SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GLYDA 10 (Dapagliflozin Tablets 10mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of Dapagliflozin.

3. PHARMACEUTICAL FORM

Tablets

GLYDA 10mg (Dapagliflozin Tablets 10mg)

Pink, round, biconvex, film-coated tablets de-bossed with “D33” on one side and “H” on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Dapagliflozin Tablets is indicated sections or subsections omitted from the full prescribing information are not listed. 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 either established cardiovascular disease or multiple cardiovascular risk factors. 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. To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

4.2 Posology and method of administration

Prior to Initiation of Dapagliflozin Tablets

Assess renal function prior to initiation of Dapagliflozin Tablets therapy and then as clinically indicated

Assess volume status and, if necessary, correct volume depletion prior to initiation of Dapagliflozin

Recommended Dosage

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1: Recommended Dosage

eGFR (mL/min/1.73 m^2)	Recommended Dose

eGFR 45 or greater	To improve glycemic control, the recommended starting dose is 5 mg orally once daily. Dose can be increased to 10 mg orally once daily for additional glycemic control. For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	10 mg orally once daily*.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

* Dapagliflozin Tablets is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m. Dapagliflozin Tablets is likely to be ineffective in this setting based upon its mechanism of action.

4.3 Contraindications

- History of a serious hypersensitivity reaction to Dapagliflozin Tablets, such as anaphylactic reactions or angioedema .
- Patients on dialysis.

4.4 Special warnings and precautions for use

- **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 Tablets. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. Fatal cases of ketoacidosis have been reported in patients taking Dapagliflozin Tablets. Dapagliflozin is not indicated for the treatment of patients with type 1 diabetes mellitus.

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.

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.

- **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 m), 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.

- **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.

- **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 . 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. Monitor and treat appropriately.

4.5 Undesirable effects

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

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

- **Clinical Studies 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, in patients with heart failure, and in patients with chronic kidney disease. 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.

- **Clinical Trials in Patients with Type 2 Diabetes Mellitus**

  Pool of 12 Placebo-Controlled Studies for Dapagliflozin 5 and 10 mg for Glycemic Control

  The data in Table 2 is derived from 12 glycemic control placebo-controlled studies in patients with type 2 diabetes mellitus ranging from 12 to 24 weeks. In 4 studies Dapagliflozin was used as monotherapy, and in 8 studies Dapagliflozin was used as add-on to background antidiabetic therapy or as combination therapy with metformin.

  These data reflect exposure of 2338 patients to Dapagliflozin with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), Dapagliflozin 5 mg (N=1145), or Dapagliflozin 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean hemoglobin A1c (HbA1c) of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately Ketoacidosis in Patients with Diabetes Mellitus Volume Depletion Urosepsis and Pyelonephritis Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) Genital Mycotic Infections 2 impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m).

  Table 2 shows common adverse reactions associated with the use of Dapagliflozin. These adverse reactions were not present at baseline, occurred more commonly on Dapagliflozin than on placebo, and occurred in at least 2% of patients treated with either Dapagliflozin 5 mg or Dapagliflozin 10 mg.

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control Reported in ≥2% of Patients Treated with Dapagliflozin

Adverse Reaction	**% of Patients**		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	**Dapagliflozin 5 mg N=1145**	**Dapagliflozin 10mg N=1193**
Female genital mycotic infections	1.5	8.4	8.4
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination	1.7	2.9	3.8
Male genital mycotic infections	0.3	2.8	2.7
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1

Pain in extremity	1.4	2.0	1.7

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, Dapagliflozin 5mg=581, Dapagliflozin 10 mg=598).

†Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

‡ increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716, DAPAGLIFLOZIN 5 mg=564, DAPAGLIFLOZIN 10 mg=595).

Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg for Glycemic Control

Dapagliflozin 10 mg was also evaluated in a larger glycemic control placebo-controlled study pool in patients with type 2 diabetes mellitus. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with Dapagliflozin 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m).

- **Volume Depletion**

Dapagliflozin causes an osmotic diuresis, which may lead to a reduction in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) in patients with type 2 diabetes mellitus for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3 .

Table 3: Adverse Reactions Related to Volume Depletion in Clinical Studies in Patients with Type 2 Diabetes Mellitus with Dapagliflozin

	Pool of 12 Placebo controlled studies			Pool of 13 Placebo controlled studies		Declaration Study	
	Placebo	**Dapagliflozin 5 mg**	**Dapagliflozin10 mg**	**Placbo**	**Dapagliflozin10 mg**	**Placebo**	**Dapagliflozin10 mg**
Overall Population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=551 (1.8%)	n=400	n=313 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)	n=934 57 (6.1%)	n=866 57 (6.6%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m2	n=1072 (1.9%)	n=1071 (0.9%)	n=891 (1.1%)	n=2684 (1.5%)	n=2655 (1.9%)	n=658 30 (4.6%)	n=60435 (5.8%)
Patients ≥65 years of age	n=2761 (0.4%)	n=2161 (0.5%)	n=2043 (1.5%)	n=7116 (0.8%)	n=66511 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

- **Hypoglycemia**

  The frequency of hypoglycemia by study in patients with type 2 diabetes mellitus is shown in Table 4. Hypoglycemia was more frequent when Dapagliflozin was added to sulfonylurea or insulin

Table 4: Incidence of Severe Hypoglycaemia and Hypoglycaemia with Glucose <54mg/dL in controlled Glycaemic Control Clinical Studies in Patients with type 2 Diabetes Mellitus

	Placebo/Active Control	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**
Monotherapy (24 weeks)	**N=75**	**N=64**	**N=70**
Severe [n (%)]	0	0	0
Glucose<54 mg/dL [n (%)]	0	0	0
Add-on to Metformin (24 weeks)	**N=137**	**N=137**	**N=135**
Severe [n (%)]	0	0	0
Glucose < 54mg/dL [n(%)]	0	0	0
Add-on to Glimepiride (24 weeks)	**N=146**	**N=145**	**N=151**
Severe [n (%)]	0	0	0
Glucose < 54mg/dL [n(%)]	1 (0.7)	3 (2.1)	5 (3.3)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	**N=109**	**-**	**N=109**
Severe [n (%)]	0	**-**	0
Glucose < 54mg/dL [n(%)]	3 (2.8)	**-**	7(6.4)
Add-on to Pioglitazone (24 weeks)	**N=139**	**N=141**	**N=140**
Severe [n (%)]	0	0	0
Glucose < 54mg/dL [n(%)]	0	**1 (0.7)**	0
Add-on to DPP4 inhibitor (24 weeks)	**N=226**	**-**	**N=225**
Severe [n (%)]	0	**-**	1 (0.4)
Glucose < 54mg/dL [n(%)]	1 (0.4)	**-**	1 (0.4)
Add-on to Insulin with or without other OADs (24 weeks)	**N=197**	**N=212**	**N=196**
Severe [n (%)]	1 (0.5)	2 (0.9)	2 (1.0)
Glucose < 54mg/dL [n(%)]	43 (21.8)	55 (25.9)	45 (23.0)

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level. Episodes of hypoglycemia with glucose level.

† Episodes of hypoglycemia with glucose <54 mg/dL (3mmol/L) were defined as reported epsiodes of hypoglycema meeting the glucose criteria that did not qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with Dapagliflozin and 83 (1.0%) out of 8569 patients treated with placebo.

- **Genital Mycotic Infections**

In the glycemic control trials, genital mycotic infections were more frequent with Dapagliflozin treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on Dapagliflozin 5 mg, and 4.8% on Dapagliflozin 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with Dapagliflozin 10 mg. Infections were more frequently reported in females than in males. The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, Dapagliflozin 5 mg, and Dapagliflozin 10 mg, respectively). In the DECLARE study, serious genital mycotic infections were reported in <0.1% of Patients treated with Dapagliflozin and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% patients treated with Dapagliflozin and <0.1% of patients treated with placebo.

- **Hypersensitivity Reactions**

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with Dapagliflozin treatment. In glycemic control studies, serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of Dapagliflozin -treated patients. If hypersensitivity reactions occur, discontinue use of Dapagliflozin; treat per standard of care and monitor until signs and symptoms resolve.

- **Ketoacidosis in Patients with Diabetes Mellitus**

In the DECLARE study and Clinical Studies (14.2)], events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the Dapagliflozin -treated group and 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

- **Laboratory Tests**

Increases in Serum Creatinine and Decreases in eGFR

Initiation of SGLT2 inhibitors, including Dapagliflozin causes a small increase in serum creatinine and decrease in eGFR. These changes in serum creatinine and eGFR generally occur within two weeks of starting therapy and then stabilize regardless of baseline kidney function. Changes that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury. In two studies that included patients with type 2 diabetes mellitus with moderate renal impairment, the acute effect on eGFR reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with Dapagliflozin.

Increase in Hematocrit

In the pool of 13 placebo-controlled studies of glycemic control, increases from baseline in mean hematocrit values were observed in Dapagliflozin -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 −0.33% in the placebo group and 2.30% in the Dapagliflozin 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of Dapagliflozin 10 mg-treated patients.

Increase in Low-Density Lipoprotein Cholesterol

In the pool of 13 placebo-controlled studies of glycemic control, changes from baseline in mean lipid values were reported in Dapagliflozin -treated patients compared to placebotreated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and Dapagliflozin 10 mg groups, respectively. In the DECLARE study , mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and 2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in Dapagliflozin -treated and the placebo groups, respectively.

Decrease in Serum Bicarbonate

In a study of concomitant therapy of Dapagliflozin 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the Dapagliflozin and exenatide-extended release treatment groups.

DAPA-HF Heart Failure Study

No new adverse reactions were identified in the DAPA-HF heart failure study.

DAPA-CKD Chronic Kidney Disease Study

No new adverse reactions were identified in the DAPA-CKD study in patients with chronic kidney disease.

4.6 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of Dapagliflozin in patients with diabetes mellitus. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene)
- Rash

4.7 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

- **Mechanism of Action**

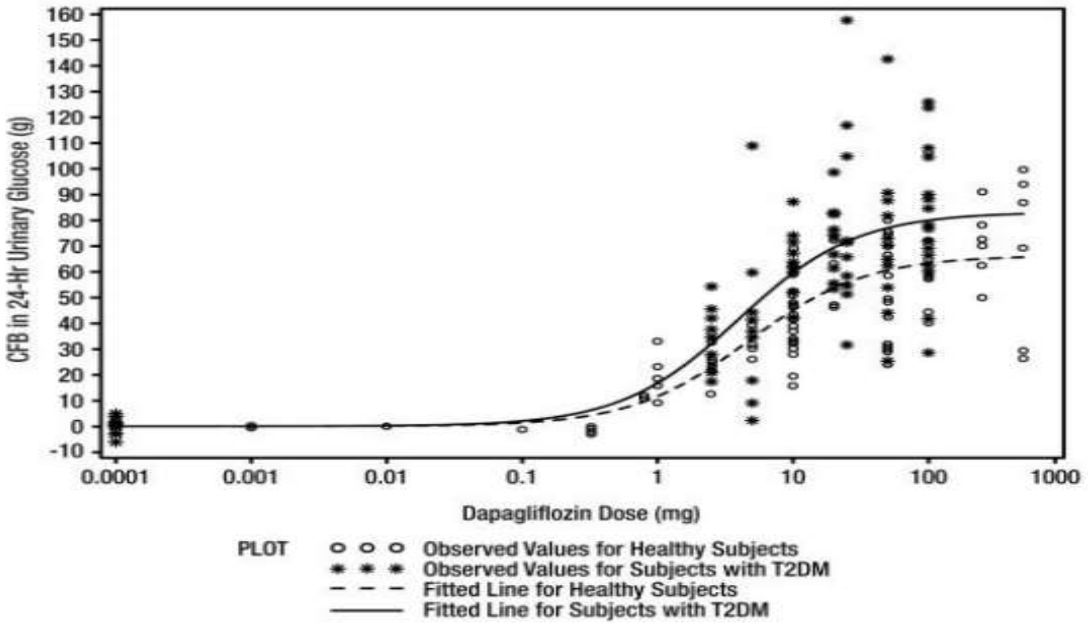
  Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, Dapagliflozin reduces reabsorption of filtered glucose and thereby promotes 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, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.

5.2 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 . 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. 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.

5.3 Pharmacokinetics

Absorption

Following oral administration of Dapagliflozin, the maximum plasma concentration (C) is usually attained within 2 hours under fasting state. The C and AUC values increase max max 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 C by up to 50% and prolongs T by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered 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 [C]- 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 [C]-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 (t) 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%, 100%, and 200% higher, respectively, as compared to patients with type 2 diabetes mellitus with normal renal function. There was no meaningful difference in exposure between patients with chronic kidney disease with and without type 2 diabetes. 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, Warnings and Precautions (5.2), Use in Specific Populations (8.6), and Clinical Studies.

Hepatic Impairment

In subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean C and AUC of Dapagliflozin were up to 12% and 36% higher, respectively, as max 14 14 ½ max compared to healthy matched control subjects following single-dose administration of 10 mg Dapagliflozin. These differences were not considered clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean C 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.

Drug Interactions

In Vitro Assessment of Drug Interactions

In in vitro studies, Dapagliflozin and Dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and Dapagliflozin 3-Oglucuronide 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.

Effects of Other Drugs on Dapagliflozin

Table 6 shows the effect of coadministered drugs on the pharmacokinetics of Dapagliflozin. No dose adjustments are recommended for Dapagliflozin.

Table 6: Effects of Co-administered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	**Dapagliflozin(Dose Regimen)***	**Effect on Coadministered Drug Exposure (%Change [90% CI])**	
		C_{max}	**AUC†**
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	↔	↔
Pioglitazone (45 mg)	50mg	↔	↔
Sitagliptin (100 mg)	20mg	↔	↔
Glimepiride (4 mg)	20mg	↔	↔
Voglibose (0.2 mg three times daily)	10mg	↔	↔
Other Medications			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10 mg once daily for 7 days	↔	↔
Valsartan (320 mg)	20mg	↓12% [↓3%, ↓20%]	↔
Simvastatin (40 mg)	20mg	↔	↔

Anti-infective Agent			
Rifampin (600 mg once daily for 6 days)	10mg	↓7% [↓22%, ↑11%]	↓22% [↓27%, ↓17%]
Nonsteroidal Anti-inflammatory Agent			
Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10mg	↑13% [↑3%, ↑24%]	↑51% [↑44%, ↑58%]

↔ = no change (geometric mean ratio of test: reference within 0.80 to 1.25); ↓ or ↑ = Parameter was lower or higher, respectively, with co-administration compared to Dapagliflozin administered alone (geometric mean ratio of test: reference was lower than 0.80 or higher than 1.25)

* Single dose unless otherwise noted.

† AUC = AUC (INF) for drugs given as single dose and AUC = AUC (TAU) for drugs given in multiple Doses.

Effects of Dapagliflozin on Other Drugs

Table 7 shows the effect of Dapagliflozin on other co-administered drugs. Dapagliflozin Did not meaningfully affect the pharmacokinetics of the coadministered drugs.

Table 7: Effects of Dapagliflozin on the Systemic Exposures of Co-administered Drugs

Coadministered Drug (Dose Regimen)*	**Dapagliflozin(Dose Regimen)***	**Effect on Coadministered Drug Exposure (% Change [90% CI])**	
		C_{max}	**AUC†**
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	↔	↔
Pioglitazone (45 mg)	50mg	↓7% [↓25%, ↑15%]	↔
Sitagliptin (100 mg)	20mg	↔	↔
Glimepiride (4 mg)	20mg	↔	↑13% [0%, ↑29%]
Other Medications			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10 mg once daily for 7 days	↑13% [↓2%, ↑31%]	↑13% [↓1%, ↑30%]
Valsartan (320 mg)	20mg	↓6% [↓24%, ↑16%]	↑5% [↓15%, ↑29%]
Simvastatin (40 mg)	20mg	↔	↑19%

Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	↔	↔
Warfarin (25 mg)	20 mg loading dose then 10 mg once daily for 7 days	↔	↔

↔ = no change (geometric mean ratio of test: reference within 0.80 to 1.25); ↓ or ↑ = parameter was lower or higher, respectively, with co-administration compared to the other medicine administered alone (geometric mean ratio of test: reference was lower than 0.80 or higher than 1.25).

* Single dose unless otherwise noted.

† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

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.

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 Single dose unless otherwise noted. AUC = AUC(INF)

for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses. 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.

Table 8: 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 (95% CI)	−0.7§ (−1.0, −0.4)	−0.5 (−0.8,	
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
Difference from placebo (adjusted (95% CI)	−24.7§ (−35.7, −13.6)	−19.9 (−31.3,	

* 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. 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 9: 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**	**Dapagliflozin 10mg**	**Metformin XR**
	N=211†	**N=219†**	**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)	−13.9§ (−20.9, −7.0)		
Difference from metformin XR (adjusted mean‡) (95% CI)	−25.5§ (−32.6, −18.5)	−11.6 (−18.6, −4.6)	
Body Weight (kg)			
Baseline (mean)	88.6	88.5	87.2
Change from baseline (adjusted	−3.3		−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.

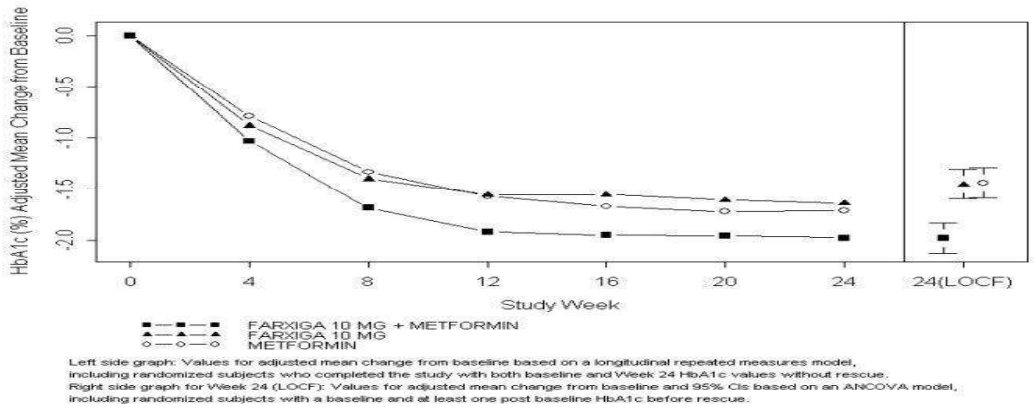
‡ Least squares mean adjusted for baseline value.

§ 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



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.

Table 10: Results at Week 24 (LOCF) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter	**Dapagliflozin5 mg+ Metformin XR**	**Dapagliflozin 5 mg**	**Metformin XR**
	N=194†	**N=203**	**N=201†**
HbA1c (%)			
Baseline (mean)	9.2	9.1	9.1
Change from baseline	−2.1	−1.2	−1.4
Difference from (95% CI)	−0.9§ (−1.1, −0.6)		
Difference from mean‡) (95% CI)	−0.7§ (-0.9, -0.5)		
Percent of patients achieving HbA1c <7%	52.4%¶	22.5%	34.6%
FPG (mg/dL)			
Baseline (mean)	193.4	190.8	196.7
Change from baseline	-61.0	-42.0	-33.6
Difference from (95% CI)	-19.1§ (-26.7, -11.4)		
Difference from mean‡) (95% CI)	-27.5§ (-35.1, -19.8)		
Body Weight (kg)			
Baseline (mean)	84.2	86.2	85.8
Change from baseline	-2.7	-2.6	-1.3
Difference from 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, singleblind, 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. 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 11: Results of a 24-Week (LOCF) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin

Efficacy Parameter	Dapagliflozin 10mg + Metformin N=135†	Dapagliflozin 5mg + 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 (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 (95% CI)	-17.5§ (-25.0, -10.0)	-15.5§ (-22.9, -8.1)	

Change from baseline at (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	-2.9	-3.0	-0.9
Difference from placebo (95% CI)	-2.0§ (-2.6, -1.3)	-2.2§ (-2.8, -1.5)	

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

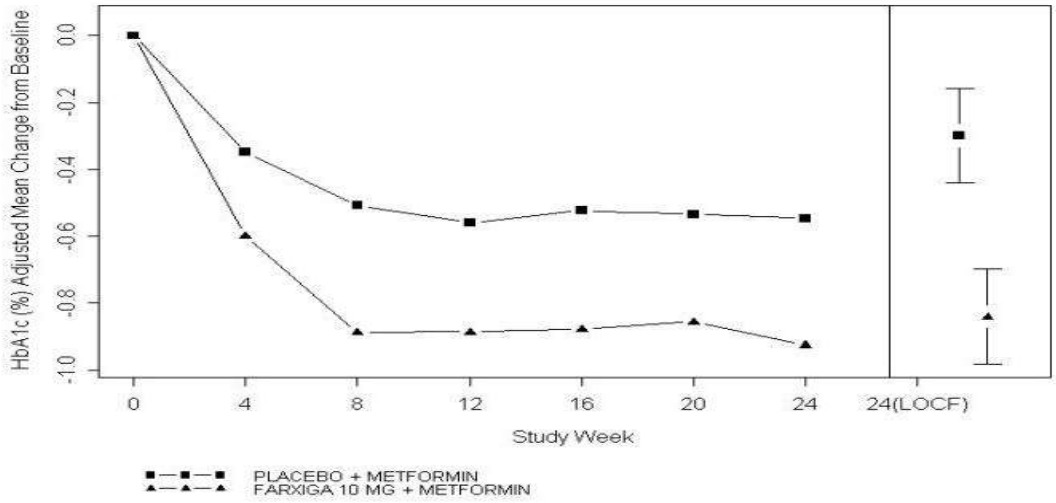
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 versus placebo + 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



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.

Active Glipizide-Controlled Study Add-On to Metformin

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, non-inferiority 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 non-inferiority. 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 12: Results at Week 52 (LOCF) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-On to Metformin

Efficacy Parameter	**Dapagliflozin + Metformin N=400†**	**Glipizide+Metformin N=401†**
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 post-baseline 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. 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 8-week 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. Downtitration 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 13). 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 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 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. 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 ; 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 13: Results of 24-Week (LOCF) Placebo-Controlled Studies of Dapagliflozin in Combination with Antidiabetic Agents

Efficacy Parameter	**Dapagliflozin 10mg**	**Dapagliflozin 5mg**	**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 basel	31.7%§	30.3%§	13.0%
FPG (mg/dL)			
Baseline (mean)	172.4	174.5	172.7
Change from baseline (adjusted mean‡)	-28.5	-21.2	-2.0
Difference from placebo (adjusted mean‡)	-26.5§	-19.3§	
(95% CI)	(-33.5, -19.5)	(-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‡)	-49.1§	-43.0§	
(95% CI)	(-64.1, -34.1)	(–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‡)	-1.5§	-0.8§	
(95% CI)	(-2.2, -0.9)	(-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‡#)	-0.69§	-	
(95% CI)	(-0.89, -0.49)		
Percent of patients achieving HbA1c <7% adjusted for baseline	31.8%§	-	11.1%
FPG (mg/dL)			
Baseline (mean)	167.4	-	180.3
Change from baseline (adjusted mean‡)	-34.2	-	-0.8
Difference from placebo (adjusted mean‡)	-33.5§	-	
(95% CI)	(-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‡)	-2.07§	-	
(95% CI)	(-2.79, -1.35)		
In Combination with Thiazolidinedione (Pioglitazone)			
Intent-to-Treat Population	N=140Þ	N=141Þ	N=139Þ
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‡)	-0.6§	-0.4§	
(95% CI)	(-0.8, -0.3)	(-0.6, -0.2)	
Percent of patients achieving HbA1c <7%	38.8%ß	32.5%ß	22.4%
adjusted for baseline			
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‡)	-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
Difference from placebo (adjusted mean‡) (95% CI)	-1.89§ (-2.37, -1.40)	–	
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 doubleblind, 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 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 14).

Table 14: Results at Week 24 of Placebo-Controlled Study for Dapagliflozin in Patients with Type2 Diabetes Mellitus and Renal Impairment (eGFR 45 to less than 60 mL/min/1.73 m)

	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 cardiovascular (CV) outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either established CV disease 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 CV disease and 10186 (59.4%) did not have established CV disease. 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 . 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 . At baseline, 10% of patients had a history of heart failure.

Most patients (98.1%) used one or more antihyperglycemic 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 if non-inferiority was demonstrated, to test for superiority on the two primary endpoints: 1) the composite of hospitalization for heart failure or CV death, and 2) MACE.

The incidence rate of MACE was similar in both treatment arms: 2.30 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% CI of (0.84, 1.03). The upper bound of this confidence interval, 1.03, excluded the pre-specified non-inferiority margin of 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 15 and Figures 4 and 5).

Table 15: 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,
Composite Endpoint of CV Death, MI, Ischemic Stroke	756 (8.8)	803 (9.4)	0.93 (0.84,
Components of the composite endpoints‡			
Hospitalization for Heart Failure	212 (2.5)	286 (3.3)	0.73 (0.61,

CV Death	245 (2.9)	249 (2.9)	0.98 (0.82,
Myocardial Infarction	393 (4.6)	441 (5.1)	0.89 (0.77,
Ischemic Stroke	235 (2.7)	231 (2.7)	1.01 (0.84,

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

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* 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

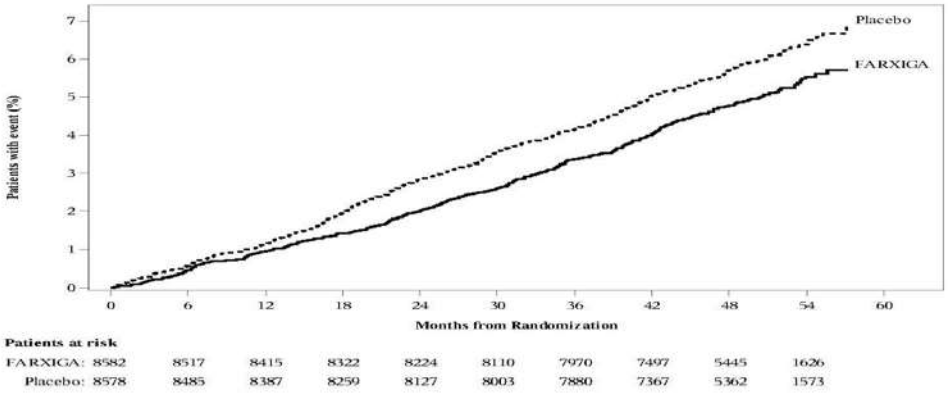
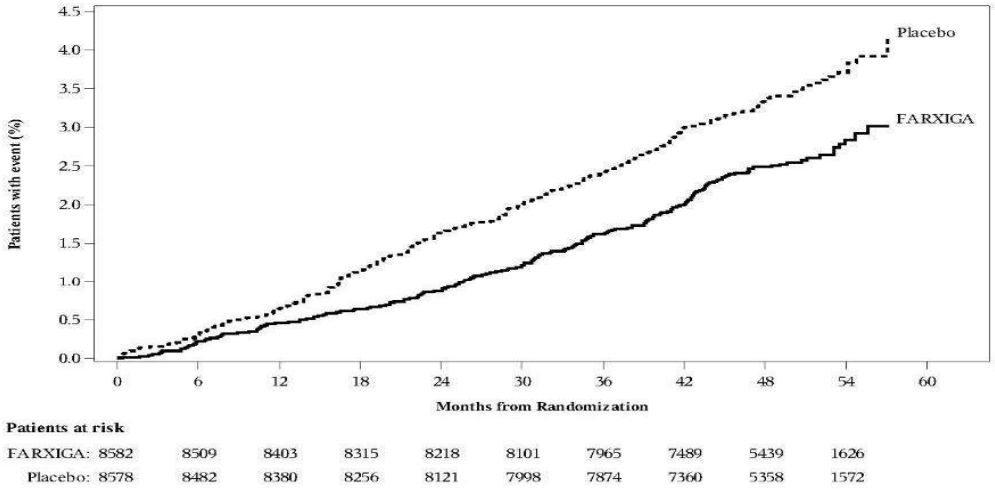


Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Study



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 receptorneprilysin 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 16, Figures 6A, 6B and 6C).

Table 16: 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)	0.82 (0.69, 0.98)	
Hospitalization for Heart Failure or Urgent Heart Failure Visit	237 (7.1)	326 (10.1)	0.70 (0.59, 0.83)	
Hospitalization for Heart Failure	231 (6.9)	318 (9.8)	0.70 (0.59, 0.83)	
Urgent Heart Failure Visit	10 (0.3)	23 (0.7)	0.43	
Al -Cause Mortality	276 (7.9)	329 (9.5)	0.83 (0.71, 0.97)	

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

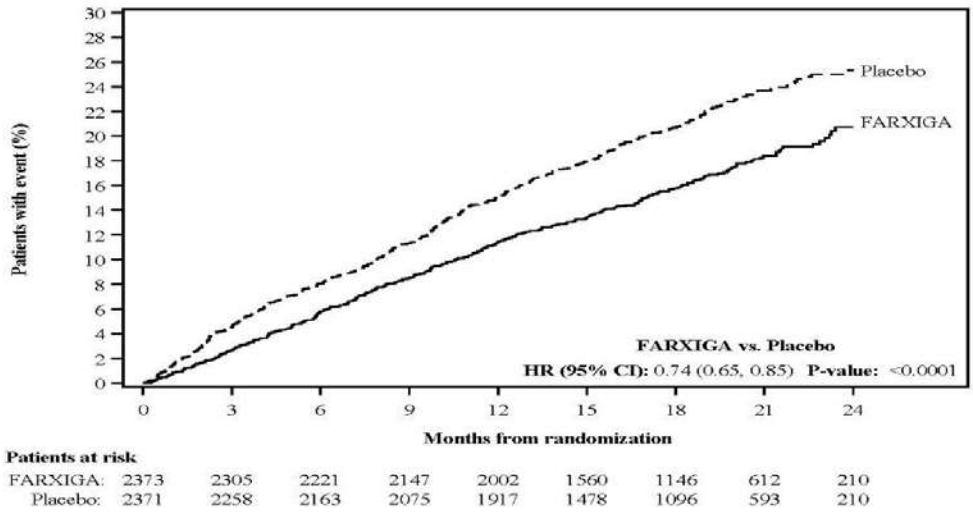
* Full analysis set.

† 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 folow-up.

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

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



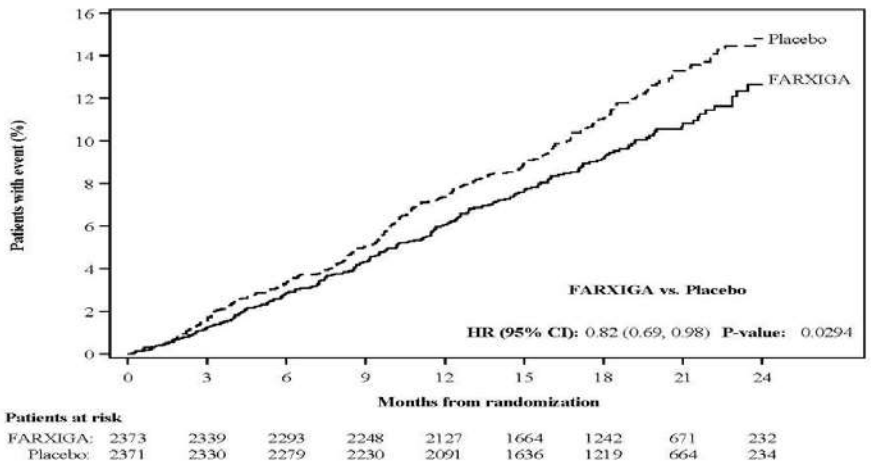
NOTE: An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g., in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

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

HR=Hazard ratio,

CI=Confidence interval.

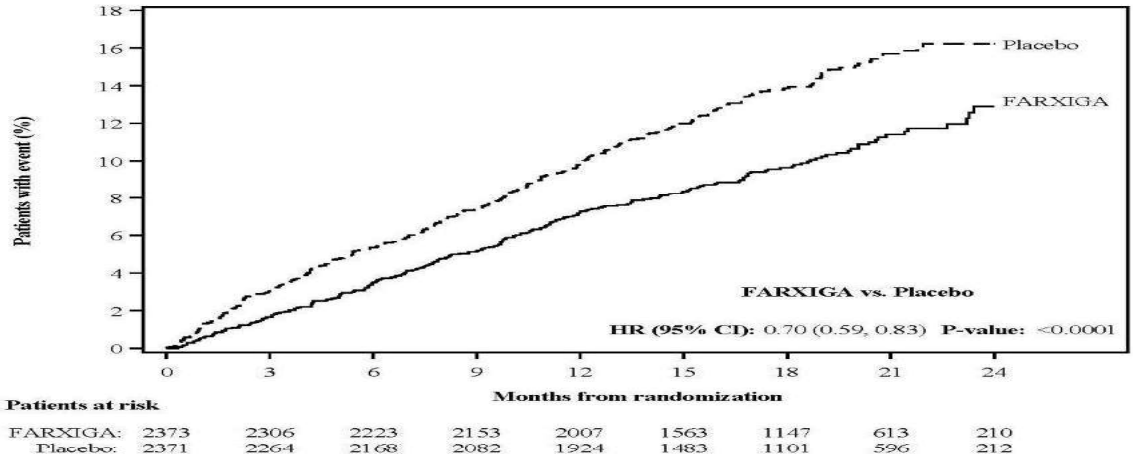
Figure 6B: Time to the First Occurrence of Cardiovascular Death



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



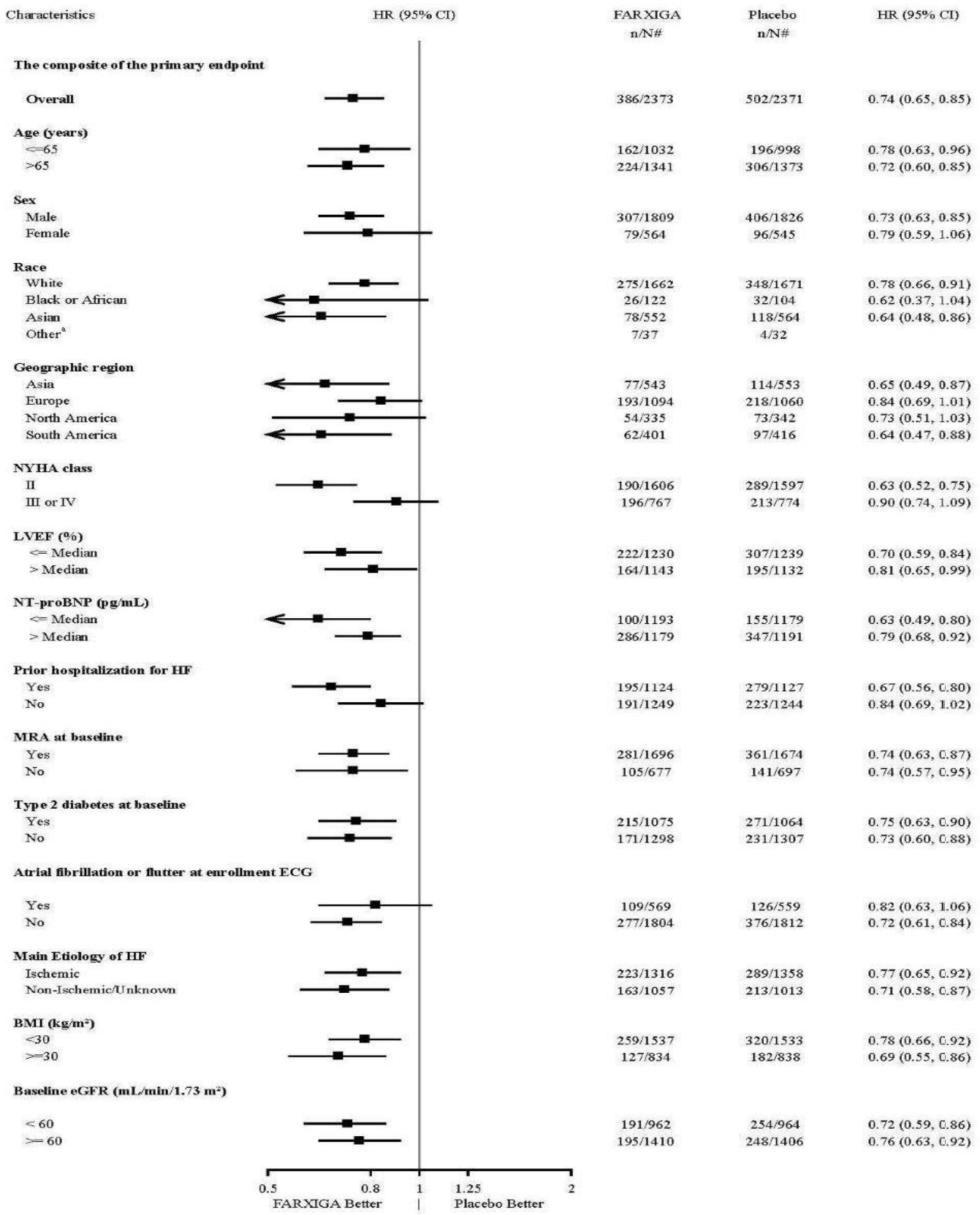
Patients at risk is the number of patients at risk at the beginning of the period.

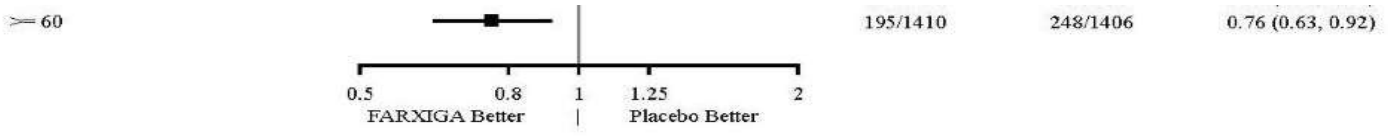
HR=Hazard ratio, CI=Confidence interval.

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)


Characteristics
HR (95% CI)
FARXIGA n/N#
Placebo n/N#
HR (95% CI)
The composite of the primary endpoint
Overall 386/2373 502/2371 0.74 (0.65, 0.85)
Age (years)
<=65 162/1032 196/998 0.78 (0.63, 0.96)
>65 224/1341 306/1373 0.72 (0.60, 0.85)
Sex
Male 307/1809 406/1826 0.73 (0.63, 0.85)
Female 79/564 96/545 0.79 (0.59, 1.06)
Race
White 275/1662 348/1671 0.78 (0.66, 0.91)
Black or African 26/122 32/104 0.62 (0.37, 1.04)
Asian 78/552 118/564 0.64 (0.48, 0.86)
Other[a] 7/37 4/32
Geographic region
Asia 77/543 114/553 0.65 (0.49, 0.87)
Europe 193/1094 218/1060 0.84 (0.69, 1.01)
North America 54/335 73/342 0.73 (0.51, 1.03)
South America 62/401 97/416 0.64 (0.47, 0.88)
NYHA class
II 190/1606 289/1597 0.63 (0.52, 0.75)
III or IV 196/767 213/774 0.90 (0.74, 1.09)
LVEF (%)
<= Median 222/1230 307/1239 0.70 (0.59, 0.84)
> Median 164/1143 195/1132 0.81 (0.65, 0.99)
NT-proBNP (pg/mL)
<= Median 100/1193 155/1179 0.63 (0.49, 0.80)
> Median 286/1179 347/1191 0.79 (0.68, 0.92)
Prior hospitalization for HF
Yes 195/1124 279/1127 0.67 (0.56, 0.80)
No 191/1249 223/1244 0.84 (0.69, 1.02)
MRA at baseline
Yes 281/1696 361/1674 0.74 (0.63, 0.87)
No 105/677 141/697 0.74 (0.57, 0.95)
Type 2 diabetes at baseline
Yes 215/1075 271/1064 0.75 (0.63, 0.90)
No 171/1298 231/1307 0.73 (0.60, 0.88)
Atrial fibrillation or flutter at enrollment ECG
Yes 109/569 126/559 0.82 (0.63, 1.06)
No 277/1804 376/1812 0.72 (0.61, 0.84)
Main Etiology of HF
Ischemic 223/1316 289/1358 0.77 (0.65, 0.92)
Non-Ischemic/Unknown 163/1057 213/1013 0.71 (0.58, 0.87)
BMI (kg/m²)
<30 259/1537 320/1533 0.78 (0.66, 0.92)
>=30 127/834 182/838 0.69 (0.55, 0.86)
Baseline eGFR (mL/min/1.73 m²)
< 60 191/962 254/964 0.72 (0.59, 0.86)
>= 60 195/1410 248/1406 0.76 (0.63, 0.92)
0.5
0.8
1
1.25
2
FARXIGA Better
Placebo Better



[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.

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, NCT03036150) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients with chronic kidney disease (CKD) (eGFR between 25 and 75 mL/min/1.73 m^2) and albuminuria (urine albumin creatinine ratio [UACR] between 200 and 5000 mg/g) who were receiving standard of care background therapy, including a maximally tolerated, labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The trial excluded patients with autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis, or ANCA-associated vasculitis and patients requiring cytotoxic, immunosuppressive, or immunomodulatory therapies in the preceding 6 months.

The primary objective was to determine whether Dapagliflozin reduces the incidence of the composite endpoint of ≥50% sustained decline in eGFR, progression to end-stage kidney disease (ESKD) (defined as sustained eGFR<15 mL/min/1.73 m^2 , initiation of chronic dialysis treatment or renal transplant), CV or renal death.

A total of 4304 patients were randomized equally to Dapagliflozin 10 mg or placebo and were followed for a median of 28.5 months.

The mean age of the study population was 62 years and 67% were male. The population was 53% White, 4% Black or African-American, and 34% Asian; 25% were of Hispanic or Latino ethnicity.

At baseline, mean eGFR was 43 mL/min/1.73 m^2 , 44% of patients had an eGFR 30 mL/min/1.73m^2 to less than 45 mL/min/1.73m^2 , and 15% of patients had an eGFR less than 30 mL/min/1.73m^2 . Median UACR was 950 mg/g. A total of 68% of the patients had type 2 diabetes mellitus at randomization. The most

common etiologies of CKD were diabetic nephropathy (58%), ischemic/hypertensive nephropathy (16%), and IgA nephropathy (6%).

At baseline, 97% of patients were treated with ACEi or ARB. Approximately 44% were taking antiplatelet agents, and 65% were on a statin.

Dapagliflozin reduced the incidence of the primary composite endpoint of ≥50% sustained decline in eGFR, progression to ESKD, CV or renal death (HR 0.61 [95% CI 0.51,0.72]; p<0.0001). The Dapagliflozin and placebo event curves separate by Month 4 and continue to diverge over the study period. The treatment effect reflected a reduction in ≥50% sustained decline in eGFR, progression to ESKD, and CV death. There were few renal deaths during the trial (Table 17, Figure 8).

Dapagliflozin also reduced the incidence of the composite endpoint of CV death or 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).

Table 17: Treatment Effect for the Primary Composite Endpoint, its Components, and Secondary Composite Endpoints, in the DAPA-CKD Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**Dapagliflozin 10 mg N=2152**	**Placebo N=2152**	**Hazard ratio (95% CI)**	**p-value**
Composite of ≥50% sustained eGFR decline, ESKD, CV or renal death	197 (4.6)	312 (7.5)	0.61 (0.51, 0.72)	<0.0001
≥50% sustained eGFR decline	112 (2.6)	201 (4.8)	0.53 (0.42, 0.67)	
ESKD*	109 (2.5)	161 (3.8)	0.64 (0.50, 0.82)	
CV Death	65 (1.4)	80 (1.7)	0.81 (0.58, 1.12)	
Renal Death	2 (0.0)	6 (0.1)		
≥50% sustained eGFR decline, ESKD or renal death	142 (3.3)	243 (5.8)	0.56 (0.45, 0.68)	<0.0001

CV death or Hospitalization for Heart Failure	100 (2.2)	138 (3.0)	0.71 (0.55, 0.92)	0.0089
Hospitalization for Heart Failure	37 (0.8)	71 (1.6)	0.51 (0.34, 0.76)	
Al -Cause Mortality	101 (2.2)	146 (3.1)	0.69 (0.53, 0.88)	0.0035

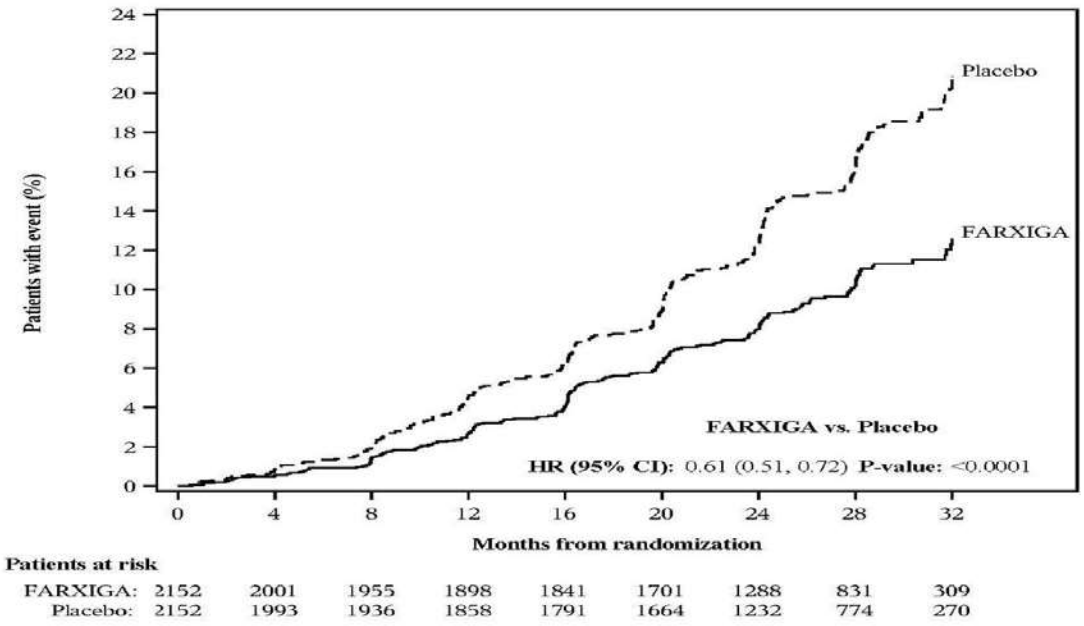
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, ESKD=End stage kidney disease.

NOTE: Time to first event was analyzed in a Cox proportional hazards model. Event rates are presented as the number of subjects with event per 100 patient years of folow-up.

There were too few events of renal death to compute a reliable hazard ratio.

* ESKD is defined as sustained eGFR<15 mL/min/1.73 m2, initiation of chronic dialysis treatment, or transplant.

Figure 8: Time to First Occurrence of the Primary Composite Endpoint, ≥50% Sustained Decline in eGFR, ESKD, CV or Renal Death (DAPA-CKD Study)



Patients at risk is the number of subjects at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. HR, CI and p-value are from the Cox proportional hazard model.

HR=hazard ratio; CI=confidence interval; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; CV=cardiovascular; vs=versus.

The results of the primary composite endpoint were consistent across the subgroups examined, including CKD patients with and without type 2 diabetes mellitus, causes of CKD, age, biological sex, race, UACR, and eGFR.

DAPA-CKD enrolled a population with relatively advanced CKD at high risk of progression. Exploratory analyses of a randomized, double-blind, placebo-controlled trial conducted to determine the effect of Dapagliflozin on CV outcomes (the DECLARE trial) support the conclusion that Dapagliflozin is also likely to be effective in patients with less advanced CKD.

6. Pharmaceutical Particulars:

6.1 List of excipients

Microcrystalline Cellulose, Anhydrous Lactose, Crospovidone (Kollidon CL), Silicon Dioxide (Syloid 244 FP), Magnesium stearate (Ligamed-MF-2-V), Opadry II Pink

Opadry II Pink Composition: Poly vinyl alcohol-Part hydrolysed, Titanium dioxide, Macrogol/PEG, Talc, Iron oxide Red, Ferrosoferric Oxide /Black Iron Oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Glyda are Supplied in 10's Alu\Alu Blister Pack.

7. Marketing authorization holder

Hetero Labs Limited
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Email: contact@heterodrugs.com A.

8. Registration Number

Not applicable

9. Date of Publication of this Package Insert

Not applicable