Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Dapagliflozin 5mg
Dapagliflozin 10mg

2. Qualitative and quantitative composition

Dapagliflozin Tablets, 5 mg

Each tablet contains the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol Dapagliflozin Tablets, 10 mg

Each tablet contains the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol

Excipient with known effect: Lactose

3. Pharmaceutical form

Tablets

Dapagliflozin Tablets, 5 mg

Pink, biconvex, round, film-coated tablets with "C388" engraved on one side and plain on the other side.

Dapagliflozin Tablets, 10 mg

Pink, biconvex, diamond-shaped, film -coated tablets with "C389" engraved on one side and plain on the other side

4. Clinical particulars

4.1 Therapeutic indications

Type 2 diabetes mellitus

Dapagliflozin is indicated:

• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

• to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

Heart failure

Dapagliflozin is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (nyha class ii-iv) with reduced ejection fraction.

Limitations of use Dapagliflozin is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

4.2 Posology and method of administration

Prior to initiation of dapagliflozin

Assess renal function prior to initiation of Dapagliflozin therapy and then as clinically indicated (See section 4.4).

In patients with volume depletion, correct this condition prior to initiation of (See section 4.4 and 5.1)

Type 2 diabetes mellitus

To improve glycemic control, the recommended starting dose of dapagliflozin is 5 mg orally once daily, taken in the morning, with or without food. In patients tolerating dapagliflozin 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg

once daily. To reduce the risk of hospitalization for heart failure in patients with type 2 diabetes mellitus and established CVD or multiple CV risk factors, the recommended dose of dapagliflozin is 10 mg orally once daily.

Heart failure
The recommended dose of dapagliflozin is 10 mg orally once daily

Special populations

Renal impairment

No dose adjustment is required based on renal function.

It is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m^2.

In patients with type 2 diabetes mellitus, the glucose lowering efficacy of dapagliflozin is reduced when eGFR is < 45 mL/min/1.73m^2, and is likely absent in patients with severe renal impairment. Therefore, if eGFR falls below 45 mL/min/1.73m^2, additional glucose lowering treatment should be considered in patients with type 2 diabetes mellitus (see sections 4.4, 4.8, 5.1 and 5.2).

Hepatic impairment

No dose adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg (see sections 4.4 and 5.2).

Elderly (≥ 65 years)

No dose adjustment is recommended based on age.

Paediatric population

No dose adjustment is required for the treatment of type 2 diabetes mellitus in children aged 10 years and above (see sections 5.1 and 5.2). No data are available for children below 10 years of age.

The safety and efficacy of dapagliflozin for the treatment of heart failure or for the treatment of chronic kidney disease in children < 18 years have not yet been established. No data are available

Method of administration

Dapagliflozin 5mg and 10mg can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

-History of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema (See section 4.8)
-Patients who are being treated for glycemic control without established CVD or multiple CV risk factors with severe renal impairment, (eGFR less than 30 mL/min/1.73 m2 (See section 5.1)
- Patients on dialysis (See section 5.1)

4.4 Special warnings and precautions for use

Volume depletion

Dapagliflozin can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating dapagliflozin in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

Ketoacidosis in patients with diabetes mellitus

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including dapagliflozin (See section 4.8). Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus (See section 4.1)

Patients treated with dapagliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with dapagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, dapagliflozin should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.
Before initiating dapagliflozin, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.
For patients who undergo scheduled surgery, consider temporarily discontinuing dapagliflozin for at least 3 days prior to surgery (See

sections 5.1 and 5.2)
Consider monitoring for ketoacidosis and temporarily discontinuing dapagliflozin in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting dapagliflozin.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue dapagliflozin and seek medical attention immediately if signs and symptoms occur.

Urosepsis and pyelonephritis
Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (See section 4.8).

Hypoglycemia with concomitant use with insulin and insulin secretagogues Insulin and insulin secretagogues are known to cause hypoglycemia. dapagliflozin may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue (See section 4.8). (See section 4.8). Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with dapagliflozin.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with dapagliflozin presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue dapagliflozin, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.
Genital mycotic infections
Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections (See section 4.8). Monitor and treat appropriately.
Lactose
This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose

malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Positive Urine Glucose

Test Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.

Use alternative methods to monitor glycemic control.

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

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

4.6 Pregnancy and Lactation

Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, dapagliflozin is not recommended during the second and third trimesters of pregnancy.

Limited data with dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes and untreated heart failure in pregnancy.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose (see Data).

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications.

Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed in utero and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to 29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.
In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose,

Breast-feeding

It i unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring (see section 5.3). A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

4.7 Effects on ability to drive and use machines

Dapagliflozin has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

The following important adverse reactions are described below and elsewhere in the labeling:

- Volume Depletion (See section 4.4)
- Ketoacidosis in Patients with Diabetes Mellitus (See section 4.4)
- Urosepsis and Pyelonephritis (See section 4.4)
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues (See section 4.4)
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) (See section 4.4)
- Genital Mycotic Infections (See section 4.4)

Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Dapagliflozin has been evaluated in clinical trials in patients with type 2 diabetes mellitus and in patients with heart failure. The overall safety profile of dapagliflozin was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

Type 2 diabetes mellitus

In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.

In the dapagliflozin cardiovascular outcomes study in type 2 diabetes mellitus, DECLARE study, 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

Heart failure

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF study), 2,368 patients were treated with dapagliflozin 10 mg and 2,368 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 > 40% (DELIVER), 3,126 patients were treated with dapagliflozin 10 mg and 3,127 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.

The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

Chronic kidney disease

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m^2. Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m^2.

The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).

Table 1. Adverse reactions in placebo-controlled clinical studies[a] and postmarketing experience

System organ class	**Very common**	**Common***	**Uncommon****	**Rare**	**Very rare**
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[*,b,c] Urinary tract infection[*,b,d]	Fungal infection**		Necrotising fasciitis of the perineum (Fournier's gangrene)[b,i]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion[b,e] Thirst**	Diabetic ketoacidosis (when used in type 2 diabetes mellitus)[b,i,k]	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation** Dry mouth**		
Skin and subcutaneous tissue disorders		Rash[j]			Angioedema
Musculoskeletal and connective tissue disorders		Back pain*			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia**		Tubulointerstitial nephritis

Reproductive system and breast disorders			Vulvovaginal pruritus** Pruritus genital**		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[h]	Blood creatinine increased during initial treatment[**,b] Blood urea increased** Weight decreased**		

[a]The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

[b]See corresponding subsection below for additional information.

[c]Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

[d]Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

[f]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

[g]Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus – 0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

[h]Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: 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%.

[j]Adverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.

[k]Reported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.

*Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

**Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the DECLARE study, the numbers of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

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

In the DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes.

Cases of phimosis/acquired phimosis have been reported concurrent with genital infections and in some cases, circumcision was required.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin (see section 4.4).

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

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in the clinical studies in diabetes mellitus.

For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia (see section 4.5).

In an add-on to glimepiride study, at weeks 24 and 48, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0% and 7.9%, respectively) than in the placebo plus glimepiride group (2.1% and 2.1%, respectively).

In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects treated with dapagliflozin 10 mg plus insulin at weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at weeks 24 and 104. At weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea.

In the DECLARE study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

In the DAPA-HF study, major events of hypoglycaemia were reported in 4 (0.2%) patients in both the dapagliflozin and placebo treatment groups. In the DELIVER study, major events of hypoglycaemia were reported in 6 (0.2%) patients in the dapagliflozin group and 7 (0.2%) in the placebo group. Major events of hypoglycaemia were only observed in patients with type 2 diabetes mellitus.

In the DAPA-CKD study, major events of hypoglycaemia were reported in 14 (0.7%) patients in the dapagliflozin group and 28 (1.3%) patients in the placebo group and observed only in patients with type 2 diabetes mellitus.

Volume depletion

In the 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo (see section 4.4).

In the DECLARE study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and angiotensin converting enzyme inhibitors (ACE-I)/angiotensin II type 1 receptor blockers (ARB) use. In patients with eGFR < 60 mL/min/1.73 m^2 at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

In the DAPA-HF study, the numbers of patients with events suggestive of volume depletion were 170 (7.2%) in the dapagliflozin group and 153 (6.5%) in the placebo group. There were fewer patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group (23 [1.0%]) compared with the placebo group (38 [1.6%]). Results were similar irrespective of presence of diabetes at baseline and baseline eGFR. In the DELIVER study, the numbers of patients with serious events of symptoms suggestive of volume depletion were 35 (1.1%) in the dapagliflozin group and 31 (1.0%) in the placebo group.

In the DAPA-CKD study, the numbers of patients with events suggestive of volume depletion were 120 (5.6%) in the dapagliflozin group and 84 (3.9%) in the placebo group. There were 16 (0.7%) patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 15 (0.7%) patients in the placebo group.

Diabetic ketoacidosis in type 2 diabetes mellitus

In the DECLARE study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 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 dapagliflozin 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).

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

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

Urinary tract infections

In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus 3.5%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

In the DECLARE study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

In the DAPA-HF study, the numbers of patients with serious adverse events of urinary tract infections were 14 (0.6%) in the dapagliflozin group and 17 (0.7%) in the placebo group. There were 5 (0.2%) patients with adverse events leading to discontinuations due to urinary tract infections in each of the dapagliflozin and placebo groups. In the DELIVER study the numbers of patients with serious adverse events of urinary tract infections were 41 (1.3%) in the dapagliflozin group and 37 (1.2%) in the placebo group. There were 13 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 9 (0.3%) in the placebo group.

In the DAPA-CKD study, the numbers of patients with serious adverse events of urinary tract infections were 29 (1.3%) in the dapagliflozin group and 18 (0.8%) in the placebo group. There were 8 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 3 (0.1%) in the placebo group. The numbers of patients without diabetes reporting serious adverse events of urinary tract infections or adverse events leading to discontinuation due to urinary tract infections were similar between treatment groups (6 [0.9%] versus 4 [0.6%] for serious adverse events, and 1 [0.1%] versus 0 for adverse events leading to discontinuation, in the dapagliflozin and placebo groups, respectively).

Increased creatinine

Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). In the 13-study safety pool, this grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 mL/min/1.73 m^2) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73 m^2 (18.5% dapagliflozin 10 mg versus 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 44 micromoles/L (≤ 0.5 mg/Dl) from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the DECLARE study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m^2), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

In the DAPA-HF and DELIVER studies, eGFR decreased over time in both the dapagliflozin group and the placebo group. In DAPA-HF, the initial decrease in mean eGFR was -4.3 mL/min/1.73 m^2 in the dapagliflozin group and -1.1 mL/min/1.73 m^2 in the placebo group. At 20 months, change from baseline in eGFR was similar between the treatment groups: -5.3

mL/min/1.73 m^2 for dapagliflozin and -4.5 mL/min/1.73 m^2 for placebo. In DELIVER, the decrease in mean eGFR at one month was -3.7 mL/min/1.73 m^2 in the dapagliflozin group and -0.4 mL/min/1.73 m^2 in the placebo group. At 24 months, change from baseline in eGFR was similar between treatment groups: -4.2 mL/min/1.73 m^2 in the dapagliflozin group and -3.2 mL/min/1.73 m^2 in the placebo group.

In the DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 m^2 in the dapagliflozin group and -0.8 mL/min/1.73 m^2 in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m^2 in the dapagliflozin group and -8.6 mL/min/1.73 m^2 in the placebo group.

Paediatric population

The dapagliflozin safety profile observed in a clinical study in children aged 10 years and above with type 2 diabetes mellitus (see section 5.1) was similar to that observed in the studies in adults.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

Overdose

There were no reports of overdose during the clinical development program for dapagliflozin. In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

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

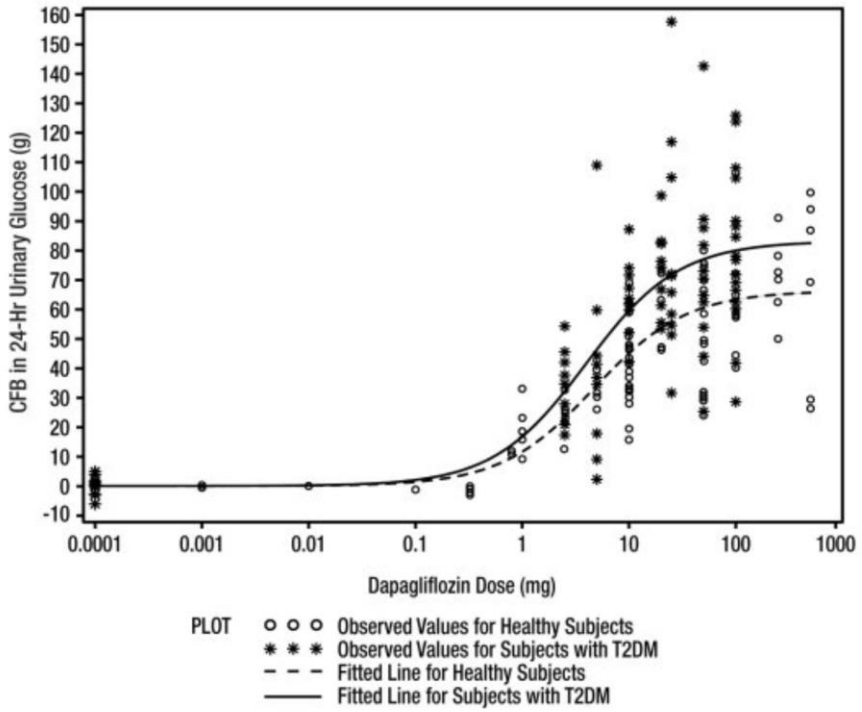
Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre-and afterload of the heart and downregulation of sympathetic activity.

Pharmacodynamics

General

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (see Figure 1). Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day at Week 12. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume (See section 4.8). After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.

Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-Hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM) (Semi-Log Plot)



Cardiac electrophysiology

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

Clinical studies

Glycemic Control in Patients with Type 2 Diabetes Mellitus

Overview of clinical studies of dapagliflozin for type 2 diabetes mellitus

Dapagliflozin has been studied as monotherapy, in combination with metformin, pioglitazone, sulfonylurea (glimepiride), sitagliptin (with or without metformin), metformin plus a sulfonylurea, or insulin (with or without other oral antidiabetic therapy), compared to a sulfonylurea (glipizide), and in combination with a GLP-1 receptor agonist (exenatide extended-release) added-on to metformin. dapagliflozin has also been studied in patients with type 2 diabetes mellitus and moderate renal impairment.

Treatment with dapagliflozin as monotherapy and in combination with metformin, glimepiride, pioglitazone, sitagliptin, or insulin produced statistically significant improvements in mean change from baseline at Week 24 in HbA1c compared to control. Reductions in HbA1c were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI).

Monotherapy

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

In 1 monotherapy study, a total of 558 treatment-naive patients with inadequately controlled diabetes participated in a 24-week study (NCT00528372). Following a 2-week diet and exercise placebo lead- in period, 485 patients with HbA1c ≥7% and ≤10% were randomized to dapagliflozin 5 mg or dapagliflozin 10 mg once daily in either the morning (QAM, main cohort) or evening (QPM), or placebo.

At Week 24, treatment with dapagliflozin 10 mg QAM provided significant improvements in HbA1c and the fasting plasma glucose (FPG) compared with placebo (see Table 5).

Table 5: Results at Week 24 (LOCF) in a Placebo-Controlled Study of dapagliflozin Monotherapy in Patients with Type 2 Diabetes Mellitus (Main Cohort AM Doses)*

Efficacy Parameter	**Dapagliflozin 10 mg N=70†**	**Dapagliflozin 5 mg N=64†**	**Placebo N=75†**
HbA1c (%)			
Baseline (mean)	8.0	7.8	7.8
Change from baseline (adjusted mean‡)	−0.9	−0.8	−0.2
Difference from placebo (adjusted mean‡) (95% CI)	−0.7§ (−1.0, −0.4)	−0.5 (−0.8, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	50.8%¶	44.2%¶	31.6%
FPG (mg/dL)			
Baseline (mean)	166.6	157.2	159.9
Change from baseline (adjusted mean‡)	−28.8	−24.1	−4.1

Table 5: Results at Week 24 (LOCF*) in a Placebo-Controlled Study of dapagliflozin Monotherapy in Patients with Type 2 Diabetes Mellitus (Main Cohort AM Doses)

Efficacy Parameter	Dapagliflozin 10 mg N=70†	Dapagliflozin 5 mg N=64†	Placebo N=75†
Difference from placebo (adjusted mean‡) (95% CI)	−24.7§ (−35.7, −13.6)	−19.9 (−31.3, −8.5)	

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

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

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 versus placebo. Sensitivity analyses yielded smaller estimates of treatment difference with placebo.

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

Initial Combination Therapy with Metformin XR

A total of 1236 treatment-naive patients with inadequately controlled type 2 diabetes mellitus (HbA1c ≥7.5% and ≤12%) participated in 2 active-controlled studies of 24-week duration to evaluate initial therapy with dapagliflozin 5 mg (NCT00643851) or 10 mg (NCT00859898) in combination with metformin extended-release (XR) formulation.

In 1 study, 638 patients randomized to 1 of 3 treatment arms following a 1-week lead-in period received: dapagliflozin 10 mg plus metformin XR (up to 2000 mg per day), dapagliflozin 10 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 10 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 6 and Figure 2). dapagliflozin 10 mg as monotherapy also provided statistically significant improvements in FPG and statistically significant reduction in body weight compared with metformin alone and was noninferior to metformin XR monotherapy in lowering HbA1c

Table 6: Results at Week 24 (LOCF[*]) in an Active-Controlled Study of dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter	**Dapagliflozin 10 mg + Metformin XR N=211[†]**	**Dapagliflozin 10 mg N=219[†]**	**Metformin XR N=208[†]**
HbA1c (%)			
Baseline (mean)	9.1	9.0	9.0
Change from baseline (adjusted mean[‡])	−2.0	−1.5	−1.4
Difference from dapagliflozin (adjusted mean[‡]) (95% CI)	−0.5[§] (−0.7, −0.3)		
Difference from metformin XR (adjusted mean[‡]) (95% CI)	−0.5[§] (−0.8, −0.3)	0.0 (−0.2[¶], 0.2)	
Percent of patients achieving HbA1c <7 % adjusted for baseline	46.6%[#]	31.7%	35.2%
FPG (mg/dL)			
Baseline (mean)	189.6	197.5	189.9
Change from baseline (adjusted mean[‡])	−60.4	−46.4	−34.8
Difference from dapagliflozin (adjusted mean[‡]) (95% CI)	−13. (−20.99[§], −7.0)		
Difference from metformin XR (adjusted mean[‡]) (95% CI)	−25. (−32.65[§], −18.5)	−11.6[#] (−18.6, −4.6)	
Body Weight (kg)			
Baseline (mean)	88.6	88.5	87.2
Change from baseline (adjusted mean[‡])	−3.3	−2.7	−1.4
Difference from metformin XR (adjusted mean[‡]) (95% CI)	−2.0[§] (−2.6, −1.3)	−1.4[§] (−2.0, −0.7)	

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

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

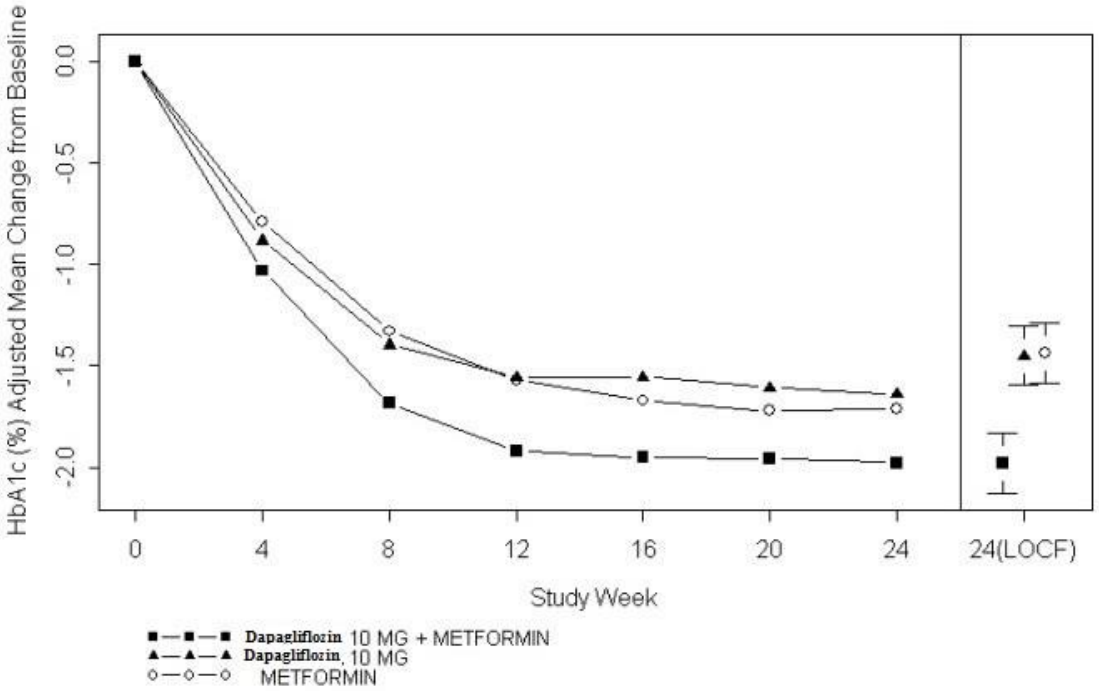
[‡] Least squares mean adjusted for baseline value.

[§] p-value <0.0001.

[¶] Noninferior versus metformin XR.

[#] p-value <0.05.

Figure 2: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Active- Controlled Study of dapagliflozin Initial Combination Therapy with Metformin XR



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed the study with both baseline and Week 24 HbA1c values without rescue.
Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

In a second study, 603 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: dapagliflozin 5 mg plus metformin XR (up to 2000 mg per day), dapagliflozin 5 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 5 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 7).

Table 7: Results at Week 24 (LOCF) in an Active-Controlled Study of dapagliflozin Initial Combination Therapy with Metformin XR*

Efficacy Parameter	**Dapagliflozin 5 mg + Metformin XR N=194**†	**Dapagliflozin 5 mg N=203**†	**Metformin XR N=201**†
HbA1c (%)			
Baseline (mean)	9.2	9.1	9.1
Change from baseline (adjusted mean‡)	−2.1	−1.2	−1.4
Difference from dapagliflozin (adjusted mean‡) (95% CI)	−0.9§ (−1.1, −0.6)		

Difference from metformin XR (adjusted mean‡) (95% CI)	−0.7§ (−0.9, −0.5)		
Percent of patients achieving HbA1c <7% adjusted for baseline	52.4%¶	22.5%	34.6%
FPG (mg/dL)			
Baseline (mean)	193.4	190.8	196.7
Change from baseline (adjusted mean‡)	−61.0	−42.0	−33.6
Difference from dapagliflozin (adjusted mean‡) (95% CI)	−19.1§ (−26.7, −11.4)		
Difference from metformin XR (adjusted mean‡) (95% CI)	−27.5§ (−35.1, −19.8)		
Body Weight (kg)			
Baseline (mean)	84.2	86.2	85.8
Change from baseline (adjusted mean‡)	−2.7	−2.6	−1.3
Difference from metformin XR (adjusted mean‡) (95% CI)	−1.4§ (−2.0, −0.7)		

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

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

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ p-value <0.05.

Add-On to Metformin

A total of 546 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled study to evaluate dapagliflozin in combination with metformin (NCT00528879). Patients on metformin at a dose of at least 1500 mg per day were randomized after completing a 2-week, single-blind, placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, dapagliflozin 10 mg provided statistically significant improvements in HbA1c and FPG, and statistically significant reduction in body weight compared with placebo at Week 24 (see Table 8 and Figure 3). Statistically significant (p <0.05 for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus metformin were −4.5 mmHg and −5.3 mmHg with dapagliflozin 5 mg and 10 mg plus metformin, respectively

Table 8: Results of a 24-Week (LOCF) Placebo-Controlled Study of dapagliflozin in Add-On Combination with Metformin*

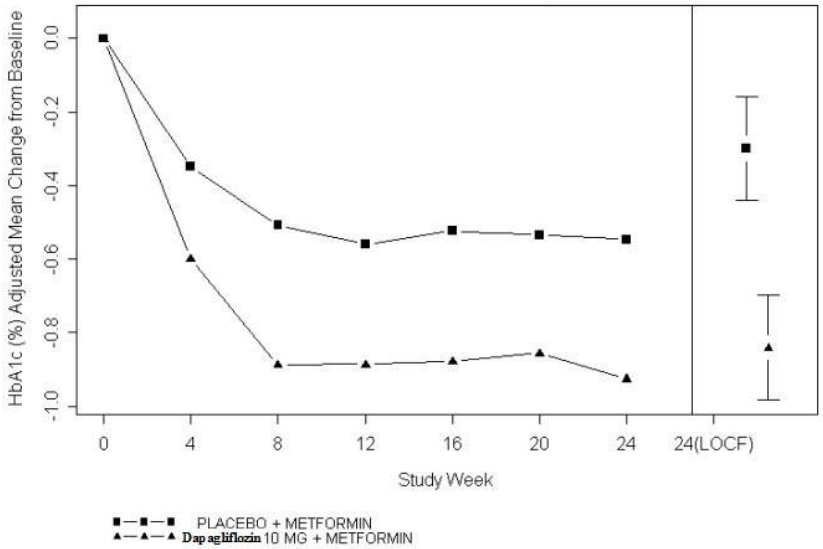
Efficacy Parameter	**Dapagliflozin 10 mg + Metformin N=135†**	**Dapagliflozin 5 mg + Metformin N=137†**	**Placebo + Metformin N=137†**
HbA1c (%)			
Baseline (mean)	7.9	8.2	8.1
Change from baseline (adjusted mean‡)	−0.8	−0.7	−0.3
Difference from placebo (adjusted mean‡) (95% CI)	−0.5§ (−0.7, −0.3)	−0.4§ (−0.6, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%¶	37.5%¶	25.9%
FPG (mg/dL)			
Baseline (mean)	156.0	169.2	165.6
Change from baseline at Week 24 (adjusted mean‡)	−23.5	−21.5	−6.0
Difference from placebo (adjusted mean‡) (95% CI)	−17.5§ (−25.0, −10.0)	−15.5§ (−22.9, −8.1)	
Change from baseline at Week 1 (adjusted mean‡)	−16.5§ (N=115)	−12.0§ (N=121)	1.2 (N=126)
Body Weight (kg)			
Baseline (mean)	86.3	84.7	87.7
Change from baseline (adjusted mean‡)	−2.9	−3.0	−0.9
Difference from placebo (adjusted mean‡) (95% CI)	−2.0§ (−2.6, −1.3)	−2.2§ (−2.8, −1.5)	

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001 versus placebo + metformin.

¶ p-value <0.05 versus placebo + metformin

Figure 3: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Placebo- Controlled Study of dapagliflozin in Combination with Metformin

Active Glipizide-Controlled Study Add-On to Metformin



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed Short-Term Period with both baseline and Week 24 HbA1c values without rescue. Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

A total of 816 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, glipizide-controlled, noninferiority study to evaluate dapagliflozin as add-on therapy to metformin (NCT00660907). Patients on metformin at a dose of at least 1500 mg per day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 mg or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and dapagliflozin 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down- titration to prevent hypoglycemia.

At the end of the titration period, 87% of patients treated with dapagliflozin had been titrated to the maximum study dose (10 mg) versus 73% treated with glipizide (20 mg). dapagliflozin led to a similar mean reduction in HbA1c from baseline at Week 52 (LOCF), compared with glipizide, thus demonstrating noninferiority (see Table 9). Dapagliflozin treatment led to a statistically significant mean reduction in body weight from baseline at Week 52 (LOCF) compared with a mean increase in body weight in the glipizide group. Statistically significant (p<0.0001) mean change from baseline in systolic blood pressure relative to glipizide plus metformin was −5.0 mmHg with dapagliflozin plus metformin. **Table 9: Results at Week 52 (LOCF*) in an Active-Controlled Study Comparing dapagliflozin to Glipizide as Add-On to Metformin**

Efficacy Parameter	**Dapagliflozin + N=401†**	**Glipizide + Metformin N=401†**

	Metformin N=400[†]	
HbA1c (%)		
Baseline (mean)	7.7	7.7

Change from baseline (adjusted mean‡)	−0.5	−0.5
Difference from glipizide + metformin (adjusted mean‡) (95% CI)	0.0§ (−0.1, 0.1)	
Body Weight (kg)		
Baseline (mean)	88.4	87.6
Change from baseline (adjusted mean‡)	−3.2	1.4
Difference from glipizide + metformin (adjusted mean‡) (95% CI)	−4.7¶ (−5.1, −4.2)	

* LOCF: last observation carried forward.
† Randomized and treated patients with baseline and at least 1 postbaseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
§ Noninferior to glipizide + metformin.
¶ p-value <0.0001.

Add-On Combination Therapy with Other Antidiabetic Agents *Add-On Combination Therapy with a Sulfonylurea*

A total of 597 patients with type 2 diabetes mellitus and inadequate glycemic control (HbA1c ≥7% and ≤10%) were randomized in this 24-week, placebo-controlled study to evaluate dapagliflozin in combination with glimepiride (a sulfonylurea) (NCT00680745).

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

In combination with glimepiride, dapagliflozin 10 mg provided statistically significant improvement in HbA1c, FPG, and 2-hour PPG, and statistically significant reduction in body weight compared with placebo plus glimepiride at Week 24 (see Table 10). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus glimepiride were −2.8 mmHg and −3.8 mmHg with dapagliflozin 5 mg and 10 mg plus glimepiride, respectively.

Add-on Combination Therapy with Metformin and a Sulfonylurea

A total of 218 patients with type 2 diabetes mellitus and inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week, placebo-controlled study to evaluate dapagliflozin in combination with metformin and a sulfonylurea (NCT01392677). Patients on a stable dose of metformin (immediate- or extended-release formulations) ≥1500 mg/day plus

maximum tolerated dose, which must be at least half the maximum dose, of a sulfonylurea for at least 8 weeks prior to enrollment were randomized after an 8week placebo lead-in period to dapagliflozin 10 mg or placebo. Dose-titration of dapagliflozin or metformin was not permitted during the 24–week treatment period. Down-titration of the sulfonylurea was permitted to prevent hypoglycemia, but no up-titration was permitted. As add-on treatment to combined metformin and a sulfonylurea, treatment with dapagliflozin 10 mg provided statistically significant improvements in HbA1c and FPG and statistically significant reduction in body weight compared with placebo at Week 24 (Table 10). A statistically significant ($p < 0.05$) mean change from baseline in systolic blood pressure relative to placebo in combination with metformin and a sulfonylurea was -3.8 mmHg with dapagliflozin 10 mg in combination with metformin and a sulfonylurea at Week 8.

Add-On Combination Therapy with a Thiazolidinedione

A total of 420 patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c ≥7% and
≤10.5%) participated in a 24-week, placebo-controlled study to evaluate dapagliflozin in combination with pioglitazone (a thiazolidinedione [TZD]) alone (NCT00683878). Patients on a stable dose of pioglitazone of 45 mg per day (or 30 mg per day, if 45 mg per day was not tolerated) for 12 weeks were randomized after a 2-week lead-in period to 5 or 10 mg of dapagliflozin or placebo in addition to their current dose of pioglitazone. Dose titration of dapagliflozin or pioglitazone was not permitted during the study.

In combination with pioglitazone, treatment with dapagliflozin 10 mg provided statistically significant improvements in HbA1c, 2-hour PPG, FPG, the proportion of patients achieving HbA1c

<7%, and a statistically significant reduction in body weight compared with the placebo plus pioglitazone treatment groups (see Table 10) at Week 24. A statistically significant (p <0.05) mean change from baseline in systolic blood pressure relative to placebo in combination with pioglitazone was −4.5 mmHg with dapagliflozin 10 mg in combination with pioglitazone.

Add-On Combination Therapy with a DPP4 Inhibitor

A total of 452 patients with type 2 diabetes mellitus who were drug naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycemic control (HbA1c ≥7.0% and ≤10.0% at randomization), participated in a 24-week, placebo-controlled study to evaluate dapagliflozin in combination with sitagliptin (a DPP4 inhibitor) with or without metformin (NCT00984867).

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

In combination with sitagliptin (with or without metformin), dapagliflozin 10 mg provided statistically significant improvements in HbA1c, FPG, and a statistically significant reduction in body weight compared with the placebo plus sitagliptin (with or without metformin) group at Week 24 (see Table 10). These improvements were also seen in the stratum of patients who received dapagliflozin 10 mg plus sitagliptin alone (placebo-corrected mean change for HbA1c −0.56%; n=110) compared with placebo plus sitagliptin alone (n=111), and the stratum of patients who received dapagliflozin 10 mg plus sitagliptin and metformin (placebo-corrected mean change for HbA1c −0.40; n=113) compared with placebo plus sitagliptin with metformin (n=113).

Add-On Combination Therapy with Insulin

A total of 808 patients with type 2 diabetes mellitus who had inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) were randomized in a 24-week, placebo-controlled study to evaluate dapagliflozin as add-on therapy to insulin (NCT00673231). Patients on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior to enrollment and on a maximum of 2 oral antidiabetic medications (OADs), including metformin, were

randomized after completing a 2-week enrollment period to receive either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable. Patients were stratified according to the presence or absence of background OADs. Up-or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycemic goals. Dose modifications of blinded study medication or OAD(s) were not allowed during the treatment phase, with the exception of decreasing OAD(s) where there were concerns over hypoglycemia after cessation of insulin therapy.

In this study, 50% of patients were on insulin monotherapy at baseline, while 50% were on 1 or 2 OADs in addition to insulin. At Week 24, dapagliflozin 10 mg dose provided statistically significant improvement in HbA1c and reduction in mean insulin dose, and a statistically significant reduction in body weight compared with placebo in combination with insulin, with or without up to 2 OADs (see Table 10); the effect of dapagliflozin on HbA1c was similar in patients treated with insulin alone and patients treated with insulin plus OAD. Statistically significant ($p<0.05$) mean change from baseline in systolic blood pressure relative to placebo in combination with insulin was −3.0 mmHg with dapagliflozin 10 mg in combination with insulin.

At Week 24, dapagliflozin 5 mg (−5.7 IU, difference from placebo) and 10 mg (−6.2 IU, difference from placebo) once daily resulted in a statistically significant reduction in mean daily insulin dose ($p<0.0001$ for both doses) compared to placebo in combination with insulin, and a statistically significantly higher proportion of patients on dapagliflozin 10 mg (19.6%) reduced their insulin dose by at least 10% compared to placebo (11.0%).

Table 10: Results of 24-Week (LOCF) Placebo-Controlled Studies of dapagliflozin in Combination with Antidiabetic Agents*

Efficacy Parameter	**Dapagliflozin 10 mg**	**Dapagliflozin 5 mg**	**Placebo**
In Combination with Sulfonylurea (Glimepiride)			
Intent-to-Treat Population	**N=151**†	**N=142**†	**N=145**†
HbA1c (%)			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean‡)	−0.8	−0.6	−0.1
Difference from placebo (adjusted mean‡) (95% CI)	−0.7§ (−0.9, −0.5)	−0.5§ (−0.7, −0.3)	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.7%§	30.3%§	13.0%
FPG (mg/dL)			
Baseline (mean)	172.4	174.5	172.7
Efficacy Parameter	**Dapagliflozin 10 mg**	**Dapagliflozin 5 mg**	**Placebo**
Change from baseline (adjusted mean‡)	−28.5	−21.2	−2.0
Difference from placebo (adjusted mean‡) (95% CI)	−26.5§ (−33.5, −19.5)	−19.3§ (−26.3, −12.2)	
2-hour PPG¶ (mg/dL)			
Baseline (mean)	329.6	322.8	324.1
Change from baseline (adjusted mean‡)	−60.6	−54.5	−11.5
Difference from placebo (adjusted mean‡) (95% CI)	−49.1§ (−64.1, −34.1)	−43.0§ (−58.4, −27.5)	
Body Weight (kg)			
Baseline (mean)	80.6	81.0	80.9
Change from baseline (adjusted mean‡)	−2.3	−1.6	−0.7
Difference from placebo (adjusted mean‡) (95% CI)	−1.5§ (−2.2, −0.9)	−0.8§ (−1.5, −0.2)	
In Combination with Metformin and a Sulfonylurea			
Intent-to-Treat Population	**N=108**†	-	**N=108**†
HbA1c (%)			
Baseline (mean)	8.08	-	8.24
Change from baseline (adjusted mean‡ #)	−0.86	-	−0.17
Difference from placebo (adjusted mean‡ #) (95% CI)	−0.69§ (−0.89, −0.49)	-	
Percent of patients achieving HbA1c <7% adjusted for	31.8%§	-	11.1%

baseline			
FPG (mg/dL)			
Baseline (mean)	167.4	-	180.3
Change from baseline (adjusted mean‡)	−34.2	-	−0.8
Difference from placebo (adjusted mean‡) (95% CI)	−33.5§ (−43.1, −23.8)		
Body Weight (kg)			
Baseline (mean)	88.57	-	90.07
Change from baseline (adjusted mean‡)	−2.65	-	−0.58
Difference from placebo (adjusted mean‡) (95% CI)	−2.07§ (−2.79, −1.35)	-	
In Combination with Thiazolidinedione (Pioglitazone)			
Intent-to-Treat Population	**N=140 Þ**	**N=141 Þ**	**N=139 Þ**
HbA1c (%)			
Baseline (mean)	8.4	8.4	8.3
Change from baseline (adjusted mean‡)	−1.0	−0.8	−0.4

Difference from placebo (adjusted mean‡) (95% CI)	−0.6§ (−0.8, −0.3)	−0.4§ (−0.6, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	38.8% ß	32.5% ß	22.4%
FPG (mg/dL)			
Baseline (mean)	164.9	168.3	160.7
Change from baseline (adjusted mean‡)	−29.6	−24.9	−5.5
Difference from placebo (adjusted mean‡) (95% CI)	−24.1§ (−32.2, −16.1)	−19.5§ (−27.5, −11.4)	
2-hour PPG¶ (mg/dL)			
Baseline (mean)	308.0	284.8	293.6
Change from baseline (adjusted mean‡)	−67.5	−65.1	−14.1
Difference from placebo (adjusted mean‡) (95% CI)	−53.3§ (−71.1, −35.6)	−51.0§ (−68.7, −33.2)	
Body Weight (kg)			
Baseline (mean)	84.8	87.8	86.4
Change from baseline (adjusted mean‡)	−0.1	0.1	1.6
Difference from placebo (adjusted mean‡) (95% CI)	−1.8§ (−2.6, −1.0)	−1.6§ (−2.3, −0.8)	
In Combination with DPP4 Inhibitor (Sitagliptin) with or without Metformin			
Intent-to-Treat Population	**N=223†**	**–**	**N=224†**
HbA1c (%)			
Baseline (mean)	7.90	–	7.97
Change from baseline (adjusted mean‡)	−0.45	–	0.04
Difference from placebo (adjusted mean‡) (95% CI)	−0.48§ (−0.62, −0.34)	–	
Patients with HbA1c decrease ≥0.7% (adjusted percent)	35.4%	–	16.6%
FPG (mg/dL)			
Baseline (mean)	161.7	–	163.1
Change from baseline at Week 24 (adjusted mean‡)	−24.1	–	3.8
Difference from placebo (adjusted mean‡) (95% CI)	−27.9§ (−34.5, −21.4)	–	
Body Weight (kg)			
Baseline (mean)	91.02	–	89.23
Change from baseline (adjusted mean‡)	−2.14	–	−0.26

In Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies			
Intent-to-Treat Population	**N=194**†	**N=211**†	**N=193**†
HbA1c (%)			
Baseline (mean)	8.6	8.6	8.5
Change from baseline (adjusted mean‡)	−0.9	−0.8	−0.3
Difference from placebo (adjusted mean‡) (95% CI)	−0.6§ (−0.7, −0.5)	−0.5§ (−0.7, −0.4)	
FPG (mg/dL)			
Baseline (mean)	173.7	NTà	170.0
Change from baseline (adjusted mean‡)	−21.7	NTà	3.3
Difference from placebo (adjusted mean‡) (95% CI)	−25.0§ (−34.3, −15.8)	NTà	
Body Weight (kg)			
Baseline (mean)	94.6	93.2	94.2
Change from baseline (adjusted mean‡)	−1.7	−1.0	0.0

Difference from placebo (adjusted mean‡) (95% CI)	−1.7§ (−2.2, −1.2)	−1.0§ (−1.5, −0.5)	

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

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

‡ Least squares mean adjusted for baseline value based on an ANCOVA model.

§ p-value <0.0001 versus placebo.

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

Least squares mean adjusted for baseline value based on a longitudinal repeated measures model.

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

ß p-value <0.05 versus placebo.

à NT: Not formally tested because of failing to achieve a statistically significant difference in an endpoint that was earlier in the testing sequence.

Combination Therapy with Exenatide-Extended Release as Add-On to Metformin

A total of 694 adult patients with type 2 diabetes mellitus and inadequate glycemic control (HbA1c ≥8.0 and ≤12.0%) on metformin, were evaluated in a 28-week double-blind, active-controlled study to compare dapagliflozin in combination with exenatide extended-release (a GLP-1 receptor agonist) to dapagliflozin alone and exenatide extended-release alone, as add-on to metformin (NCT02229396). Patients on metformin at a dose of at least 1,500 mg per day were randomized following a 1-week placebo lead-in period to receive either dapagliflozin 10 mg once daily (QD) in combination with exenatide extended-release 2 mg once weekly (QW), dapagliflozin 10 mg QD, or exenatide extended– release 2 mg QW.

At Week 28, dapagliflozin in combination with exenatide extended-release provided statistically significantly greater reductions in HbA1c (-1.77%) compared to dapagliflozin alone (-1.32%, p=0.001) and exenatide extended-release alone (-1.42%, p=0.012). Dapagliflozin in combination with exenatide extended-release provided statistically significantly greater reductions in FPG (-57.35 mg/dL) compared to dapagliflozin alone (-44.72 mg/dL, p=0.006) and exenatide extended-release alone (-40.53, p <0.001).

Use in Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment

Dapagliflozin was assessed in two placebo-controlled studies of

patients with type 2 diabetes mellitus and moderate renal impairment.

Patients with type 2 diabetes mellitus and an eGFR between 45 to less than 60 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy participated in a 24-week, double-blind, placebo- controlled clinical study (NCT02413398). Patients were randomized to either dapagliflozin 10 mg or placebo, administered orally once daily. At Week 24, dapagliflozin provided statistically significant reductions in HbA1c compared with placebo (Table 11).

Table 11: Results at Week 24 of Placebo-Controlled Study for dapagliflozin in Patients with Type 2 Diabetes Mellitus and Renal Impairment (eGFR 45 to less than 60 mL/min/ 1.73 m^2)

	Dapagliflozin 10 mg	**Placebo**
Number of patients:	**N=160**	**N=161**
HbA1c (%)		
Baseline (mean)	8.3	8.0
Change from baseline (adjusted mean*)	-0.4	-0.1
Difference from placebo (adjusted mean*) (95% CI)	-0.3† (-0.5, -0.1)	

* Least squares mean adjusted for baseline value; at Week 24, HbA1c was missing for 5.6% and 6.8% of individuals treated with dapagliflozin and placebo, respectively. Retrieved dropouts, i.e. observed HbA1c at Week 24 from subjects who discontinued treatment, were used to impute missing values in HbA1c.

† p-value =0.008 versus placebo.

Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Dapagliflozin Effect on Cardiovascular Events (DECLARE, NCT01730534) was an international, multicenter, randomized, double-blind, placebo-controlled, clinical study conducted to determine the effect of dapagliflozin relative to placebo on CV outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either established CVD or two or more 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). Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

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

Approximately 80% of the trial population was White, 4% Black or African-American, and 13% Asian. The mean age was 64 years, and approximately 63% were male.

Mean duration of diabetes was 11.9 years and 22.4% of patients had diabetes for less than 5 years. Mean eGFR was 85.2 mL/min/1.73 m^2. At baseline, 23.5% of patients had microalbuminuria (UACR ≥30 to ≤300 mg/g) and 6.8% had macroalbuminuria (UACR >300 mg/g). Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2. At baseline, 10% of patients had a history of heart failure.

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 receptor agonist.

Approximately 81.3% of patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 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.

A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio (HR) of the composite of CV death, myocardial infarction (MI), or ischemic stroke [MACE] and to test for superiority on the dual primary endpoints: the composite of hospitalization for heart failure or CV death, and MACE, if non-

inferiority was demonstrated.

The incidence rate of MACE was similar in both treatment arms: 2.3 MACE events per 100 patient- years on dapagliflozin vs. 2.46 MACE events per 100 patient-years on placebo. The estimated hazard ratio of MACE associated with dapagliflozin relative to placebo was 0.93 with a 95.38% confidence interval of (0.84,1.03). The upper bound of this confidence interval, 1.03, excluded a risk margin larger than 1.3.

Dapagliflozin was superior to placebo in reducing the incidence of the primary composite endpoint of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]).

The treatment effect was due to a significant reduction in the risk of hospitalization for heart failure in subjects randomized to dapagliflozin (HR 0.73 [95% CI 0.61, 0.88]), with no change in the risk of CV death (Table 12 and Figures 4 and 5).

Table 12: Treatment Effects for the Primary Endpoints and Their Components* in the DECLARE Study*

	Patients with events n (%)	

Efficacy Variable (time to first occurrence)	**Dapagliflozin 10 mg N=8582**	**Placebo N=8578**	**Hazard ratio (95% CI)**
Primary Endpoints			
Composite of Hospitalization for Heart Failure, CV Death†	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)
Composite Endpoint of CV Death, MI, Ischemic Stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)
Components of the composite endpoints‡			
Hospitalization for Heart Failure	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)
CV Death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)
Myocardial Infarction	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)
Ischemic Stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)

N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction.

*Full analysis set.

† p-value =0.005 versus placebo.

‡ total number of events presented for each component of the composite endpoints

Figure 4: Time to First Occurrence of Hospitalization for Heart Failure or CV Death in the DECLARE Study

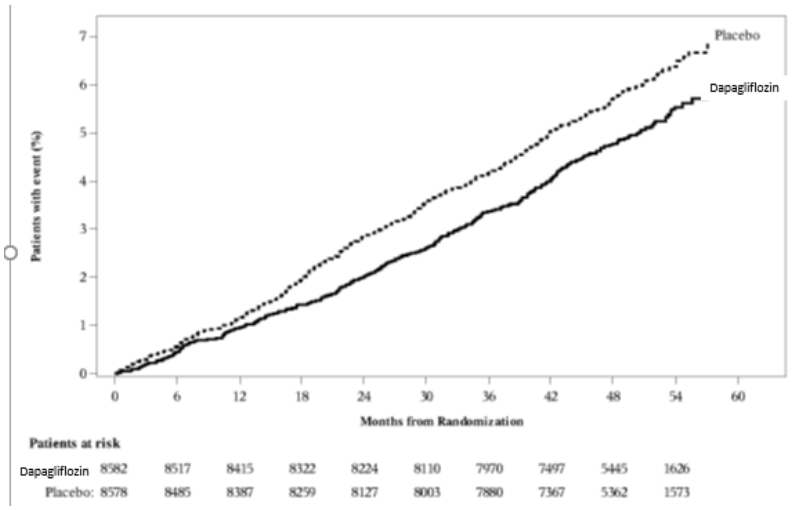
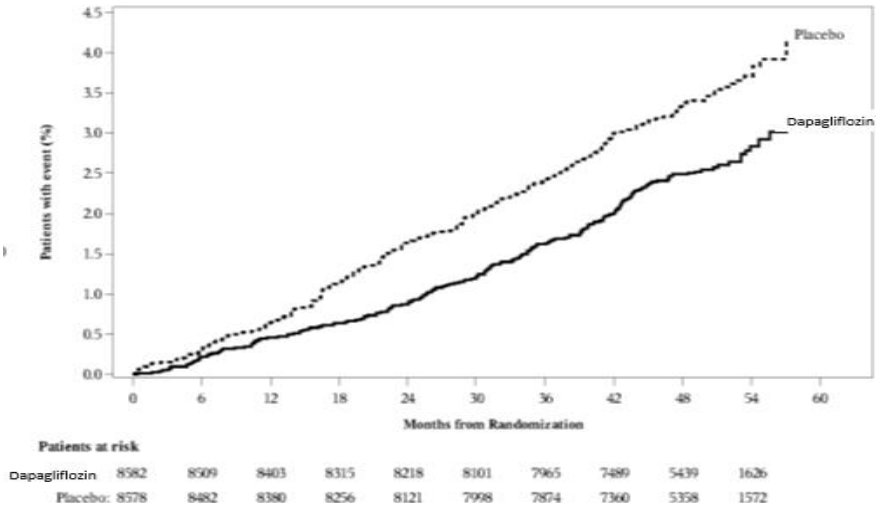


Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Study



Heart failure with reduced ejection fraction

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF, NCT03036124) 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% or less) to determine whether dapagliflozin reduces the risk of cardiovascular death and hospitalization for heart failure.

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

At baseline, 68% patients were classified as NYHA class II, 32% class III, and 1% class IV; median LVEF was 32%. History of type 2 diabetes mellitus was present in 42%, and an additional 3% had type 2 diabetes mellitus based on a HbA1c ≥6.5% at both enrollment and randomization.

At baseline, 94% of patients were treated with ACEi, ARB or angiotensin receptor-neprilysin inhibitor (ARNI, including sacubitril/valsartan 11%), 96% with beta-blocker, 71% with mineralocorticoid receptor antagonist (MRA), 93% with diuretic, and 26% had an implantable device.

Dapagliflozin 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). All three components of the primary composite endpoint individually contributed to the treatment effect. The dapagliflozin and placebo event curves separated early and continued to diverge over the study period (Table 13, Figures 6A, 6B and 6C).

Table 13: Treatment Effect for the Primary Composite Endpoint, its Components* and All- Cause Mortality in the DAPA-HF Study*

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**Dapagliflozin 10 mg N=2373**	**Placebo N=2371**	**Hazard ratio (95% CI)**	**p-value†**
Composite of Hospitalization for Heart Failure, CV Death or Urgent Heart Failure Visit	386 (11.6)	502 (15.6)	0.74 (0.65, 0.85)	<0.0001
Composite of CV Death or Hospitalization for Heart Failure	382 (11.4)	495 (15.3)	0.75 (0.65, 0.85)	<0.0001
Components of the composite endpoints				
CV Death	227 (6.5)	273 (7.9)		

Hospitalization for Heart Failure or Urgent Heart Failure Visit	237 (7.1)	326 (10.1)		
Hospitalization for Heart Failure	231 (6.9)	318 (9.8)		

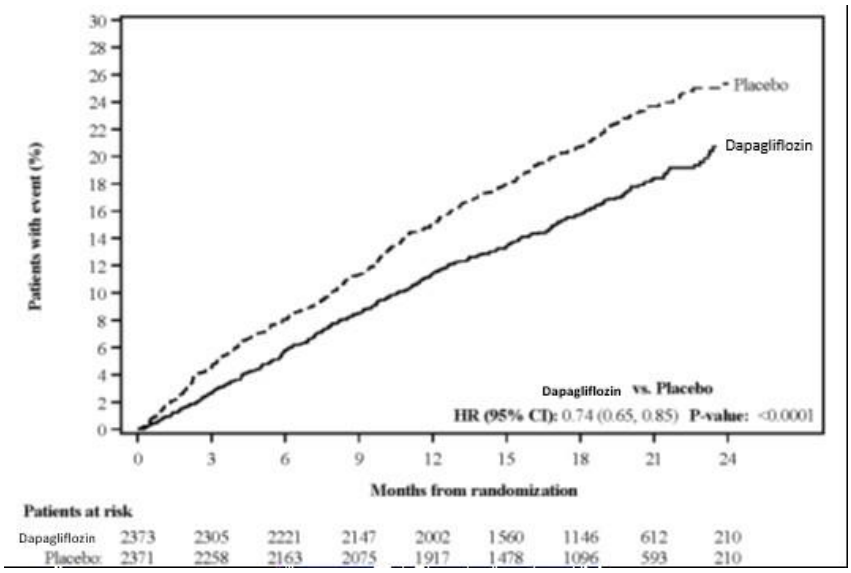
Table 13: Treatment Effect for the Primary Composite Endpoint*, its Components* and All-Cause Mortality in the DAPA-HF Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**Dapagliflozin 10 mg N=2373**	**Placebo N=2371**	**Hazard ratio (95% CI)**	**p-value**
Urgent Heart Failure Visit	10 (0.3)	23 (0.7)	0.43 (0.20, 0.90)	
All-Cause Mortality	276 (7.9)	329 (9.5)	0.83 (0.71, 0.97)	

N=Number of patients, CI=Confidence interval, CV=Cardiovascular.
*Full analysis set.
† Two-sided p-values. NOTE: 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. Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

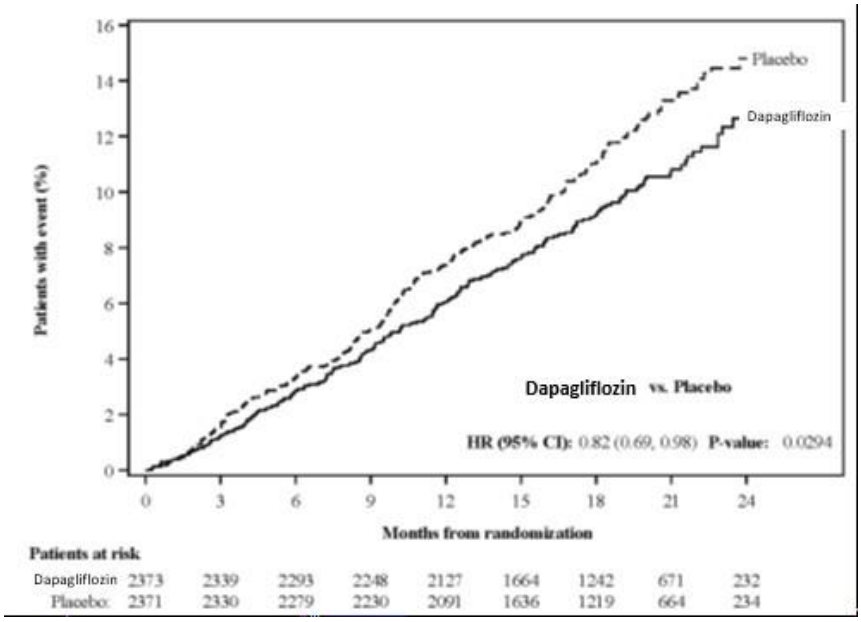
Figure 6: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C)

Figure 6A: Time to the First Occurrence of the Composite of Cardiovascular Death, Hospitalization for Heart Failure or Urgent Heart Failure Visit



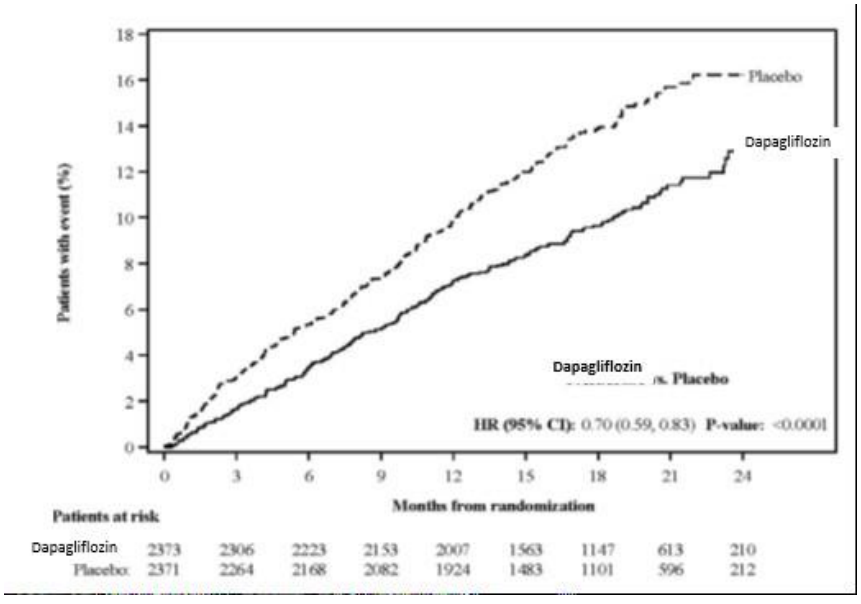
NOTE: An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician,
e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics). Patients at risk is the number of patients at risk at the beginning of the period. HR=Hazard ratio, CI=Confidence interval.

Figure 6B: Time to the First Occurrence of Cardiovascular Death



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

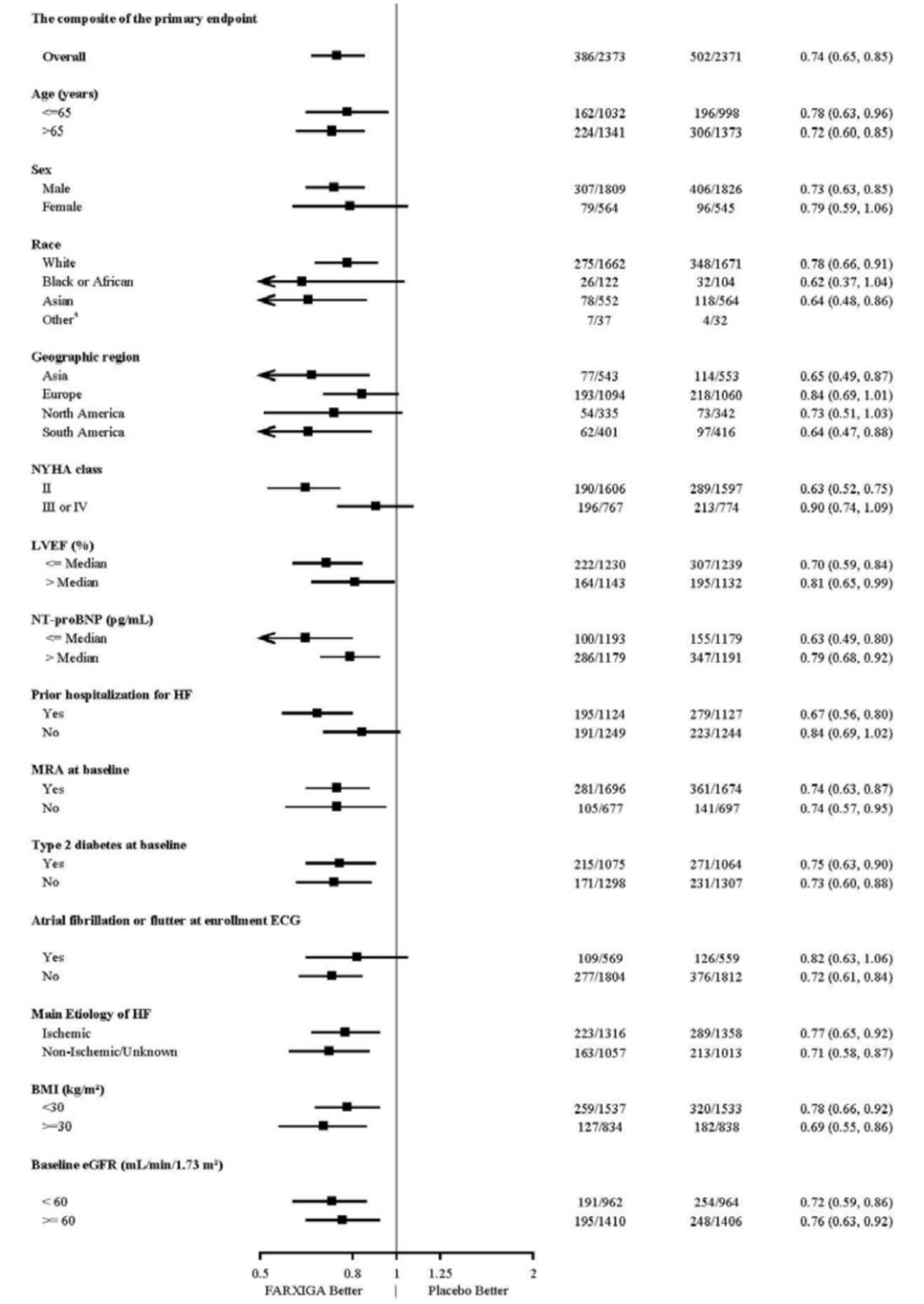
Figure 6C: Time to the First Occurrence of Heart Failure Hospitalization



Dapagliflozin reduced the total number of hospitalizations for heart failure (first and recurrent) events and CV death, with 567 and 742 total events in the dapagliflozin -treated vs placebo group (Rate Ratio 0.75 [95% CI 0.65, 0.88]; p=0.0002).

The results of the primary composite endpoint were consistent across the subgroups examined, including heart failure patients with and without type 2 diabetes mellitus (Figure 7).

Figure 7: Treatment Effects for Primary Composite Endpoint (Cardiovascular Death and Heart Failure Events) Subgroup Analysis (DAPA-HF Study)



[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, MRA = mineralocorticoid receptor antagonist,

ECG = electrocardiogram, eGFR = estimated glomerular filtration rate.

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over- interpreted.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metabolism

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Specific Populations

Renal Impairment

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes mellitus with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes mellitus and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patients with type 2 diabetes mellitus with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known (See sections 4.2, 4.4, and 5.1)

Hepatic Impairment

In subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean Cmax and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Effects of Age, Gender, Race, and Body Weight on Pharmacokinetics

Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.

Pediatric

Pharmacokinetics in the pediatric population has not been

studied.

Elderly (≥ 65 years)

There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. 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.

Gender

The mean dapagliflozin AUC_{ss} in females was estimated to be about 22% higher than in males.

Race

There were no clinically relevant differences in systemic exposures between White, Black or Asian races.

Body weight

Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72-times (males) and 105-times (females) the clinical dose of 10 mg per day, based on AUC exposure. In rats, the highest dose was approximately 131-times (males) and 186-times (females) the clinical dose of 10 mg per day, based on AUC exposure.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of in vitro clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of in vivo studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose.
There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline cellulose
Copovidone
Isopropyl Alcohol
Anhydrous Lactose
Silicon Dioxide
Magnesium Stearate
Opadry II Complete Film Coating System 85F94333 Pink
Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

24 Months

6.4 Special Precautions for storage

Store in tightly closed container at a temperature not exceeding 30°C.

6.5 Nature and Content of container

30 tablets in HDPE container

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. Marketing Authorization Holder

Cipla Limited
Cipla House,
Peninsula Business Park,
Ganpatrao Kadam Marg, Lower Parel, Mumbai – 400 013, India
Tel: (9122) 24826000
Fax: (9122) 24826120

8. Marketing Authorization Number

H2024/CTD9450/20665

9. Date of first authorization/renewal of the authorization

30/07/2024

10. Date of revision of the text

11/05/2025