of FORXIGA in combination with insulin with or without up to 2 oral anti-diabetic therapies excluding data after insulin up titration



Add-on to Sitagliptin Alone or in Combination with Metformin

A total of 452 patients with type 2 diabetes who were drug naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycemic control (HbA1c ≥7.0% and ≤10.0% at randomization), participated in a 24-week, placebo-controlled study with a 24-week extension period to evaluate FORXIGA in combination with sitagliptin (a DPP4 inhibitor) with or without metformin.

Eligible patients were stratified based on the presence or absence of background metformin (≥1500 mg/day) and within each stratum were randomized to either FORXIGA 10 mg plus sitagliptin 100 mg once daily or placebo plus sitagliptin 100 mg once daily. Endpoints were tested for FORXIGA 10 mg *versus* placebo for the total study group (sitagliptin with and without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin). Thirty-seven percent (37%) of patients were drug naive, 32% were on metformin alone, 13% were on a DPP4 inhibitor alone, and 18% were on a DPP4 inhibitor plus metformin. Dose titration of FORXIGA, sitagliptin or metformin was not permitted during the study.

In combination with sitagliptin (with and without metformin), FORXIGA 10 mg provided significant improvements in HbA1c, HbA1c in patients with baseline HbA1c ≥8%, and FPG, and significant reduction in body weight compared with the placebo plus sitagliptin (with or without metformin) group at Week 24 (Table 7). These improvements were also seen in the stratum of patients who received FORXIGA 10 mg plus sitagliptin alone (n=110) compared with placebo plus sitagliptin alone (n=111), and the stratum of patients who received FORXIGA 10 mg plus sitagliptin and metformin (n=113) compared with placebo plus sitagliptin with metformin (n=113) (Table 7).

At Week 48, adjusted mean change from baseline in HbA1c, HbA1c in patients with HbA1c ≥8% at baseline, FPG, PPG, and body weight were −0.30%, −0.72%, −19.7 mg/dL, −43.0 mg/dL, and −2.03 kg, respectively, for patients treated with FORXIGA 10 mg plus sitagliptin with or without metformin, and 0.38%, 0.26%, 13.4 mg/dL,−12.1 mg/dL, and 0.18 kg for patients treated with placebo plus sitagliptin with or without metformin based on the longitudinal repeated measures analysis excluding data after rescue. At Week 48, for the stratum of patients without metformin, adjusted mean change from baseline in HbA1c for patients treated with FORXIGA 10 mg plus sitagliptin was 0.00% and placebo plus sitagliptin was 0.85%; and for the stratum of patients with metformin, adjusted mean change from baseline in HbA1c for patients treated with FORXIGA 10 mg plus sitagliptin was −0.44% and placebo plus sitagliptin was 0.15% based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients at Week 24 and Week 48 who were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher for sitagliptin with or without metformin (41.5% and 56.6%, respectively) than for FORXIGA with or without metformin (18.8% and 32.7%, respectively) .

Table 7: Results of a 24-Week (LOCF*) Placebo-Controlled Study of FORXIGA in Add-On Combination with Sitagliptin with or without Metformin (Full Analysis Set and Strata without or with Metformin)

Efficacy Parameter	**FORXIGA 10 mg + Sitagliptin + or –Met**	**Placebo + Sitagliptin + or –Met**	**FORXIGA 10 mg + Sitagliptin**	**Placebo + Sitagliptin**	**FORXIGA 10 mg + Sitagliptin + Met**	**Placebo + Sitagliptin + Met**
	N=223[†]	**N=224**[†]	**N=110**[†]	**N=111**[†]	**N=113**[†]	**N=113**[†]
HbA1c (%)						
Baseline (mean)	7.90	7.97	7.99	8.07	7.80	7.87
Change from baseline (adjusted mean[‡])	−0.45	0.04	−0.47	0.10	−0.43	−0.02
Difference from placebo (adjusted mean[‡]) (95% CI)	−0.48§ (−0.62, −0.34)		−0.56§ (−0.79, −0.34)		−0.40§ (−0.58, −0.23)	
Change from baseline in HbA1c in patients with baseline HbA1c ≥8% (adjusted mean[‡])	−0.80¶ (N= 94)	0.03 (N= 99)	−0.81§	0.06	−0.79§	0.0
FPG (mg/dL)						
Baseline (mean)	161.7	163.1	157.3	161.5	165.9	164.7
Change from baseline at Week 24 (adjusted mean[‡])	−24.1	3.8	−22.0	4.6	−26.2	3.0
Difference from placebo (adjusted mean[‡]) (95% CI)	−27.9§ (−34.5, −21.4)		−26.6§ (−36.3, −16.85)		−29.2§ (−38.0, −20.4)	
Body Weight (kg)						
Baseline (mean)	91.02	89.23	88.01	84.20	93.95	94.17

Change from baseline (adjusted mean‡)	−2.14	−0.26	−1.91	−0.06	−2.35	−0.47
Difference from placebo (adjusted mean‡) (95% CI)	−1.89§ (−2.37, −1.40)		−1.85§ (−2.47, −1.23)		−1.87§ (−2.61, −1.13)	
Seated SBP at Week 8 in patients with baseline seated SBP ≥130 mmHg (mmHg)						
Baseline (mean)	140.5 (N=111)	139.3 (N=101)	138.5	137.9	141.9	140.3
Change from baseline (adjusted mean‡)	−6.0	−5.1	−6.6	−4.2	−5.3	−5.5
Difference from placebo (adjusted mean‡) (95% CI)	−0.86 (−3.8, 2.0)		−2.4 (−6.4, 1.7)		0.2 (−3.85, 4.32)	
2-hour PPG¶ (mg/dL)						
Baseline (mean)	227.8	226.3	225.3	231.2	230.2	221.0
Change from baseline (adjusted mean‡)	−47.7	−4.8	−46.3	−2.6	−48.9	−7.2
Difference from placebo (adjusted mean‡) (95% CI)	−42.9 (−52.1, −33.8)		−43.7 (−55.9, −31.5)		−41.6 (−55.4, −27.8)	
Patients with HbA1c decrease	35.4	16.6%	42.8	17.2	28.0	16.0

≥0.7% (adjusted %)						

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 *versus* placebo.

¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

Concomitant Initiation of Saxagliptin and FORXIGA in Patients Inadequately Controlled on Metformin

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycemic control on metformin alone (HbA1c ≥8% and ≤12%), participated in this 24-week randomized, double blind, active comparator-controlled superiority trial to compare the combination of saxagliptin and FORXIGA added concurrently to metformin, *versus* saxagliptin (DPP4 inhibitor) or FORXIGA added to metformin. Patients were randomized to one of three double-blind treatment groups to receive saxagliptin 5 mg and FORXIGA 10 mg added to metformin XR, saxagliptin 5 mg and placebo added to metformin XR, or FORXIGA 10 mg and placebo added to metformin XR.

The saxagliptin and FORXIGA combination group achieved significantly greater reductions in HbA1c *versus* either saxagliptin group or FORXIGA group at 24 weeks. Forty-one percent (41%) of patients in the saxagliptin and FORXIGA combination group achieved HbA1c levels of less than 7% compared to 18% patients in the saxagliptin group and 22% patients in the FORXIGA group.

Table 8: HbA1c at week 24 (LRM*) in active-controlled study comparing the combination of saxagliptin and FORXIGA added concurrently to metformin with saxagliptin or FORXIGA added concurrently to metformin

Efficacy Parameter	Saxagliptin 5 mg + FORXIGA 10 mg + Metformin XR N=179†	Saxagliptin 5 mg + Metformin XR N=176†	FORXIGA10 mg + Metformin XR N=179†
HbA1c (%) at week 24 (LRM)*			
Baseline (mean)	8.93	9.03	8.87

Change from baseline (adjusted mean[‡]) (95% CI) for adjusted mean change from baseline	−1.47 (−1.62, −1.31)	−0.88 (−1.03, −0.72)	−1.20 (−1.35, −1.04)
Difference from saxagliptin + metformin (adjusted mean[‡]) (95% CI)	−0.59[§] (−0.81, −0.37)	-	-
Difference from FORXIGA + metformin (adjusted mean[‡]) (95% CI)	−0.27[¶] (−0.48, −0.05)	-	-

* LRM = Longitudinal repeated measures (*using values prior to rescue)*

† Randomized and treated patients with baseline and at least 1 postbaseline efficacy measurement

‡ Least squares mean adjusted for baseline value

§ p-value<0.0001.

¶ p-value=0.0166

The adjusted mean change in body weight at 24 weeks was −2.05 kg (95% CI [-2.52, -1.58]) in the saxagliptin and FORXIGA plus metformin group and −2.39 kg (95% CI [-2.87, -1.91]) in the FORXIGA plus metformin group. The adjusted mean change for body weight in the saxagliptin plus metformin group had no change 0.00 kg (95% CI [-0.48, 0.49]).

Add-on therapy with FORXIGA in patients inadequately controlled on saxagliptin plus metformin

A 24-week randomized, double-blind, placebo-controlled study compared the sequential addition of 10 mg FORXIGA to 5 mg saxagliptin and metformin to the addition of placebo to 5 mg saxagliptin (DPP4 inhibitor) and metformin in patients with type 2 diabetes mellitus and inadequate glycemic control (HbA1c ≥7% and ≤10.5%). 320 subjects were randomized equally into either the FORXIGA added to saxagliptin plus metformin treatment group or placebo plus saxagliptin plus metformin treatment group.

The group with FORXIGA sequentially added to saxagliptin and metformin achieved statistically significant (p-value <0.0001) greater reductions in HbA1c *versus* the group with placebo sequentially added to saxagliptin plus metformin group at 24 weeks (see Table 9).

Table 9: Results of a week 24 (LRM*) placebo-controlled study of FORXIGA in add-on combination with saxagliptin and metformin

Efficacy Parameter	FORXIGA 10 mg + Saxagliptin 5 mg + Metformin (N=160)†	Placebo + Saxagliptin 5 mg + Metformin (N=160)†
HbA1c (%) at week 24*		
Baseline (mean)	8.24	8.16
Change from baseline (adjusted mean‡) (95% CI)	−0.82 (−0.96, 0.69)	−0.10 (−0.24, 0.04)
Comparison of FORXIGA added to saxa + met *versus* placebo + saxa + met: Adjusted mean* (95% CI)	−0.72 (−0.91, 0.53) §	
FPG (mg/dL)		
Baseline (mean)	178.5	176.6
Change from baseline (adjusted mean‡) (95% CI)	−32.7 (−38.3, −27.2)	−5.3 (−11.1, 0.6)
Comparison of FORXIGA added to saxa + met *versus* placebo + saxa + met: Adjusted mean* (95% CI)	−27.5 (−35.4, −19.6) §	
2-hour PPG¶ (mg/dL)		
Baseline (mean)	239.8	241.3
Change from baseline (adjusted mean‡) (95% CI)	−73.5 (−81.5, −65.5)	−38.0 (−46.1, −29.9)
Comparison of FORXIGA added to saxa + met *versus*	−35.5§	

placebo + saxa + met: Adjusted mean¶ (95% CI)	(−46.3, −24.7)

* LRM = Longitudinal repeated measures (using values prior to rescue).

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

¶ LOCF: last observation (prior to rescue for rescued patients) carried forward.

§ p-value <0.0001 *versus* placebo.

saxa= saxagliptin; met=metformin

The proportion of patients achieving HbA1c <7.0% at Week 24 was higher in the FORXIGA plus saxagliptin plus metformin group 38.0% (95% CI [30.9, 45.1]) compared to the placebo plus saxagliptin plus metformin group 12.4% (95% [7.0, 17.9]).

The adjusted changes from baseline at Week 24 in body weight were −1.91 kg (95% CI [−2.34, −1.48]), in the FORXIGA plus saxagliptin plus metformin group and -0.41 kg (95% CI [−0.86, −0.04]), in the placebo plus saxagliptin plus metformin group.

The effects in HbA1C, FPG and body weight observed at Week 24 were sustained at Week 52. Adjusted mean change from baseline in HbA1c, FPG, and body weight were −0.74% (95% CI [−0.90, −0.57]), -26.8 mg/dL (95% CI [-34.2, -19.4]) and −2.13 kg (95% CI[-2.70, 1.56]), respectively, for patients treated with FORXIGA 10 mg plus saxagliptin with metformin, and 0.07% (95% CI [−0.13, 0.27]), 10.2 mg/dL (95% CI[1.6, 18.8]) and −0.37 kg (95% CI[-1.01, 0.26]) for patients treated with placebo plus saxagliptin with metformin based on the longitudinal repeated measures analysis excluding data after rescue.

Cardiovascular and renal outcomes

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicenter, randomized, double-blind, placebo-controlled clinical study conducted to determine the effect of FORXIGA compared with placebo on CV and renal outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension or current tobacco use) without having had a CV event at baseline (primary prevention) or established CV disease (secondary prevention). DECLARE was designed to ensure inclusion of a broad population.

Of 17160 randomized patients, 6974 (40.6%) had established CV disease and 10186 (59.4%) did not have established CV disease. 8582 patients were randomized to FORXIGA 10 mg and 8578 to placebo and were followed for a median of 4.2 years.

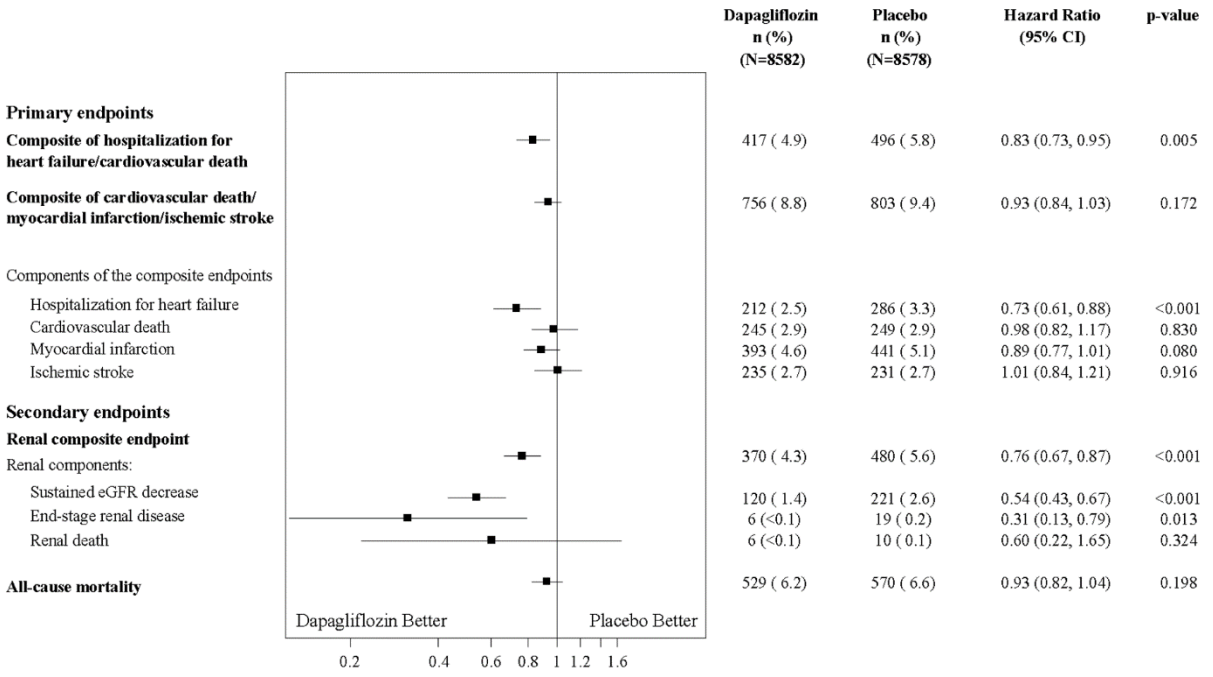
The mean age of the study population was 63.9 years, 37.4% were female, 79.6% were White, 3.5% Black or African-American and 13.4% Asian. In total, 22.4% had had diabetes for ≤5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 $mL/min/1.73m^2$, 7.4% of patients had eGFR <60$mL/min/1.73m^2$ and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ration [UACR] ≥30 to ≤300 mg/g or >300 mg/g, respectively).

Most patients (98.1%) used one or more diabetic medications at baseline, 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 agonist.

Approximately 81.3% of patients were treated with ACEi or ARB, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics and 10.5% with loop diuretics. Results on primary and secondary endpoints are displayed in Figures 11 and 12.

Figure 11: Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components

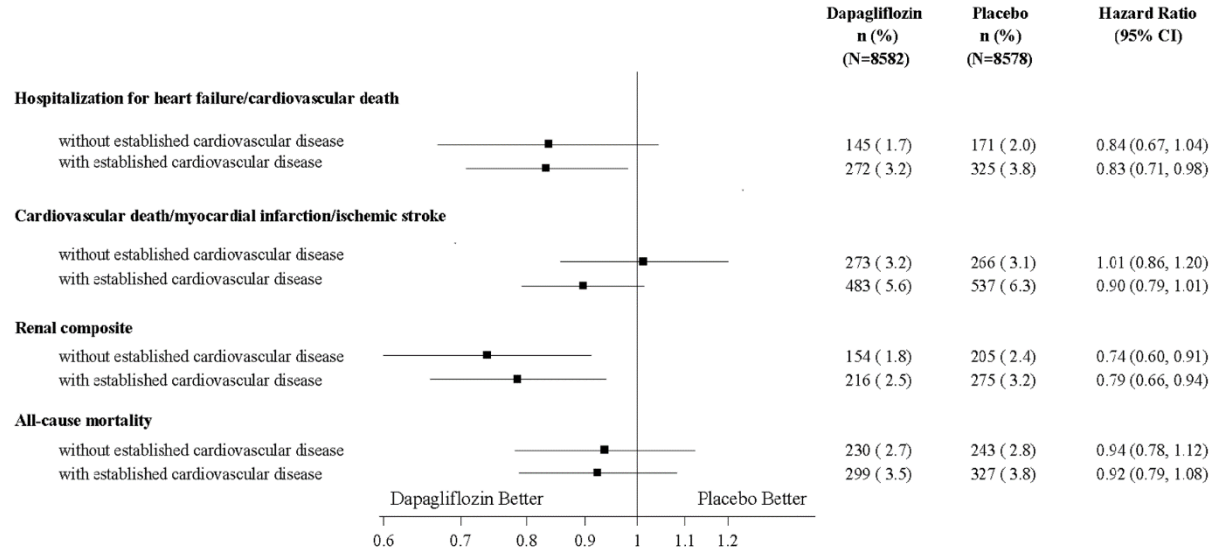


p-values are two-sided p-values for primary endpoints and nominal p-values for secondary endpoints and single components. Time to first event was analyzed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

Renal composite endpoint is defined as sustained confirmed ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESKD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73m^2) and/or renal or CV death.

CI=confidence interval.

Figure 12: Treatment effects for the primary and secondary endpoints in patients with and without established CV disease



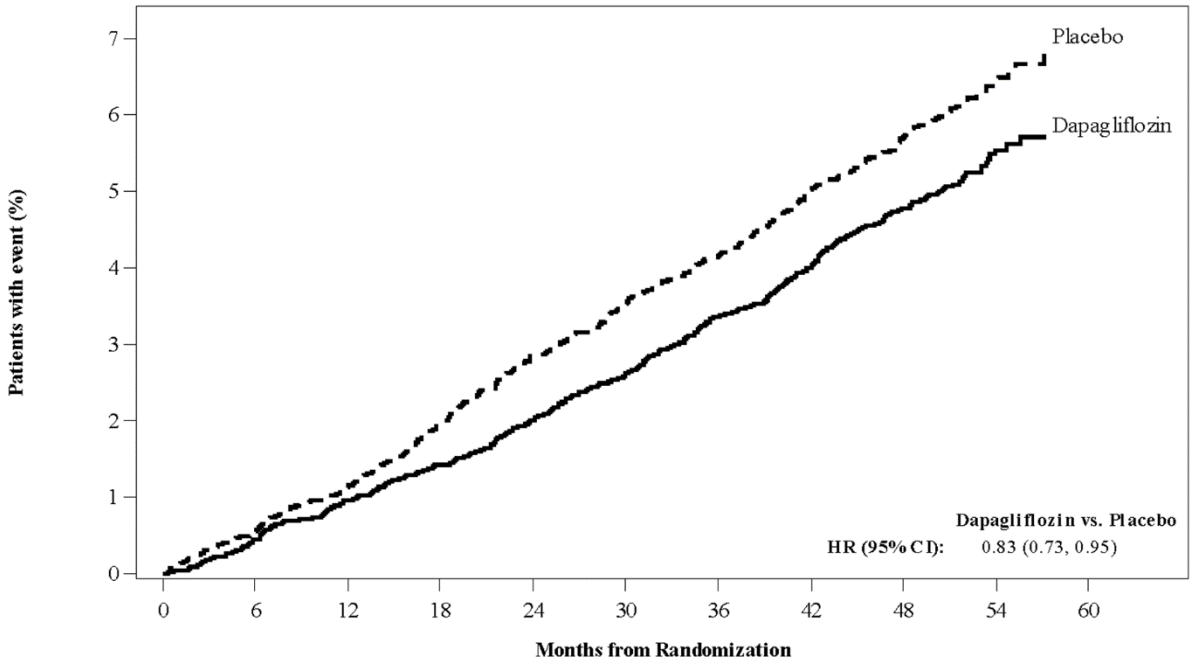
Renal composite defined as: sustained confirmed ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESKD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73m^2) and/or renal or CV death. Time to first event was analyzed in a Cox proportional hazards model.
CI=confidence interval

Heart failure or cardiovascular death

FORXIGA 10 mg was superior to placebo in preventing the primary composite endpoint of hospitalization for heart failure or CV death (Hazard Ratio [HR] 0.83 [95% CI 0.73, 0.95]; p=0.005) (Figure 13).

Exploratory analyses of the single components suggest that the difference in treatment effect was driven by hospitalization for heart failure (HR 0.73 [95% CI 0.61, 0.88]) (Figure 11), with no clear difference in CV death (HR 0.98 [95% CI 0.82 to 1.17]).

Figure 13: Time to first occurrence of hospitalization for heart failure or cardiovascular death



Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

Patients at risk is the number of patients at risk at the beginning of the period.
CI = Confidence interval
HR = Hazard ratio.

Major adverse cardiovascular events

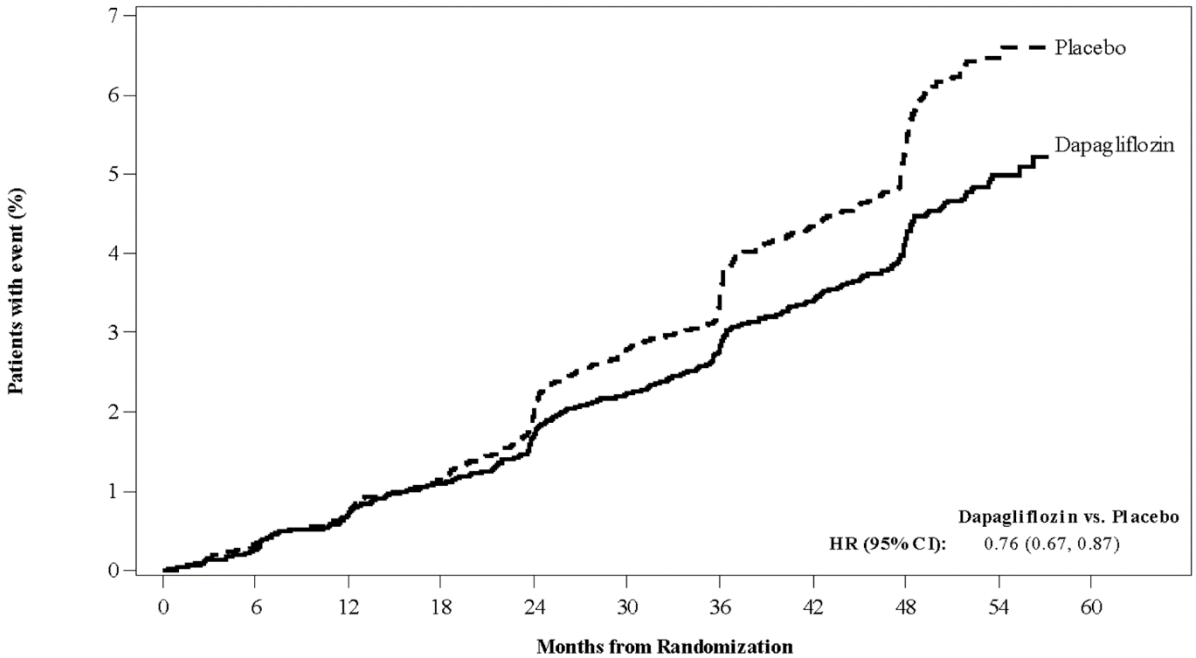
FORXIGA demonstrated cardiovascular safety (tested as non-inferiority versus placebo for the composite of CV death, myocardial infarction or ischemic stroke [MACE]; one-sided p <0.001).

There were numerically fewer MACE events in the FORXIGA group compared with the placebo group (HR 0.93 [95% CI 0.84, 1.03]; p=0.172) (Figures 11 and 12).

Nephropathy

FORXIGA reduced the incidence of events of the composite of confirmed sustained eGFR decrease, ESKD, renal or CV death (HR 0.76 [95% CI 0.67, 0.87]; nominal p<0.001, Figure 14). The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESKD and renal death (Figure 11), and was observed both in patients with and without CV disease (Figure 12).

Figure 14: Time to first occurrence of sustained eGFR decrease, ESKD, renal or CV death



Patients at risk is the number of patients at risk at the beginning of the period.

Renal composite endpoint defined as sustained confirmed eGFR decrease ≥40% to eGFR <60 mL/min/1.73m^2 and/or ESKD and/or renal or CV death.
CI = Confidence interval
HR = Hazard ratio.

When evaluating the renal components, there were 127 and 238 events of new or worsening nephropathy (sustained eGFR decrease, ESKD or renal death) in patients in the FORXIGA and placebo groups, respectively. The HR for time to nephropathy was 0.53 (95% CI 0.43, 0.66) for FORXIGA versus placebo.

Beneficial effects of FORXIGA on renal outcomes were also observed for albuminuria, e.g.,

- In patients without pre-existing albuminuria, FORXIGA reduced the incidence of sustained albuminuria (UACR >30 mg/g) compared with placebo (HR 0.79 [95% CI 0.72, 0.87], nominal p<0.001).
- In patients without pre-existing macroalbuminuria, new onset of macroalbuminuria (UACR >300 mg/g) was reduced in the FORXIGA group compared with the placebo group (HR 0.54 [95% CI 0.45, 0.65], nominal p<0.001).
- In patients with pre-existing macroalbuminuria, regression of macroalbuminuria was greater in the FORXIGA group compared with the placebo group (HR 1.82 [95% CI 1.51, 2.20], nominal p<0.001).

The treatment benefit of FORXIGA over placebo was observed both in patients with and without existing renal impairment.

Supportive Studies

Dual Energy X-ray Absorptiometry in Type 2 Diabetic Patients

Due to the mechanism of action of FORXIGA, a study was done to evaluate body composition and bone mineral density in 182 patients with type 2 diabetes. Treatment with FORXIGA 10 mg added on to metformin over a 24-week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: −2.96 kg *versus* −0.88 kg); waist circumference (mean change from baseline: −2.51 cm *versus* −0.99 cm), and body-fat mass as measured by DXA (mean change from baseline −2.22 kg *versus* −0.74 kg) rather than lean tissue or fluid loss. FORXIGA plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (change

from baseline −322.6 cm3 *versus* −8.7 cm3) in an MRI substudy. Week 24 was analyzed using last observation carried forward (LOCF) analysis including data after rescue.

At Week 24, 2 patients (2.2%) in the placebo plus metformin group and no patients in the FORXIGA 10 mg plus metformin group were rescued for lack of glycemic control.

At Week 50 and Week 102, improvements were sustained in the FORXIGA 10 mg added on to metformin group compared with the placebo plus metformin group for body weight (adjusted mean change from baseline at Week 50: −4.39 kg *versus* −2.03 kg; adjusted mean change from baseline at Week 102: −4.54 kg *versus* −2.12 kg), waist circumference (adjusted mean change from baseline at Week 50: −5.0 cm *versus* −3.0 cm; adjusted mean change from baseline at Week 102: −5.0 cm *versus* −2.9 cm), and body-fat mass as measured by DXA at Week 102 (mean change from baseline: −2.80 kg *versus* −1.46 kg) based on the longitudinal repeated measures analysis including data after rescue. In an MRI sub-study at Weeks 50 and 102, FORXIGA plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (adjusted mean change from baseline at Week 50: −120.0 cm^3 *versus* 61.5 cm^3; adjusted mean change from baseline at Week 102: −214.9 cm^3 *versus* −22.3 cm^3).

The proportion of patients at Week 50 (unadjusted for baseline HbA1c) and Week 102 (adjusted for baseline HbA1c) who were rescued or discontinued for lack of glycemic control was higher in the placebo plus metformin group (6.6% and 33.2%, respectively) than in the FORXIGA 10 mg plus metformin group (2.2% and 13.5%, respectively).

In an extension of this study to Week 50, there was no change in bone mineral density (BMD) for the lumbar spine, femoral neck, or total hip seen in either treatment group (mean change from baseline for all anatomical regions <0.5%). There was also no change in BMD in either treatment group up to Week 102 (mean decrease from baseline for all anatomical regions <1.0%). There were no clinically meaningful changes in markers of bone resorption or bone formation.

Clinical Safety

Hypoglycemia

The incidence of hypoglycemia as seen in controlled clinical studies with dapagliflozin in different combinations is shown in Table 10.

Table 10: Incidence of Major[a] and Minor[b] Hypoglycemia in Controlled Clinical Studies

	Placebo/Active control	FORXIGA 10 mg
CV Outcomes Trial (48 months median exposure)		
All	**N=8569**	**N=8574**
Major [n(%)]	83 (1.0)	58 (0.7)
Patients treated with insulin	**N=4606**	**N=4177**
Major [n(%)]	64 (1.4)	52 (1.2)
Patients treated with a sulfonylurea	**N=4521**	**N=4118**
Major [n(%)]	23 (0.5)	14 (0.3)
Monotherapy (24 weeks)	**N=75**	**N=70**
Major [n (%)]	0	0
Minor [n (%)]	0	0
Add-on to Metformin (24 weeks)	**N=137**	**N=135**
Major [n (%)]	0	0
Minor [n (%)]	0	1 (0.7)
Active Control Add-on to Metformin *versus* Glipizide (52 weeks)	**N=408**	**N=406**
Major [n (%)]	3 (0.7)	0
Minor [n (%)]	147 (36.0)	7 (1.7)
Add-on to Glimepiride (24 weeks)	**N=146**	**N=151**
Major [n (%)]	0	0
Minor [n (%)]	3 (2.1)	9 (6.0)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	**N=109**	**N=109**
Major [n (%)]	0	0
Minor [n (%)]	4 (3.7)	14 (12.8)
Add-on to Pioglitazone (24 weeks)	**N=139**	**N=140**
Major [n (%)]	0	0

Minor [n (%)]	0	0
Add-on to DPP4 inhibitor (24 weeks)	**N=226**	**N=225**
Major [n (%)]	0	1 (0.4)
Minor [n (%)]	3 (1.3)	4 (1.8)
Add-on to Insulin with or without other OADs[c] (24 weeks)	**N=197**	**N=196**
Major [n (%)]	1 (0.5)	1 (0.5)
Minor [n (%)]	67 (34.0)	79 (40.3)

[a] Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration.

[b] Minor episodes of hypoglycemia were defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.

[c] OAD = oral antidiabetic therapy.

Events related to decreased renal function

In the 13-study, short-term, placebo-controlled pool, mean serum creatinine levels increased a small amount at Week 1 (mean change from baseline: 0.041 mg/dL FORXIGA 10 mg *versus* 0.008 mg/dL placebo) and decreased toward baseline by Week 24 (mean change from baseline: 0.019 mg/dL FORXIGA 10 mg *versus* 0.008 mg/dL placebo). There were no further changes through Week 102.

In the CV outcomes study, there were fewer patients with marked laboratory abnormalities of creatinine, creatinine clearance, eGFR, and UACR in the FORXIGA group compared with the placebo group. Fewer renal events (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine, and decreased glomerular filtration rate) were reported in the FORXIGA group compared with the placebo group: 422 (4.9%) and 526 (6.1%), respectively. There were fewer patients with events reported as acute kidney injury in the FORXIGA group compared with the placebo group: 125 (1.5%) and 175 (2.0%), respectively. There were fewer patients with SAEs of renal events in the FORXIGA group compared with the placebo group: 80 (0.9%) and 136 (1.6%), respectively

Laboratory Findings

Hematocrit

In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observed in FORXIGA-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were 2.30% in the FORXIGA 10 mg group *versus* −0.33% in the placebo group. At Week 102, the mean changes were 2.68% *versus* −0.46% respectively. By Week 24, hematocrit values >55% were reported in 1.3% of FORXIGA 10 mg–treated patients *versus* 0.3% of placebo-treated patients. Results were similar during the short-term plus long-term phase (the majority of patients were exposed to treatment for more than one year).

Serum Inorganic Phosphorus

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in FORXIGA 10 mg–treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL *versus* 0.04 mg/dL, respectively). Similar results were seen at Week 102. Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if age ≥66) were reported in FORXIGA 10 mg group *versus* placebo at Week 24 (1.7% *versus* 0.9%, respectively) and during the short-term plus long-term phase (3.0% *versus* 1.6%, respectively). The clinical relevance of these findings is unknown.

Lipids

In the pool of 13 placebo-controlled studies, small changes from baseline in mean lipid values were reported at Week 24 in FORXIGA 10 mg–treated patients compared with placebo-treated patients. Mean percent change from baseline at Week 24 for FORXIGA 10 mg *versus* placebo, respectively, was as follows: total cholesterol, 2.5% *versus* 0.0%; HDL cholesterol, 6.0% *versus* 2.7%; LDL cholesterol, 2.9% *versus* −1.0%; triglycerides, -2.7% *versus* -0.7%. Mean percent change from baseline at Week 102 for FORXIGA 10 mg *versus* placebo, respectively, was as follows: total cholesterol, 2.1% *versus* −1.5%; HDL cholesterol, 6.6% *versus* 2.1%; LDL cholesterol, 2.9% *versus* -2.2%; triglycerides, −1.8% *versus* -1.8%. The ratio between LDL cholesterol and HDL cholesterol decreased for all treatment groups at Week 24.

In the CV outcomes study, no clinical important differences in total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides were seen.

Glycemic control in special populations

Use in patients with type 2 diabetes and hypertension

In two 12-week, placebo-controlled studies, a total of 1062 patients with inadequately controlled type 2 diabetes and hypertension were treated with FORXIGA 10 mg or placebo. Patients with inadequately controlled hypertension (seated systolic blood pressure ≥140 and <165 mmHg, seated diastolic blood pressure ≥85 and <105 mmHg, and a 24-hour mean blood pressure of ≥130/80 mmHg) despite pre-existing stable treatment with an ACEi or ARB (alone [Study 1] or in combination with an additional antihypertensive [Study 2]) as well as inadequate glycemic control (HbA1c ≥7.0% and ≤10.5%) despite pre-existing stable treatment with OADs or insulin (alone or in combination) prior to entry, were eligible for these studies. During the studies, no adjustments in antidiabetic and antihypertensive medications were allowed. Across the 2 studies, 527 patients were treated with FORXIGA 10 mg and 535 with placebo. Patients treated with FORXIGA 10 mg or placebo also received the following medications for blood pressure control, which were balanced between treatment groups: ACEs (64%), ARBs (36%), thiazide diuretics (16%), calcium channel blockers (9%), and beta-blockers (6%).

At Week 12 for both studies, FORXIGA 10 mg plus usual treatment provided significant improvement in HbA1c and significant reduction in seated systolic blood pressure compared with placebo plus usual treatment (see Table 11). Consistent reductions were seen in mean 24-hour ambulatory systolic blood pressure in patients treated with FORXIGA 10 mg treatment compared with placebo. There was a small reduction in mean seated diastolic blood pressure in patients treated with FORXIGA 10 mg that was not statistically significant compared with placebo.

Table 11: Results at week 12 in 2 placebo-controlled studies of FORXIGA in patients with type 2 diabetes and hypertension

	Study 1		Study 2	
Efficacy Parameter	**FORXIGA 10 mg + Usual Treatment**	**Placebo + Usual Treatment**	**FORXIGA 10 mg + Usual Treatment**	**Placebo + Usual Treatment**
	N=302†	**N=311†**	**N=225†**	**N=224†**

HbA1c (%) (LRM)*				
Baseline (mean)	8.1	8.0	8.1	8.0
Change from baseline (adjusted mean‡)	−0.6	−0.1	−0.6	0.0
Difference from placebo (adjusted mean‡) (95% CI)	−0.5§ (−0.6, −0.3)		−0.6§ (−0.8, −0.5)	
Seated Systolic Blood Pressure (mmHg) (LRM) *				
Baseline (mean)	149.8	149.5	151.0	151.3
Change from baseline (adjusted mean‡)	−10.4	−7.3	−11.9	−7.6
Difference from placebo (adjusted mean‡) (95% CI)	−3.1¶ (−4.9, −1.2)		−4.3¶ (−6.5, −2.0)	

* LRM: longitudinal repeated measures analysis.

† All randomized patients who took at least one dose of double-blind study medication during the short-term, double-blind period

‡ Least squares mean adjusted for baseline value

§ p-value <0.0001. ¶ p-value <0.05

\# LOCF: last observation carried forward

Use in patients with type 2 diabetes and cardiovascular disease

In two 24-week, placebo-controlled studies with 80-week extension periods, a total of 1887 patients with type 2 diabetes and CVD were treated with FORXIGA 10 mg or placebo.

Patients with established CVD and inadequate glycemic control (HbA1c ≥7.0% and ≤10.0%), despite pre-existing, stable treatment with OADs or insulin (alone or in combination) prior to entry, were eligible for these studies and were stratified according to age (<65 years or ≥65 years), insulin use (no or yes), and time from most recent qualifying cardiovascular event (>1 year or <1 year prior to enrollment). Across the 2 studies, 942 patients were treated with FORXIGA 10 mg and 945 with placebo. Ninety-six percent (96%) of patients treated with FORXIGA 10 mg across the 2 studies had hypertension at entry, the majority for more than 10

years duration; the most common qualifying cardiovascular events were coronary heart disease (76%) or stroke (20%). Approximately 19% of patients received loop diuretics at entry and 15% had congestive heart failure (2% had NYHA Class III). Approximately 37% of patients treated with FORXIGA 10 mg also received metformin plus one additional OAD (sulfonylurea, thiazolidinedione, DPP4-inhibitor, or other OAD with or without insulin at entry), 39% received insulin plus at least one OAD, and 18% received insulin alone.

At Week 24 for both studies, when added to pre-existing antidiabetic treatments, treatment with FORXIGA 10 mg provided significant improvement to coprimary endpoints of HbA1c and composite clinical benefit compared with placebo. Composite clinical benefit was defined as the proportion of patients with an absolute drop from baseline of 0.5% in HbA1c, and a relative drop from baseline of at least 3% in total body weight, and an absolute drop from baseline of at least 3 mmHg in seated SBP (Table 12). Significant reductions in total body weight and seated systolic blood pressure were also seen in patients treated with FORXIGA 10 mg compared with placebo.

At Week 52 and Week 104 for Study 1, adjusted mean change from baseline in HbA1c, seated systolic blood pressure, and adjusted percent change from baseline in body weight were −0.44% and −0.41%, −3.40 mmHg and −2.64 mmHg, and −2.89% and −3.53%, respectively, for patients treated with FORXIGA 10 mg plus usual treatment based on the longitudinal repeated measures analysis. Corresponding numbers for patients treated with placebo plus usual treatment were 0.22% and 0.50%, 0.18 mmHg and 1.54 mmHg, and −0.29% and −0.02%. At Week 52 and Week 104, percent composite clinical benefit was still higher in the FORXIGA 10 mg group (6.6% and 3.8%) than in the placebo group (0.7% and 0.5%).

At Week 24, Week 52, and Week 104 for Study 1, the proportion of patients who were rescued for lack of glycemic control (adjusted for baseline HbA1c) was higher in the placebo plus usual treatment group (24.0%, 51.8%, and 57.3%, respectively) than in the FORXIGA 10 mg plus usual treatment group (7.9%, 24.6%, and 31.8%, respectively).

At Week 52 and Week 104 for Study 2, adjusted mean change from baseline in HbA1c, seated systolic blood pressure, and adjusted percent change from baseline in body weight were −0.47% and −0.37%, −3.56 mmHg and −1.96 mmHg, and −3.20% and −3.51%, respectively, for

patients treated with FORXIGA 10 mg plus usual treatment based on the longitudinal repeated measures analysis. Corresponding numbers for patients treated with placebo plus usual treatment were 0.03% and −0.18%, −0.91 mmHg and −0.37 mmHg, and −1.12% and −0.65%. At Week 52 and Week 104, percent composite clinical benefit was still higher in the FORXIGA 10 mg group (10.6% and 4.2%) than in the placebo group (3.1% and 1.1%).

At Week 24, Week 52, and Week 104 for Study 2, the proportion of patients who were rescued for lack of glycemic control (adjusted for baseline HbA1c) was higher in the placebo plus usual treatment group (22.3%, 43.6%, and 50.5%, respectively) than in the FORXIGA 10 mg plus usual treatment group (7.6%, 18.7%, and 27.5%, respectively).

Table 12: Results at Week 24 (LOCF*) in Two Placebo-Controlled Studies Comparing FORXIGA to placebo in patient with type 2 diabetic and cardiovascular Disease

	Study 1		Study 2	
Efficacy Parameter	**FORXIGA 10 mg + Usual Treatment**	**PLACEBO + Usual Treatment**	**FORXIGA 10 mg + Usual Treatment**	**PLACEBO + Usual Treatment**
	N=455†	**N=459†**	**N=480†**	**N=482†**
HbA1c (%)				
Baseline mean	8.18	8.08	8.04	8.07
Change from baseline (adjusted mean‡)	−0.38	0.08	−0.33	0.07
Difference from placebo (adjusted mean‡) (95% CI)	−0.46§ (−0.56, −0.37)		−0.40§ (−0.50, −0.30)	
Responders of Composite Clinical Benefit (%)	11.7	0.9	10.0	1.9
Difference from placebo (adjusted %)	9.9§		7.0§	
Components of Composite Endpoint (%)				
Patients with absolute reduction HbA1c ≥0.5% (adjusted %)	45.3	20.6	42.4	21.1

Patients with body weight decrease of at least 3% from baseline (adjusted %)	40.0	13.9	41.3	15.4
Patients with absolute reduction in SBP ≥3 mmHg (adjusted %)	49.1	41.6	46.1	40.9
Body Weight (kg)				
Baseline mean	92.63	93.59	94.53	93.22
Change from baseline (adjusted percent‡)	−2.56	−0.30	−2.53	−0.61
Difference from placebo (adjusted percent‡) (95% CI)	−2.27§ (−2.64, −1.89)		−1.93§ (−2.31, −1.54)	
Body weight decrease of at least 5% in patients with baseline BMI ≥27 kg/m^2 (%)	16.5§	4.0	18.4§	4.8
Seated Systolic Blood Pressure (mmHg)				
Change from baseline at Week 24 (adjusted mean‡)	−2.99	−1.03	−2.70	0.32
Difference from placebo (adjusted mean‡) (95%CI)	−1.95¶ (−3.56, −0.34)		−3.02¶ (−4.59, −1.46)	
Change from baseline seated SBP (mmHg) at week 8 in patients with baseline SBP ≥130 mmHg (adjusted mean‡)	-	-	−5.33¶	−1.89

* LOCF: last observation carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ p-value <0.05.

At week 24, patients treated with FORXIGA 10 mg in the predefined age groups (<65 and ≥65 years of age) also showed significant improvements in the coprimary endpoints of HbA1c and

composite clinical benefit compared with placebo in both studies. A significant reduction in total body weight was also seen in both age groups and a significant reduction of seated SBP in patients <65 years treated with FORXIGA 10 mg compared with placebo at Week 24. These effects were maintained at Week 52 and Week 104.

The safety profile of FORXIGA in these studies was consistent with that of FORXIGA in the general clinical study population through 104 weeks of treatment (see section 4.8 Undesirable effects).

Use in patients with type 2 diabetes and renal impairment

Patients with mild renal impairment (eGFR ≥60 to <90 mL/min/1.73m^2)

In the clinical trial program more than 3000 patients with mild renal impairment were treated with dapagliflozin. Efficacy was assessed in a pooled analysis across 9 clinical studies consisting of 2226 patients with mild renal impairment. The mean change from baseline in hemoglobin A1c (HbA1c) and the placebo-corrected mean HbA1c change at 24 weeks was −1.03% and −0.54%, respectively, for FORXIGA 10 mg (n=562). The safety profile in patients with mild renal impairment is similar to that in the overall population.

Patients with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73m^2)

The glycemic efficacy and safety of FORXIGA was evaluated in two dedicated studies of patients with moderate renal impairment and in two subgroup analyses of pooled clinical studies.

In a randomized, double blind, placebo-controlled trial a total of 321 adult patients with type 2 diabetes mellitus and eGFR ≥45 to <60 mL/min/1.73m^2 (moderate renal impairment subgroup CKD 3A), with inadequate glycemic control on current treatment regimen, were treated with FORXIGA 10 mg or placebo. At Week 24, FORXIGA 10 mg (n=159) provided significant improvements in HbA1c, FPG, Body Weight and SBP compared with placebo (n=161) (Table 13). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change was −0.37% and −0.34%, respectively. The mean change from baseline in FPG and the placebo-corrected mean FPG was -21.46 mg/dL and -16.59 mg/dL, respectively. The mean body weight reduction (percentage) and the placebo-corrected mean body weight reduction was -3.42% and -1.43 %, respectively. The mean reduction in seated systolic blood pressure

(SBP) and the placebo-corrected mean reduction in SBP was -4.8 mmHg and -3.1 mmHg, respectively.

Table 13: Results at Week 24 in a Placebo-Controlled Study of FORXIGA Treatment in Diabetic Patients with Moderate Renal Impairment (Class 3A, eGFR ≥45 to <60 mL/min/1.73m^2)

Efficacy Parameter	FORXIGA 10 mg N=159	Placebo N=161
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline (adjusted mean*)	-0.37	-0.03
Difference from placebo (adjusted mean*)	-0.34§	
(95% CI)	(-0.53, -0.15)	
FPG (mg/dL)		
Baseline (mean)	183.04	173.28
Change from baseline (adjusted mean*)	-21.46	-4.87
Difference from placebo (adjusted mean*)	-16.59§	
(95% CI)	(-26.73, -6.45)	
Body Weight (percentage)		
Baseline (mean)	92.51	88.30
% Change from baseline (adjusted mean*)	-3.42	-2.02
Difference from placebo (adjusted mean*)	-1.43§	
(95% CI)	(-2.15, -0.69)	
Seated Systolic Blood Pressure (mmHg)		
Baseline (mean)	135.7	135.0
Change from baseline (adjusted mean*)	-4.8	-1.7
Difference from placebo (adjusted mean*)	-3.1¶	
(95% CI)	(-6.3, 0.0)	

* Least squares mean adjusted for baseline value.

§ p-value ≤0.001.

¶ p-value <0.05.

The safety profile of dapagliflozin in the study was consistent with that in the general population of patients with type 2 diabetes. Mean eGFR decreased initially during the

treatment period in the dapagliflozin group and subsequently remained stable during the 24-week treatment period (FORXIGA: -3.39 mL/min/1.73m^2 and placebo: -0.90 mL/min/1.73m^2). At 3 weeks after termination of FORXIGA, the mean change from baseline in eGFR in the dapagliflozin group was similar to the mean change in the placebo group (FORXIGA: 0.57 mL/min/1.73m^2 and placebo: -0.04 mL/min/1.73m^2).

Efficacy in patients with moderate renal impairment was assessed in a pooled analysis across 9 clinical studies (366 patients, 87% with eGFR ≥45 to <60 mL/min/1.73m^2) ; this pool did not include the two dedicated studies of diabetic patients with moderate renal impairment. The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change at 24 weeks was −0.87% and −0.39%, respectively, for FORXIGA 10 mg (n=85).

Safety in patients with moderate renal impairment was assessed in a pooled analysis of 12 clinical studies (384 patients, 88% with eGFR ≥45 to <60 mL/min/1.73m^2); this pool does not include the dedicated study of diabetic patients with moderate renal impairment. At Week 24, safety was similar to that seen in the overall program of clinical studies except for a higher proportion of patients reporting at least one event related to renal impairment or failure (7.9% FORXIGA 10 mg *versus* 5.6% placebo). Of these events, increased serum creatinine was the most frequently reported (6.7% FORXIGA 10 mg *versus* 2.8% placebo). Increases in mean parathyroid hormone (PTH) and serum phosphorus observed with FORXIGA in the overall program of clinical studies were also seen in the pooled analysis. No imbalance in bone fractures was observed in this analysis. In the short-term plus long-term safety pool up to 102 weeks, the safety profile remained similar.

The efficacy and safety of FORXIGA was also assessed in a study of 252 diabetic patients with eGFR ≥30 to <60 mL/min/1.73m^2 (moderate renal impairment subgroup CKD 3A and CKD 3B). FORXIGA treatment did not show a significant placebo corrected change in HbA1c in the overall study population (CKD 3A and CKD 3B combined) at 24 weeks. In an additional analysis of the subgroup CKD 3A, FORXIGA 10 mg (n=32) provided a placebo-corrected mean HbA1c change at 24 weeks of −0.33%. At Week 52, FORXIGA was associated with changes from baseline in mean eGFR (FORXIGA 10 mg −4.46 mL/min/1.73m^2 and placebo −2.58 mL/min/1.73m^2). At Week 104, these changes persisted (eGFR: FORXIGA 10 mg −3.50 mL/min/1.73m^2 and placebo −2.38 mL/min/1.73m^2). With FORXIGA 10 mg, this eGFR reduction was evident at Week 1 and

remained stable through Week 104, while placebo-treated patients had a slow continuous decline through Week 52 that stabilized through Week 104.

At Week 52 and persisting through Week 104, greater increases in mean PTH and serum phosphorus were observed in this study with FORXIGA 10 mg compared to placebo, where baseline values of these analytes were higher. Elevations of potassium of ≥6 mEq/L were more common in patients treated with placebo (12.0%) than those treated with FORXIGA 5 mg and 10 mg (4.8% for both groups) during the cumulative 104-week treatment period. The proportion of patients discontinued for elevated potassium, adjusted for baseline potassium, was higher for the placebo group 14.3%) than for the FORXIGA groups (6.9% and 6.7% for the 5 mg and 10 mg groups, respectively).

Overall, there were 13 patients with an adverse event of bone fracture reported in this study up to Week 104 of which 8 occurred in the FORXIGA 10 mg group, 5 occurred in the FORXIGA 5 mg group, and none occurred in the placebo group. Eight (8) of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1.73m^2 and 10 of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the site of fracture. No imbalance in bone fractures was observed in the safety analysis of the 12-study pool data and no bone fractures were reported in the dedicated study of patients with eGFR ≥45 to <60 mL/min/1.73m^2 (CKD 3A).

Use in elderly patients with type 2 diabetes

A total of 2403 (26%) of 9339 treated patients were 65 years and older and 327 (5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies of FORXIGA assessing the safety and efficacy of FORXIGA in improving glycemic control. After controlling for level of renal function (eGFR), there was no conclusive evidence suggesting that age is an independent factor affecting efficacy. Overall, the proportion of patients reporting adverse events was consistent between those ≥65 and <65 years of age.

Clinical trial information – heart failure

Clinical efficacy

DAPA-HF study: Heart failure with reduced left ventricular ejection fraction (LVEF ≤40%)

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients with heart failure (New York Heart Association [NYHA] functional class II-IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤40%) to determine the effect of FORXIGA compared with placebo, when added to background standard of care therapy, on the incidence of CV death and worsening heart failure.

Of 4744 patients, 2373 were randomized to FORXIGA 10 mg and 2371 to placebo and followed for a median of 18 months. The mean age of the study population was 66 years, 77% were male, 70% White, 5% Black or African-American and 24% Asian.

At baseline, 67.5% patients were classified as NYHA class II, 31.6% class III and 0.9% class IV, median LVEF was 32%, 42% of the patients in each treatment group had a history of type 2 diabetes mellitus, and an additional 3% of the patients in each group were classified as having type 2 diabetes mellitus based on a HbA1c ≥6.5% at both enrollment and randomization.

Patients were on standard of care therapy; 94% of patients were treated with ACEi, ARB, or angiotensin receptor-neprilysin inhibitor (ARNI, 11%), 96% with beta-blocker, 71% with mineralocorticoid receptor antagonist (MRA), 93% with diuretic and 26% had an implantable device.

Patients with eGFR ≥30 mL/min/1.73m^2 at enrollment were included in the study. The mean eGFR was 66 mL/min/1.73m^2, 41% of patients had eGFR <60mL/min/1.73m^2 and 15% had eGFR <45 mL/min/1.73m^2.

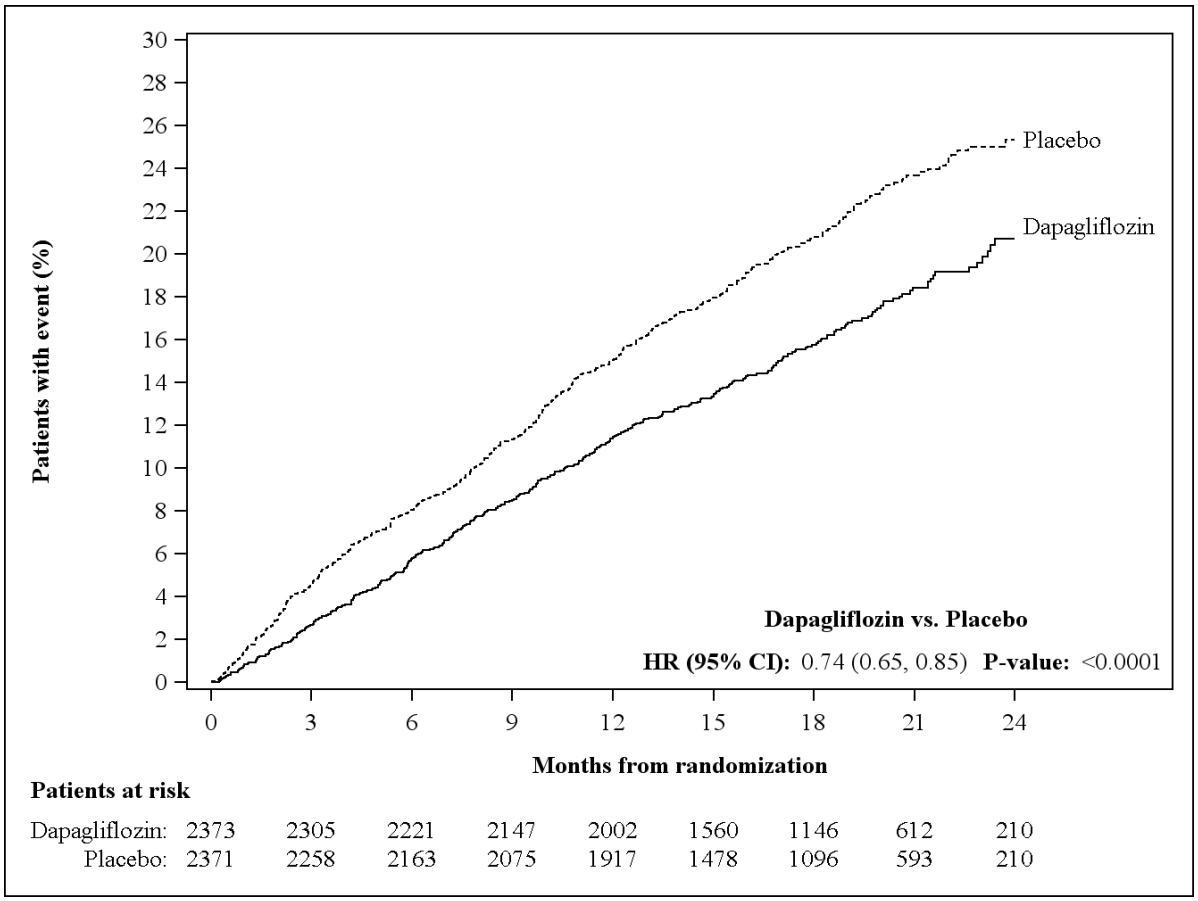
The DAPA-HF outcomes study compared FORXIGA versus placebo in a population representative of that found in clinical practice. The overall study objective was to determine whether FORXIGA prevents cardiovascular death and worsening heart failure, and if FORXIGA improves heart failure symptoms.

Cardiovascular death and worsening heart failure

FORXIGA 10 mg was superior to placebo in preventing CV death and worsening heart failure, with consistent treatment effect on primary and secondary endpoints.

FORXIGA reduced the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit (HR 0.74 [95% CI 0.65, 0.85]; p<0.0001). The number needed to treat per year was 26 (95% CI 18, 46). The FORXIGA and placebo event curves separated early and continued to diverge over the study period (Figure 15).

Figure 15: Time to first occurrence of the composite hospitalization of cardiovascular death, hospitalization for heart failure or urgent heart failure visit

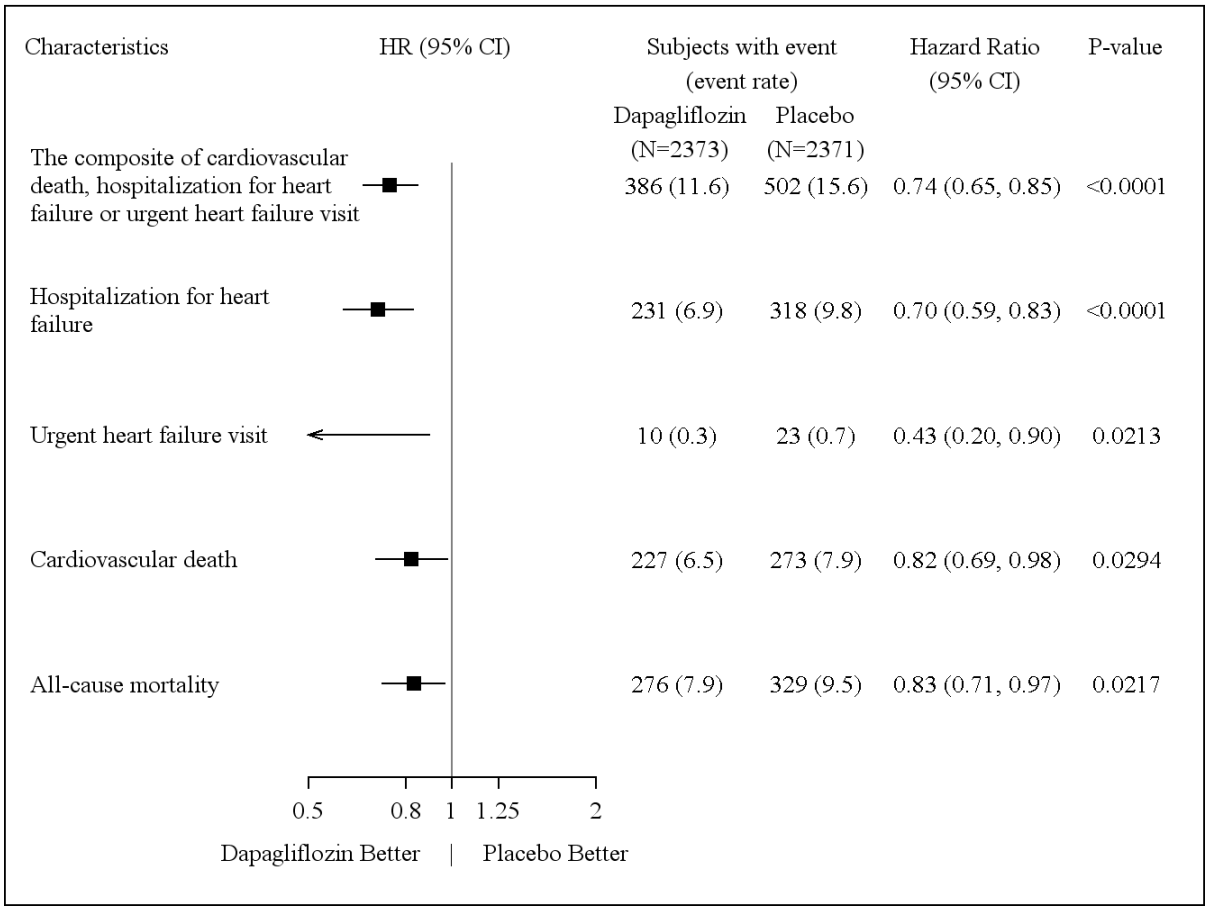


An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

Patients at risk is the number of patients at risk at the beginning of the period.

All three components of the primary composite endpoint individually contributed to the treatment effect (Figure 16). There were few urgent heart failure visits. FORXIGA also reduced the incidence of cardiovascular death or hospitalization for heart failure (HR 0.75 [95% CI 0.65, 0.85], p<0.0001).

Figure 16: Treatment effects for the primary composite endpoint, its components and all-cause mortality



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

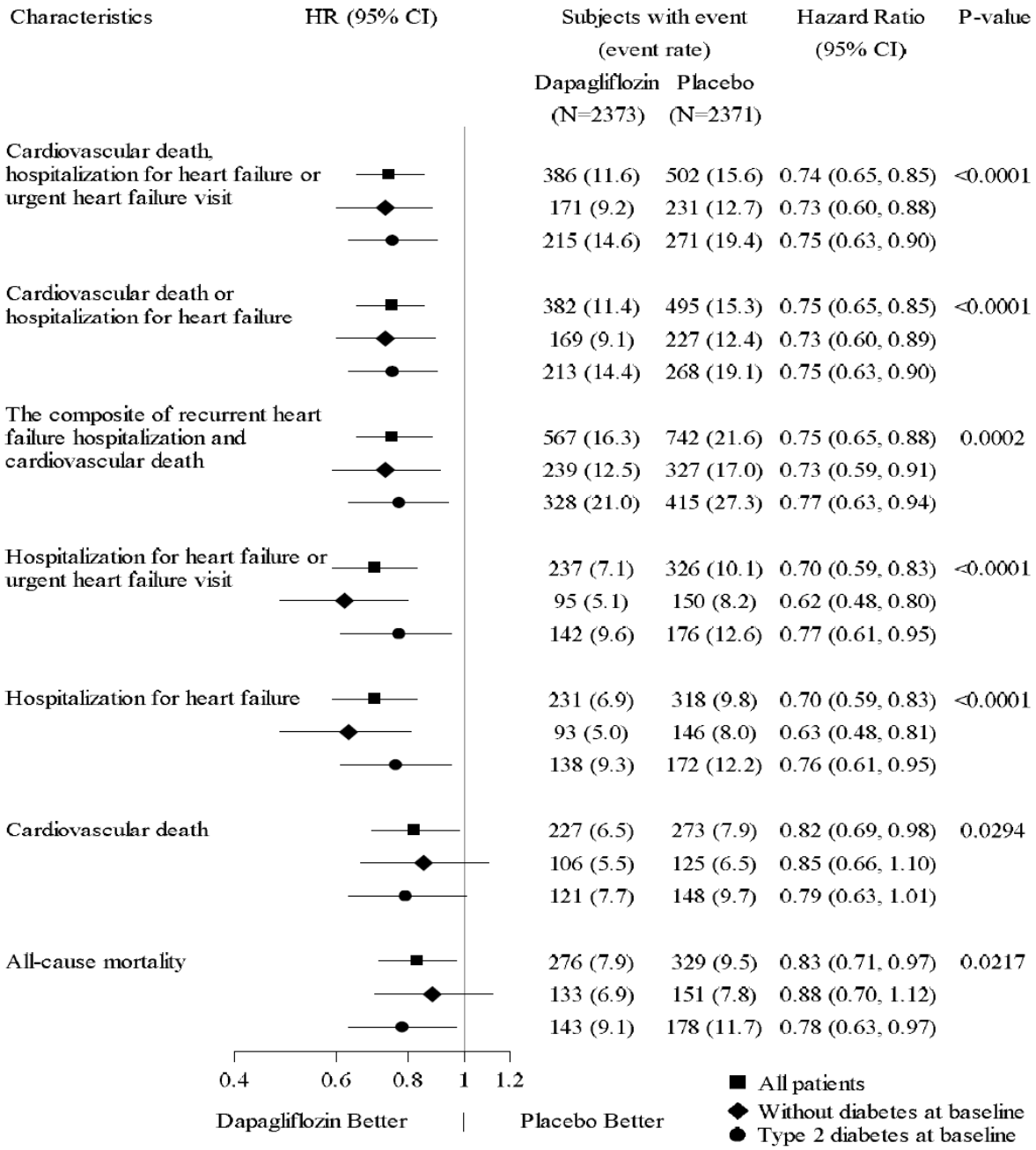
Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

p-values for single components and all-cause mortality are nominal.

FORXIGA also reduced the total number of events of hospitalizations for heart failure (first and recurrent) and cardiovascular death; there were 567 events in the FORXIGA group versus 742 events in the placebo group (Rate Ratio 0.75 [95% CI 0.65, 0.88]; p=0.0002).

The treatment benefit of FORXIGA was observed in heart failure patients both with type 2 diabetes mellitus and without diabetes (Figure 17).

Figure 17: Treatment effects in all patients, in patients with type 2 diabetes mellitus and in patients without diabetes



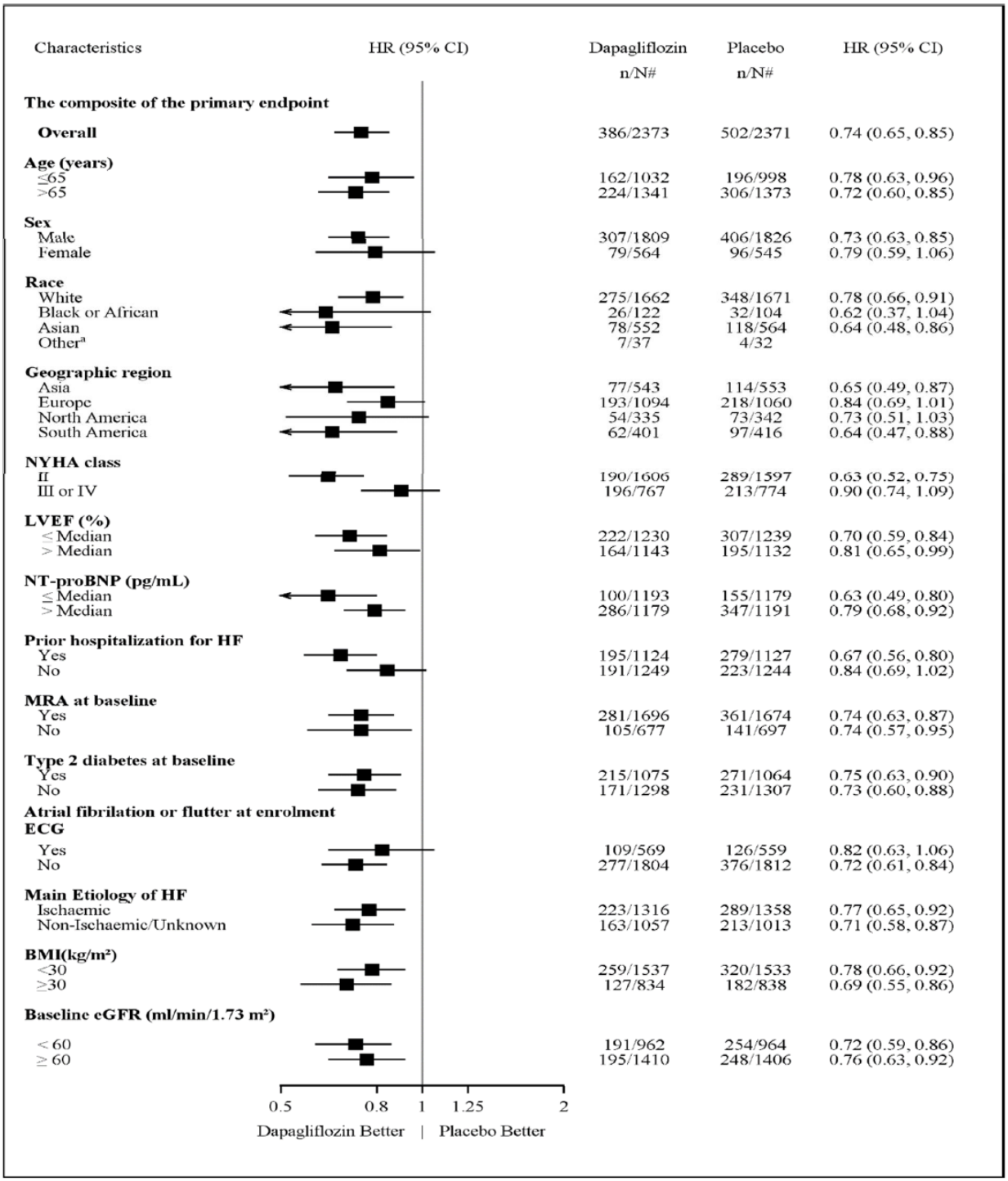
An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

For the composite of recurrent hospitalizations for heart failure and cardiovascular death, rate ratios are presented rather than hazard ratios and the numbers of events are shown rather than subjects with event.

The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.
Event rates are presented as the number of subjects with event per 100 patient years of follow-up, or, for the composite of recurrent heart failure hospitalizations and CV death, as the average number of events per 100 patient years.
p-values for components of the primary composite endpoint and for all-cause mortality are nominal.

The treatment benefit of FORXIGA over placebo on the primary endpoint was also consistent across other key subgroups (Figure 18).

Figure 18: Treatment effects for the primary composite endpoint by sub-groups



a Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

n/N# Number of subjects with event/number of subjects in the subgroup.

NT-proBNP = N-terminal pro b-type natriuretic peptide.

HF = Heart failure

Patient reported outcome – heart failure symptoms

The treatment effect of FORXIGA on heart failure symptoms was assessed by the Total Symptom Score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS), which quantifies heart failure symptom frequency and severity, including fatigue, peripheral edema, dyspnea and orthopnea. The score ranges from 0 to 100, with higher scores representing better health status.

Treatment with FORXIGA resulted in a statistically significant and clinically meaningful benefit over placebo in heart failure symptoms, as measured by change from baseline to Month 8 in the KCCQ-TSS, (Win Ratio 1.18 [95% CI 1.11, 1.26]; p<0.0001). Both symptom frequency and symptom burden contributed to the results. Benefit was seen both in improving heart failure symptoms and in preventing deterioration of heart failure symptoms.

In responder analyses, the proportion of patients with a clinically meaningful improvement on the KCCQ-TSS from baseline at 8 months, defined as 5 points or more, was higher for the FORXIGA treatment group compared with placebo. The proportion of patients with a clinically meaningful deterioration, defined as 5 points or more, was lower for the FORXIGA treatment group compared to placebo. The benefits observed with FORXIGA remained when applying more conservative cut-offs for larger clinically meaningful change (Table 14).

Table 14: Number and percent of patients with clinically meaningful improvement and deterioration on the KCCQ-TSS at 8 months

Change from baseline at 8 months:	**Dapagliflozin 10 mg n[a]=2086**	**Placebo n[a]=2062**		
Improvement	**n (%) improved[b]**	**n (%) improved[b]**	**Odds ratio[c] (95% CI)**	**p-value[f]**
≥5 points (small improvement)	1198 (57.4)	1030 (50.0)	1.15 (1.08, 1.23)	<0.0001
≥10 points (moderate to large improvement)	1124 (53.9)	968 (46.9)	1.15 (1.08, 1.22)	<0.0001
≥15 points (large improvement)	1120 (53.7)	984 (47.7)	1.14 (1.07,1.22)	<0.0001

Deterioration	n (%) deteriorated[d]	n (%) deteriorated[d]	Odds ratio[e] (95% CI)	p-value[f]
≥5 points (small deterioration)	524 (25.1)	682 (33.1)	0.84 (0.78, 0.90)	<0.0001
≥10 points (moderate to large deterioration)	385 (18.5)	495 (24.0)	0.85 (0.79, 0.92)	<0.0001

[a] Number of patients with an observed KCCQ-TSS or who died prior to 8 months

[b] Number of patients who had an observed improvement of at least 5, 10 or 15 points from baseline. Patients who died prior to the given timepoint are counted as not improved. Patients with a KCCQ-TSS at baseline which was too high for them to experience an improvement were defined as improved if they remained there at 8 months.

[c] For improvement, an odds ratio >1 favours dapagliflozin 10 mg.

[d] Number of patients who had an observed deterioration of at least 5 or 10 points from baseline. Patients who died prior to the given timepoint are counted as deteriorated. Patients with a KCCQ-TSS at baseline which was too low for them to experience a deterioration were defined as deteriorated if they remained there at 8 months.

[e] For deterioration, an odds ratio <1 favours dapagliflozin 10 mg.

[f] p-values are nominal.

Nephropathy

There were 28 and 39 events of the composite of confirmed sustained ≥50% eGFR decrease, ESKD, or renal death in patients in the FORXIGA and placebo groups, respectively, (HR 0.71 [95% CI 0.44, 1.16]).

All-cause mortality

The incidence of all-cause mortality was lower in the FORXIGA treatment group compared with placebo (HR 0.83; 95% CI [0.71, 0.97], Figure 16).

DELIVER study: Heart failure with left ventricular ejection fraction >40%

Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (DELIVER) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients aged ≥40 years with heart failure (NYHA class II-IV) with LVEF >40% and evidence of structural heart disease to determine the effect of FORXIGA compared with placebo on the incidence of CV death and worsening heart failure.

Of 6263 patients, 3131 were randomized to FORXIGA 10 mg and 3132 to placebo and

followed for a median of 28 months. The study included 654 (10%) subacute heart failure patients (defined as randomized during hospitalization for heart failure or within 30 days of discharge).

The mean age of the study population was 72 years, 56% were male, 71% White, 3% Black or African-American and 20% Asian.

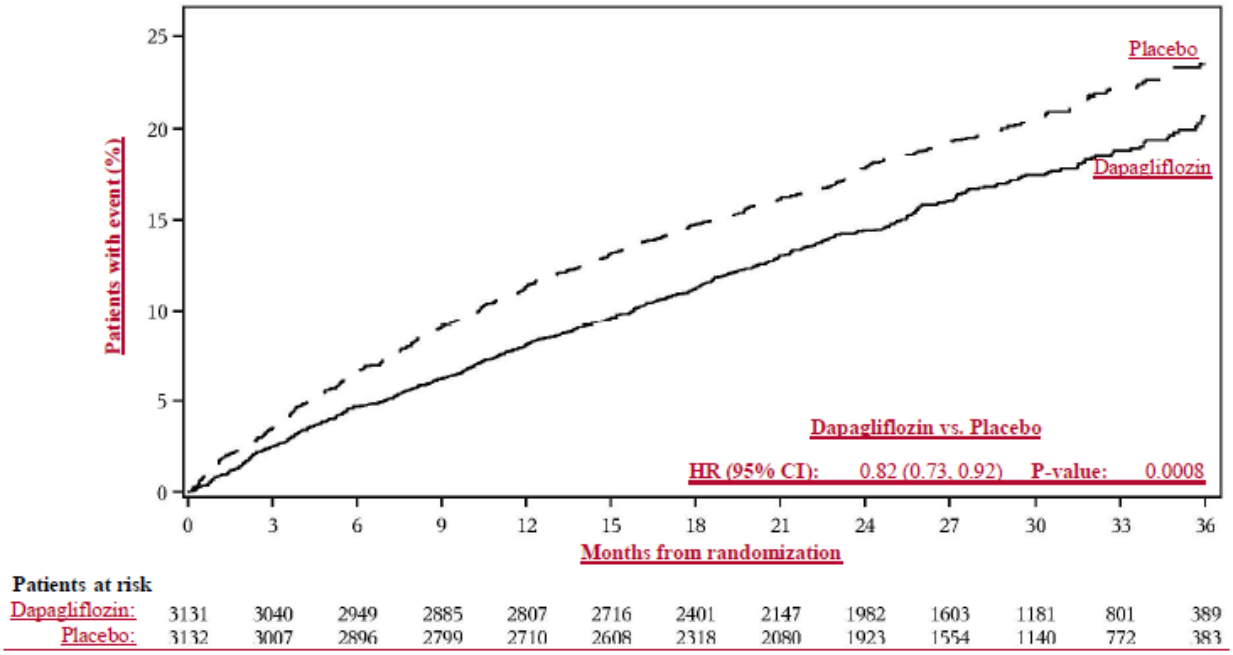
At baseline, 75% patients were classified as NYHA class II, 24% class III and 0.3% class IV. Median LVEF was 54%, 34% of the patients had LVEF ≤49%, 36% had LVEF 50-59% and 30% had LVEF ≥60%. In each treatment group, 45% had a history of type 2 diabetes mellitus. Baseline therapy included ACEi/ARB/ARNI (77%), beta-blockers (83%) diuretics (98%) and MRA (43%).

Patients with eGFR ≥25 mL/min/1.73 m2 at enrollment were included in the study. The mean eGFR was 61 mL/min/1.73 m2, 49% of patients had eGFR <60 mL/min/1.73 m2, 23% had eGFR <45 mL/min/1.73 m2, and 3% had eGFR <30 mL/min/1.73 m2.

Cardiovascular death or worsening heart failure

FORXIGA was superior to placebo in reducing the incidence of the primary composite endpoint of cardiovascular death, hospitalization for heart failure or urgent heart failure visit (HR 0.82 [95% CI 0.73, 0.92]; p=0.0008). The number needed to treat per study duration (median follow-up 28 months) was 32 (95% CI 20,82). The FORXIGA and placebo event curves diverged early and the separation was maintained throughout the study (Figure 19).

Figure 19 Time to first occurrence of the composite of cardiovascular death, hospitalization for heart failure or urgent heart failure visit

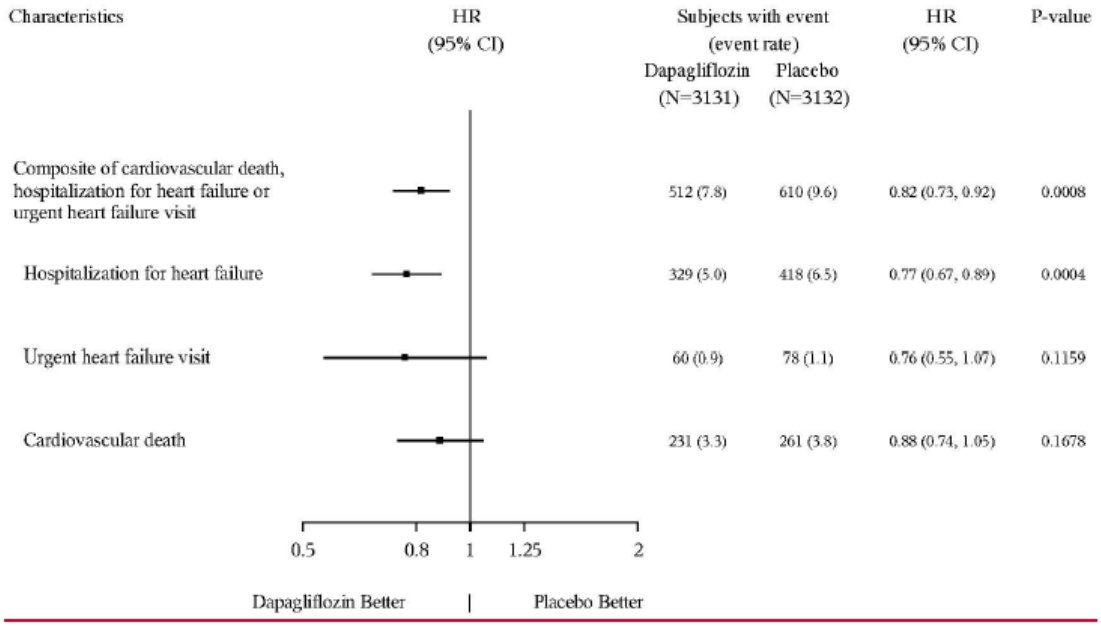


An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

Patients at risk is the number of patients at risk at the beginning of the period.

All three components of the primary composite endpoint individually contributed to the treatment effect (Figure 20).

Figure 20 Treatment effects for the primary composite endpoint and its components

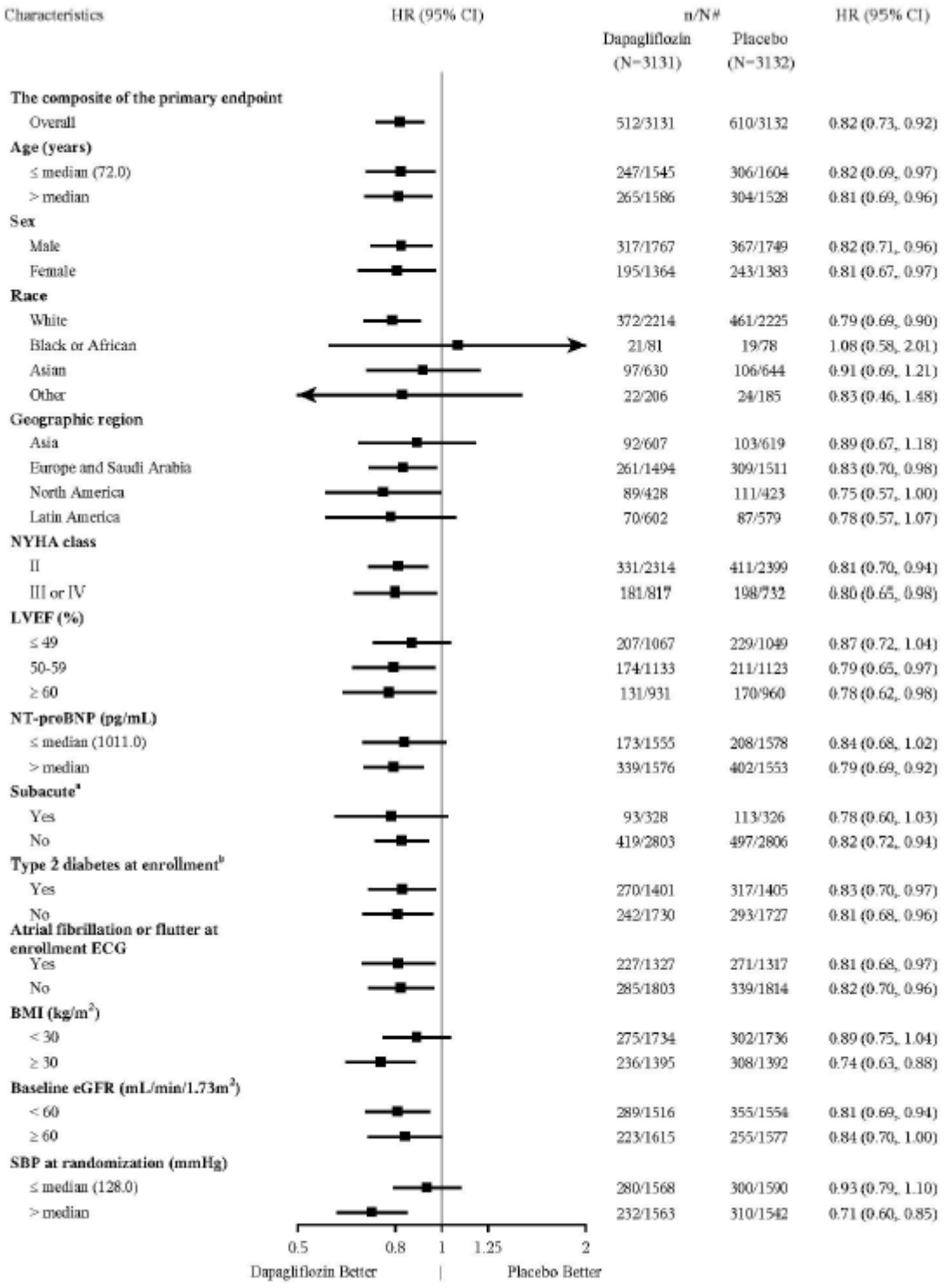


An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).
The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.
Event rates are presented as the number of subjects with event per 100 patient years of follow-up.
p-values for single components are nominal. Cardiovascular death, here presented as a component of the primary endpoint, was also tested under formal Type 1 error control as a secondary endpoint.

FORXIGA was superior to placebo in reducing the total number of heart failure events (first and recurrent hospitalization for heart failure or urgent heart failure visits) and cardiovascular death; there were 815 events in the FORXIGA group versus 1057 events in the placebo group (Rate Ratio 0.77 [95% CI 0.67, 0.89]; p=0.0003).

The treatment benefit of FORXIGA over placebo on the primary endpoint was observed across subgroups of patients with LVEF ≤49%, 50–59%, and ≥60%. Effects were also consistent across other key subgroups (Figure 21).

Figure 21 Treatment effects for the primary composite endpoint by sub-groups



[a] Defined as randomized during hospitalization for heart failure or within 30 days of discharge.

[b] Defined as history of type 2 diabetes mellitus. This analysis does not include type 2 diabetes mellitus as a stratification factor.

n/N# Number of subjects with event/number of subjects in the subgroup.

Patient reported outcome – heart failure symptoms

Treatment with FORXIGA resulted in a statistically significant benefit over placebo in heart failure symptoms, as measured by change from baseline at Month 8 in the KCCQ-TSS, (Win Ratio 1.11 [95% CI 1.03, 1.21]; p=0.0086). Both symptom frequency and symptom burden contributed to the results.

In responder analyses, clinically meaningful deterioration, defined as 5 points or more, was lower for the FORXIGA treatment group compared with placebo. The benefit observed with FORXIGA remained when applying a more conservative cut-off. The proportion of patients with a clinically meaningful improvement on the KCCQ-TSS from baseline at 8 months did not differ between treatment groups (Table 15).

Table 15 Number and percent of patients with clinically meaningful deterioration and improvement on the KCCQ-TSS at 8 months

Change from baseline at 8 months:	Dapagliflozin 10 mg n[a]=1316	Placebo n[a]=1311		
Deterioration	n (%) deteriorated[b]	n (%) deteriorated[b]	Odds ratio[c] (95% CI)	p-value
≥5 points (moderate deterioration)	264 (24.1)	317 (29.1)	0.78 (0.64, 0.95)	0.0127
≥14 points (large deterioration)	148 (13.5)	201 (18.4)	0.70 (0.55, 0.88)	0.0026
Improvement	n (%) improved[d]	n (%) improved[d]	Odds ratio[e] (95% CI)	p-value[f]
≥13 points (small to moderate improvement)	531 (48.4)	498 (45.6)	1.13 (0.95, 1.33)	0.1608
≥17 points (large improvement)	486 (44.3)	478 (43.8)	1.06 (0.89, 1.26)	0.5137

[a] Number of patients with an observed KCCQ-TSS or who died prior to 8 months. Number includes patients with an 8-month assessment (Visit 5) planned or performed prior to 11 March 2020, when COVID-19 was declared a pandemic by the WHO. Data for patients with planned but not performed assessment prior to 11 March 2020 was imputed.

[b] Number of subjects who died prior to the given time point or had an observed deterioration from baseline equal to or exceeding the given threshold. Patients with a KCCQ-TSS at baseline which was too low to possibly experience a deterioration were defined as deteriorated if their score at 8 months was not higher than baseline.

[c] For deterioration, an odds ratio <1 favours dapagliflozin 10 mg.

[d] Number of subjects who had an observed improvement of at least 13 or 17 points from baseline. Patients who died prior to the given timepoint are counted as not improved. Patients with a KCCQ-TSS at baseline

which was too high to possibly experience an improvement were defined as improved if their score at 8 months was not lower than baseline.

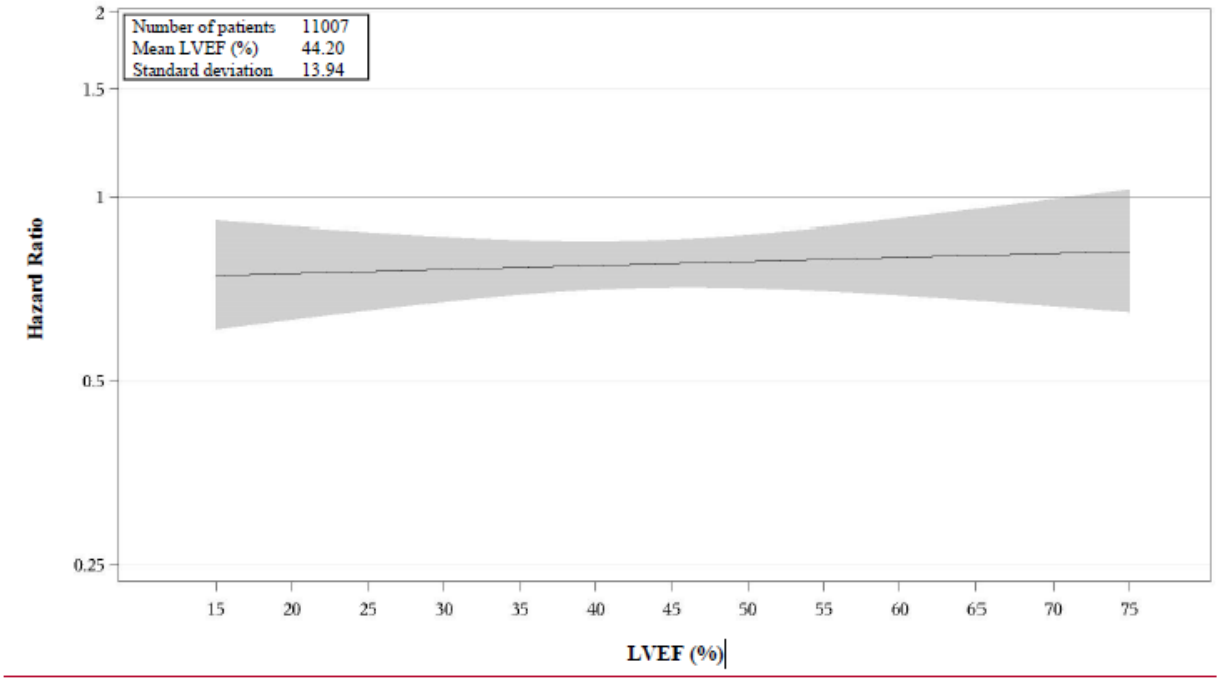
[e] For improvement, an odds ratio >1 favours dapagliflozin 10 mg.

[f] p-values are nominal

Heart failure across DAPA-HF and DELIVER studies

In a pooled analysis of DAPA-HF and DELIVER, the treatment effect of FORXIGA on the composite endpoint of cardiovascular death, hospitalization for heart failure or urgent heart failure visit was consistent across the LVEF range (Figure 22).

Figure 22 Treatment effect for the primary composite endpoint (cardiovascular death, hospitalization for heart failure or urgent heart failure visit) by baseline LVEF

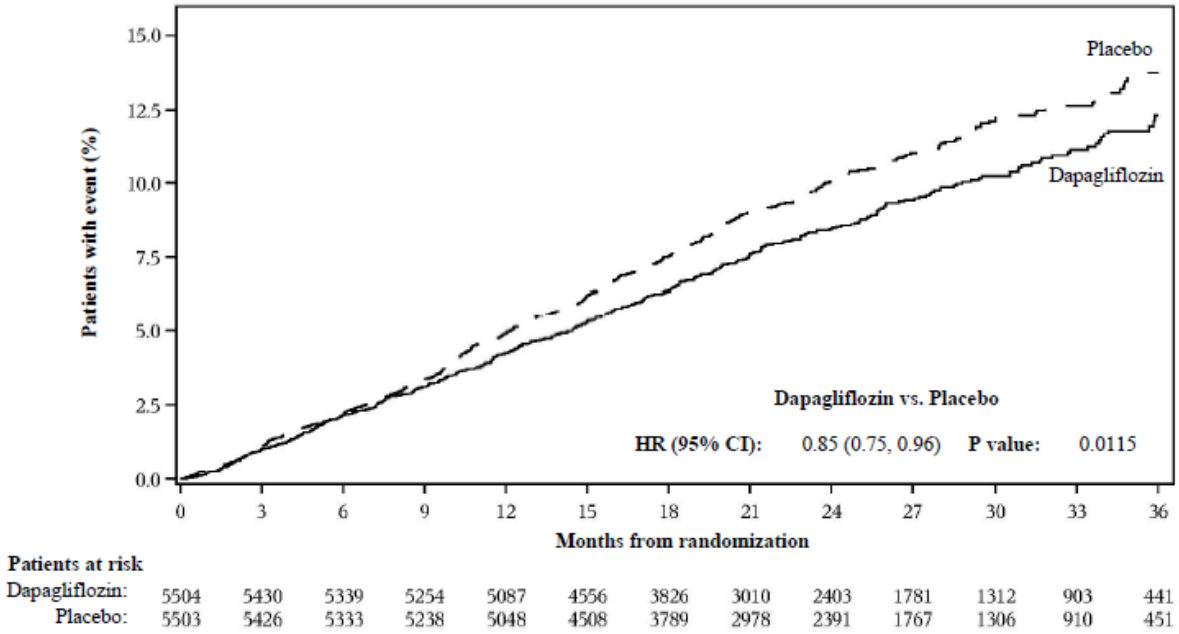


Definitions of the primary endpoints from each study are used. In DAPA-HF the primary endpoint included death with undetermined cause of death. In DELIVER the primary endpoint did not include death with undetermined cause of death.

Data for LVEF between 15% and 75% are presented in the figure. At baseline, 0.5% of patients had LVEF <15% and 0.7% had LVEF >75%.

In a pre-specified subject level pooled analysis of the DAPA-HF and DELIVER studies, FORXIGA compared with placebo reduced the risk of cardiovascular death (HR 0.85 [95% CI 0.75, 0.96], p=0.0115) (Figure 23). Both studies contributed to the effect.

Figure 23 Time to first occurrence of cardiovascular death (pooled analysis of DAPA-HF and DELIVER studies)



Definitions of CV death from each study is used. In DAPA-HF, CV death included death with undetermined cause of death.

In DELIVER, CV death did not include death with undetermined cause of death.

Patients at risk is the number of patients at risk at the beginning of the period.

Clinical trial information - chronic kidney disease

Clinical efficacy

The Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD) was an international, multicenter, event-driven, randomized, double-blind, parallel-group, placebo-controlled study comparing FORXIGA with placebo, when added to background standard of care therapy, in chronic kidney disease (CKD) patients with eGFR ≥25 to ≤75 mL/min/1.73m^2 and albuminuria (urine albumin creatinine ratio [UACR] ≥200 and ≤5000 mg/g). The primary objective was to determine the effect of FORXIGA compared with placebo in reducing the incidence of the composite endpoint of ≥50% sustained decline in eGFR, end stage kidney disease (ESKD) (defined as sustained eGFR <15 mL/min/1.73 m^2, chronic dialysis treatment or receiving a renal transplant), CV or renal death.

A total of 4304 patients were randomised to FORXIGA 10 mg (N=2152) or placebo (N=2152) once daily and followed for a median of 28.5 months. Treatment was continued if eGFR fell to levels below 25 mL/min/1.73m^2 during the study and could be continued in cases when dialysis was needed.

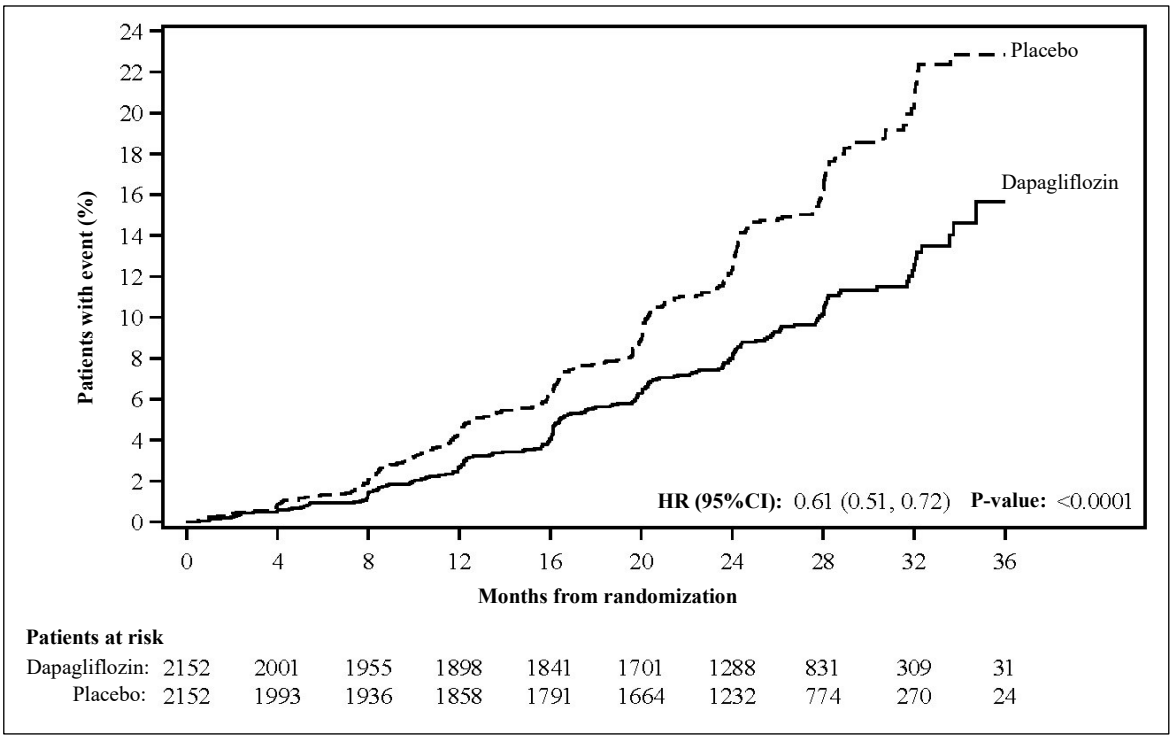
At baseline, mean eGFR was 43.1 mL/min/1.73m^2 and median UACR was 949.3 mg/g, 44.1% of patients had eGFR 30 to <45 mL/min/1.73m^2 and 14.5% had eGFR <30 mL/min/1.73m^2. 67.5% of the patients had type 2 diabetes mellitus.

Patients were on standard of care (SOC) therapy; 97.0% of patients were treated with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

The mean age of the study population was 61.8 years, 66.9% were male, 53.2% White, 4.4% Black or African-American, and 34.1% Asian.

FORXIGA was superior to placebo in reducing the incidence of the primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, CV or renal death (HR 0.61 [95% CI 0.51, 0.72]; p<0.0001). The number needed to treat per 27 months was 19 (95% CI 15, 27). Based on the Kaplan-Meier plot, the FORXIGA and placebo event curves began to separate early (4 months) and continued to diverge over the study period (Figure 24).

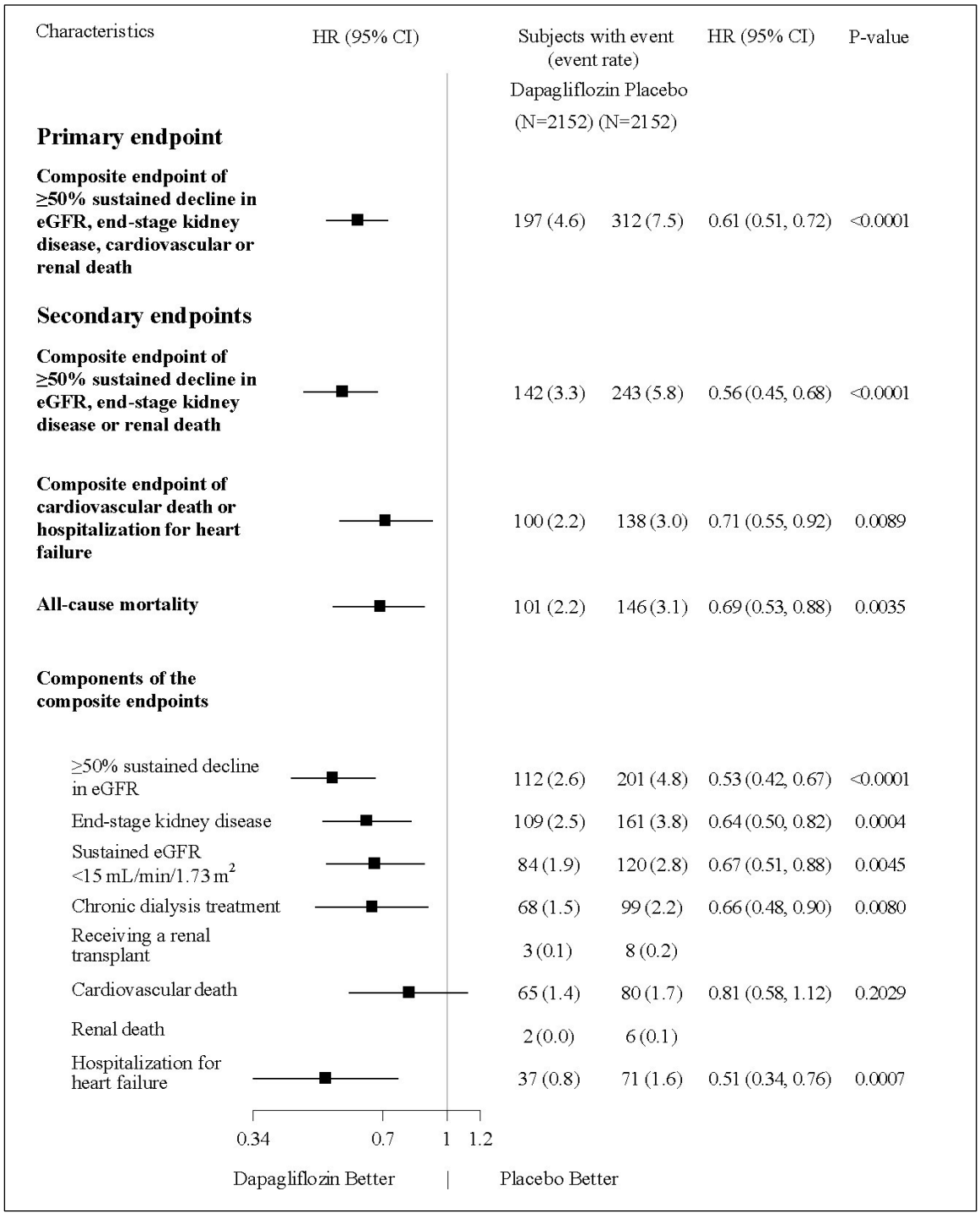
Figure 24 Time to first occurrence of the primary composite endpoint, ≥50% sustained decline in eGFR, ESKD, CV or renal death



Patients at risk is the number of patients at risk at the beginning of the period.

All four components of the primary composite endpoint individually contributed to the treatment effect (Figure 25). FORXIGA also reduced the incidence of the composite endpoint of ≥50% sustained decline in eGFR, ESKD or renal death (HR 0.56 [95% CI 0.45, 0.68], p<0.0001), the composite endpoint of CV death and hospitalization for heart failure (HR 0.71 [95% CI 0.55, 0.92], p=0.0089), and all-cause mortality (HR 0.69 [95% CI 0.53, 0.88], p=0.0035).

Figure 25: Treatment effects for the primary and secondary composite endpoints, their individual components, and all-cause mortality



The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

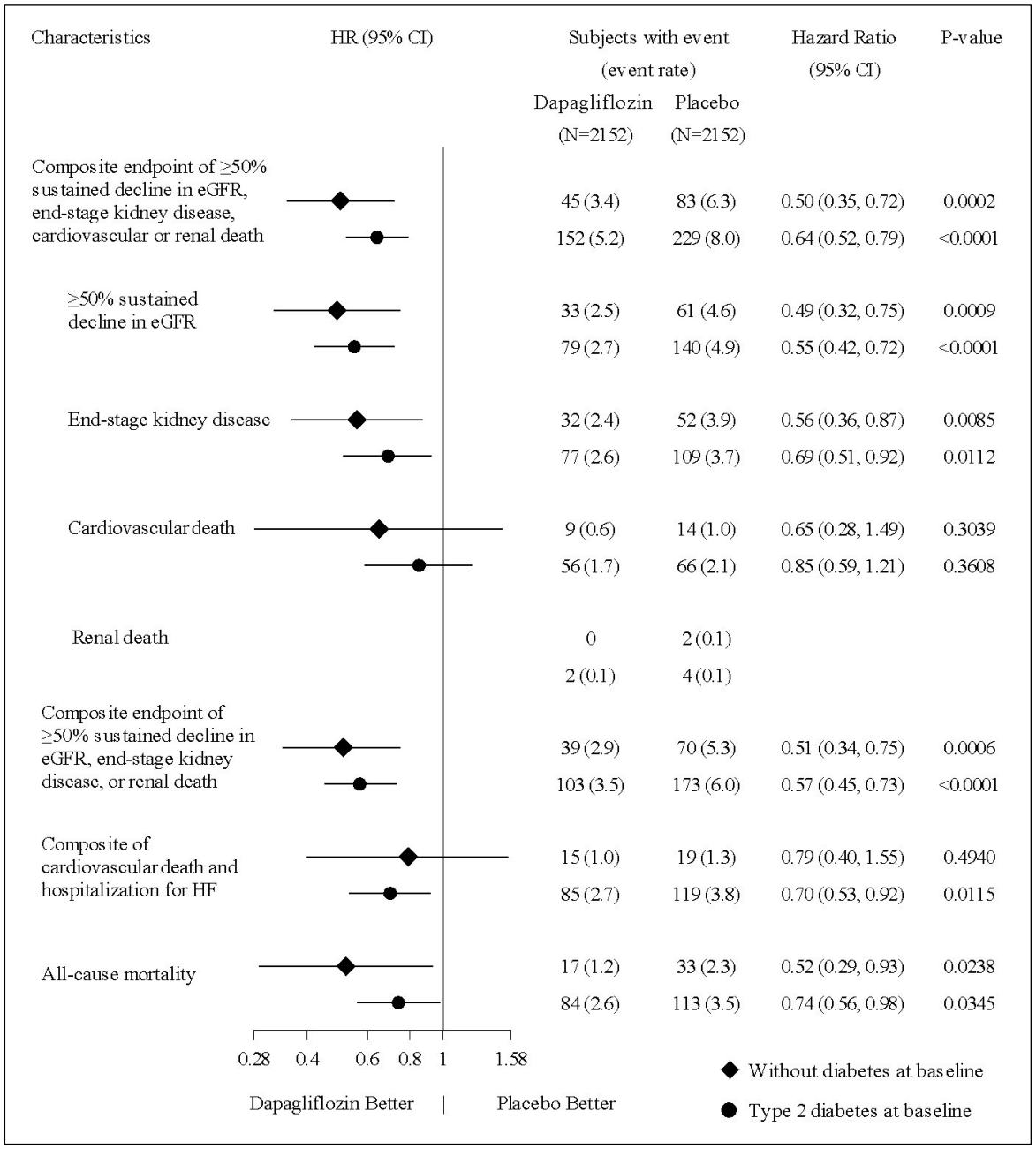
Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

p-values for components of the composite endpoints are nominal.

The treatment effect of FORXIGA was consistent in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes (Figure 26).

Figure 26: Treatment effects in patients with type 2 diabetes mellitus and in patients without diabetes



The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

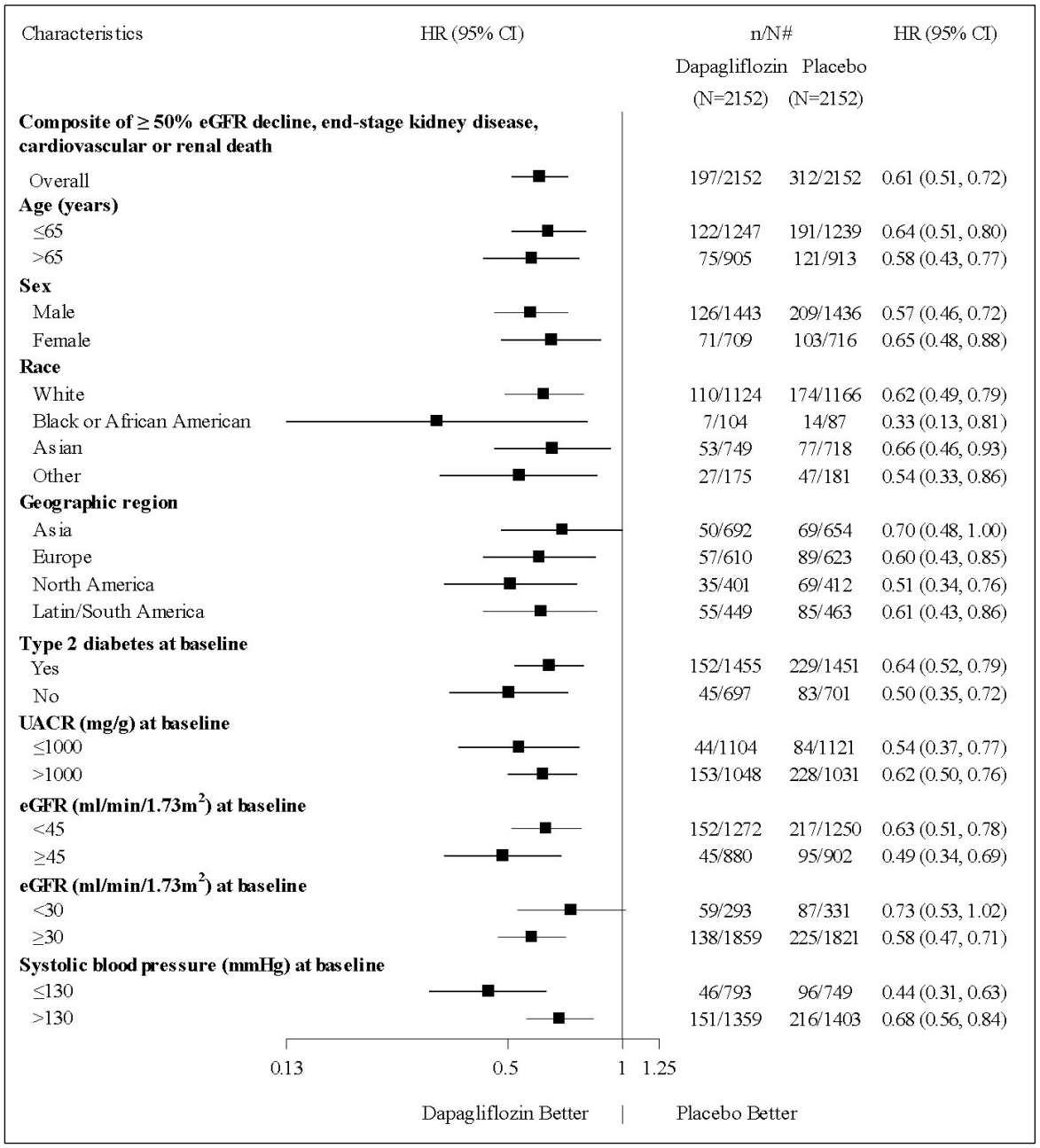
Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

p-values are nominal.

The treatment benefit of FORXIGA over placebo on the primary composite endpoint was consistent across key subgroups (Figure 27).

Figure 27: Treatment effects for the primary composite endpoint by sub-groups



n/N# Number of subjects with event/number of subjects in the subgroup.

The treatment benefit of FORXIGA was also observed for exploratory endpoints;

- A greater reduction in UACR was demonstrated for FORXIGA compared with placebo. The effect was observed as early as 14 days and was maintained throughout the study. At 36 months, the adjusted mean percent change from baseline in UACR (mg/g) was -41% in patients treated with FORXIGA and -20% in patients treated with placebo, with a difference between treatment groups of -26.3% ([95% CI -36.8, -14.0], nominal p=0.0001).

The incidence of doubling of serum creatinine since the most recent laboratory measurement (an evaluation of acute worsening in kidney function), was reduced in the FORXIGA group compared with the placebo group (HR 0.68 [95% CI 0.49, 0.94], nominal p=0.0187).

5.2 Pharmacokinetics

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged Tmax by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (eg, renal or hepatic impairment).

Metabolism

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean

plasma terminal half-life ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounts for 61% of a 50 mg [14C]-dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42% (based on AUC [0-12 hour]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounted for >5% of the total plasma radioactivity. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After administration of 50 mg [14C]-dapagliflozin dose, 96% was recovered; 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

Special Populations

No dosage adjustments based on pharmacokinetic analyses are recommended for mild, moderate and severe renal impairment; mild, or moderate hepatic impairment; age; gender; race; and body weight.

Renal Impairment

At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes and mild, moderate, or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60%, and 87% higher, respectively, than those of patients with type 2 diabetes and normal renal function. At dapagliflozin 20 mg once-daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal-glucose clearance or 24-hour glucose excretion. The renal-glucose clearance and 24-hour glucose excretion were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function, and 85, 52, 18, and 11 g of glucose/day was excreted by patients

with type 2 diabetes mellitus and normal renal function or mild, moderate, or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of hemodialysis on dapagliflozin exposure is not known.

The effect of reduced renal function on systemic exposure was evaluated in a population pharmacokinetic model. Consistent with previous results, model predicted AUC was higher in patients with chronic kidney disease compared with patients with normal renal function, and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes.

Hepatic impairment

For dosing recommendations for patients with moderate or severe hepatic impairment see section 4.2 Posology and method of administration. A single-dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate, or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between patients with hepatic impairment compared to healthy subjects. In patients with mild or moderate hepatic impairment, mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively. No dose adjustment is required for patients with severe hepatic impairment. However, the benefit- risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

Age

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to

patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI; 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI; 123, 129%). These differences in systemic exposure were considered to not be clinically meaningful.

Pediatric and adolescent patients

Pharmacokinetics in the pediatric and adolescent population have not been studied.

Gender

No dosage adjustment from the dose of 10 mg once daily is recommended for dapagliflozin on the basis of gender. Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUCss in females (n=619) was estimated to be 22% higher than in males (n=634) (90% CI; 117,124).

Race

No dosage adjustment from the dapagliflozin dose of 10 mg once daily is recommended on the basis of race. Race (White, Black, or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to Whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures (90% CI range; 3.7% lower, 1% higher). Compared to Whites, Black subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures (90% CI range; 7.7% lower, 3.7% lower).

Body weight

No dose adjustments from the proposed dapagliflozin dose of 10 mg once daily is recommended in patient with diabetes mellitus or in patient without diabetes on the basis of weight.

In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high-body-weight subjects (≥120 kg, n=91) were estimated to be 78.3% (90% CI; 78.2, 83.2%) of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed

dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥120 kg) is recommended.

Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low-body-weight subjects were estimated to be 29% higher than subjects with the reference group body weight. This difference is considered to be small, and based on these findings, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (<50 kg) is recommended.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were equivalent to AUC exposure multiples of approximately 72× (males) and 105× (females) the human AUC at MRHD of 10 mg/day. In rats, AUC exposures were approximately 131× (males) and 186× (females) the human AUC at the MRHD.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in an *in vitro* clastogenicity assay, but only in the presence of S9 activation and at concentrations ≥100 μg/mL. Importantly, dapagliflozin was negative for clastogenicity in vivo in a series of studies evaluating micronuclei or DNA repair in rats at exposure multiples >2100× the human exposure at the MRHD. These studies, along with the absence of tumor findings in the rat and mouse carcinogenicity studies, support that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin-related gene transcription changes were evaluated in kidney, liver, adipose, and skeletal muscle of Zucker Diabetic Fatty (ZDF) rats treated daily with dapagliflozin for 5 weeks. These organs were specifically selected as they represent target organs in the treatment of

diabetes. There was no evidence that dapagliflozin caused transcriptional changes that are predictive of tumor promoters.

Dapagliflozin and its primary human metabolite (3-O-glucuronide) did not enhance the *in vitro* growth of six human urinary bladder transitional cell carcinomas (TCC) cell lines at concentrations ≥100× human C_{max} at the MRHD. In a mouse xenograft study, dapagliflozin administered daily to male and female nude mice implanted with human TCC tumors did not significantly enhance the size of tumors at exposures up to 75× and up to 0.9× clinical exposures at the MRHD for dapagliflozin and its 3-O-glucuronide metabolite, respectively. These studies provide evidence that dapagliflozin and its primary human metabolite do not enhance urinary bladder tumor growth.

In a 15-month phenotyping study, there was no evidence of any difference in survival, body weights, clinical pathology parameters, or histopathologic findings observed between SGLT2 KO mice and their wild-type (WT) counterparts. SGLT2 KO mice had glucosuria, unlike the WT mice. Despite a lifetime of glucosuria, there was no evidence of any alteration of renal function or proliferative changes observed in the kidneys or urinary bladders of SGLT2 KO mice. This data strongly suggests that high levels of urinary glucose do not induce urinary tract tumors or accelerate age-related urinary tract pathology.

In a study of fertility and early embryonic development in rats, doses of 15, 75, or 300/210 mg/kg/day dapagliflozin were administered to males (the 300 mg/kg/day dose was lowered to 210 mg/kg/day after 4 days), and doses of 3, 15, or 75 mg/kg/day were administered to females. Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated males or females at any dose tested (at exposure multiples ≤1708× and 998× the MRHD in males and females, respectively). However, at 300/210 mg/kg/day, seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were low numbers of morphologically abnormal sperm.

Teratogenicity and impairment of early development

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy and lactation (time periods corresponding to the second and third trimesters of

pregnancy with respect to human renal maturation) are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥15× the MRHD. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of prenatal and postnatal development, maternal rats were dosed from gestation day (GD) 6 through PND 21 (also at 1, 15, or 75 mg/kg/day), and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups). Increased incidence or severity of renal pelvic dilatation was again observed in adult offspring of treated dams, although only at 75 mg/kg/day (associated maternal and pup dapagliflozin exposures were 1415× and 137×, respectively, the human values at the MRHD). Additional developmental toxicity was limited to dose-related reductions in pup body weights and observed only at doses ≥15 mg/kg/day (associated with pup exposures that are ≥29× the human values at the MRHD). Maternal toxicity was evident only at 75 mg/kg/day, and limited to transient reductions in body weight and food consumption at dose initiation. The no-adverse-effect level (NOAEL) for developmental toxicity, 1 mg/kg/day, is associated with a maternal systemic exposure multiple that is approximately 19× the human value at the MRHD.

In additional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested (20, 60, or 180 mg/kg/day); 180 mg/kg/day is associated with a systemic exposure multiple of approximately 1191× the MRHD. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441× the MRHD). Doses ≥150 mg/kg/day (≥2344× the human values at the MRHD) were associated with both maternal and developmental toxicities. Maternal toxicity included mortality, adverse clinical signs, and decrements in body weight and

food consumption. Developmental toxicity consisted of increased embryo-fetal lethality, increased incidences of fetal malformations and skeletal variations, and reduced fetal body weights. Malformations included a low incidence of great vessel malformations, fused ribs and vertebral centras, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

Animal toxicology

Most of the effects observed in pivotal repeat-dose toxicity studies in both rats and dogs were considered to be secondary to pharmacologically mediated increases in urinary glucose, and included decreases in body weights and/or body weight gains, increased food consumption, and increases in urine volumes due to osmotic diuresis. Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of ≤25 mg/kg/day (≥346×the human exposures at the MRHD) and in dogs for up to 12 months at doses of ≤120 mg/kg/day (≥3200× the human exposures at the MRHD). Also, single-dose studies with dapagliflozin indicated that the dapagliflozin 3-O-glucuronide metabolite would have been formed in both rat and dog toxicity studies at exposure levels (AUCs) that are greater than, or approximately equal to, anticipated human dapagliflozin 3-O-glucuronide exposures following administration of dapagliflozin at the MRHD. In rats, the most noteworthy nonclinical toxicity finding of increased trabecular bone and tissue mineralization (associated with increased serum calcium) was only observed at high-exposure multiples (≥2100× based on human exposures at the MRHD). Despite achieving exposure multiples of ≥3200× the human exposure at the MRHD, there was no dose-limiting or target-organ toxicities identified in the 12-month dog study.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Each film-coated tablet of FORXIGA contains 10 mg of dapagliflozin and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Storage

Store below 30°C

6.5 Dosage forms and packaging available

A carton containing Alu/Alu blisters of 30 film-coated tablets (3 blisters of 10 film-coated tablets each).

7. NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER

AstraZeneca (Thailand) Ltd., Bangkok, Thailand

8. DATE OF REVISION OF PACKAGE INSERT

March 2023