# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

FORXIGA® 10 mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

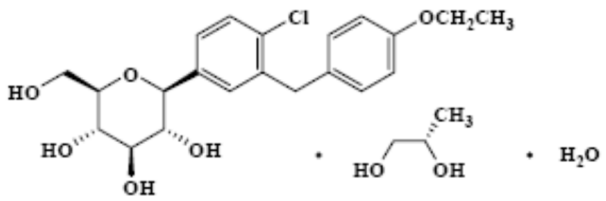
FORXIGA 10 mg: Each film-coated tablet contains 10 mg dapagliflozin as dapagliflozin propanediol

For the full list of excipients see section 6.1 - List of Excipients.

## 3. PHARMACEUTICAL FORM

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

Dapagliflozin propanediol is described chemically as D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-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

*Glycaemic control*

FORXIGA is indicated in adults with type 2 diabetes mellitus:

- as monotherapy as an adjunct to diet and exercise in patients for whom metformin is otherwise indicated but was not tolerated.

- as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycaemic control when diet and exercise have failed to provide adequate glycaemic control and there are poor prospects for response to metformin monotherapy.

- in combination with other anti-hyperglycaemic agents to improve glycaemic control, when these together with diet and exercise, do not provide adequate glycaemic control (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety, and 4.4 Special Warnings and Precautions for Use for available data on different add-on combination therapies).

*Prevention of hospitalisation for heart failure*

FORXIGA is indicated in adults with type 2 diabetes mellitus and established cardiovascular disease or risk factors for cardiovascular disease to reduce the risk of hospitalisation for heart failure (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety)

*Prevention of new or worsening nephropathy*

FORXIGA is indicated in adults with type 2 diabetes mellitus and established cardiovascular disease or risk factors for cardiovascular disease for the prevention of new or worsening nephropathy (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety).

### Heart failure

FORXIGA is indicated in adults for the treatment of symptomatic heart failure (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety).

### Chronic kidney disease

FORXIGA is indicated in adults for the treatment of chronic kidney disease (see section 5.1 Pharmacodynamic Properties – Clinical Efficacy and Safety).

## 4.2 DOSE AND METHOD OF ADMINISTRATION

### Type 2 diabetes mellitus

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

When FORXIGA is used as an add-on therapy with insulin or an insulin secretagogue (e.g. sulphonylurea), a lower dose of insulin or an insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

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 glycaemic control on this starting dose should have their metformin dose increased according to approved metformin Product Information.

### Heart failure

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

### Chronic kidney disease

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

## Special patient populations

*Renal impairment*

No dosage adjustment 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 sections 4.4 Special Warnings and Precautions for Use, and 5.1 Pharmacodynamic Properties). Therefore, if eGFR falls below 45 mL/min/1.73 $m^2$, additional glucose lowering treatment should be considered in patients with diabetes mellitus.

*Hepatic Impairment*

No dosage adjustment for FORXIGA is necessary for patients with mild or moderate hepatic impairment. FORXIGA should not be used in patients with severe hepatic impairment (see section 4.4 Special Warnings and Precautions for Use).

*Paediatric and adolescent*

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

*Elderly*

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 Precautions for Use).

## Method of administration

FORXIGA can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

## 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 listed in section 6.1

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

FORXIGA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

## Use in Patients with Renal Impairment

There is limited experience with initiating treatment with FORXIGA in patients with eGFR <25 mL/min/1.73 $m^2$.

Initiation of dapagliflozin may transiently increase serum creatinine and decrease eGFR (see section 4.8 Undesirable Effects).

The glucose lowering efficacy of dapagliflozin is dependent on renal function, and is reduced in patients where eGFR is <45 mL/min/1.73 $m^2$ (see section 4.2 Dose and Method of Administration).

## Use in Patients with Severe Hepatic Impairment

There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment. FORXIGA should not be used in patients with severe hepatic impairment (see sections 4.2 Dose and Method of Administration and 5.2 Pharmacokinetic Properties).

## 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.

Treatment of ketoacidosis generally requires insulin, fluid and carbohydrate replacement.

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

In patients where the decision is made to restart FORXIGA after an episode of ketoacidosis, any potential risk for DKA should be managed by the physician. If a patient taking dapagliflozin requires major surgery, the need for interruption of treatment should be considered taking into account local guidelines.

## Use with Medications Known to Cause Hypoglycaemia

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

## Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8 Undesirable Effects). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise.

Patients treated with FORXIGA who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotising fasciitis.' 'Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis.

If Fournier's gangrene is suspected, FORXIGA should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

### Urinary tract infections

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis in patients receiving SGLT2 inhibitors.

### Cardiac failure

There is limited clinical experience in patients with NYHA class IV.

## 4.5 INTERACTION WITH OTHER MEDICINES 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 CYP 1A2, 2A6, 2B6, 2C8, 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 (an $\alpha$-glucosidase inhibitor), 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 inhibitors 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 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 Normalised Ratio; [INR]).

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

### Other Interactions

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

### Effects on Laboratory Tests

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

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

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Pregnancy

Category D

There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 4.4 Special Warnings and Precautions for Use). Therefore, FORXIGA must not be used during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with FORXIGA should be discontinued.

In conventional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the period of organogenesis in humans. An increased incidence of embryo-foetal lethality, decreased foetal weight and an increased incidence of foetal visceral and skeletal anomalies were seen in rats at maternotoxic doses (oral doses greater than or equal to 150 mg/kg/day). The no observed effect level for embryo-foetal effects in rats was an oral dose of 75 mg/kg/day (1530 times the exposure in patients at the maximum recommended human dose [MRHD]). No developmental toxicities were observed in rabbits at oral doses up to 180 mg/kg/day (1265 times the exposure in patients at the MRHD).

### Breast-feeding

FORXIGA must not be used by breastfeeding women. It is not known whether dapagliflozin or its metabolites are excreted in human milk. Studies in rats have shown excretion of dapagliflozin in milk. Direct and indirect exposure of dapagliflozin 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. 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, dapagliflozin-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.

### Effects on Fertility

In a study of fertility in rats, no effects on mating, fertility, or early embryonic development were seen when males received oral doses up to 210 mg/kg/day or when females received oral doses up to 75 mg/kg/day (yielding plasma AUC values at least 1000 times the clinical exposure at the maximum recommended human dose [MRHD] of 10 mg/day). However, at 210 mg/kg/day, a dose associated with profound toxicity (including mortality), seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were increased numbers of morphologically abnormal sperm. No adverse effects on sperm or male reproductive organs were seen at 75 mg/kg/day (700 times the clinical exposure at the MRHD).

## 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, 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 – Clinical Efficacy and Safety.

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).

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 ≥ 30 mL/min/1.73 $m^2$. 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 $m^2$.

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/1.73 $m^2$. Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 $m^2$.

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]<br>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 dapaglifozin 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 reactions

*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 more frequently reported 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.

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.

*Necrotising fasciitis of the perineum (Fournier's gangrene)*

In the dapagliflozin cardiovascular outcomes study with 17,160 patients with type 2 diabetes mellitus and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported on treatment, one in the dapagliflozin-treated group and 5 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.

*Events Related to Decreased Renal Function*

There have been post-marketing reports of acute kidney injury (including acute renal failure) in patients receiving dapagliflozin. In the DECLARE study, there was no increased risk for events of acute kidney injury in FORXIGA-treated patients compared with the placebo group.

In development, the 13-study, short-term, placebo-controlled pool, use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR. These changes were observed to reverse after treatment discontinuation.

*Diabetic ketoacidosis (DKA)*

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 Warnings 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.

### REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

### 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 hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension 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 haemodialysis has not been studied.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2) inhibitors, ATC code: A10BK01

## Mechanism of action

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium glucose co-transporter 2 (SGLT2) that improves glycaemic 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 reduces 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 plasma glucose (FPG) and postprandial plasma glucose (PPG) 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 hypoglycaemia, 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 hypoglycaemia. 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 the weight reduction was 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 approximately 1,000 - 3,000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

## Pharmacodynamic effects

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. 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. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10mg/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 18.3 to 48.3 µmol/L.

## 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 Efficacy and Safety – Type 2 Diabetes Mellitus

More than 28,000 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 15,000 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), thiazolidinedione (pioglitazone), sitagliptin (with or without metformin), prolonged release exenatide when initiated concomitantly with FORXIGA (on a background of 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 – Glycaemic control in 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.

*Monotherapy*

A double-blind, placebo-controlled study of 24-week duration (with an additional extension period) was conducted to evaluate the safety and efficacy of monotherapy with FORXIGA in subjects with inadequately controlled type 2 diabetes mellitus. Once-daily treatment with FORXIGA resulted in statistically significant ($p < 0.0001$) reductions in HbA1c compared to placebo (Table 2).

In the extension period, HbA1c reductions were sustained through Week 102 (-0.61% and -0.17% adjusted mean change from baseline for FORXIGA 10 mg and placebo, respectively).

**Table 2: Results at Week 24 (LOCF[a]) in a Placebo-Controlled Study of FORXIGA Monotherapy**

| | Monotherapy | |
|---|---|---|
| **Efficacy Parameter** | **FORXIGA 10 mg** | **Placebo** |

| N[b] | 70 | 75 |
|---|---|---|
| **HbA1c (%)** | | |
| Baseline (mean) | 8.01 | 7.79 |
| Change from baseline[c] | −0.89 | −0.23 |
| Difference from placebo[c] (95% CI) | −0.66[*] (−0.96, −0.36) | |
| **Subjects (%) achieving: HbA1c <7%** | | |
| Adjusted for baseline | 50.8[§] | 31.6 |
| **Body Weight (kg)** | | |
| Baseline (mean) | 94.13 | 88.77 |
| Change from baseline[c] | −3.16 | −2.19 |
| Difference from placebo[c] (95% CI) | −0.97 (−2.20, 0.25) | |

[a] LOCF: Last observation (prior to rescue for rescued patients) carried forward.

[b] All randomised patients who took at least one dose of double-blind study medication during the short-term double-blind period.

[c] Least squares mean adjusted for baseline value.

[*] p-value <0.0001 vs. placebo.

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

*Combination Therapy*

FORXIGA was studied as add-on to metformin, add-on to a sulphonylurea (glimepiride), add-on to metformin and a sulphonylurea, add-on to a DPP-4 inhibitor (sitagliptin [with or without metformin]), add-on to insulin (with or without other antidiabetic therapies) and when initiated concomitantly with a glucagon-like peptide 1 (GLP-1) receptor agonist (prolonged-release exenatide) on a background of metformin.

*Initial Combination Therapy with Metformin*

638 patients randomised 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 dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg. The patients were treatment-naïve, defined as either never having received diabetes medication or having had such for less than 24 weeks since the diagnosis of diabetes, not for more than 14 days during the 12 weeks prior to enrolment, and not at all during the 4 weeks prior to enrolment.

The combination treatment of FORXIGA 10 mg plus metformin provided significant improvements in HbA1c and FPG, compared with either of the monotherapy treatments and significant improvements in body weight compared with metformin alone (Table 3). FORXIGA 10 mg as monotherapy also provided significant improvements in FPG and body weight compared with metformin alone and was non-inferior to metformin monotherapy in lowering HbA1c. The proportion of patients who were rescued or discontinued for lack of glycaemic control during the 24 week double-blind treatment period (adjusted for baseline HbA1c) was higher on treatment with metformin plus placebo (13.5%) than on FORXIGA 10 mg plus placebo and FORXIGA 10 mg plus metformin (7.8%, and 1.4%).

**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 (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 |
| **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 (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 randomised 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.
[#] p-value <0.05.

*Add-on combination therapy with other anti-hyperglycaemic agents*

In a 52-week, active-controlled non-inferiority study (with 52- and 104-week extension periods), FORXIGA was evaluated as add-on therapy to metformin compared with a sulphonylurea (glipizide) as add-on therapy to metformin in subjects with inadequate glycaemic control (HbA1c >6.5% and ≤10%). The results showed a similar mean reduction in HbA1c from baseline to Week 52, compared to glipizide, thus demonstrating non-inferiority (Table 4). At Week 104, adjusted mean change from baseline in HbA1c was -0.32% for FORXIGA and -0.14% for glipizide. At Week 208, the secondary endpoint of adjusted mean change from baseline in HbA1c was -0.10% for FORXIGA and 0.20% for glipizide (see Figure 1). At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with FORXIGA (3.5%, 4.3% and 5.0% respectively) experienced at least one event of hypoglycaemia compared to the group treated with glipizide (40.8%, 47.0% and 50.0% respectively). The proportions of subjects remaining in the study at Week 104 and at Week 208 were 56.2% and 39% respectively for the group treated with FORXIGA and 50.0% and 34.6% respectively for the group treated with glipizide.

**Table 4. Results at Week 52 (LOCF[a]) in an active-controlled study comparing FORXIGA to glipizide as add-on to metformin**

| Parameter | FORXIGA +metformin | Glipizide+metformin |
|---|---|---|
| **N**[b] | 400 | 401 |
| **HbA1c (%)** | | |
| Baseline (mean) | 7.69 | 7.74 |
| Change from baseline[c] | -0.52 | -0.52 |
| Difference from glipizide + metformin[c] | 0.00[d] | |
| (95% CI) | (-0.11, 0.11) | |
| **Body weight (kg)** | | |
| Baseline (mean) | 88.44 | 87.60 |
| Change from baseline[c] | -3.22 | 1.44 |
| Difference from glipizide + metformin[c] | -4.65[*] | |
| (95% CI) | (-5.14, -4.17) | |

[a]LOCF: Last observation carried forward

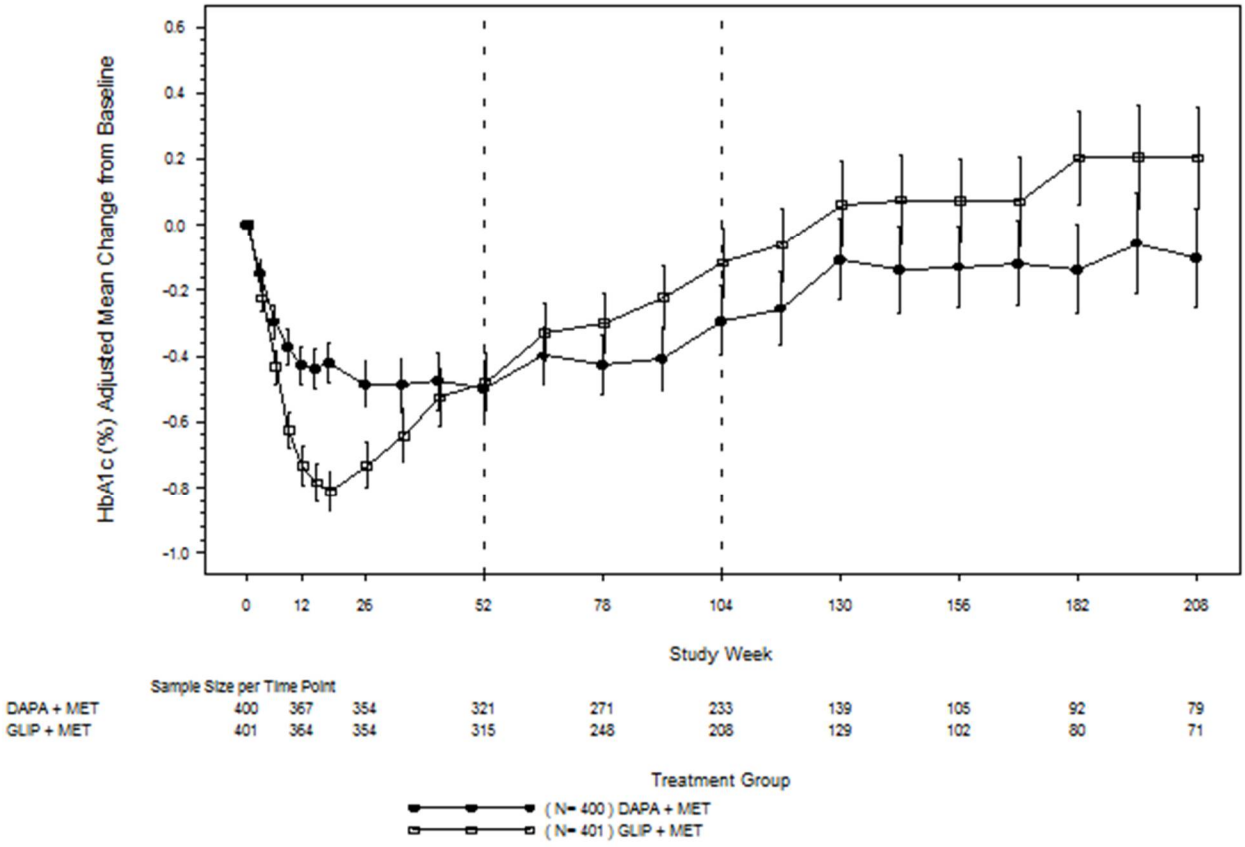
[b]Randomised and treated subjects with baseline and at least 1 post-baseline efficacy measurement

[c]Least squares mean adjusted for baseline value

[d]Non-inferior to glipizide + metformin

[*]p-value <0.0001

**Figure 1: 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)**




Subjects in the full analysis set.
Mean value based on repeated measures analysis model:
post-baseline = baseline treatment week week*treatment week*baseline.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping.

FORXIGA as an add-on with either metformin, metformin and a sulfonylurea, glimepiride, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo ($p < 0.0001$; Tables 5, 6 and 7).

**Table 5. Results of 24-week (LOCF[a]) placebo-controlled studies of FORXIGA in add-on combination with metformin or sitagliptin (with or without metformin)**

| | Add-on combination | | | |
|---|---|---|---|---|
| | Metformin[1] | | DPP-4 Inhibitor (sitagliptin[3]) ±Metformin[1] | |
| | FORXIGA 10 mg | Placebo | FORXIGA 10 mg | Placebo |
| N[b] | 135 | 137 | 223 | 224 |
| **HbA1c (%)** | | | | |
| Baseline (mean) | 7.92 | 8.11 | 7.90 | 7.97 |
| Change from baseline[c] | -0.84 | -0.30 | -0.45 | 0.04 |
| Difference from placebo[c] | -0.54* | | -0.48* | |
| (95% CI) | (-0.74, -0.34) | | (-0.62, -0.34) | |
| **Subjects (%) achieving: HbA1c <7%** | | | | |
| Adjusted for baseline | 40.6** | 25.9 | | |
| **Body weight (kg)** | | | | |
| Baseline (mean) | 86.28 | 87.74 | 91.02 | 89.23 |
| Change from baseline[c] | -2.86 | -0.89 | -2.14 | -0.26 |
| Difference from placebo[c] | -1.97* | | -1.89* | |
| (95% CI) | (-2.63, -1.31) | | (-2.37, -1.40) | |

[1] Metformin ≥ 1500 mg/day; [2]glimepiride 4 mg/day; [3]sitagliptin 100 mg/day

[a] LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

[c] Least squares mean adjusted for baseline value

*p-value <0.0001 versus placebo + oral glucose-lowering medicinal product

**p-value <0.05 versus placebo + oral glucose-lowering medicinal product

**Table 6. Results of 24-week placebo-controlled studies of dapagliflozin in add-on combination with sulphonylurea (glimepiride) or metformin and a sulphonylurea**

| | Add-on combination | | | |
|---|---|---|---|---|
| | Sulphonylurea (glimepiride[1]) | | Sulphonylurea + metformin[2] | |
| | Dapagliflozin 10 mg | Placebo | Dapagliflozin 10 mg | Placebo |
| **N**[a] | 151 | 145 | 108 | 108 |
| **HbA1c (%)**[b] | | | | |
| Baseline (mean) | 8.07 | 8.15 | 8.08 | 8.24 |
| Change from Baseline[c] | -0.82 | -0.13 | -0.86 | -0.17 |
| Difference from Placebo[c] | -0.68* | | −0.69* | |
| (95% CI) | (-0.86, -0.51) | | (−0.89, −0.49) | |
| **Subjects (%) achieving: HbA1c < 7% (LOCF)**[d] | | | | |
| Adjusted for baseline | 31.7* | 13.0 | 31.8* | 11.1 |
| **Body weight (kg) (LOCF)**[d] | | | | |
| Baseline (mean) | 80.56 | 80.94 | 88.57 | 90.07 |
| Change from Baseline[c] | -2.26 | -0.72 | -2.65 | -0.58 |
| Difference from Placebo[c] | -1.54* | | −2.07* | |
| (95% CI) | (-2.17, -0.92) | | (−2.79, −1.35) | |

[1]glimepiride 4 mg/day; [2]metformin (immediate- or prolonged-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulphonylurea for at least 8 weeks prior to enrolment.

[a]Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[b]Columns 1 and 2, HbA1c analyzed using LOCF (see footnote d); Columns 3 and 4, HbA1c analyzed using LRM (see footnote e)

[c]Least squares mean adjusted for baseline value

[d]LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[e]LRM: Longitudinal repeated measures analysis

*p-value <0.0001 versus placebo + oral glucose-lowering medicinal product(s)

**Table 7. Results at Week 24 (LOCF[a]) in a placebo-controlled study of FORXIGA in combination with insulin (alone or with oral glucose-lowering medicinal products)**

| Parameter | FORXIGA 10 mg +insulin ±oral glucose-lowering medicinal products[2] | Placebo +insulin ±oral glucose-lowering medicinal products[2] |
|---|---|---|
| **N**[b] | 194 | 193 |
| **HbA1c (%)** | | |
| Baseline (mean) | 8.58 | 8.46 |
| Change from baseline[c] | -0.90 | -0.30 |
| Difference from placebo[c] | -0.60[*] | |
| (95% CI) | (-0.74, -0.45) | |
| **Body weight (kg)** | | |
| Baseline (mean) | 94.63 | 94.21 |
| Change from baseline[c] | -1.67 | 0.02 |
| Difference from placebo[c] | -1.68[*] | |
| (95% CI) | (-2.19, -1.18) | |
| **Mean daily insulin dose (IU)**[1] | | |
| Baseline (mean) | 77.96 | 73.96 |
| Change from baseline[c] | -1.16 | 5.08 |
| Difference from placebo[c] | -6.23[*] | |
| (95% CI) | (-8.84, -3.63) | |
| Subjects with mean daily insulin dose reduction of at least 10% (%) | 19.6[**] | 11.0 |

[a]LOCF: Last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward

[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

[c]Least squares mean adjusted for baseline value and presence of oral glucose-lowering medicinal product

[*]p-value <0.0001 versus placebo + insulin ±oral glucose-lowering medicinal product

[**]p-value <0.05 versus placebo + insulin ±oral glucose-lowering medicinal product

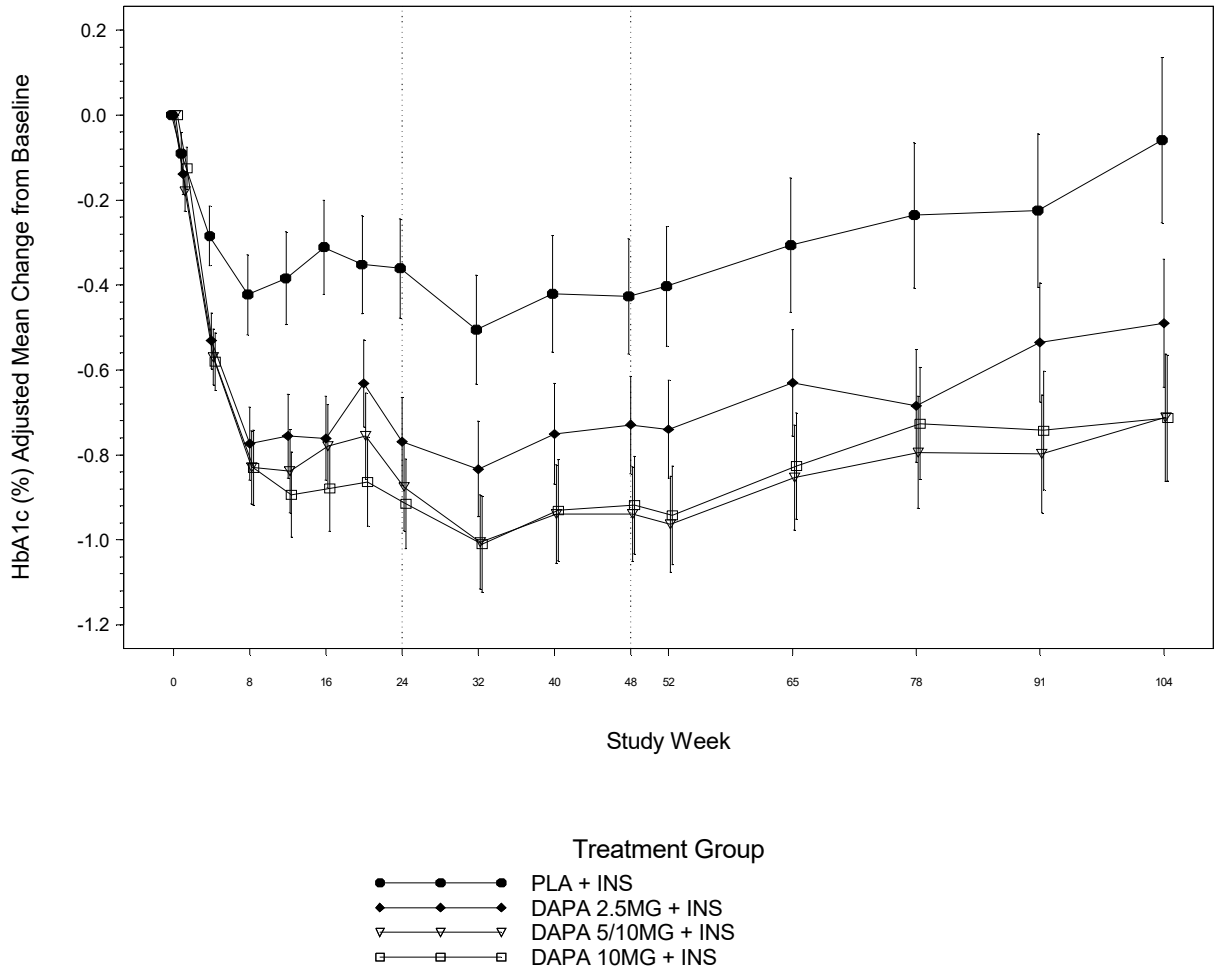
[1]Up-titration of insulin regimens (including short-acting, intermediate, and basal insulin) was only allowed if subjects met pre-defined FPG criteria.

[2]Fifty percent of subjects were on insulin monotherapy at baseline; 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group, 80% were on metformin alone, 12% were on metformin plus sulphonylurea therapy, and the rest were on other oral glucose-lowering medicinal products.

The reductions in HbA1c observed at Week 24 were sustained in add-on combination studies (glimepiride and insulin) with 48-week data (glimepiride) and up to 104-week data (insulin, see Figure 2). At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for FORXIGA 10 mg and placebo was -0.30% and 0.38%, respectively. For the add-on to metformin study, HbA1c reductions were sustained through Week 102 (-0.78% and 0.02% adjusted mean change from baseline for 10 mg and placebo, respectively, see also Figure 3). At Week 104 for insulin (with or without additional oral glucose-lowering medicinal products), the HbA1c reductions were -0.71% and -0.06% adjusted mean change from baseline for FORXIGA 10 mg and placebo, respectively. At Weeks 48 and 104, the insulin

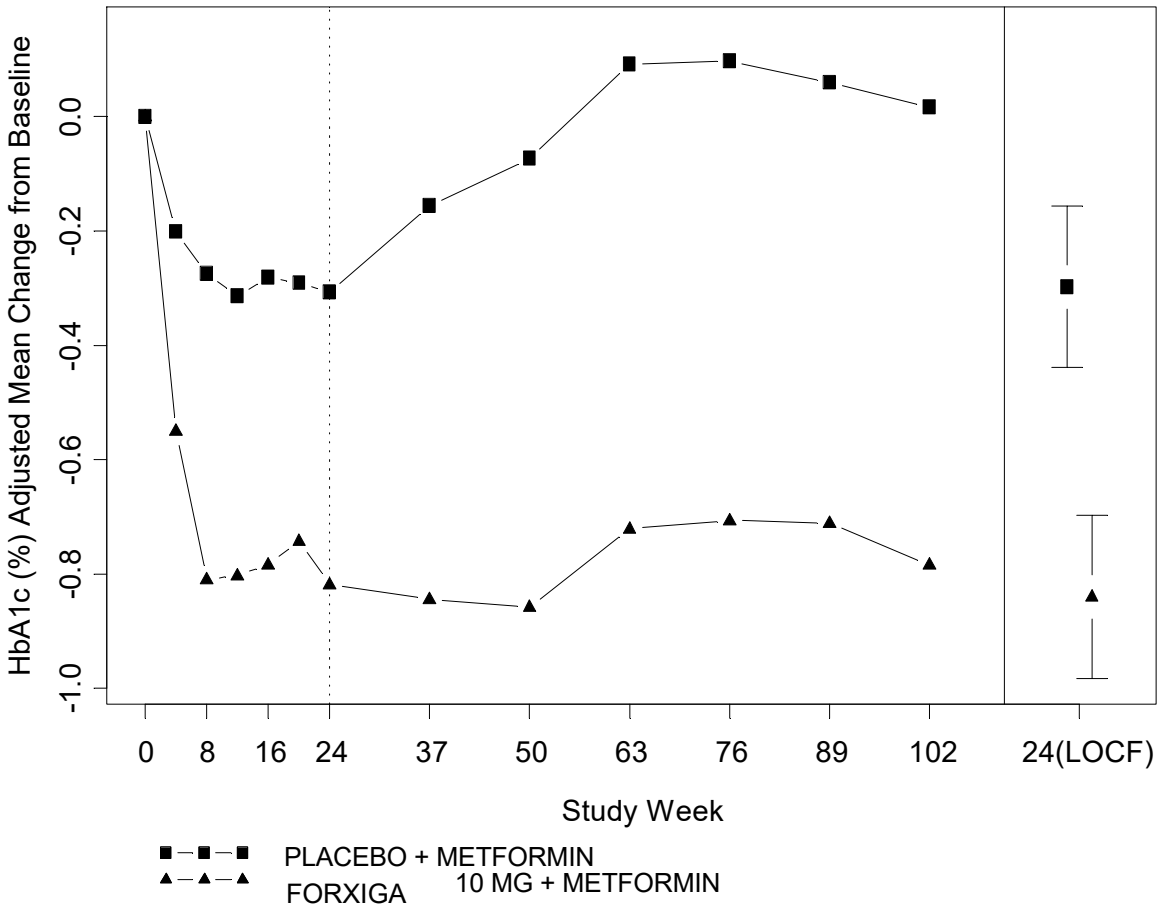
dose remained stable compared to baseline in subjects treated with FORXIGA 10 mg at an average dose of 76 IU/day (see Fig 4). In the placebo group there was a mean increase of 10.5 IU/day and 18.3 IU/day from baseline at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4% for the group treated with FORXIGA 10 mg and 54.8% for the placebo group.

**Figure 2: HbA1c (%) Adjusted Mean Change from Baseline Over Time Short-term and Long-term Treatment Period in a 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.**



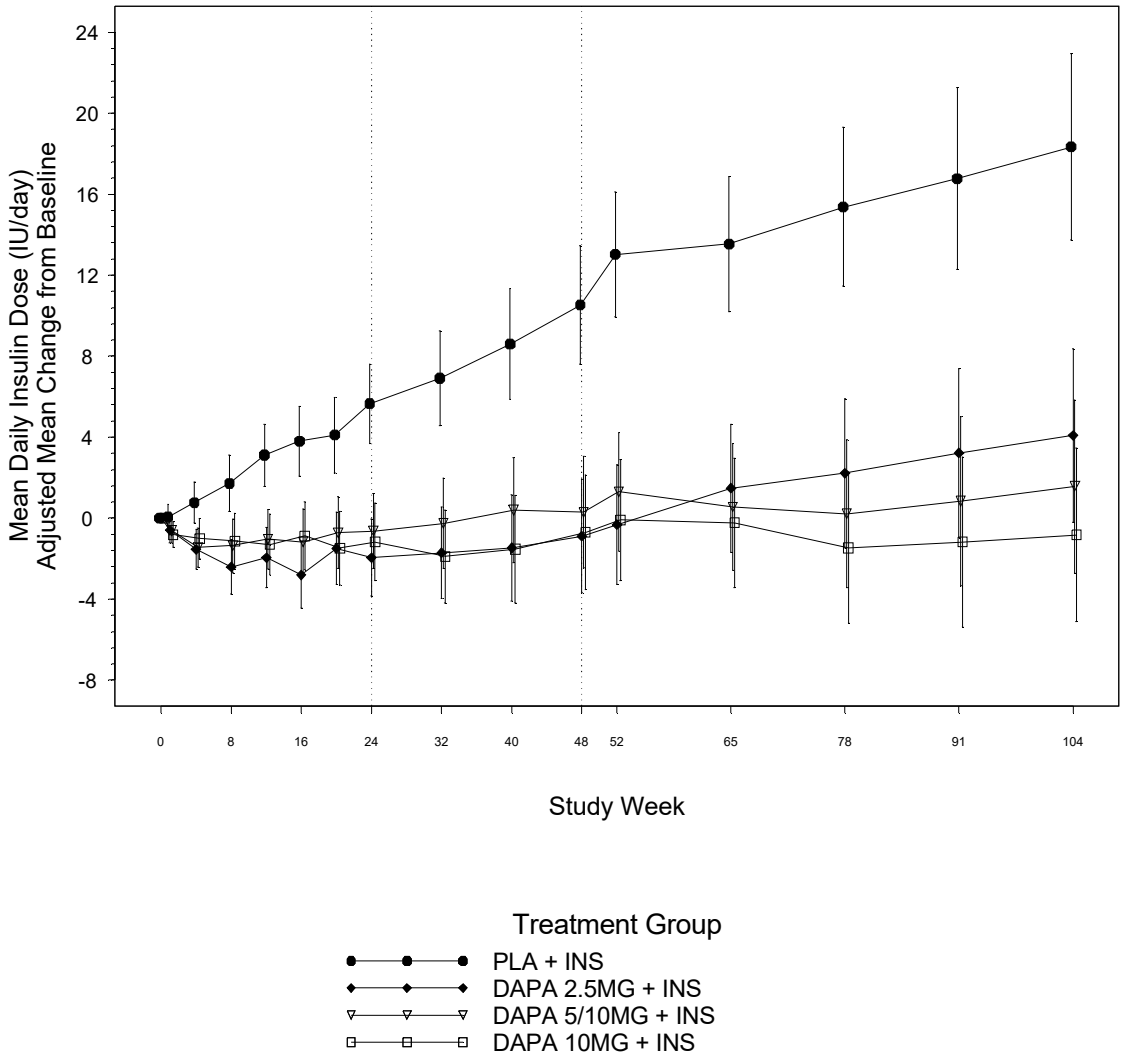

Error bars represent 95% confidence intervals for the adjusted mean change from baseline

**Figure 3: 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)**




LOCF: Last observation (prior to rescue for rescued subjects) carried forward
Values for 24(LOCF) represent adjusted mean and 95% confidence intervals based on an ANCOVA model
Values for other weeks represent adjusted means based on a longitudinal repeated measures model

**Figure 4: Mean Daily Insulin Dose (IU/day) Adjusted Mean Change from Baseline Over Time in a Placebo-controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Short-term and Long-term Treatment Period Including Data After Insulin Up-titration**




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

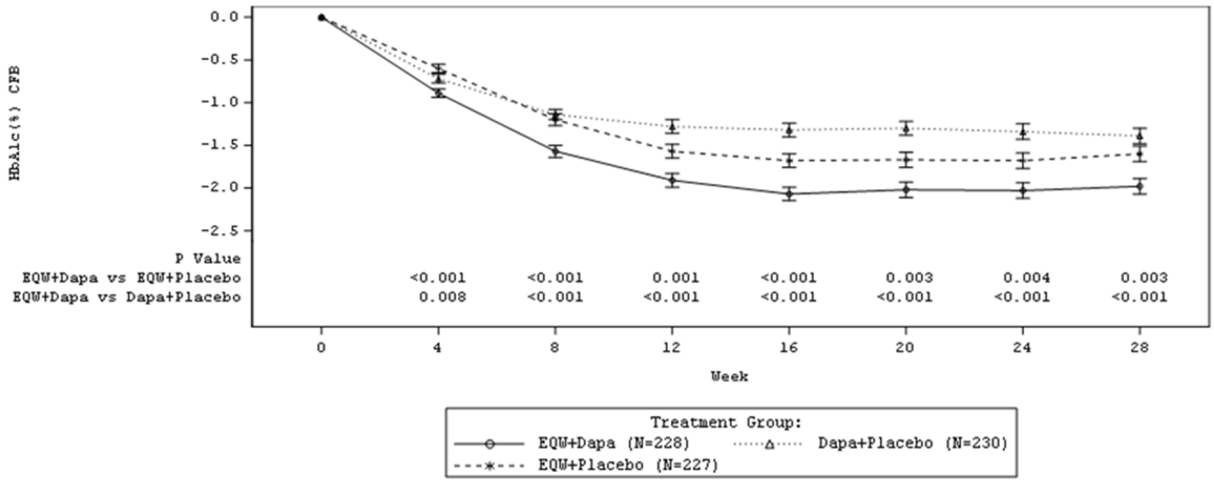
*Concomitant Initiation of FORXIGA and Prolonged-Release Exenatide in Patients Inadequately Controlled on Metformin*

A total of 694 adult patients with type 2 diabetes mellitus and inadequate glycaemic control (HbA1c ≥8.0 and ≤12.0%) on metformin alone (≥1,500 mg/day) participated in this 28-week randomised, double-blind, active-controlled trial to compare the concomitant initiation of FORXIGA 10 mg once daily and prolonged-release exenatide 2 mg once weekly (GLP-1 receptor agonist) on a background of metformin versus prolonged-release exenatide 2 mg once weekly alone and FORXIGA 10 mg once daily alone, when added to metformin. Following a 1-week placebo lead-in period, patients were randomised equally to one of three double-blind treatment groups to receive either FORXIGA 10 mg and prolonged-release exenatide, FORXIGA 10 mg and placebo or prolonged-release exenatide and placebo. During the treatment period, patients continued on the same type and dose of metformin as when they entered the study.

At baseline, patients had a mean age of 54.2 years and a BMI of 32.73 kg/m$^2$. Randomisation was stratified by glycated haemoglobin A1c (HbA1c) at baseline (<9.0% or ≥9.0%).

The primary endpoint was the change in HbA1c from baseline to Week 28 (Figure 5). Compared to FORXIGA 10 mg alone and to prolonged-release exenatide alone, concomitant initiation of FORXIGA 10 mg and prolonged-release exenatide resulted in statistically significant reductions in HbA1c from baseline at Week 28 (Table 8).

**Figure 5: Change in HbA1c over Time, LS Mean (SE) – 28-Week Treatment Period (Intent-to-Treat Analysis Set)**




CFB=change from baseline; EQW=exenatide 2 mg once weekly; Dapa=dapagliflozin 10 mg once daily. Baseline is defined as Week 0.

**Table 8. Results of a 28-Week Active-Controlled Trial of FORXIGA 10 mg and Prolonged- Release Exenatide Concomitant Add-On to Metformin**

| Efficacy Parameter | FORXIGA 10 mg QD + Prolonged-release exenatide 2 mg QW | FORXIGA 10 mg QD + Placebo QW | Prolonged-release exenatide 2 mg QW + Placebo QD |
|---|---|---|---|
| **Intent-to-Treat population (N)** [c] | **228** | **230** | **227** |
| **HbA1c (%)** | | | |
| Baseline (mean)[a] | 9.29 | 9.25 | 9.26 |
| Change from baseline | -1.98 | -1.39 | -1.60 |
| Mean difference in change from baseline vs. FORXIGA (95% CI) | -0.59* (-0.84, -0.34) | | |
| Mean difference in change from baseline vs. Prolonged-release exenatide QW (95% CI) | -0.38** (-0.63, -0.13) | | |
| Percent of patients achieving HbA1c < 7.0%[b] | 44.7% | 19.1% | 26.9% |
| **Body weight (kg)** | | | |
| Baseline (mean) [a] | 92.13 | 90.87 | 89.12 |
| Change from baseline | -3.55 | -2.22 | -1.56 |

| Efficacy Parameter | FORXIGA 10 mg QD + Prolonged-release exenatide 2 mg QW | FORXIGA 10 mg QD + Placebo QW | Prolonged-release exenatide 2 mg QW + Placebo QD |
|---|---|---|---|
| **Intent-to-Treat population (N)** [c] | **228** | **230** | **227** |
| Mean difference in change from baseline vs. FORXIGA (95% CI) | -1.33** (-2.12, -0.55) | | |
| Mean difference in change from baseline vs. Prolonged-release exenatide (95% CI) | -2.00* (-2.79,-1.20) | | |
| Proportion of patients achieving weight loss ≥5.0%b | 33.3% | 20.0% | 13.7% |
| Difference in proportion of patients vs. FORXIGA (%) | 13.3** | | |
| Difference in proportion of patients vs. Prolonged-release exenatide (%) | 19.7* | | |
| **FPG (mmol/L)** | | | |
| Baseline (mean)[a] | 10.9 | 10.5 | 10.5 |
| Change from baseline | -3.7 | -2.7 | -2.5 |
| Mean difference in change from baseline vs. FORXIGA (95% CI) | -0.92* (-1.36, -0.49) | | |
| Mean difference in change from baseline vs. Prolonged-release exenatide (95% CI) | -1.12* (-1.55,-0.68) | | |
| **2-hour PPG (mmol/L)** | | | |
| Standard meal test population (n) | 198 | 199 | 188 |
| Baseline (mean) [a] | 14.9 | 14.5 | 14.8 |
| Change from baseline | -4.9 | -3.4 | -3.3 |
| Mean difference in change from baseline vs. FORXIGA (95% CI) | -1.49* (-2.04,-0.93) | | |
| Mean difference in change from baseline vs. Prolonged-release exenatide (95% CI) | -1.54* (-2.10, -0.98) | | |
| **Seated systolic blood pressure (mmHg)** | | | |
| Baseline (mean) [a] | 130.7 | 129.5 | 129.3 |
| Change from baseline | -4.3 | -1.8 | -1.2 |
| Mean difference in change from baseline vs. FORXIGA (95% CI) | -2.4[#] (-4.5, -0.4) | | |

| Efficacy Parameter | FORXIGA 10 mg QD + Prolonged-release exenatide 2 mg QW | FORXIGA 10 mg QD + Placebo QW | Prolonged-release exenatide 2 mg QW + Placebo QD |
|---|---|---|---|
| **Intent-to-Treat population (N)** [c] | **228** | **230** | **227** |
| Mean difference in change from baseline vs. Prolonged-release exenatide (95% CI) | -3.0**<br>(-5.2, -0.9) | | |

QD=once daily, QW=once weekly, N=number of patients in treatment group, CI=confidence interval, FPG= fasting plasma glucose, PPG=postprandial plasma glucose

[a] Adjusted least squares means (LS Means) and treatment group difference(s) in the change from baseline values at Week 28 are modeled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (<9.0% or ≥9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.

[b] Categories are derived from continuous measurements. All patients with missing endpoint data are imputed as non-responders. Treatment comparison is based on Cochran-Mantel-Haenszel (CMH) test stratified by baseline HbA1c (<9.0% or ≥9.0%). P-values are from the general association statistics.

[c] Patients who received at least 1 dose of study medication and had at least 1 post-baseline HbA1c assessment.

*p < 0.001, **p < 0.01, #p < 0.05.

P-values are all adjusted p-values for multiplicity.

Analyses exclude measurements post rescue therapy and post premature discontinuation of study medication discontinuation, except for systolic blood pressure analysis, which includes measurements post rescue therapy but excludes data post premature discontinuation of study medication discontinuation.

Concomitant initiation therapy of Forxiga 10 mg and prolonged-release exenatide resulted in a greater proportion of patients achieving HbA1c $\leq$ 6.5% at Week 28 (30.3%) compared to Forxiga alone (10.4%) and prolonged-release exenatide alone (18.5%). The mean baseline HbA1c was 9.3%.

*Fasting plasma glucose*

Treatment with FORXIGA 10 mg as a monotherapy or as an add-on to either metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in fasting plasma glucose (-1.90 to -1.20 mmol/L) compared to placebo (-0.33 to 0.21 mmol/L) at 24 weeks. This effect was observed at Week 1 of treatment and maintained in studies extended through Week 104.

*Post-prandial glucose*

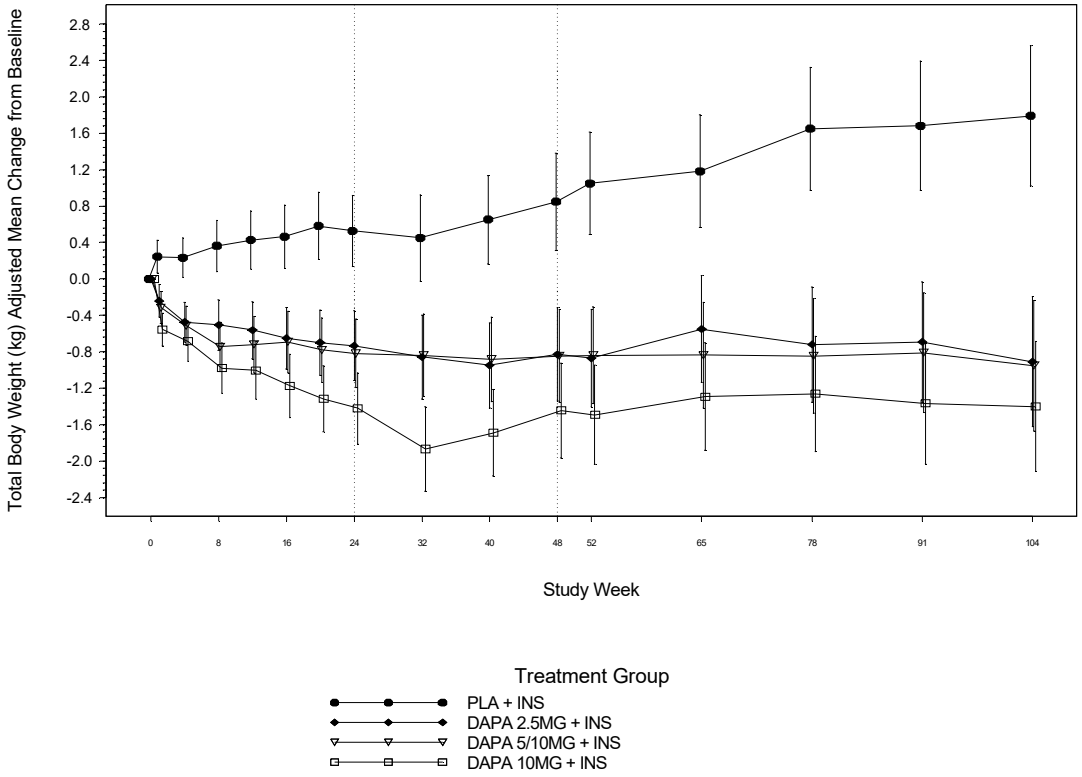
Treatment with FORXIGA 10 mg as an add-on to glimepiride resulted in statistically significant reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48. Treatment with FORXIGA 10 mg as an add-on to sitagliptin (with or without metformin) resulted in reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

*Body weight*

FORXIGA 10 mg as an add-on to metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant body weight reduction at 24 weeks (p <0.0001, Tables 5, 6 and 7) with placebo-corrected reductions of 1.97 kg (2.43%), 1.54 kg (2.07%), 2.07 kg (2.25%), 1.89 kg (2.18%) and 1.68 kg (1.83%), respectively. These effects were sustained in longer-term trials (see Figure 6 for add-on to insulin). At 48 weeks, the difference for FORXIGA as add-on to sitagliptin (with or without metformin) compared with placebo was -2.22 kg. At 102 weeks, the difference for FORXIGA as add-on to metformin compared with placebo, or as add-on to insulin (at 104 weeks) compared with placebo was -2.14 and -2.88 kg, respectively.

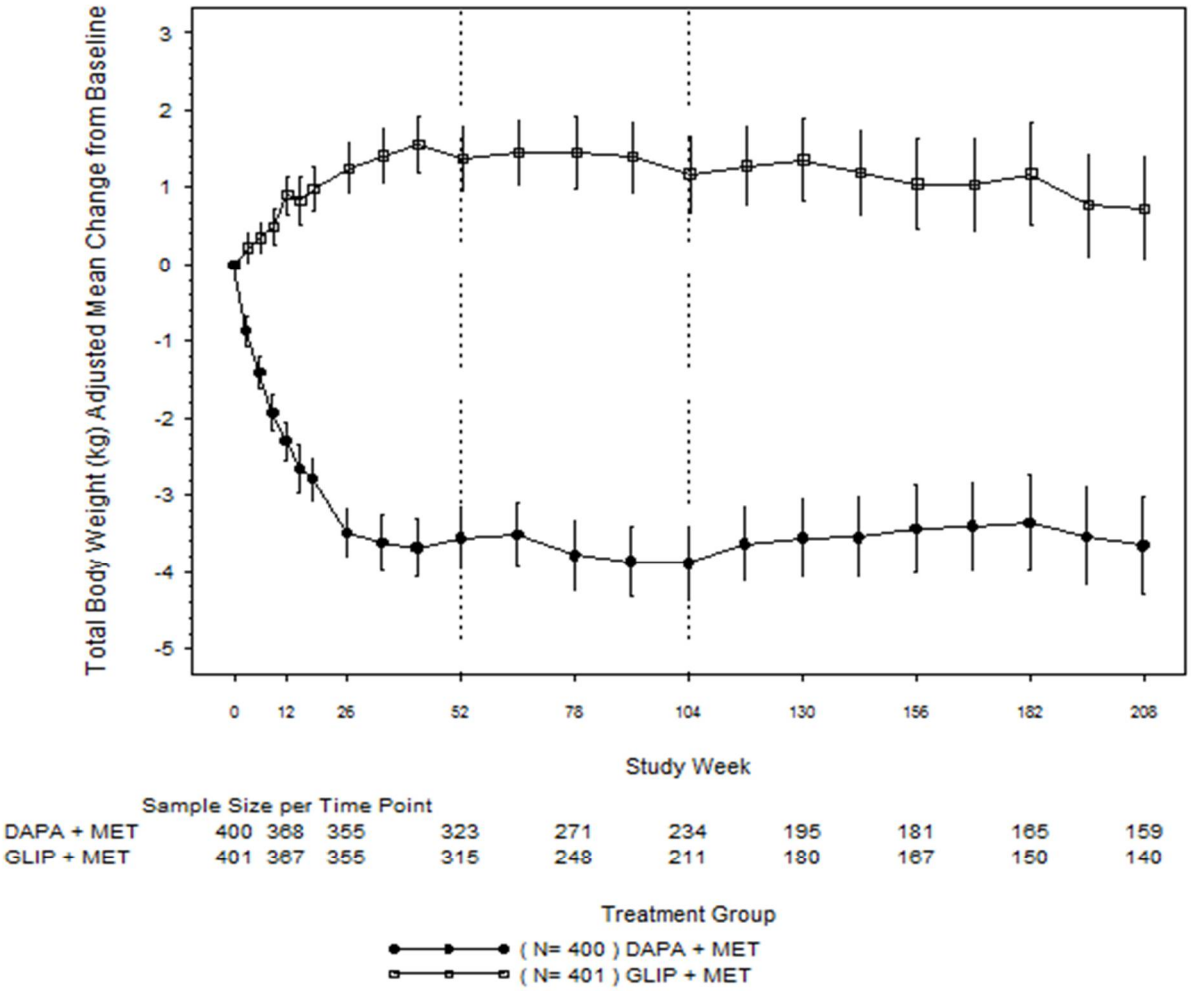
As an add-on therapy to metformin in an active-controlled non-inferiority study, FORXIGA resulted in a statistically significant body weight reduction compared with glipizide of -4.65 kg at 52 weeks (p <0.0001, Table 5) that was sustained at 104 weeks and 208 weeks (-5.06 kg and 4.38 kg respectively) (see Figure 7).

**Figure 6: Total Body Weight (kg) Adjusted Mean Change from Baseline Over Time in a Placebo-controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Short-term and Long-term Treatment Period Including Data After Insulin Up-titration**




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)**




Subjects in the full analysis set.
Mean value based on repeated measures analysis model:
post-baseline = baseline treatment week rescue week*treatment week*baseline.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

*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/$m^2$.

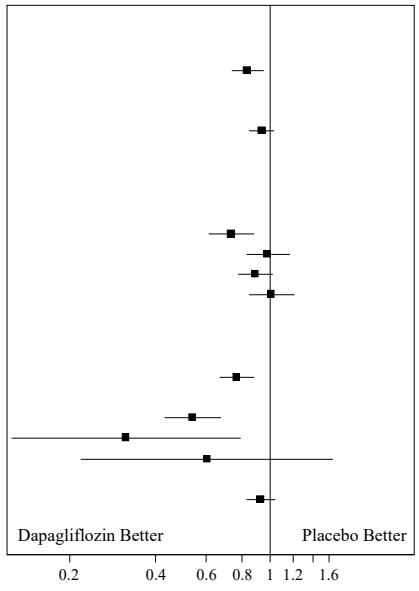
At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 $m^2$, 7.4% of patients had eGFR <60mL/min/1.73 $m^2$ and 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ration [UACR] ≥30 to ≤300 mg/g or >300 mg/g, respectively).

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 8 and 9.

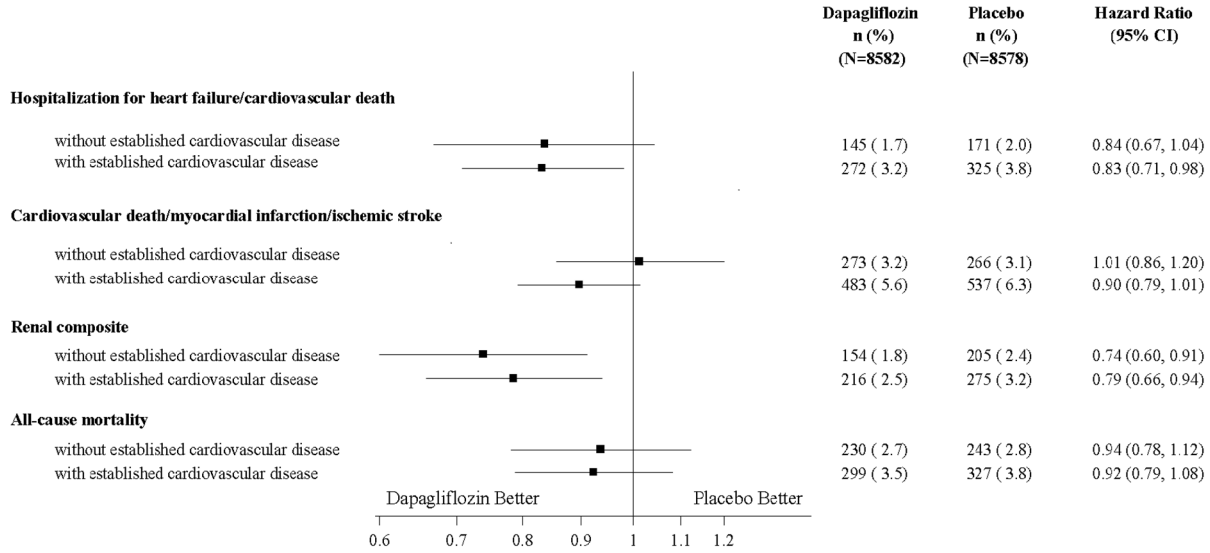
**Figure 8 Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components**




| | Dapagliflozin n (%) (N=8582) | Placebo n (%) (N=8578) | Hazard Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Primary endpoints** | | | | |
| **Composite of hospitalization for heart failure/cardiovascular death** | 417 ( 4.9) | 496 ( 5.8) | 0.83 (0.73, 0.95) | 0.005 |
| **Composite of cardiovascular death/ myocardial infarction/ischemic stroke** | 756 ( 8.8) | 803 ( 9.4) | 0.93 (0.84, 1.03) | 0.172 |
| Components of the composite endpoints | | | | |
| Hospitalization for heart failure | 212 ( 2.5) | 286 ( 3.3) | 0.73 (0.61, 0.88) | <0.001 |
| Cardiovascular death | 245 ( 2.9) | 249 ( 2.9) | 0.98 (0.82, 1.17) | 0.830 |
| Myocardial infarction | 393 ( 4.6) | 441 ( 5.1) | 0.89 (0.77, 1.01) | 0.080 |
| Ischemic stroke | 235 ( 2.7) | 231 ( 2.7) | 1.01 (0.84, 1.21) | 0.916 |
| **Secondary endpoints** | | | | |
| **Renal composite endpoint** | 370 ( 4.3) | 480 ( 5.6) | 0.76 (0.67, 0.87) | <0.001 |
| Renal components: | | | | |
| Sustained eGFR decrease | 120 ( 1.4) | 221 ( 2.6) | 0.54 (0.43, 0.67) | <0.001 |
| End-stage kidney disease | 6 (<0.1) | 19 ( 0.2) | 0.31 (0.13, 0.79) | 0.013 |
| Renal death | 6 (<0.1) | 10 ( 0.1) | 0.60 (0.22, 1.65) | 0.324 |
| **All-cause mortality** | 529 ( 6.2) | 570 ( 6.6) | 0.93 (0.82, 1.04) | 0.198 |

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/1.73 $m^2$ and/or ESKD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73 $m^2$) and/or renal or CV death.
CI=confidence interval.

**Figure 9 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/1.73 $m^2$ and/or ESKD (dialysis ≥90 days or kidney transplantation, sustained confirmed eGFR <15 mL/min/1.73 $m^2$) and/or renal or CV death. Time to first event was analyzed in a Cox proportional hazards model.
CI=confidence interval

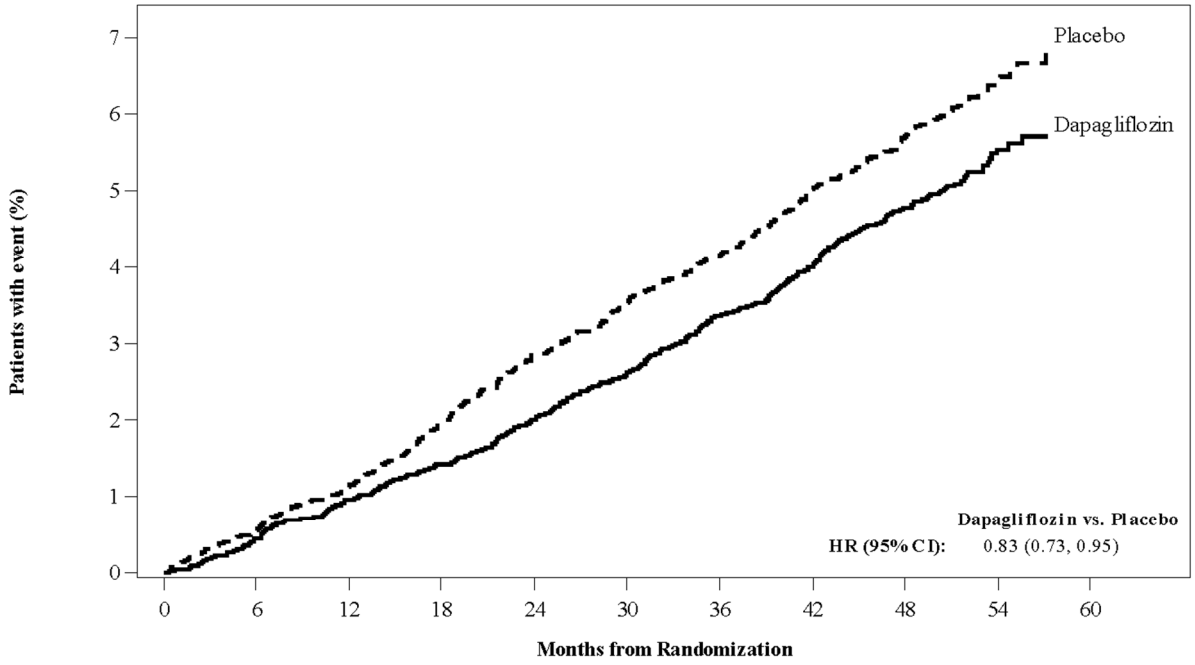
*Heart failure or cardiovascular death*

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 10).

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 8), with no clear difference in CV death (HR 0.98 [95% CI 0.82 to 1.17]).

The treatment benefit of FORXIGA over placebo was observed both in patients with and without established CV disease (Figure 9), with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR), and region.

**Figure 10 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*

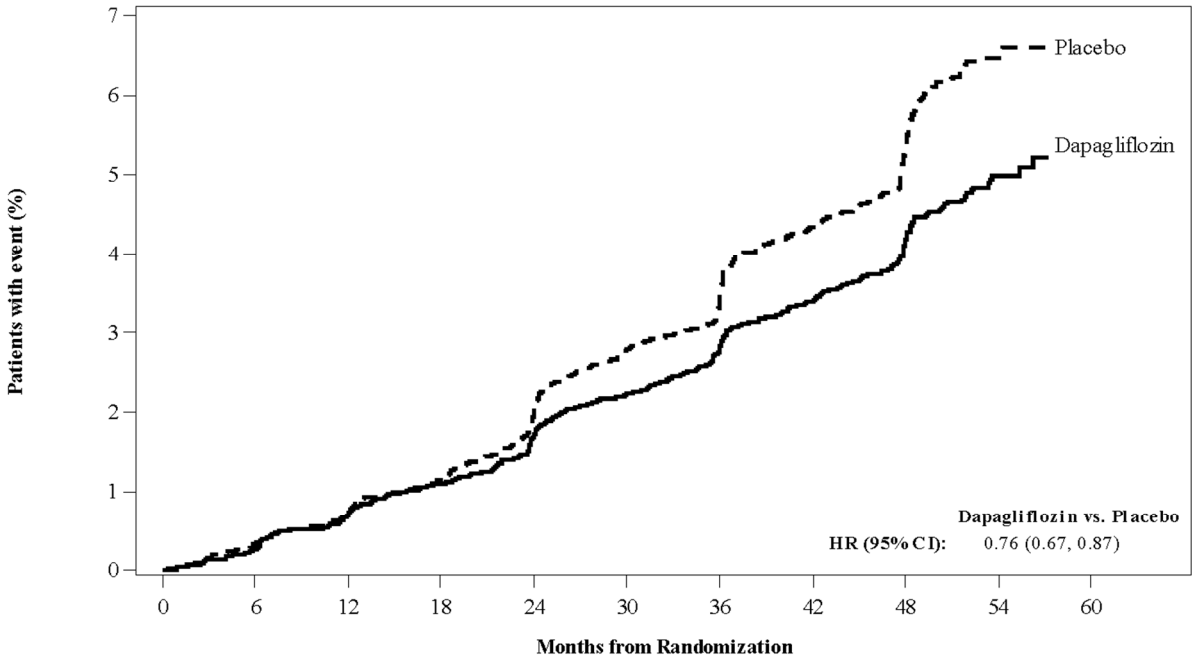
FORXIGA demonstrated cardiovascular safety (tested as non-inferiority versus placebo for the composite of CV death, myocardial infarction or ischemic stroke [MACE]; one-sided p <0.001).

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 8 and 9).

*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 11). The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, ESKD and renal death (Figure 8), and was observed both in patients with and without CV disease (Figure 9).

**Figure 11 Time to first occurrence of sustained eGFR decrease, ESKD, renal or CV death**




**Patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Dapagliflozin: | 8582 | 8533 | 8436 | 8347 | 8248 | 8136 | 8009 | 7534 | 5472 | 1637 |
| Placebo: | 8578 | 8508 | 8422 | 8326 | 8200 | 8056 | 7932 | 7409 | 5389 | 1589 |

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/1.73 $m^2$ 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 Diabetic Patients*

Due to the mechanism of action of FORXIGA a study was done to evaluate body composition and bone mineral density. FORXIGA 10 mg added on to metformin in 182 patients with type 2 diabetes over a 24 week period provided significant improvements compared with placebo plus

metformin, respectively, in body weight (mean change from baseline: -2.96 kg v. -0.88 kg); waist circumference (mean change from baseline: -2.51 cm v. -0.99 cm), and body fat mass as measured by DXA (mean change from baseline -2.22 kg v. -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 $cm^3$ v. -8.7 $cm^3$) in an MRI substudy. In an ongoing extension of this study to week 50, there was no important change in bone mineral density for the lumbar spine, femoral neck or total hip seen in either treatment group (mean change from baseline for all anatomical regions <0.5%, 7/89 dapagliflozin and 4/91 comparator subjects showed a decrease of 5% or more). These effects were sustained in a further extension of the study to 102 weeks where no important changes in BMD for the lumbar spine, femoral neck or total hip in either treatment group were observed.

*Clinical Safety*

*Hypoglycaemia*

The incidence of hypoglycaemia as seen in controlled clinical studies with dapagliflozin in different combinations is shown in Table 9.

**Table 9 Incidence of Major[a] and Minor[b] Hypoglycaemia 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 hypoglycaemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration

[b] Minor episodes of hypoglycaemia 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* 0.4% 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 both 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.

*Glycaemic control in special populations*

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

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 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/1.73 m$^2$)*

The glycaemic 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/1.73 m$^2$ (moderate renal impairment subgroup Chronic Kidney Disease [CKD] 3A), with inadequate glycaemic 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 10). 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 -1.19 mmol/L and -0.92 mmol/L, 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 10: 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/1.73 m$^2$)**

| 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*) (95% CI) | -0.34§ (-0.53, -0.15) | |
| **FPG (mmol/L)** | | |
| Baseline (mean) | 10.16 | 9.62 |
| Change from baseline (adjusted mean*) | -1.19 | -0.27 |

| Efficacy Parameter | FORXIGA 10 mg N=159 | Placebo N=161 |
|---|---|---|
| Difference from placebo (adjusted mean*) (95% CI) | -0.92§ (-1.48, -0.36) | |
| **Body Weight (percentage)** | | |
| Baseline (mean) | 92.51 | 88.30 |
| % Change from baseline (adjusted mean*) | -3.42 | -2.02 |
| Difference from placebo (adjusted mean*) (95% CI) | -1.43§ (-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*) (95% CI) | -3.1¶ (-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/1.73 $m^2$ and placebo: -0.90 mL/min/1.73 $m^2$). 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/1.73 $m^2$ and placebo: -0.04 mL/min/1.73 $m^2$).

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/1.73 $m^2$); 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/1.73 $m^2$); this pool did not include the two dedicated studies 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. 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/1.73 $m^2$ (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/1.73 $m^2$ and placebo

−2.58 mL/min/1.73 $m^2$) At Week 104, these changes persisted (eGFR: FORXIGA 10 mg −3.50 mL/min/1.73 $m^2$ and placebo −2.38 mL/min/1.73 $m^2$). 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/1.73 $m^2$ 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/1.73 $m^2$ (CKD 3A).

*Blood Pressure*

In the pre-specified pooled analysis of 13 placebo-controlled studies (see section 4.8 Undesirable Effects), treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of –3.7 mmHg and diastolic blood pressure of –1.8 mmHg versus –0.5 mmHg systolic and -0.5 mmHg diastolic blood pressure for the placebo group at Week 24. Similar reductions were observed up to 104 weeks.

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with FORXIGA 10 mg or placebo. At Week 12 for both studies, FORXIGA 10 mg plus usual antidiabetic treatment provided improvement in HbA1c, and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively.

## Clinical Efficacy and Safety – Heart Failure

*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 (with defibrillator function).

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

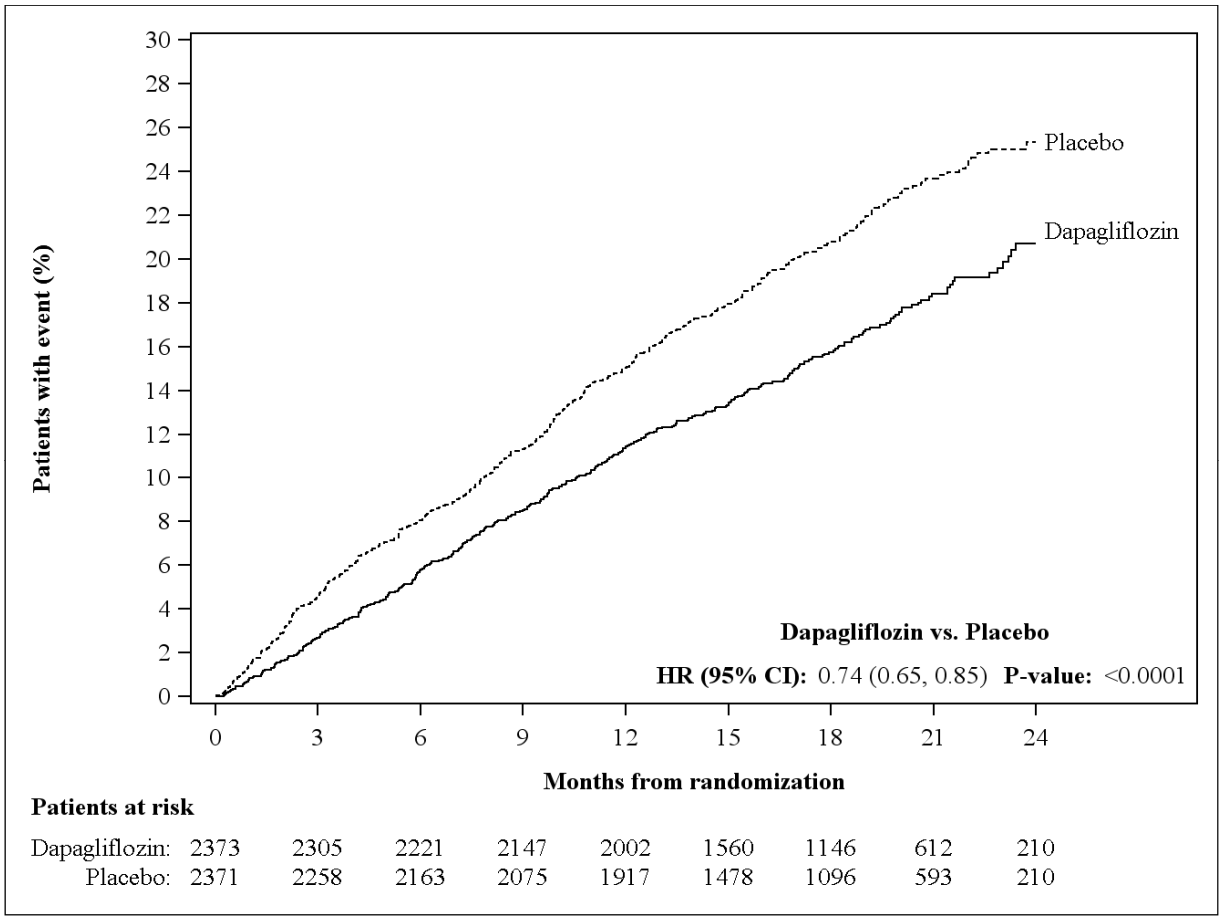
The DAPA-HF outcomes study compared FORXIGA versus placebo in a population representative of that found in clinical practice. The overall study objective was to determine whether FORXIGA prevents cardiovascular death and worsening heart failure, and if FORXIGA improves heart failure symptoms.

*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 12).

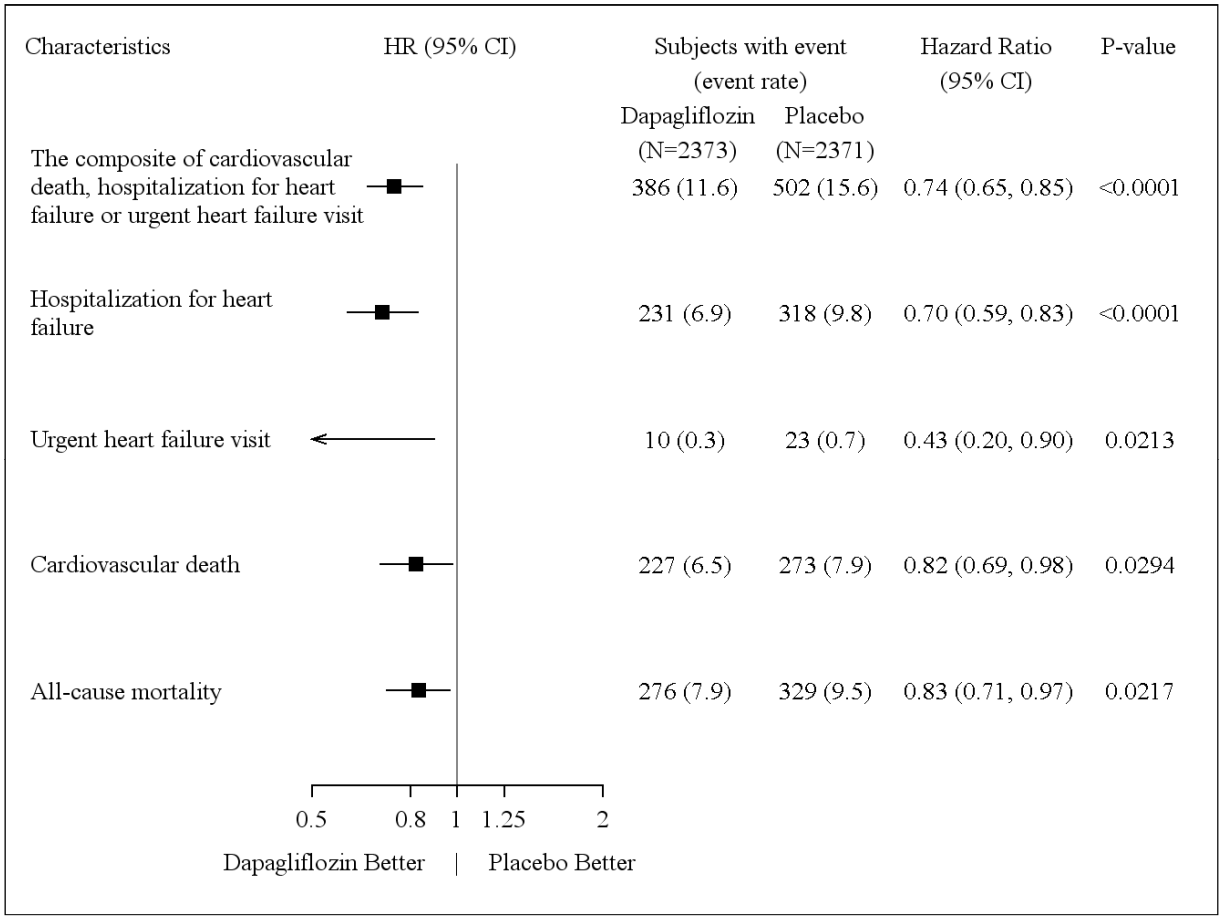
**Figure 12 Time to first occurrence of the composite hospitalization of cardiovascular death, hospitalization for heart failure or urgent heart failure visit**




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 13). 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 13 Treatment effects for the primary composite endpoint, its components and all-cause mortality**

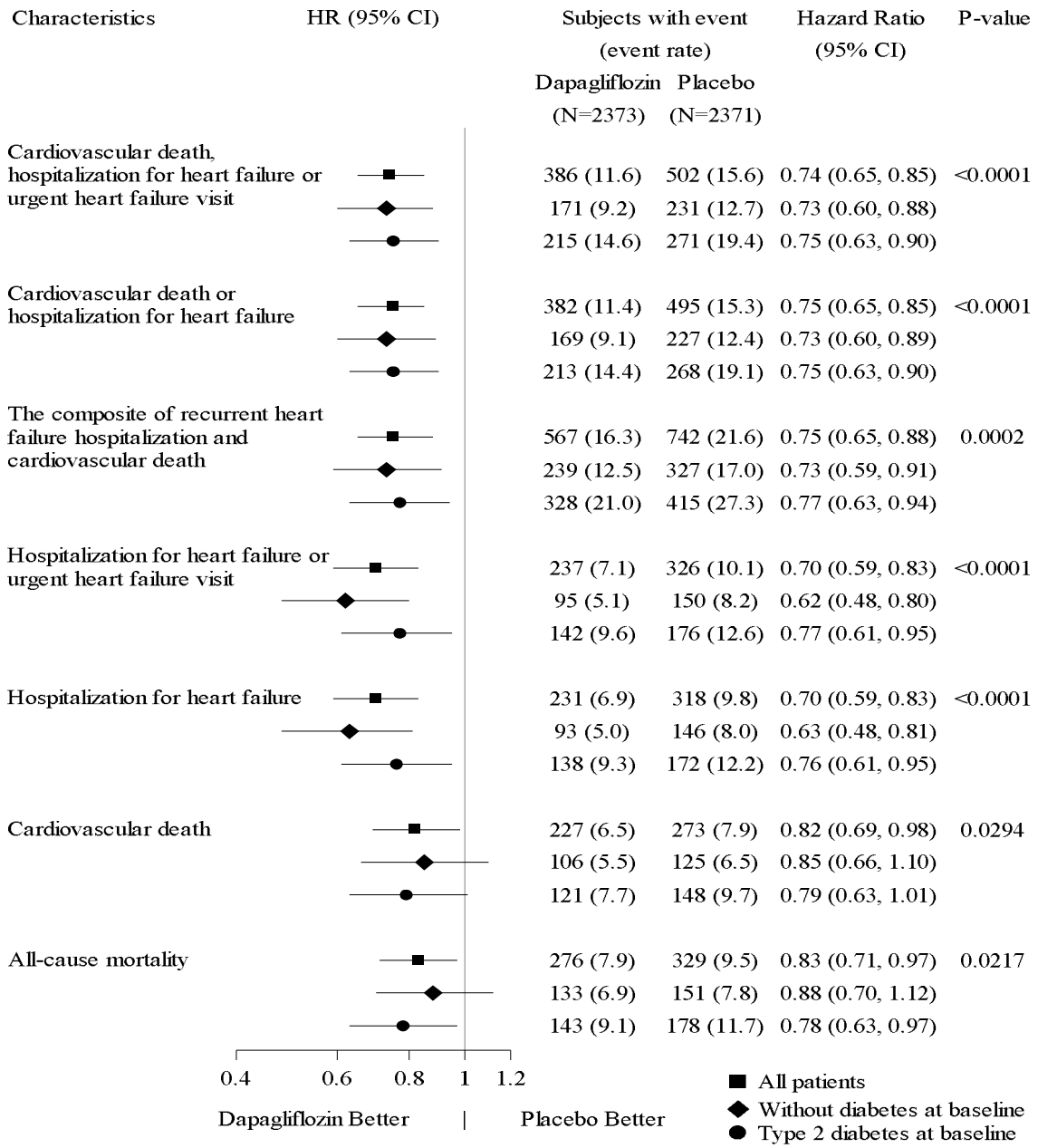



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).
The number of first events for the single components are the actual number 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 14).

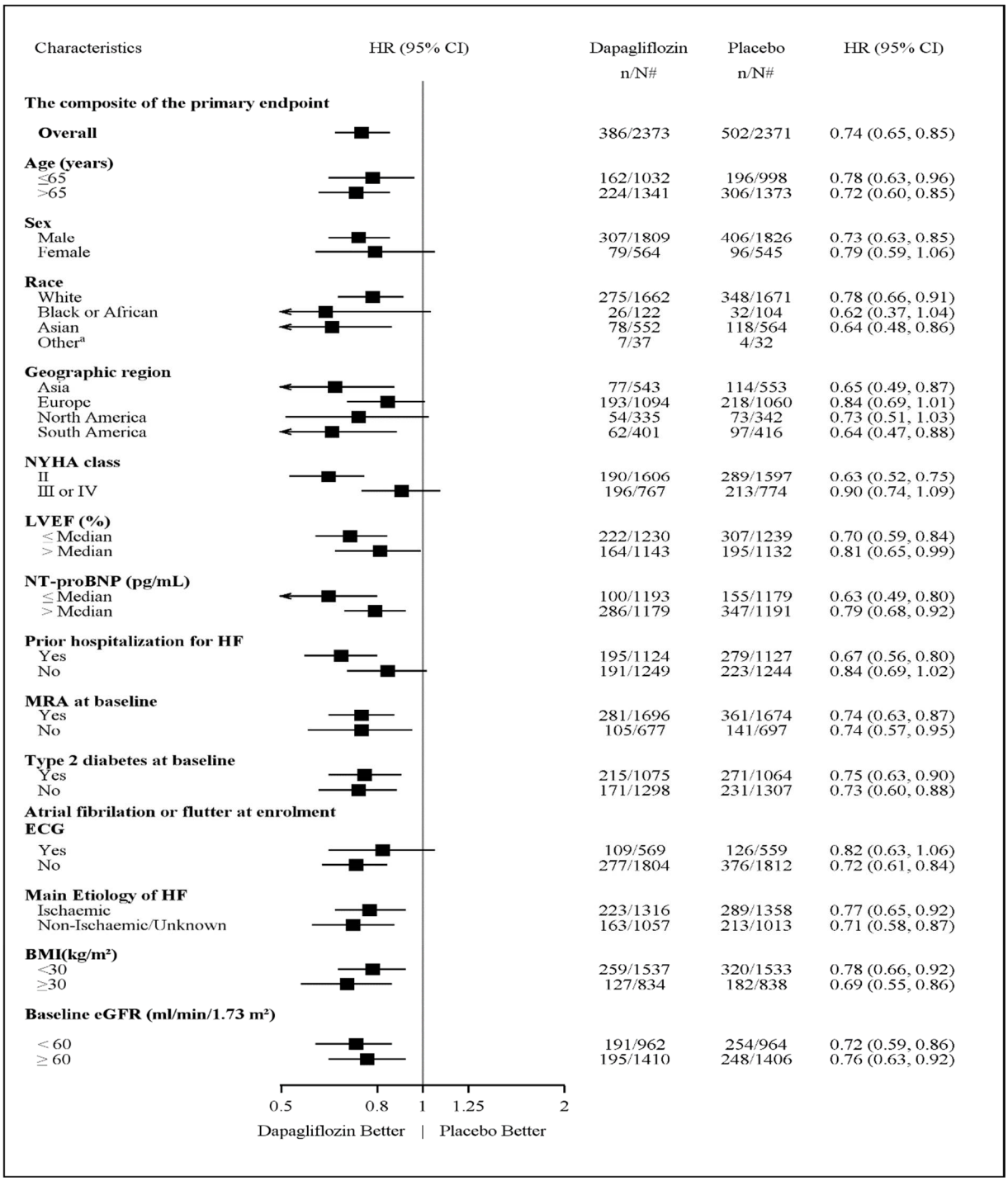
**Figure 14 Treatment effects in all patients, in patients with type 2 diabetes mellitus and in patients without diabetes**




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 15).

**Figure 15 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 11).

**Table 11 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 13).

*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.

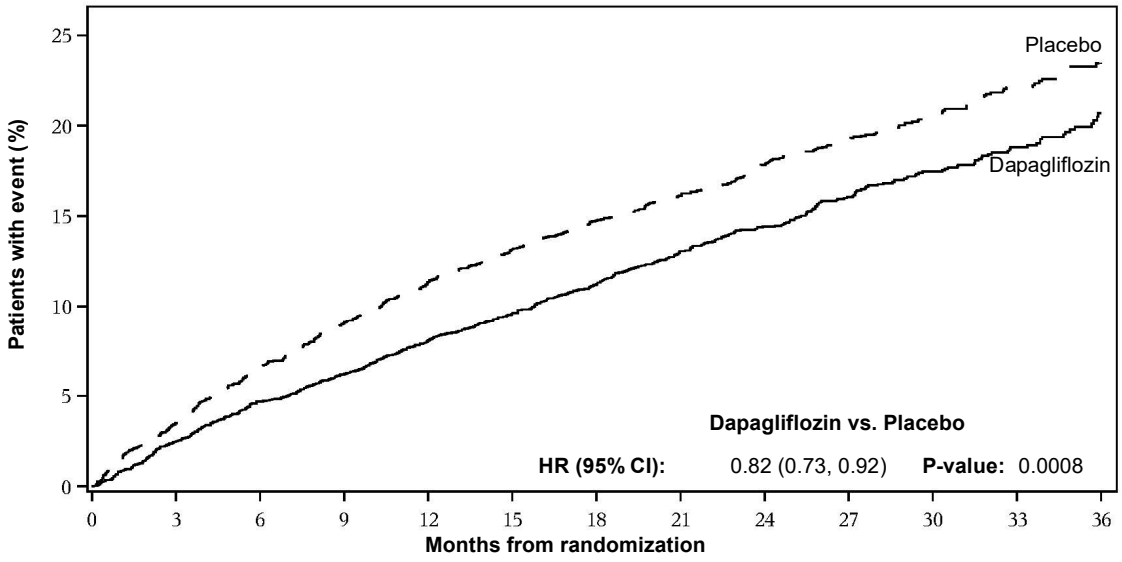
At baseline, 75% patients were classified as NYHA class II, 24% class III and 0.3% class IV. Median LVEF was 54%, 34% of the patients had LVEF ≤49%, 36% had LVEF 50-59% and 30% had LVEF ≥60%. In each treatment group, 45% had a history of type 2 diabetes mellitus. Baseline therapy included ACEi/ARB/ARNI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

Patients with eGFR ≥25 mL/min/1.73 $m^2$ at enrollment were included in the study. The mean eGFR was 61 mL/min/1.73 $m^2$, 49% of patients had eGFR <60 mL/min/1.73 $m^2$, 23% had eGFR <45 mL/min/1.73 $m^2$, and 3% had eGFR <30 mL/min/1.73 $m^2$.

*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 16).

**Figure 16 Time to first occurrence of the composite of cardiovascular death, hospitalization for heart failure or urgent heart failure visit**



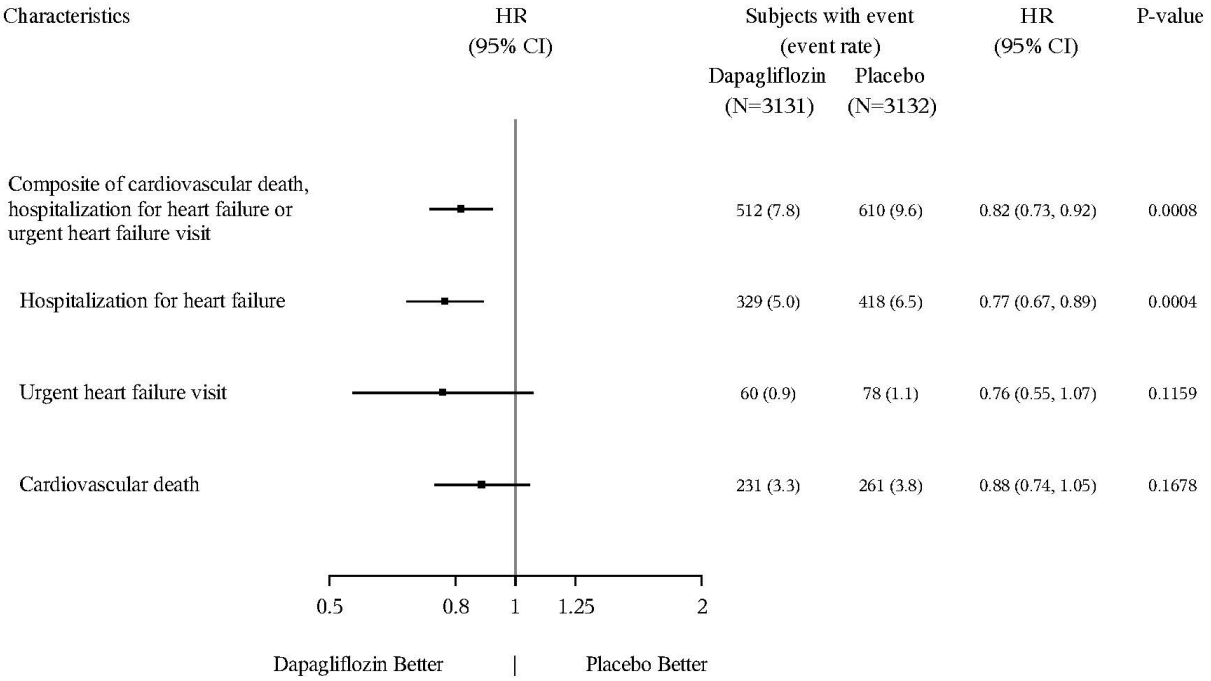

**Patients at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dapagliflozin: | 3131 | 3040 | 2949 | 2885 | 2807 | 2716 | 2401 | 2147 | 1982 | 1603 | 1181 | 801 | 389 |
| Placebo: | 3132 | 3007 | 2896 | 2799 | 2710 | 2608 | 2318 | 2080 | 1923 | 1554 | 1140 | 772 | 383 |

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 17).

**Figure 17 Treatment effects for the primary composite endpoint and its components**

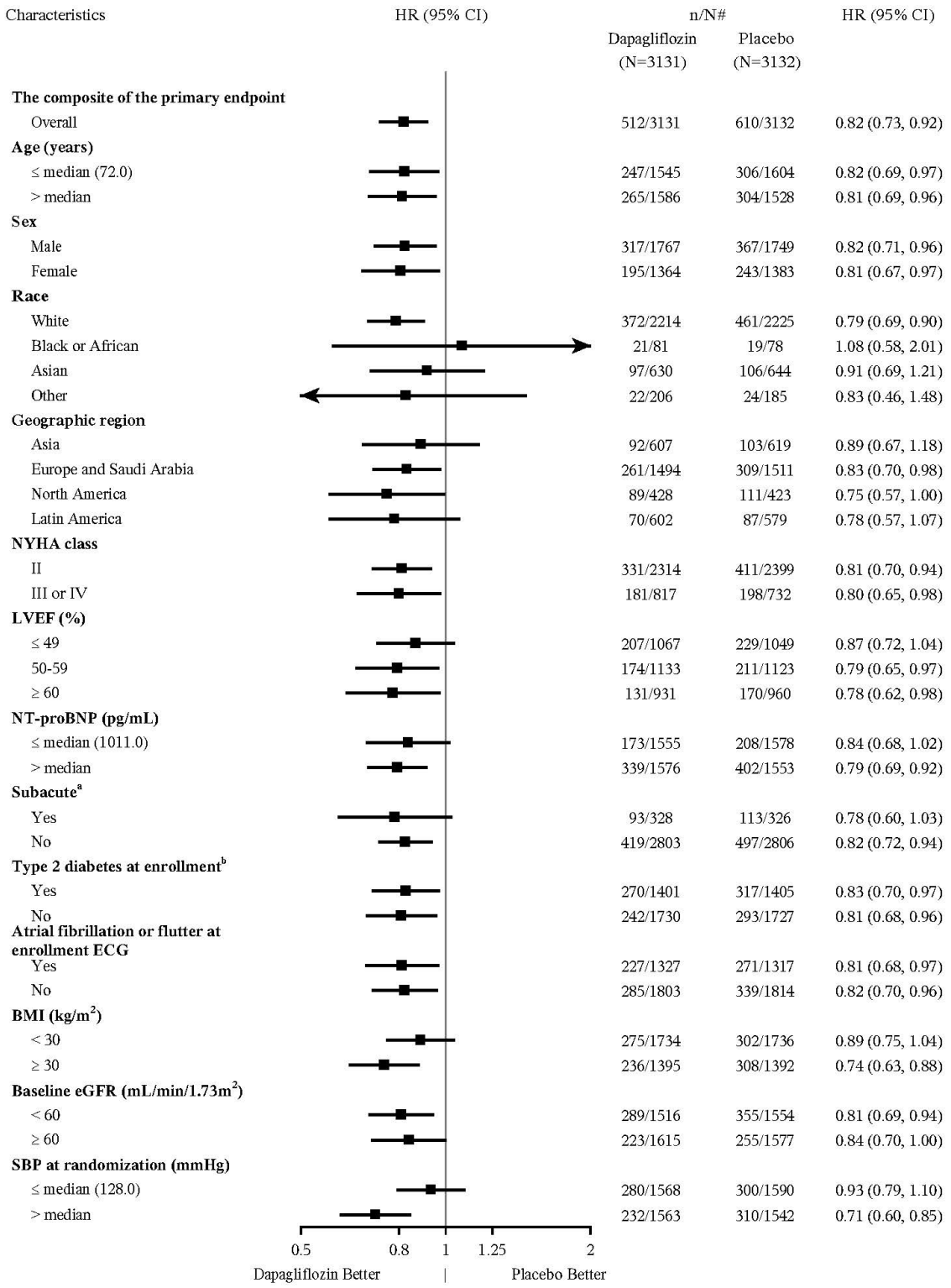



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).
The number of first events for the single components are the actual number 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 18).

## Figure 18 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 12).

**Table 12 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 |

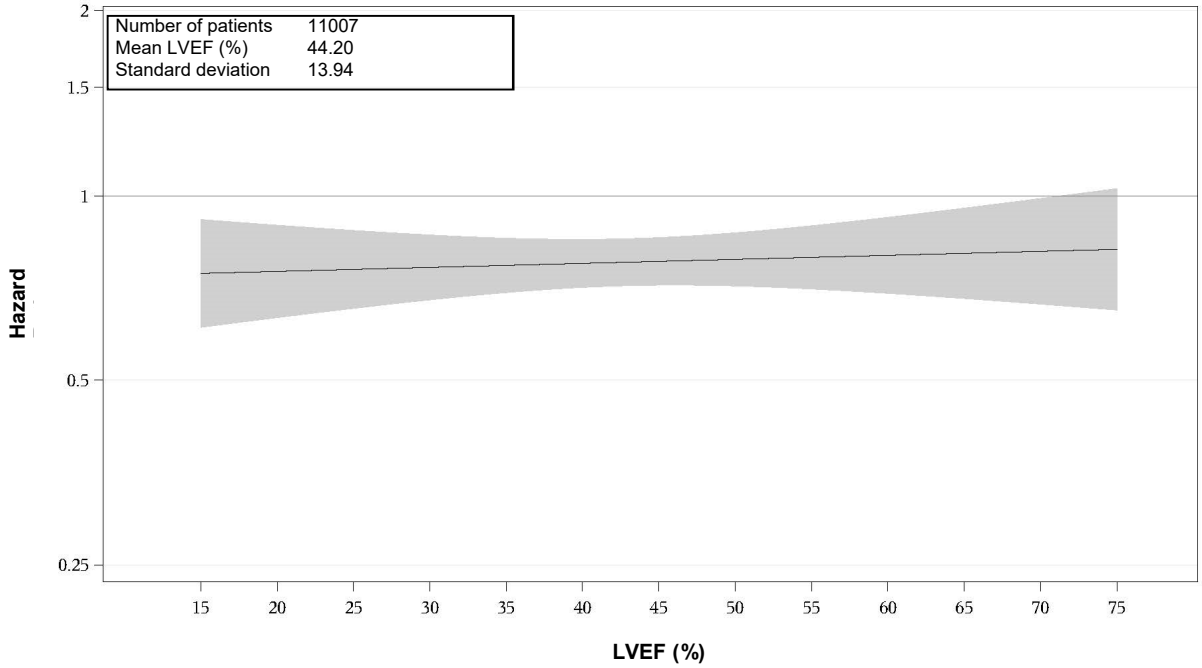
[a] Number of patients with an observed KCCQ-TSS or who died prior to 8 months. Number includes patients with an 8-month assessment (Visit 5) planned or performed prior to 11 March 2020, when COVID-19 was declared a pandemic by the WHO. Data for patients with planned but not performed assessment prior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

*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 19).

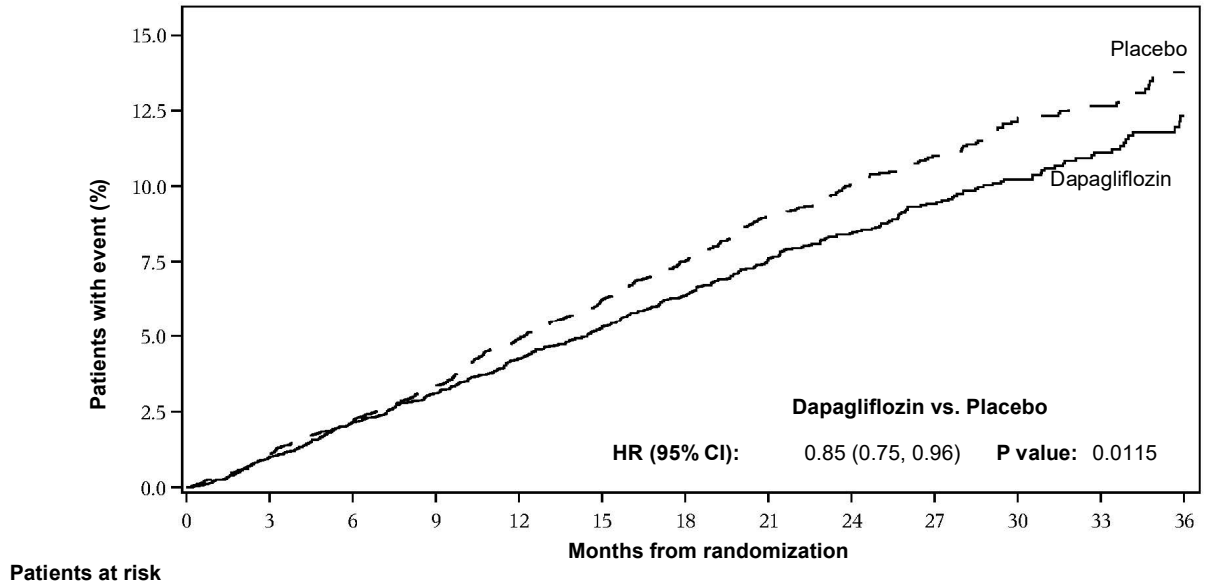
**Figure 19 Treatment effect for the primary composite endpoint (cardiovascular death, hospitalization for heart failure or urgent heart failure visit) by baseline LVEF**




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 20). Both studies contributed to the effect.

**Figure 20 Time to first occurrence of cardiovascular death (pooled analysis of DAPA-HF and DELIVER studies)**




**Patients at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dapagliflozin: | 5504 | 5430 | 5339 | 5254 | 5087 | 4556 | 3826 | 3010 | 2403 | 1781 | 1312 | 903 | 441 |
| Placebo: | 5503 | 5426 | 5333 | 5238 | 5048 | 4508 | 3789 | 2978 | 2391 | 1767 | 1306 | 910 | 451 |

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 Efficacy and Safety - Chronic kidney disease

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/1.73 $m^2$ 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/1.73 $m^2$ during the study and could be continued in cases when dialysis was needed.

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

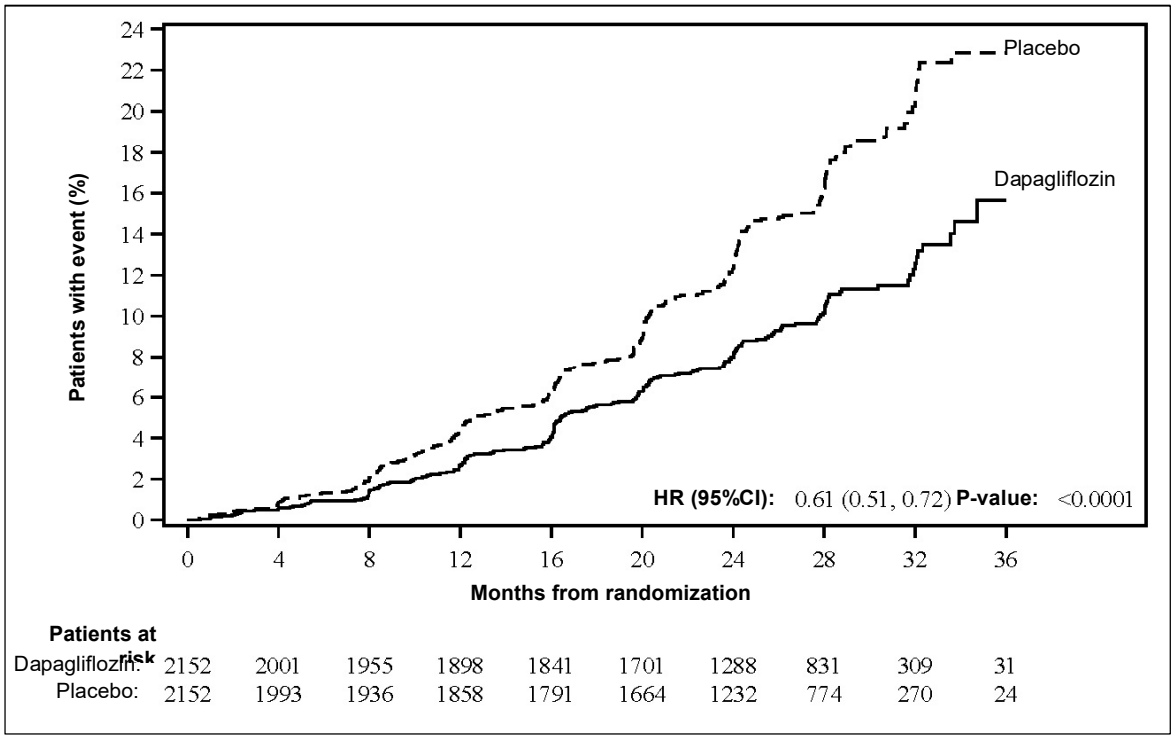
Patients were on standard of care (SOC) therapy; 97.0% of patients were treated with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

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 21).

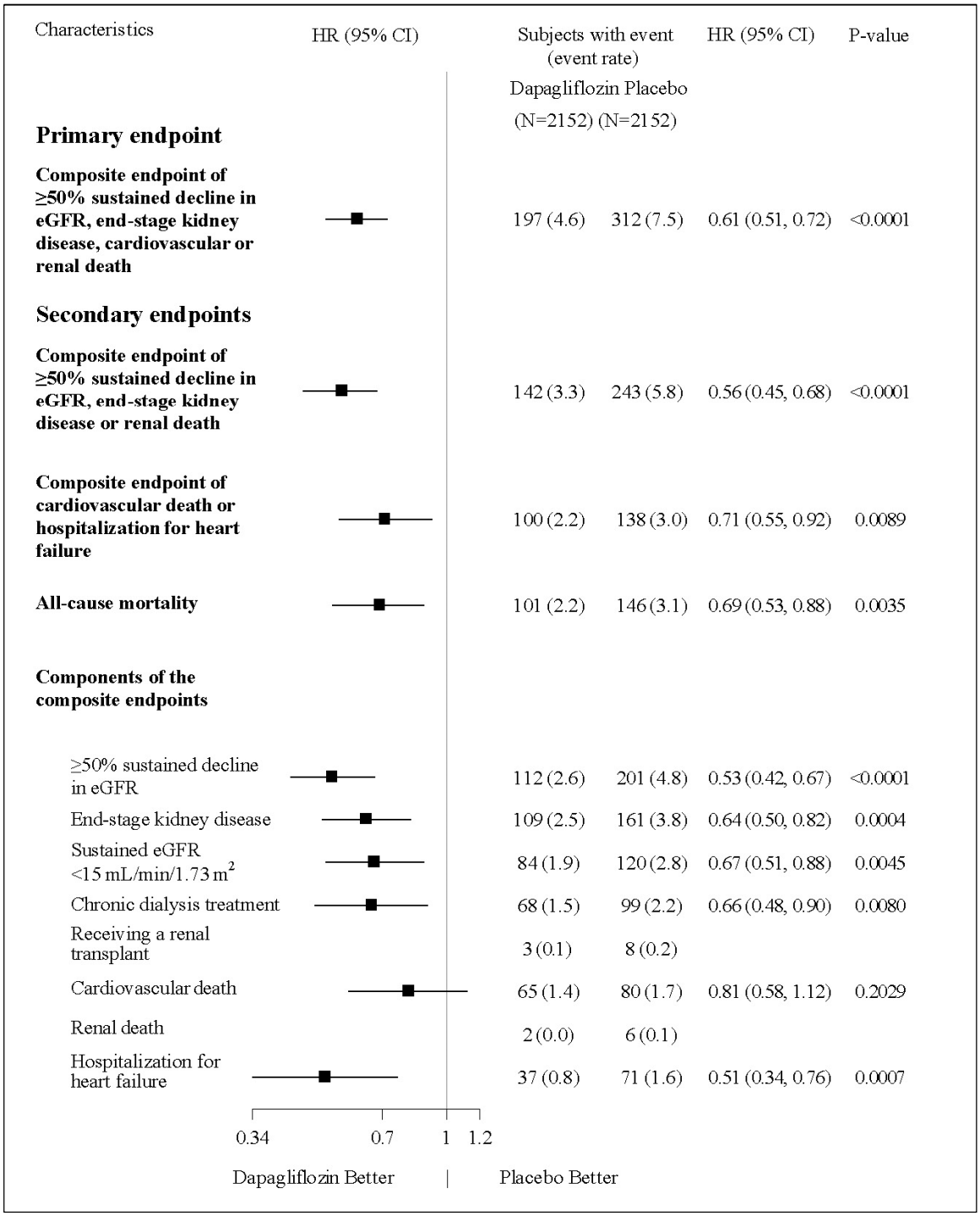
**Figure 21 Time to first occurrence of the primary composite endpoint, ≥50% sustained decline in eGFR, ESKD, CV or renal death**




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 22). 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).

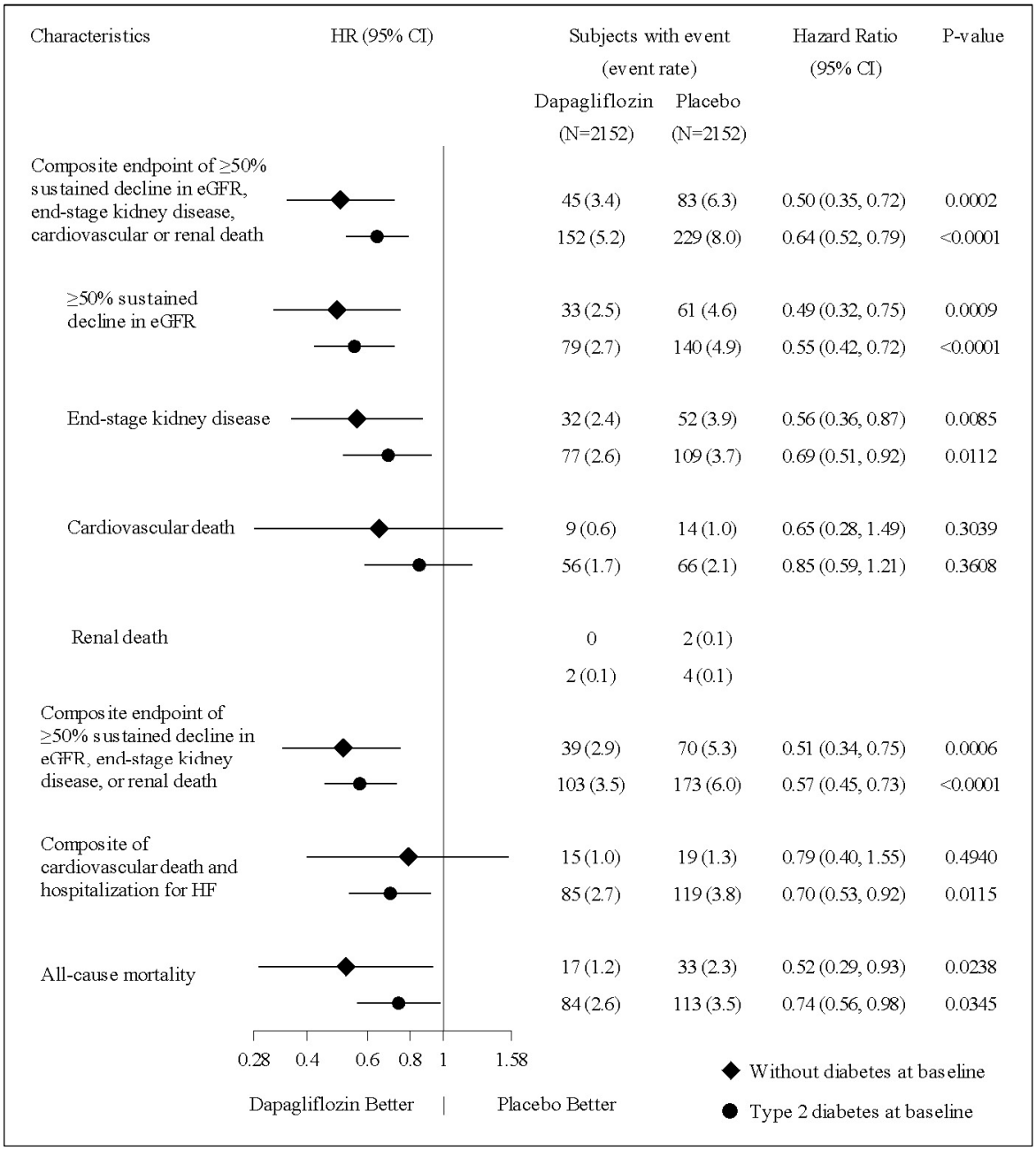
**Figure 22 Treatment effects for the primary and secondary composite endpoints, their individual components, and all-cause mortality**




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 23).

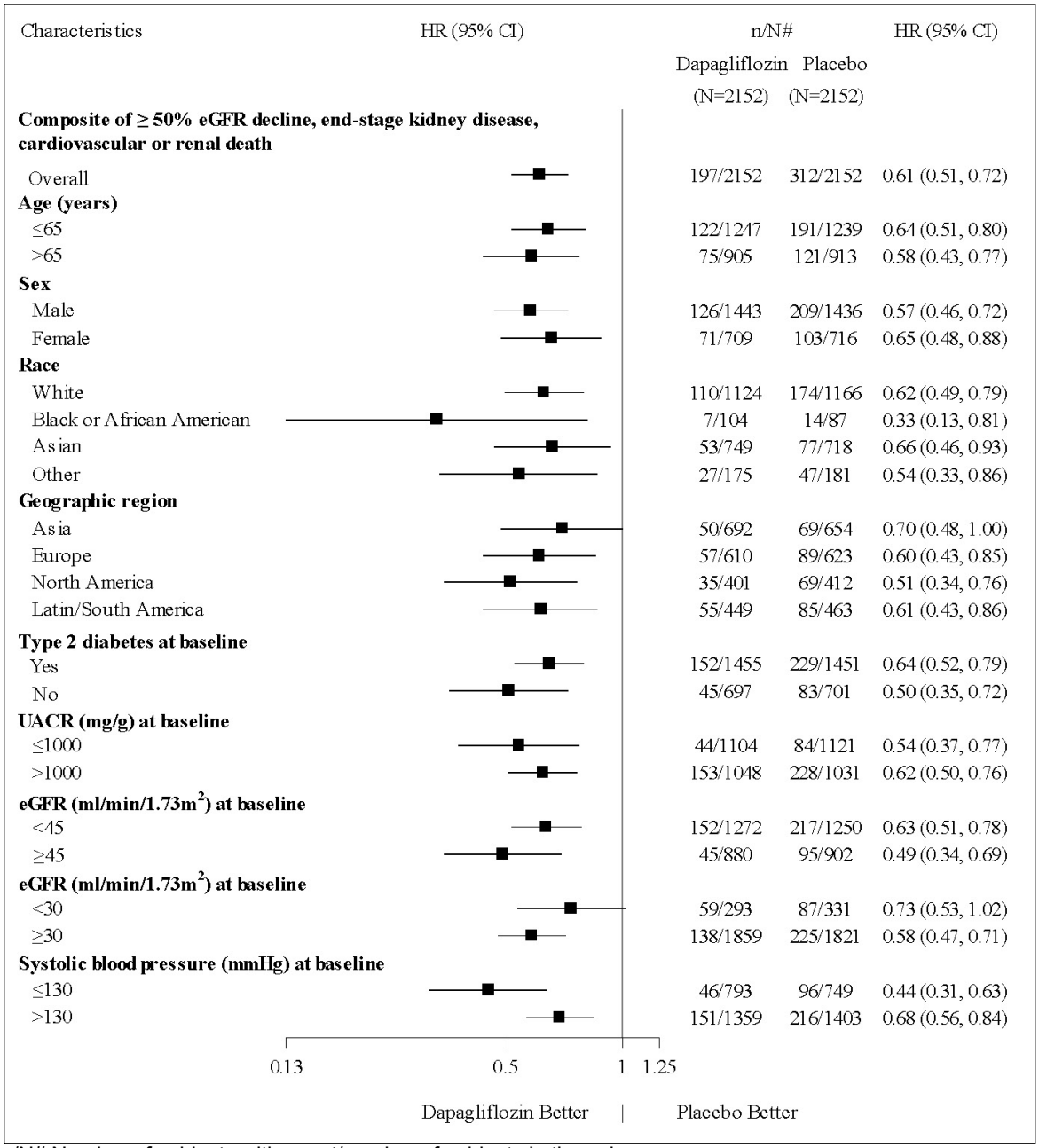
**Figure 23 Treatment effects in patients with type 2 diabetes mellitus and in patients without diabetes**




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 24).

**Figure 24 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 PHARMACOKINETIC PROPERTIES

### 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 proportional 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 $T_{max}$ 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 (e.g. renal or hepatic impairment).

### Metabolism

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide. Dapagliflozin 3-O-glucuronide, with a molar plasma AUC 52% higher than that of dapagliflozin itself at the clinical dose, is an inactive metabolite and does 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 oral administration of 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug. The mean plasma terminal half-life ($t_{½}$) for dapagliflozin was 12.9 hours following a single oral dose of FORXIGA 10 mg to healthy subjects.

### 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 was lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-h 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 haemodialysis 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 hepatic impairment see section 4.2 Dose 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 hepatic impairment groups or 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.

*Age*

No dosage adjustment for dapagliflozin 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%]. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

*Paediatric and Adolescent*

Pharmacokinetics in the paediatric 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 AUCs 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 [African descent] 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 (African descent) 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 adjustment from the proposed dapagliflozin dose of 10 mg once daily is recommended in patients with diabetes mellitus or in patients 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

#### Carcinogenicity

Dapagliflozin did not induce tumours in two-year carcinogenicity studies in mice or rats at oral doses up to 40 mg/kg/day and 10 mg/kg/day respectively. These doses correspond to AUC exposure levels at least 78 times the human AUC at the MRHD of 10 mg/day.

#### Genotoxicity

Dapagliflozin was positive in an *in-vitro* clastogenicity assay in the presence of metabolic activation. However, dapagliflozin was negative in the Ames mutagenicity assay and in a series of in-vivo clastogenicity studies evaluating micronuclei or DNA repair in rats at exposure multiples at least 2100 times the human exposure at the MRHD. The weight of evidence from these studies, along with the absence of tumour findings in the rat and mouse carcinogenicity studies, support that dapagliflozin is not genotoxic.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Each film-coated tablet of FORXIGA contains 10 mg of dapagliflozin (as dapagliflozin propanediol monohydrate) and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, 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 INCOMPATABILITIES

Not applicable.

### 6.3 SHELF LIFE

36 months

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Should be stored below 30°C.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Aluminium/aluminium blisters in pack sizes of 7 and 28 tablets.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Return unused and expired medicines to your local pharmacy for disposal.

## 7. MEDICINE SCHEDULE

Prescription Medicine.

## 8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: (09) 306 5650

## 9. DATE OF FIRST APPROVAL

6 June 2013

## 10. DATE OF REVISION OF TEXT

14 June 2023



Doc ID-003966675 v 7.0

### SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 4.1,4.2 | Extension of indications as per DELIVER study |
| 4.8 | Updated section based on DELIVER data |
| 5, 5.1 | Updated section with clinical data from DELIVER data |
| | |