FARXIGA- dapagliflozin tablet, film coated
REMEDYREPACK INC.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FARXIGA safely and effectively. See full prescribing information for FARXIGA.

FARXIGA ®(dapagliflozin) tablets, for oral use
Initial U.S. Approval: 2014

RECENT MAJOR CHANGES

Dosage and Administration (2.5)	06/2026
Warnings and Precautions (5.3)	06/2026

INDICATIONS AND USAGE

FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated:

- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular (CV) death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. (1)
- To reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure. (1)
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established CV disease or multiple CV risk factors. (1)
- As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. (1)

Limitations of use:

- Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. (1)
- Not recommended for use to improve glycemic control in patients with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action. (1)
- Not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for the treatment of kidney disease. FARXIGA is not expected to be effective in these populations. (1)

DOSAGE AND ADMINISTRATION

- Assess renal function prior to initiation and then as clinically indicated. Assess volume status and correct volume depletion before initiating. (2.1)
- To improve glycemic control, the recommended starting dosage is 5 mg orally once daily. Dosage can be increased to 10 mg orally once daily for additional glycemic control. (2.2)
- For all other indications, the recommended dosage is 10 mg orally once daily. (2.3)
- See full prescribing information for dosage recommendations in patients with renal impairment. (2.2, 2.3)
- Withhold FARXIGA for at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting. (2.4)

DOSAGE FORMS AND STRENGTHS

• Tablets: 5 mg (3)

CONTRAINDICATIONS

- History of serious hypersensitivity reaction to dapagliflozin or any of the excipients in FARXIGA. (4)

WARNINGS AND PRECAUTIONS

- *Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis:*Consider ketone monitoring in patients with type 1 diabetes mellitus and consider ketone monitoring in others at risk for ketoacidosis, as indicated. Assess for ketoacidosis regardless of presenting blood glucose levels and discontinue FARXIGA if ketoacidosis is suspected. Monitor patients for resolution of ketoacidosis before restarting. (5.1)
- *Volume depletion:*Before initiating FARXIGA, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.2)
- *Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum*

(Fournier's Gangrene), and Genital Mycotic Infections: Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated. Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis and if suspected, discontinue FARXIGA, and promptly institute appropriate medical and/or surgical intervention (5.3)
- *Hypoglycemia:* Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with FARXIGA. (5.4)

ADVERSE REACTIONS

- Most common adverse reactions (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- See full prescribing information for information on drug interactions and interference of FARXIGA with laboratory tests. (7)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation:* Not recommended when breastfeeding. (8.2)
- *Geriatrics:* Higher incidence of adverse reactions related to hypotension. (8.5)
- *Renal Impairment:* Higher incidence of adverse reactions related to volume depletion. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FARXIGA (dapagliflozin) is indicated:

- To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular (CV) death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.
- To reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure.
- To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established CV disease or multiple CV risk factors.
- As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus.

Limitations of Use

- FARXIGA is not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]* .
- FARXIGA is not recommended for use to improve glycemic control in patients with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective in this setting based upon its mechanism of action.

- FARXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FARXIGA is not expected to be effective in these populations.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of FARXIGA

- Assess renal function prior to initiation of FARXIGA and then as clinically indicated *[see Warnings and Precautions (5.2)].*
- Assess volume status. In patients with volume depletion, correct this condition before initiating FARXIGA *[see Warnings and Precautions (5.2)and Use in Specific Populations (8.5, 8.6)]* .

2.2 Recommended Dosage for Glycemic Control in Adults and Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

In adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus, the recommended starting dosage of FARXIGA is 5 mg orally once daily to improve glycemic control. For additional glycemic control, the dosage can be increased to 10 mg orally once daily.

For Adult and Pediatric Patients with Type 2 Diabetes Mellitus and Renal Impairment:

- The recommended dosage for FARXIGA in patients with an eGFR greater than or equal to 45 mL/min/1.73 $m^2$is the same as the recommended dosage in patients with normal renal function.
- FARXIGA is not recommended for use to improve glycemic control in patients with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FARXIGA is likely to be ineffective to improve glycemic control in this setting based upon its mechanism of action.

2.3 Recommended Dosage for Other Indications in Adults

The recommended dosage of FARXIGA is 10 mg orally once daily in adults for the following indications:

- To reduce the risk of sustained eGFR decline, end-stage kidney disease (ESKD), CV death, and hospitalization for heart failure (hHF) in patients with chronic kidney disease at risk of progression.
- To reduce the risk of CV death, hHF, and urgent heart failure visit in patients with heart failure.
- To reduce the risk of hHF in patients with type 2 diabetes mellitus and either established CV disease or multiple CV risk factors.

<u>For Adults with Renal Impairment Receiving FARXIGA for Indications Other than Glycemic Control:</u>

- The recommended dosage of FARXIGA in patients with an eGFR greater than or equal to 25 mL/min/1.73 $m^2$is the same as the recommended dosage in patients with normal renal function.
- Initiation with FARXIGA is not recommended in patients with an eGFR less than 25 mL/min/1.73 m^2.

- If the eGFR falls below 25 mL/min/1.73 m ^{2}while receiving treatment with FARXIGA, patients may continue FARXIGA 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.

2.4 Temporary Interruption for Surgery

- Withhold FARXIGA for at least 3 days, if possible, prior to surgery or procedures associated with prolonged fasting. Resume FARXIGA when the patient is clinically stable and has resumed oral intake [see Warnings and Precautions (5.1)and Clinical Pharmacology (12.2)].

2.5 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to take the dose as soon as possible.
- Advise patients not to double up the next dose.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 5 mg, yellow, biconvex, round, film-coated tablets with “5” engraved on one side and “1427” engraved on the other side.

4 CONTRAINDICATIONS

FARXIGA is contraindicated in patients with a history of a serious hypersensitivity reaction to dapagliflozin or any of the excipients in FARXIGA. Serious hypersensitivity reactions, including anaphylaxis and angioedema have been reported with FARXIGA *[see Adverse Reactions (6.1)]* .

5 WARNINGS AND PRECAUTIONS

5.1 Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, FARXIGA significantly increases the risk of diabetic ketoacidosis, a life-threatening event, beyond the background rate. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was markedly increased in patients who received sodium-glucose cotransporter 2 (SGLT2) inhibitors compared to patients who received placebo. FARXIGA is not indicated for glycemic control in patients with type 1 diabetes mellitus.

Type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are also risk factors for ketoacidosis. There have been postmarketing reports of fatal events of ketoacidosis in patients with type 2 diabetes mellitus using SGLT2 inhibitors, including FARXIGA.

Precipitating conditions for diabetic ketoacidosis or other ketoacidosis include under-insulinization due to insulin dose reduction or missed insulin doses, acute febrile illness, reduced caloric intake, ketogenic diet, surgery, volume depletion, and alcohol abuse.

Signs and symptoms are consistent with dehydration and severe metabolic acidosis and include nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath.

Blood glucose levels at presentation may be below those typically expected for diabetic ketoacidosis (e.g., less than 250 mg/dL). Ketoacidosis and glucosuria may persist longer than typically expected. Urinary glucose excretion persists for 3 days after discontinuing FARXIGA *[see Clinical Pharmacology (12.2)]* ; however, there have been postmarketing reports of ketoacidosis and/or glucosuria lasting greater than 6 days and some up to 2 weeks after discontinuation of SGLT2 inhibitors.

Consider ketone monitoring in patients with type 1 diabetes mellitus and consider ketone monitoring in others at risk for ketoacidosis if indicated by the clinical situation. Assess for ketoacidosis regardless of presenting blood glucose levels in patients who present with signs and symptoms consistent with severe metabolic acidosis. If ketoacidosis is suspected, discontinue FARXIGA, promptly evaluate, and treat ketoacidosis, if confirmed. Monitor patients for resolution of ketoacidosis before restarting FARXIGA.

Withhold FARXIGA, if possible, in temporary clinical situations that could predispose patients to ketoacidosis. Resume FARXIGA when the patient is clinically stable and has resumed oral intake *[see Dosage and Administration (2.4)]* .

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

5.2 Volume Depletion

FARXIGA 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 FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA 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.

5.3 Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene), and Genital Mycotic Infections

FARXIGA increases urinary glucose excretion *[see Clinical Pharmacology (12.2)]* and increases the risk of genitourinary infections including urinary tract infections and genital mycotic infections in both male and female patients *[see Adverse Reactions (6.1)]* .

Serious genitourinary infections, including urosepsis, pyelonephritis, and necrotizing fasciitis of the perineum (Fournier’s gangrene, a rare life-threatening infection requiring urgent surgical intervention), have occurred in patients receiving SGLT2 inhibitors, including FARXIGA *[see Adverse Reactions (6.2)]* . Cases have required hospitalization. In patients with Fournier’s gangrene, serious outcomes have included multiple surgeries and death.

Patients with a history of genitourinary infections are more likely to develop genitourinary infections when using FARXIGA.

Monitor patients for signs and symptoms of genitourinary infections and treat promptly, if indicated.

Immediately evaluate patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, for necrotizing fasciitis. If suspected, discontinue FARXIGA and promptly institute appropriate medical and/or surgical intervention.

5.4 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues (e.g., sulfonylureas) are known to cause hypoglycemia. FARXIGA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1)]* . 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 FARXIGA *[see Drug Interactions (7)]* .

6 ADVERSE REACTIONS

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

- Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis *[see Warnings and Precautions (5.1)]*
- Volume Depletion *[see Warnings and Precautions (5.2)]*
- Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier’s Gangrene), and Genital Mycotic Infections *[see Warnings and Precautions (5.3)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4)]*

6.1 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.

FARXIGA has been evaluated in clinical trials in adult and pediatric patients aged 10 years and older with type 2 diabetes mellitus, in adult patients with heart failure, and in adult patients with chronic kidney disease. The overall safety profile of FARXIGA was consistent across the studied indications. No new adverse reactions were identified in the DAPA-HF and DELIVER heart failure trials, or in the DAPA-CKD trial in patients with chronic kidney disease. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

Clinical Trials for Glycemic Control in Adult Patients with Type 2 Diabetes Mellitus

Pool of 12 Placebo-Controlled Adult Trials for FARXIGA 5 and 10 mg for Glycemic Control

The data in Table 1 is derived from 12 glycemic control placebo-controlled trials in adult patients with type 2 diabetes mellitus ranging from 12 to 24 weeks. In 4 trials FARXIGA was used as monotherapy, and in 8 trials FARXIGA was used as add-on to background antidiabetic therapy or as combination therapy with metformin *[see Clinical Studies (14.1)]* .

These data reflect exposure of 2338 adult patients to FARXIGA with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), FARXIGA 5 mg (N=1145), or FARXIGA 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 impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m^2).

Table 1 shows common adverse reactions in adults associated with the use of FARXIGA. These adverse reactions were not present at baseline, occurred more commonly on FARXIGA than on placebo, and occurred in at least 2% of patients treated with either FARXIGA 5 mg or FARXIGA 10 mg.

Table 1: Adverse Reactions in Placebo-Controlled Trials of Glycemic Control Reported in ≥2% of Adults Treated with FARXIGA

Adverse Reaction	**% of Patients**		
	Pool of 12 Placebo-Controlled Trials		
	Placebo N=1393	**FARXIGA 5 mg N=1145**	**FARXIGA 10 mg N=1193**
Female genital mycotic infections *	1.5	8.4	6.9
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, FARXIGA 5 mg=581, FARXIGA 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, FARXIGA 5 mg=564, FARXIGA 10 mg=595).

Pool of 13 Placebo-Controlled Adult Trials for FARXIGA 10 mg for Glycemic Control

FARXIGA 10 mg was also evaluated in a larger glycemic control placebo-controlled trial pool in adult patients with type 2 diabetes mellitus. This pool combined 13 placebo-controlled trials, including 3 monotherapy trials, 9 add-on to background antidiabetic therapy trials, and an initial combination with metformin trial. Across these 13 trials, 2360 patients were treated once daily with FARXIGA 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^2).

Other Adverse Reactions in Adult Patients with Type 2 Diabetes Mellitus

Volume Depletion

FARXIGA 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 adult patients with type 2 diabetes mellitus for the 12-trial and 13-trial, short-term, placebo-controlled pools and for the DECLARE trial are shown in Table 2 *[see Warnings and Precautions (5.2)].*

Table 2: Adverse Reactions Related to Volume Depletion *in Clinical Trials in Adults with Type 2 Diabetes Mellitus with FARXIGA

	Pool of 12 Placebo-Controlled Trials			**Pool of 13 Placebo-Controlled Trials**		**DECLARE Trial**	
	Placebo	**FARXIGA 5 mg**	**FARXIGA 10 mg**	**Placebo**	**FARXIGA 10 mg**	**Placebo**	**FARXIGA 10 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=55 1 (1.8%)	n=40 0	n=31 3 (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 m	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)	n=658 30 (4.6%)	n=604 35 (5.8%)

2							
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=3950121 (3.1%)	n=3948117 (3.0%)

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

Hypoglycemia

The frequency of hypoglycemia by trial in adult patients with type 2 diabetes mellitus *[see Clinical Studies (14.1)]* is shown in Table 3. Hypoglycemia was more frequent when FARXIGA was added to sulfonylurea or insulin *[see Warnings and Precautions (5.4)]* .

Table 3: Incidence of Severe Hypoglycemia [*]and Hypoglycemia with Glucose < 54 mg/dL [†]in Controlled Glycemic Control Clinical Trials in Adults with Type 2 Diabetes Mellitus

	Placebo/Active Control	**FARXIGA 5 mg**	**FARXIGA 10 mg**
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 <54 mg/dL [n (%)]	0	0	0
Add-on to Glimepiride (24 weeks)	**N=146**	**N=145**	**N=151**
Severe [n (%)]	0	0	0
Glucose <54 mg/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 <54 mg/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 <54 mg/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 <54 mg/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 <54 mg/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 <54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE trial *[see Clinical Studies (14.3)]* , severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 adult patients treated with FARXIGA and 83 (1.0%) out of 8569 adult patients treated with placebo.

Genital Mycotic Infections

In the glycemic control trials in adults, genital mycotic infections were more frequent with FARXIGA treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on FARXIGA 5 mg, and 4.8% on FARXIGA 10 mg, in the 12-trial placebo-controlled pool. Discontinuation from trial due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with FARXIGA 10 mg. Infections were more frequently reported in females than in males (see Table 1). 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 trial than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, FARXIGA 5 mg, and FARXIGA 10 mg, respectively). In the DECLARE trial *[see Clinical Studies (14.3)]* , serious genital mycotic infections were reported in <0.1% of patients treated with FARXIGA and <0.1% of patients treated with placebo. Genital mycotic infections that caused trial drug discontinuation were reported in 0.9% of patients treated with FARXIGA and <0.1% of patients treated with placebo.

Hypersensitivity Reactions

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

Ketoacidosis in Patients with Diabetes Mellitus

In the DECLARE trial *[see Clinical Studies (14.3)]* , events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 adult patients in the FARXIGA-treated group and 12 out of 8569 adult patients in the placebo group. The events were evenly distributed over the trial period.

Laboratory Tests in Adult Patients with Type 2 Diabetes Mellitus

Increases in Serum Creatinine and Decreases in eGFR

Initiation of SGLT2 inhibitors, including FARXIGA 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 *[see Warnings and Precautions (5.2)]* . In two trials that included adult 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 FARXIGA.

Increase in Hematocrit

In the pool of 13 placebo-controlled trials of glycemic control, increases from baseline in

mean hematocrit values were observed in FARXIGA-treated adult 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 FARXIGA 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of FARXIGA 10 mg-treated patients.

Increase in Low-Density Lipoprotein Cholesterol

In the pool of 13 placebo-controlled trials of glycemic control, changes from baseline in mean lipid values were reported in FARXIGA-treated adult patients compared to placebo-treated 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 FARXIGA 10 mg groups, respectively. In the DECLARE trial *[see Clinical Studies (14.3)]* , 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 FARXIGA-treated and the placebo groups, respectively.

Decrease in Serum Bicarbonate

In a trial of concomitant therapy of FARXIGA 10 mg with exenatide extended-release (on a background of metformin) in adults, 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 FARXIGA and exenatide-extended release treatment groups *[see Warnings and Precautions (5.1)].*

Clinical Trial in Pediatric Patients with Type 2 Diabetes Mellitus

The FARXIGA safety profile observed in a 26-week placebo-controlled clinical trial with a 26-week extension in 157 pediatric patients aged 10 years and older with type 2 diabetes mellitus was similar to that observed in adults *[see Clinical Studies (14.2)].*

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of FARXIGA. 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.

*Infections:*Necrotizing fasciitis of the perineum (Fournier’s Gangrene), urosepsis and pyelonephritis

*Metabolism and Nutrition Disorders:*Ketoacidosis

*Renal and Urinary Disorders:*Acute kidney injury

*Skin and Subcutaneous Tissue Disorders:*Rash

7 DRUG INTERACTIONS

Table 4: Clinically Relevant Interactions with FARXIGA

Insulin or Insulin Secretagogues	
Clinical	The risk of hypoglycemia may be increased when FARXIGA is

Impact	used concomitantly with insulin or insulin secretagogues (e.g., sulfonylurea) *[see Warnings and Precautions (5.4)].*
Intervention	Concomitant use may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during FARXIGA initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Limited data with FARXIGA 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 *(seeclinical considerations).*

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, based on AUC).

8.2 Lactation

Risk Summary

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats *(see Data)* . However, due to species-specific differences in lactation physiology, the clinical relevance of these data is not clear. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of FARXIGA is not recommended while breastfeeding.

Data

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.4 Pediatric Use

The safety and effectiveness of FARXIGA as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients aged 10 years and older. Use of FARXIGA for this indication is supported by a 26-week placebo-controlled trial with a 26-week extension in 157 pediatric patients aged 10 to 17 years with type 2 diabetes mellitus, pediatric pharmacokinetic data, and trials in adults with type 2 diabetes mellitus *[see Clinical Pharmacology (12.3)and Clinical Studies (14.1, 14.2)]* . The safety profile observed in the placebo-controlled trial in pediatric patients with type 2 diabetes mellitus was similar to that observed in adults *[see Adverse Reactions (6.1)]* .

The safety and effectiveness of FARXIGA for glycemic control in type 2 diabetes mellitus have not been established in pediatric patients less than 10 years of age.

The safety and effectiveness of FARXIGA have not been established in pediatric patients to reduce the risk of *[see Indications and Usage (1)]* :

- sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for heart failure in patients with chronic kidney disease at risk of progression.
- CV death, hospitalization for heart failure, and urgent heart failure visit in patients with heart failure.
- hospitalization for heart failure in patients with type 2 diabetes mellitus and either established CV disease or multiple CV risk factors.

8.5 Geriatric Use

No FARXIGA dosage change is recommended based on age.

A total of 1424 (24%) of the 5936 FARXIGA-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical trials assessing the efficacy of FARXIGA in improving glycemic control in type 2 diabetes mellitus. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with FARXIGA for glycemic control had adverse reactions of hypotension *[see Warnings and Precautions (5.2)and Adverse Reactions (6.1)]* .

In the DAPA-CKD, DAPA-HF and DELIVER trials, safety and efficacy were similar for patients aged 65 years and younger and those older than 65. In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. In the DELIVER study, 4759 (76%) out of 6263 patients with heart failure (LVEF >40%) were older than 65 years. In the DAPA-CKD study, 1818 (42%) out of 4304 patients with CKD were older than 65 years.

8.6 Renal Impairment

FARXIGA was evaluated in 4304 adult patients with chronic kidney disease (eGFR 25 to 75 mL/min/1.73 m2) in the DAPA-CKD trial. FARXIGA was also evaluated in 1926 adult patients with an eGFR of 30 to 60 mL/min/1.73 m2 in the DAPA-HF trial. The safety profile of FARXIGA across eGFR subgroups in these studies was consistent with the known safety profile [see Adverse Reactions (6.1)and Clinical Studies (14.4, 14.5)].

FARXIGA was evaluated in two glycemic control adult trials that included patients with type 2 diabetes mellitus with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m2 [see Clinical Studies (14.1)], and an eGFR of 30 to less than 60 mL/min/1.73 m2, respectively). Patients with diabetes and renal impairment using FARXIGA may be more likely to experience hypotension and may be at higher risk for acute kidney injury secondary to volume depletion. In the trial of adult patients with an eGFR 30 to less than 60 mL/min/1.73 m2, 13 patients receiving FARXIGA experienced bone fractures compared to none receiving placebo. Use of FARXIGA for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m2 [see Dosage and Administration (2.1)].

Efficacy and safety trials with FARXIGA did not enroll patients with an eGFR less than 25 mL/min/1.73 m ^{2}or on dialysis. Once enrolled in the DAPA-CKD and DELIVER trials, adult patients were not required to discontinue therapy if eGFR fell below 25 mL/min/1.73 m ^{2}or if dialysis was initiated. Once enrolled in the DAPA-HF trial, adult patients were not required to discontinue therapy if eGFR fell below 30 mL/min/1.73 m ^{2}or if dialysis was initiated *[see Dosage and Administration (2.3)and Clinical Studies (14.4,14.5)]* .

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population *[see Clinical Pharmacology (12.3)]* .

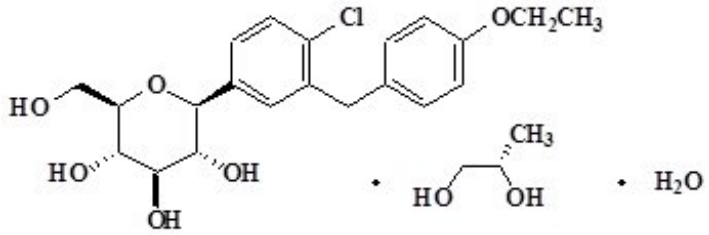
10 OVERDOSAGE

There were no reports of overdose during the clinical development program for FARXIGA.

In the event of an overdose, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. 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.

11 DESCRIPTION

Dapagliflozin, an inhibitor of SGLT2, is described chemically as D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1 *S*)-, compounded with (2 *S*)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the molecular weight is 502.98. The structural formula is:



FARXIGA is available as a film-coated tablet for oral administration containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol, and the following inactive ingredients: anhydrous lactose, crospovidone, magnesium stearate, microcrystalline cellulose, and silicon dioxide. In addition, the film coating contains the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 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.

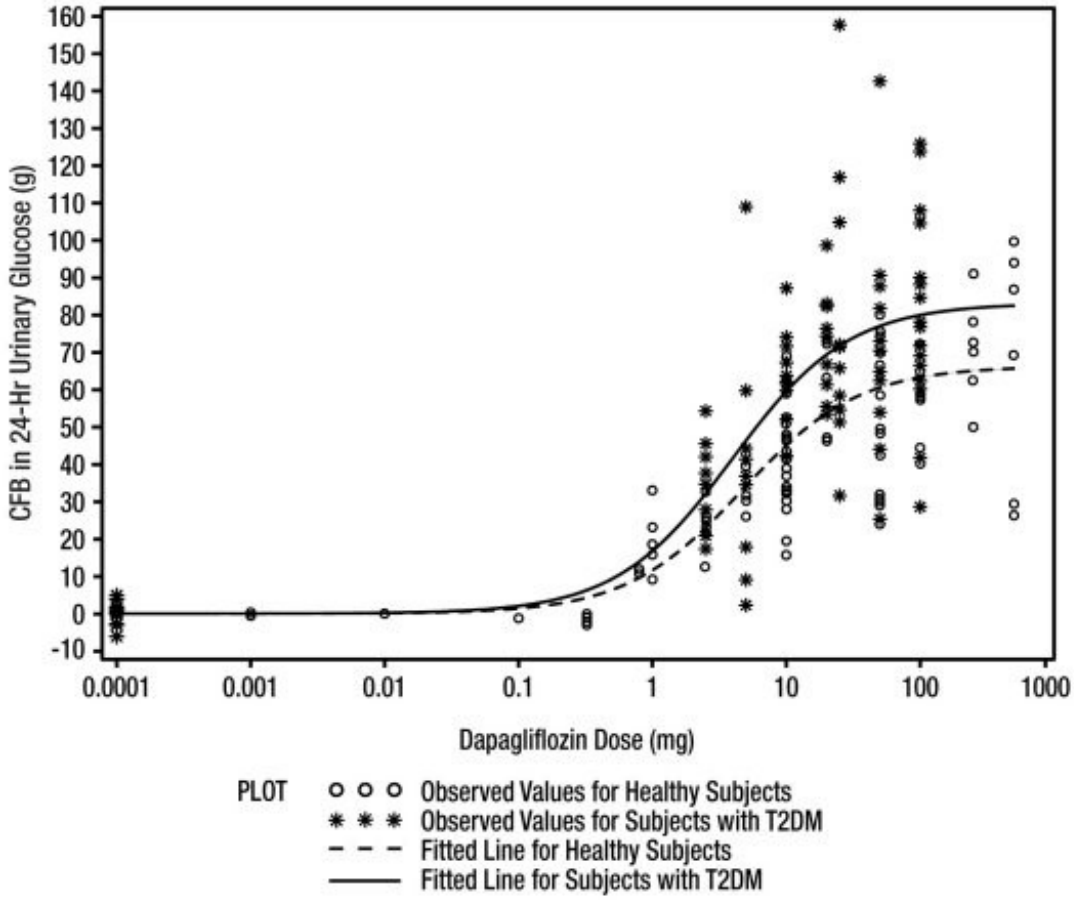
Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity, and decreased intraglomerular pressure which is believed to be mediated by increased tubuloglomerular feedback.

12.2 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 (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 dosage of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume *[see Adverse Reactions (6.1)]* . After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dosage.

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.

12.3 Pharmacokinetics

Absorption

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} 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 C_{max} by up to 50% and prolongs T_{max} 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 [^{14}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 [^{14}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 ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of FARXIGA 10 mg.

Specific Populations

Pediatric Patients

The pharmacokinetics and pharmacodynamics (glucosuria) of dapagliflozin in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus were similar to those observed in adult patients with same renal function.

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.

Patients with Renal Impairment

At steady state (20 mg once daily dapagliflozin for 7 days), adult 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 *[see Warnings and Precautions (5.2), Use in Specific Populations (8.6), and Clinical Studies (14)]*

Patients with Hepatic Impairment

In adult subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} 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 adult patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls *[see Use in Specific Populations (8.7)].*

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-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effects of Other Drugs on Dapagliflozin

Table 5 shows the effect of coadministered drugs on the pharmacokinetics of dapagliflozin in adults. No dose adjustments are recommended for dapagliflozin.

Table 5: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	**Dapagliflozin (Dose Regimen)***	**Effect on Dapagliflozin 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)	50 mg	↔	↔
Sitagliptin (100 mg)	20 mg	↔	↔
Glimepiride (4 mg)	20 mg	↔	↔
Voglibose (0.2 mg three times daily)	10 mg	↔	↔
Other Medications			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10 mg once daily for 7 days	↔	↔
Valsartan (320 mg)	20 mg	↓12% [↓3%, ↓20%]	↔
Simvastatin (40 mg)	20 mg	↔	↔
Anti-infective Agent			
Rifampin (600 mg once daily for 6 days)	10 mg	↓7% [↓22%, ↑11%]	↓22% [↓27%, ↓17%]
Nonsteroidal Anti-inflammatory Agent			
Mefenamic Acid (loading dose	10 mg	↑13%	↑51%

of 500 mg followed by 14 doses of 250 mg every 6 hours)		[↑3%, ↑24%]	[↑44%, ↑58%]

↔ = no change (geometric mean ratio of test: reference within 0.80 to 1.25); ↓ or ↑ = parameter was lower or higher, respectively, with coadministration 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 6 shows the effect of dapagliflozin on other coadministered drugs in adults. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

Table 6: Effects of Dapagliflozin on the Systemic Exposures of Coadministered 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)	50 mg	↓7% [↓25%, ↑15%]	↔
Sitagliptin (100 mg)	20 mg	↔	↔
Glimepiride (4 mg)	20 mg	↔	↑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)	20 mg	↓6% [↓24%, ↑16%]	↑5% [↓15%, ↑29%]
Simvastatin (40 mg)	20 mg	↔	↑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 coadministration 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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

14 CLINICAL STUDIES

14.1 Glycemic Control in Adults with Type 2 Diabetes Mellitus

Overview of Clinical Trials of FARXIGA in Adults with Type 2 Diabetes Mellitus

FARXIGA has been studied in adult patients 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. FARXIGA has also been studied in adult patients with type 2 diabetes mellitus and moderate renal impairment.

Treatment with FARXIGA 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 adult patients with inadequately controlled type 2 diabetes mellitus participated in 2 placebo-controlled trials to evaluate the safety and efficacy of monotherapy with FARXIGA.

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

At Week 24, treatment with FARXIGA 10 mg QAM provided significant improvements in HbA1c and the fasting plasma glucose (FPG) compared with placebo (see Table 7).

Table 7: Results at Week 24 (LOCF [*]) in a Placebo-Controlled Trial of FARXIGA Monotherapy in Adults with Type 2 Diabetes Mellitus (Main Cohort AM Doses)

Efficacy Parameter	**FARXIGA 10 mg N=70[†]**	**FARXIGA 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
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 trial 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 adult patients with inadequately controlled type 2 diabetes mellitus (HbA1c ≥7.5% and ≤12%) participated in 2 active-controlled trials of 24-week duration to evaluate initial therapy with FARXIGA 5 mg or 10 mg in combination

with metformin extended-release (XR) formulation.

In one trial (NCT00859898), 638 patients randomized to 1 of 3 treatment arms following a 1-week lead-in period received: FARXIGA 10 mg plus metformin XR (up to 2,000 mg per day), FARXIGA 10 mg plus placebo, or metformin XR (up to 2,000 mg per day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2,000 mg.

The combination treatment of FARXIGA 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 8 and Figure 2). FARXIGA 10 mg as monotherapy also provided statistically significant improvements in FPG and statistically significant reduction in body weight compared with metformin alone and was non inferior to metformin XR monotherapy in lowering HbA1c

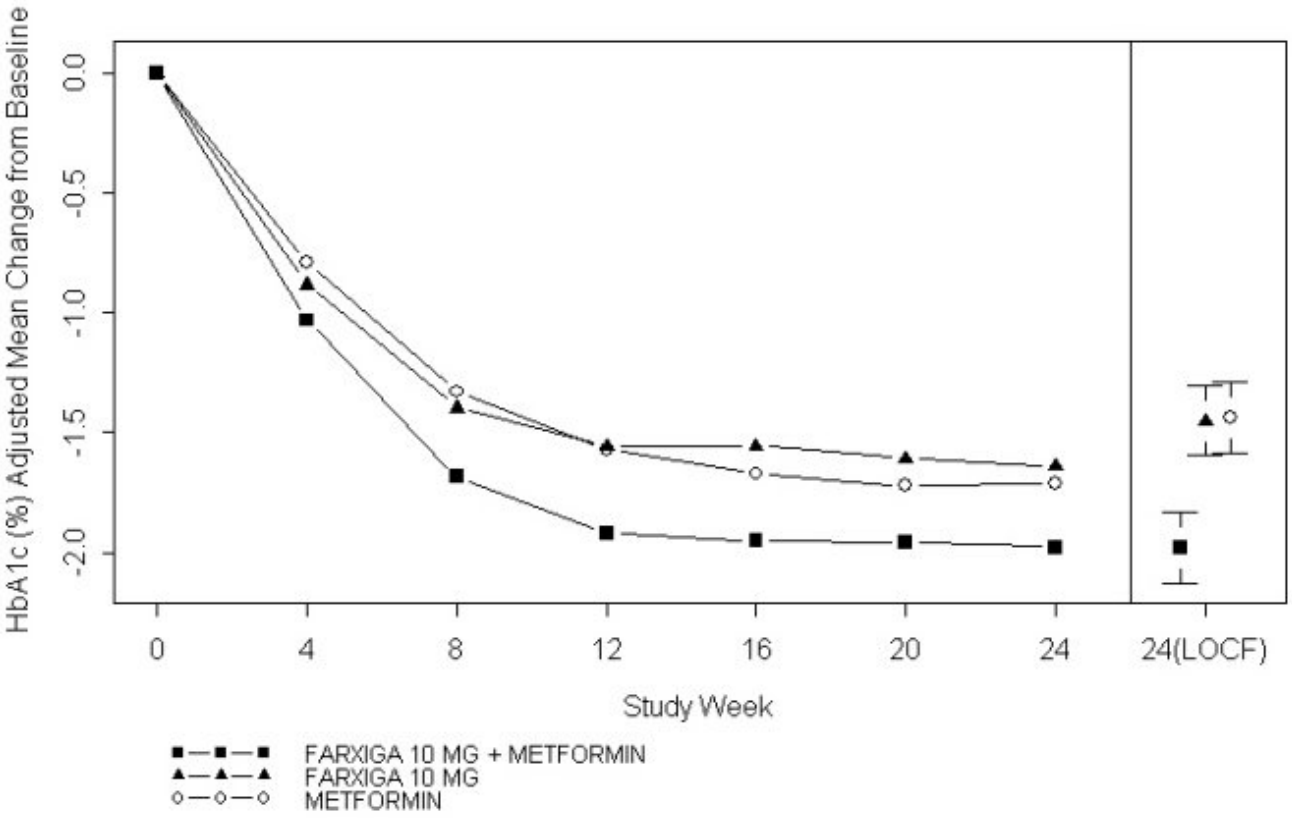
Table 8: Results at Week 24 (LOCF [*]) in an Active-Controlled Trial of FARXIGA Initial Combination Therapy with Metformin XR

Efficacy Parameter	**FARXIGA 10 mg + Metformin XR**	**FARXIGA 10 mg**	**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 FARXIGA (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 FARXIGA (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 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 trial medication during the

short-term double-blind period.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001.
¶ Non inferior versus metformin XR.
# p-value <0.05.

Figure 2: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Active-Controlled Trial of FARXIGA 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 trial (NCT00643851), 603 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: FARXIGA 5 mg plus metformin XR (up to 2,000 mg per day), FARXIGA 5 mg plus placebo, or metformin XR (up to 2,000 mg per day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2,000 mg.

The combination treatment of FARXIGA 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 9).

Table 9: Results at Week 24 (LOCF [*]) in an Active-Controlled Trial of FARXIGA Initial Combination Therapy with Metformin XR

Efficacy Parameter	FARXIGA 5 mg + Metformin XR	FARXIGA 5 mg	Metformin XR
	N=194[†]	N=203[†]	N=201[†]
HbA1c (%)			
Baseline (mean)	9.2	9.1	9.1
Change from baseline (adjusted mean [‡])	−2.1	−1.2	−1.4
Difference from FARXIGA (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 FARXIGA (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 trial 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 adult patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled trial to evaluate FARXIGA in combination with metformin (NCT00528879). Patients on metformin at a dose of at least 1,500 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 FARXIGA 5 mg, FARXIGA 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, FARXIGA 10 mg provided statistically significant

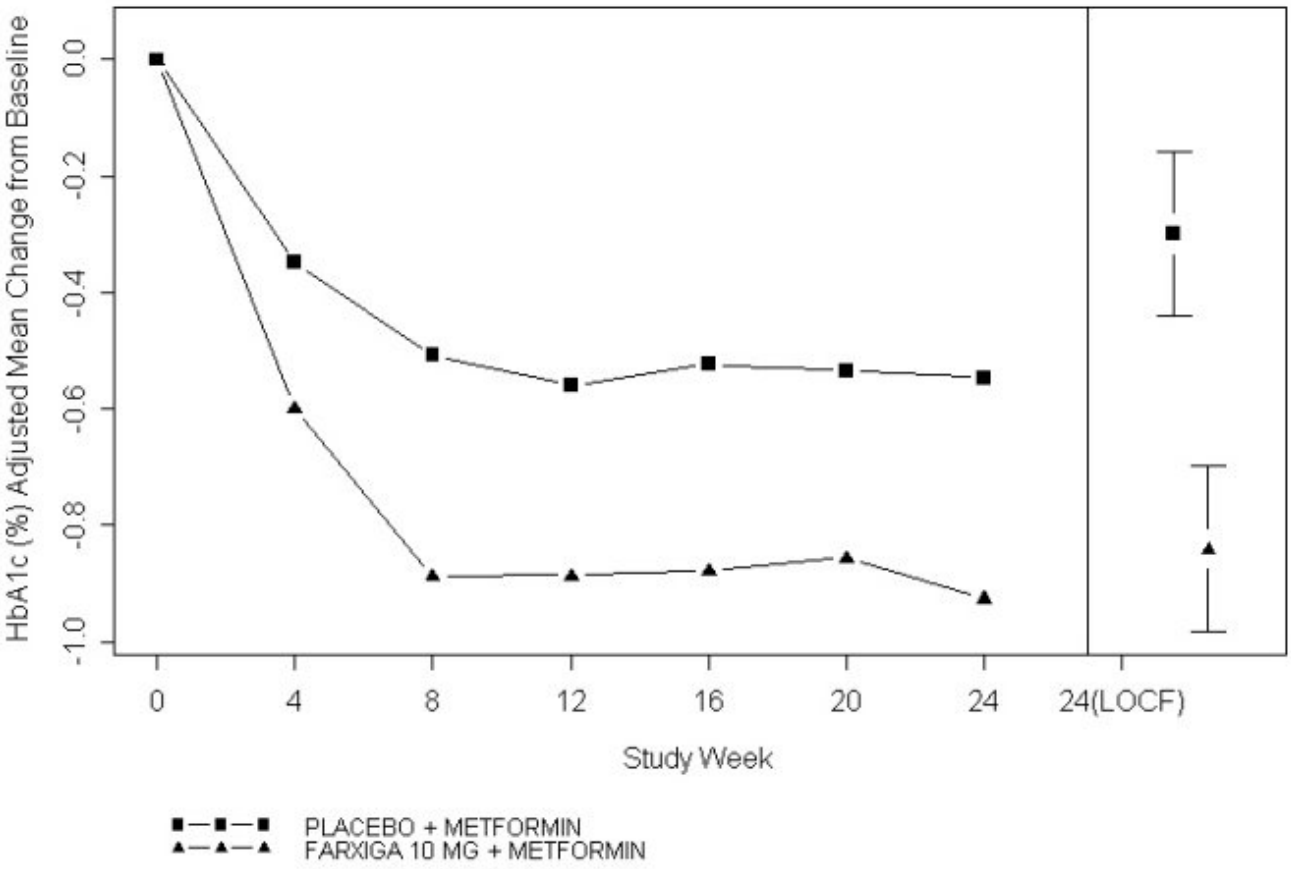
improvements in HbA1c and FPG, and statistically significant reduction in body weight compared with placebo at Week 24 (see Table 10 and Figure 3). Statistically significant ($p < 0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus metformin were −4.5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

Table 10: Results of a 24-Week (LOCF [*]) Placebo-Controlled Trial of FARXIGA in Add-On Combination with Metformin

Efficacy Parameter	FARXIGA 10 mg + Metformin N=135[†]	FARXIGA 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)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.
† All randomized patients who took at least one dose of double-blind trial 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 Trial of FARXIGA 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 Trial Add-On to Metformin

A total of 816 adult 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 trial to evaluate FARXIGA as add-on therapy to metformin (NCT00660907). Patients on metformin at a dose of at least 1,500 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 FARXIGA 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 FARXIGA had been titrated to the maximum trial dose (10 mg) versus 73% treated with glipizide (20 mg). FARXIGA led to a similar mean reduction in HbA1c from baseline at Week 52 (LOCF), compared with glipizide, thus demonstrating non inferiority (see Table 11). FARXIGA 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 FARXIGA plus metformin.

Table 11: Results at Week 52 (LOCF *) in an Active-Controlled Trial Comparing FARXIGA to Glipizide as Add-On to Metformin

Efficacy Parameter	FARXIGA + 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.
§ Non inferior 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 adult patients with type 2 diabetes mellitus and inadequate glycemic control (HbA1c ≥7% and ≤10%) were randomized in this 24-week, placebo-controlled trial to evaluate FARXIGA 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 FARXIGA 5 mg, FARXIGA 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, FARXIGA 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 12). 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 FARXIGA 5 mg and 10 mg plus glimepiride, respectively.

Add-on Combination Therapy with Metformin and a Sulfonylurea

A total of 218 adult patients with type 2 diabetes mellitus and inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week, placebo-controlled trial to evaluate FARXIGA in combination with metformin and a sulfonylurea (NCT01392677).

Patients on a stable dose of metformin (immediate- or extended-release formulations) ≥1,500 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 FARXIGA 10 mg or placebo. Dose-titration of FARXIGA 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 FARXIGA 10 mg provided statistically significant improvements in HbA1c and FPG and statistically significant reduction in body weight compared with placebo at Week 24 (Table 12). 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 FARXIGA 10 mg in combination with metformin and a sulfonylurea at Week 8.

Add-On Combination Therapy with a Thiazolidinedione

A total of 420 adult patients with type 2 diabetes mellitus with inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week, placebo-controlled trial to evaluate FARXIGA 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 FARXIGA or placebo in addition to their current dose of pioglitazone. Dose titration of FARXIGA or pioglitazone was not permitted during the trial.

In combination with pioglitazone, treatment with FARXIGA 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 12) 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 FARXIGA 10 mg in combination with pioglitazone.

Add-On Combination Therapy with a DPP4 Inhibitor

A total of 452 adult 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 trial to evaluate FARXIGA 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 (≥1,500 mg per day), and within each stratum were randomized to either FARXIGA 10 mg plus sitagliptin 100 mg once daily, or placebo plus sitagliptin 100 mg once daily. Endpoints were tested for FARXIGA 10 mg versus placebo for the total trial 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 FARXIGA, sitagliptin, or metformin was not permitted during the trial.

In combination with sitagliptin (with or without metformin), FARXIGA 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 12). These improvements were also seen in the stratum of patients who received FARXIGA 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 FARXIGA 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 adult 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 trial to evaluate FARXIGA 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 FARXIGA 5 mg, FARXIGA 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 trial 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 trial, 50% of patients were on insulin monotherapy at baseline, while 50% were on 1 or 2 OADs in addition to insulin. At Week 24, FARXIGA 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 12); the effect of FARXIGA 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 FARXIGA 10 mg in combination with insulin.

At Week 24, FARXIGA 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 FARXIGA 10 mg (19.6%) reduced their insulin dose by at least 10% compared to placebo (11.0%).

Table 12: Results of 24-Week (LOCF [*]) Placebo-Controlled Trials of FARXIGA in Combination with Antidiabetic Agents

Efficacy Parameter	**FARXIGA 10 mg**	**FARXIGA 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
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 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 ‡) (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#**	**N=141#**	**N=139#**
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%	38.8% Þ	32.5% Þ	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 ‡) (95% CI)	-24.1 ¶ (-32.2, -16.1)	-19.5 ¶ (-27.5, -11.4)	
2-hour PPGß(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	NT à	170.0

Change from baseline (adjusted mean ‡)	-21.7	NT à	3.3
Difference from placebo (adjusted mean ‡) (95% CI)	-25.0 ¶ (-34.3, -15.8)	NT à	
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.
§ Least squares mean adjusted for baseline value based on a longitudinal repeated measures model.
¶ p-value <0.0001 versus placebo.
# All randomized patients who took at least one dose of double-blind trial medication during the short-term, double-blind period.
Þ p-value <0.05 versus placebo.
ß 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).
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 trial to compare FARXIGA in combination with exenatide extended-release (a GLP-1 receptor agonist) to FARXIGA 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 FARXIGA 10 mg once daily (QD) in combination with exenatide extended release 2 mg once weekly (QW), FARXIGA 10 mg QD, or exenatide extended–release 2 mg QW.

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

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

FARXIGA was assessed in two placebo-controlled trials of adult 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 trial (NCT02413398). Patients were randomized to either FARXIGA 10 mg or placebo, administered orally once daily. At Week 24, FARXIGA provided statistically significant reductions in HbA1c compared with placebo (Table 13).

Table 13: Results at Week 24 of Placebo-Controlled Trial for FARXIGA in Adults with Type 2 Diabetes Mellitus and Renal Impairment (eGFR 45 to less than 60 mL/min/1.73 m2)

	FARXIGA 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 FARXIGA 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.

14.2 Glycemic Control in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

In a pediatric trial (NCT03199053), patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus (HbA1c ≥6.5% and ≤10.5%) were randomized to FARXIGA (81 patients) or placebo (76 patients) as add-on to metformin, insulin or a combination of metformin and insulin. In this 26-week, placebo-controlled, double-blind randomized clinical trial with a 26-week safety extension, patients received 5 mg of FARXIGA or placebo following a lead-in period. At Week 14, patients with HbA1c values <7% remained on 5 mg while patients with HbA1c values ≥7% were randomized to either continue on 5 mg or up-titrate to 10 mg.

At baseline, 88% of FARXIGA-treated patients and 89% of placebo-treated patients were on metformin with or without insulin as background medication. The mean HbA1c at baseline was 8.2% in FARXIGA-treated patients and 8.0% in placebo-treated patients, and the mean duration of type 2 diabetes mellitus was 2.3 years in FARXIGA-treated patients and 2.5 years in placebo-treated patients. The mean age was 14.4 years in FARXIGA-treated patients and 14.7 years in placebo-treated patients, and approximately 61% of FARXIGA-treated patients and 58% of placebo-treated patients were female. In FARXIGA-treated patients, approximately 52% were White, 22% were Asian, 9% were Black or African American, and 56% were of Hispanic or Latino ethnicity. In placebo-treated patients, approximately 42% were White, 32% were Asian, 4% were Black or African American, and 45% were of Hispanic or Latino ethnicity. The mean BMI was 29.7 kg/m ^{2}in FARXIGA-treated patients and 28.5 kg/m2 in placebo-treated patients, and mean BMI Z-score was 1.7 in FARXIGA-treated patients and 1.5 in placebo-treated patients. The mean eGFR at baseline was 115 mL/min/1.73 m ^{2}in FARXIGA-treated patients and 113 mL/min/1.73 m ^{2}in placebo-treated patients.

At Week 26, treatment with FARXIGA provided statistically significant improvements in HbA1c compared with placebo (Table 14). This effect was consistent across subgroups including race, ethnicity, sex, age group (≥10 to <15 years of age and ≥15 to <18 years of age), background antidiabetic treatment, and baseline BMI.

Table 14: Results at Week 26 in a Placebo-Controlled Trial of FARXIGA as Add-On to Metformin and/or Insulin in Pediatric Patients Aged 10 Years and Older with Type 2 Diabetes Mellitus

Efficacy Parameter	**FARXIGA 5 mg and 10 mg**	**Placebo**
Intent-to-Treat Population (N)*	**81**	**76**
HbA1c†(%)		
Baseline (mean)	8.2	8.0
Change from baseline (adjusted mean ‡)	-0.6	0.4
Difference from placebo (adjusted mean ‡) (95% CI)	-1.0 § (-1.6, -0.5)	
FPG (mg/dL)		
Baseline (mean)	162.2	152.0
Change from baseline (adjusted mean ‡)	-10.3	9.2
Difference from placebo (adjusted mean ‡) • (95% CI)	-19.5 ¶ (-36.4, -2.5)	
Percent of Subjects Achieving a HbA1c Level <7%	34.6%	25.0%

CI=confidence interval

* All randomized patients who received at least one dose of double-blind trial medication during the treatment period. Includes data regardless of rescue or premature treatment discontinuation.
† Multiple imputations using placebo washout approach for missing efficacy endpoint. Imputed for HbA1c (FARXIGA N=6 (7.4%), placebo N=6 (7.9%)), for FPG (FARXIGA N=6 (7.4%), placebo N=8 (10.5%)).
‡ Least squares mean adjusted for baseline value, treatment, age, gender and baseline diabetic medication.
§ p-value versus placebo <0.001. p-value is two-sided.
¶ p-value versus placebo <0.05. p-value is two-sided.

14.3 Cardiovascular Outcomes in Adults with Type 2 Diabetes Mellitus

Dapagliflozin Effect on Cardiovascular Events (DECLARE, NCT01730534) was an international, multicenter, randomized, double-blind, placebo-controlled, clinical trial conducted to determine the effect of FARXIGA relative to placebo on 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 FARXIGA 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 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.

FARXIGA 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 FARXIGA [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 Trial

	Patients with events n (%)		
Efficacy Variable (time to first occurrence)	**FARXIGA 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 Trial

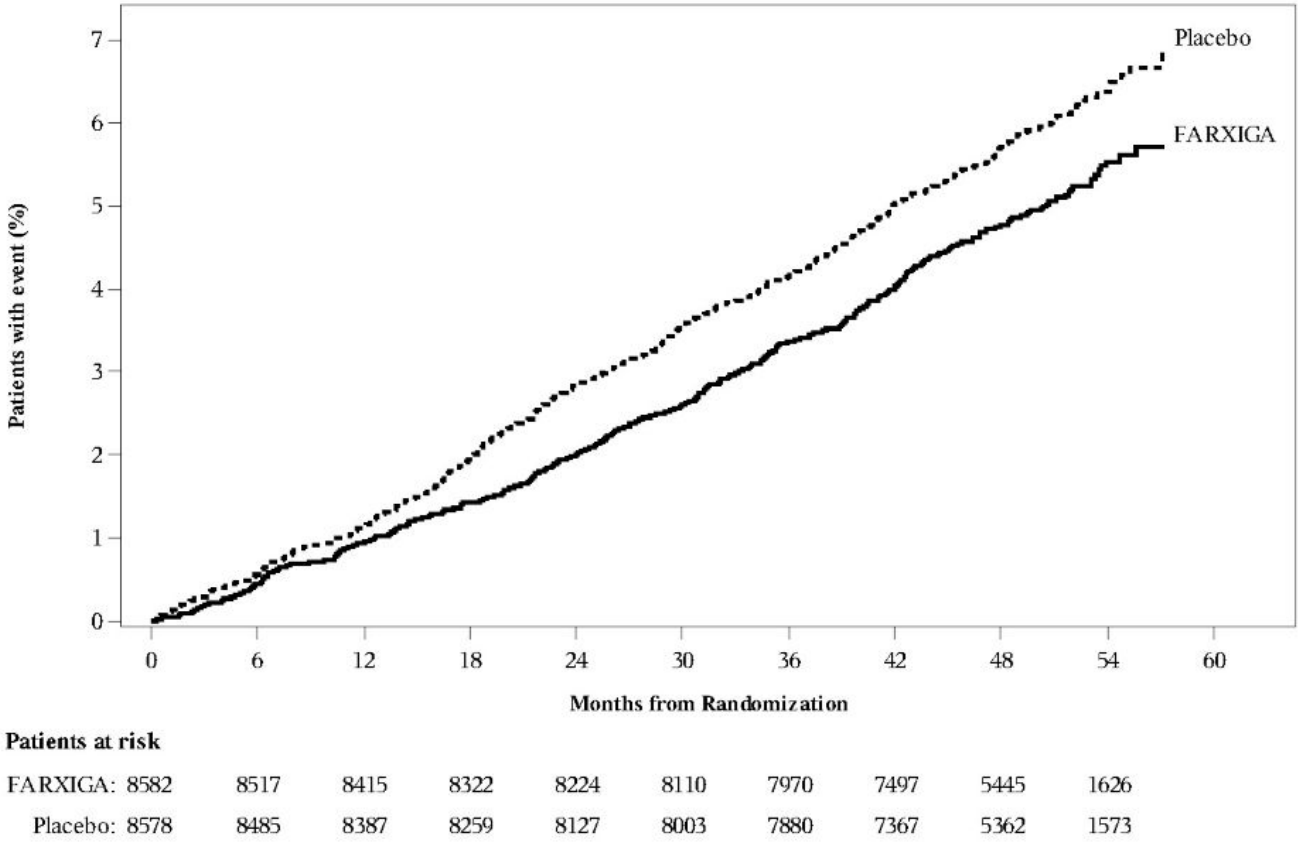
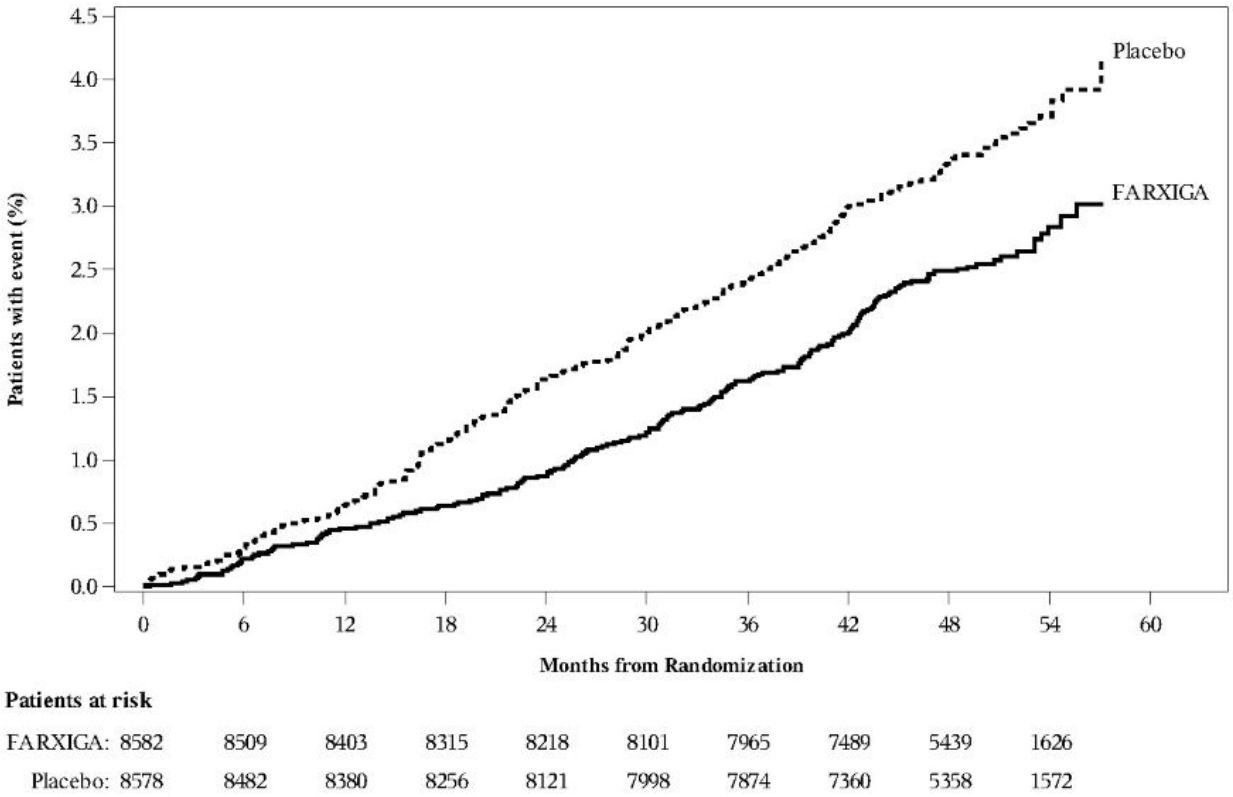


Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Trial



14.4 Chronic Kidney Disease in Adults

The Trial 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 trial in adult 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 FARXIGA 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 FARXIGA 10 mg or placebo and were followed for a median of 28.5 months.

The mean age of the trial 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/1.73 m ^{2}to less than 45 mL/min/1.73 m ^{2}, and 15% of patients had an eGFR less than 30 mL/min/1.73 m ^{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.

FARXIGA 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 FARXIGA and placebo event curves separate by Month 4 and continue to diverge over the trial 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 16, Figure 6).

FARXIGA 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 16: Treatment Effect for the Primary Composite Endpoint, its Components, and Secondary Composite Endpoints, in the DAPA-CKD Trial

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**FARXIGA 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 (<0.1)	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)	
All-Cause Mortality	101 (2.2)	146 (3.1)	0.69 (0.53, 0.88)	0.0035

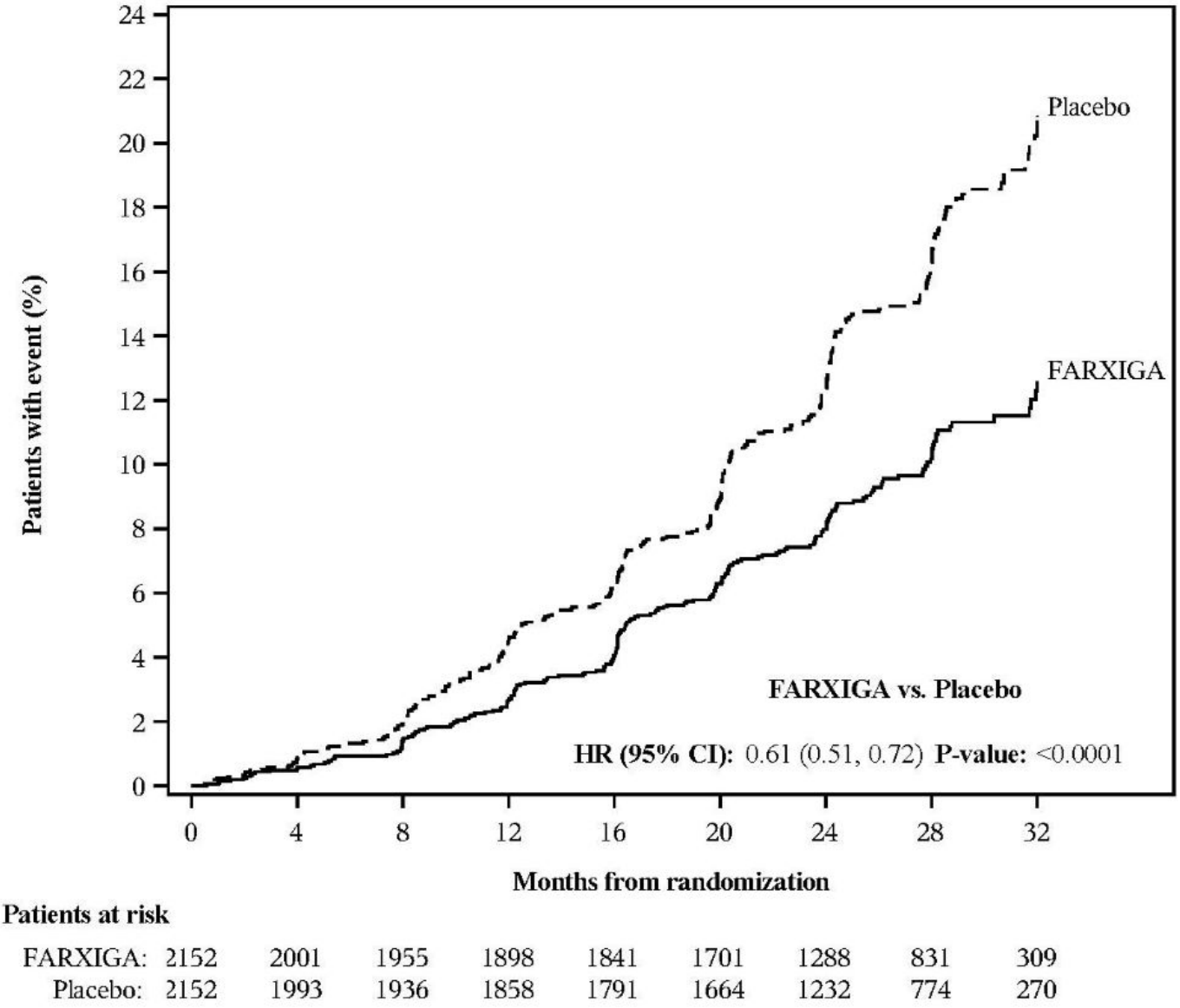
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, ESKD=End stage kidney disease.

* ESKD is defined as sustained eGFR<15 mL/min/1.73 m 2, initiation of chronic dialysis treatment, or transplant.

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

Figure 6: Time to First Occurrence of the Primary Composite Endpoint, ≥50% Sustained Decline in eGFR, ESKD, CV or Renal Death (DAPA-CKD Trial)



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 FARXIGA on CV outcomes (the DECLARE trial) support the conclusion that FARXIGA is also likely to be effective in patients with less advanced CKD.

14.5 Heart Failure in Adults

The efficacy and safety of FARXIGA 10 mg were assessed independently in two Phase 3 trials in adult patients with heart failure.

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF, NCT03036124) was an international, multicenter, randomized, double-blind, placebo-controlled trial 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 FARXIGA reduces the risk of CV death and hospitalization for heart failure. Of 4744 patients, 2373 were randomized to FARXIGA 10 mg and 2371 to placebo and were followed for a median of 18 months.

Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (DELIVER, NCT03619213) was an international, multicenter, randomized, double-blind, placebo-controlled trial in patients aged ≥40 years with heart failure (NYHA class II-IV) with LVEF >40% and evidence of structural heart disease to determine whether FARXIGA reduces the risk of CV death, hospitalization for heart failure or urgent heart failure visits. Of 6263 patients, 3131 were randomized to FARXIGA 10 mg and 3132 to placebo and were followed for a median of 28 months. The trial included 654 (10%) heart failure patients who were randomized during hospitalization for heart failure or within 30 days of discharge.

In DAPA-HF, 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 (with defibrillator function).

In DELIVER, at baseline, 77% of patients were treated with ACEi, ARB or ARNI, 83% with beta-blocker, 43% with MRA, 98% with diuretic.

In both trials, FARXIGA reduced the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit (see Table 17).

Table 17: Treatment Effect for the Primary Composite Endpoint* and its Components* in the DAPA-HF and DELIVER Trials

	DAPA-HF Trial				DELIVER Trial			
	Patients with events (event rate)		Hazard ratio (95% CI)	p-value†	Patients with events (event rate)		Hazard ratio (95% CI)	p-value†
Efficacy Variable (Time to first occurrence)	**FARXIGA 10 mg N=2373**				**Placebo N=2371**	**FARXIGA 10 mg N=3131**		**Placebo N=3132**
Composite of Hospitalization								

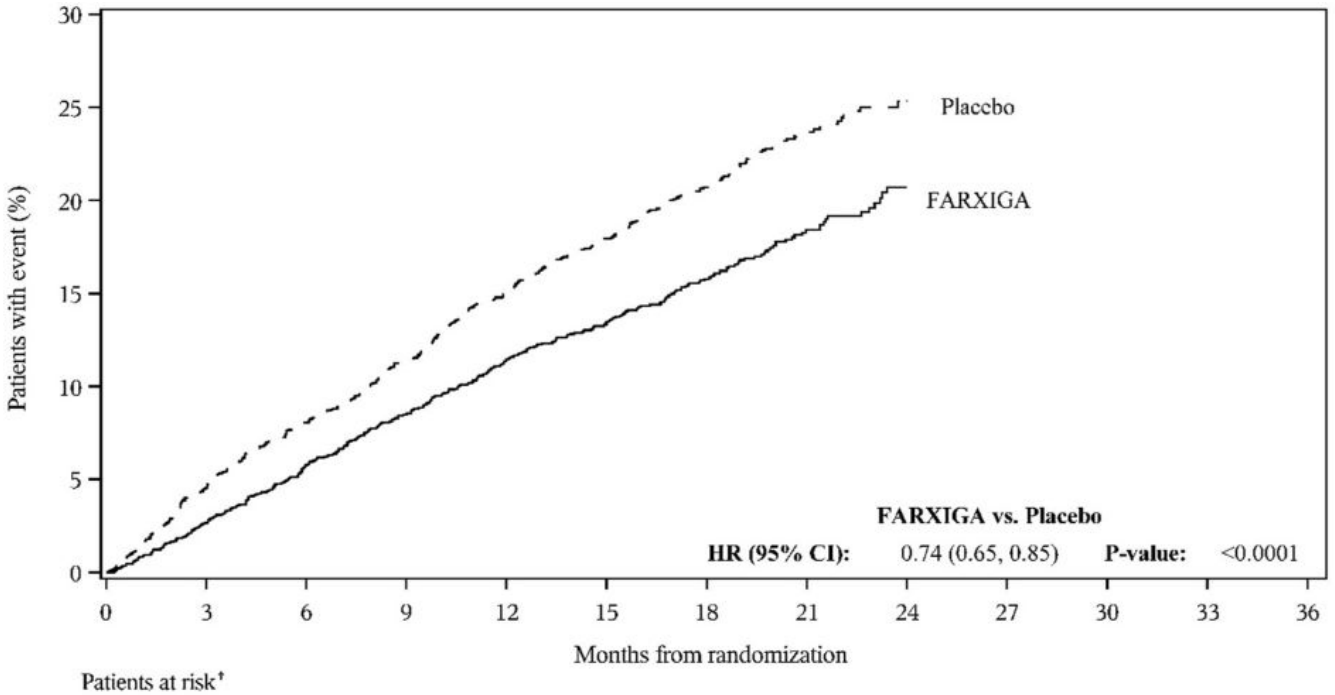
for Heart Failure, CV Death‡ or Urgent Heart Failure Visit	386 (11.6)	502 (15.6)	0.74 (0.65, 0.85)	<0.0001	512 (7.8)	610 (9.6)	0.82 (0.73, 0.92)	0.0008
Components of the composite endpoints								
CV Death‡	227 (6.5)	273 (7.9)	0.82 (0.69, 0.98)		231 (3.3)	261 (3.8)	0.88 (0.74, 1.05)	
Hospitalization for Heart Failure or Urgent Heart Failure Visit	237 (7.1)	326 (10.1)	0.70 (0.59, 0.83)		368 (5.6)	455 (7.2)	0.79 (0.69, 0.91)	
Hospitalization for Heart Failure	231 (6.9)	318 (9.8)	0.70 (0.59, 0.83)		329 (5.0)	418 (6.5)	0.77 (0.67, 0.89)	
Urgent Heart Failure Visit	10 (0.3)	23 (0.7)	0.43 (0.20, 0.90)		60 (0.9)	78 (1.1)	0.76 (0.55, 1.07)	

N=Number of patients, CI=Confidence interval, CV=Cardiovascular.
* Full analysis set.
† Two-sided p-values.
‡ In DAPA-HF, the CV death component of the primary endpoint included death of undetermined cause. In DELIVER, the CV death component of the primary endpoint excluded death of undetermined cause.
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.

In both trials, all three components of the primary composite endpoint individually contributed to the treatment effect. In both trials, the FARXIGA and placebo event curves separated early and continued to diverge over the trial period (see Figures 7 and 9).

Figure 7: Time to the First Occurrence of the Composite of CV Death*, Hospitalization for Heart Failure or Urgent Heart Failure Visit

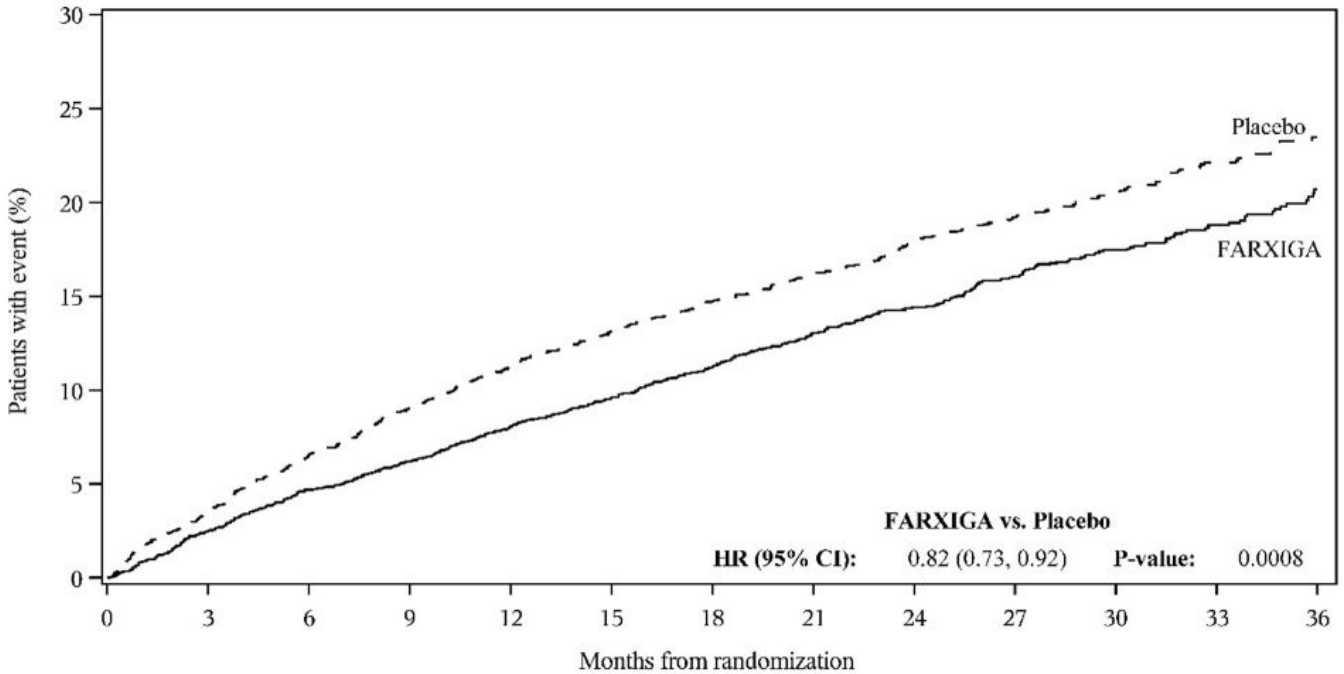
A) DAPA-HF Trial



Patients at risk†

FARXIGA:	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo:	2371	2258	2163	2075	1917	1478	1096	593	210

B) DELIVER Trial



Patients at risk†

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

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).

* In DAPA-HF, the CV death component of the primary endpoint included death of

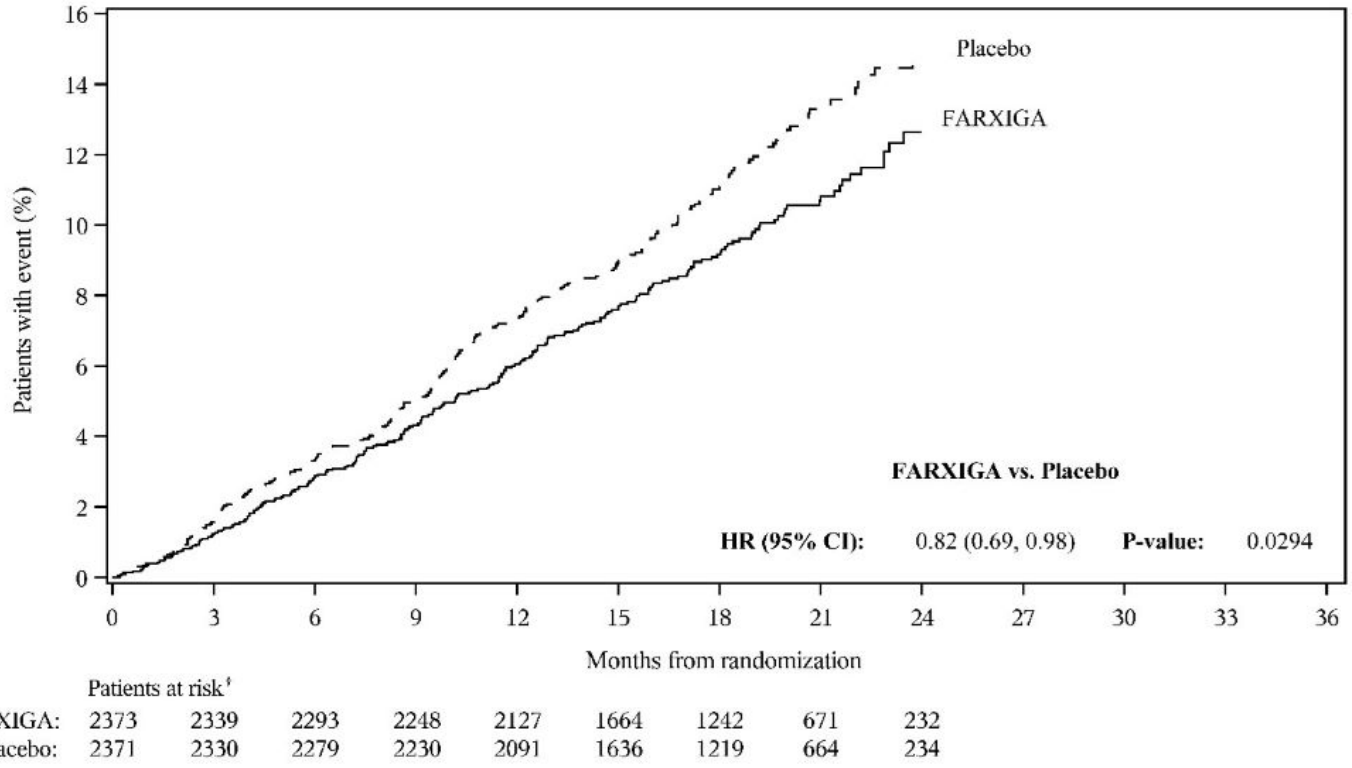
undetermined cause. In DELIVER, the CV death component of the primary endpoint excluded death of undetermined cause.

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

HR=Hazard ratio, CI=Confidence interval, CV=Cardiovascular.

Figure 8: Time to CV Death*

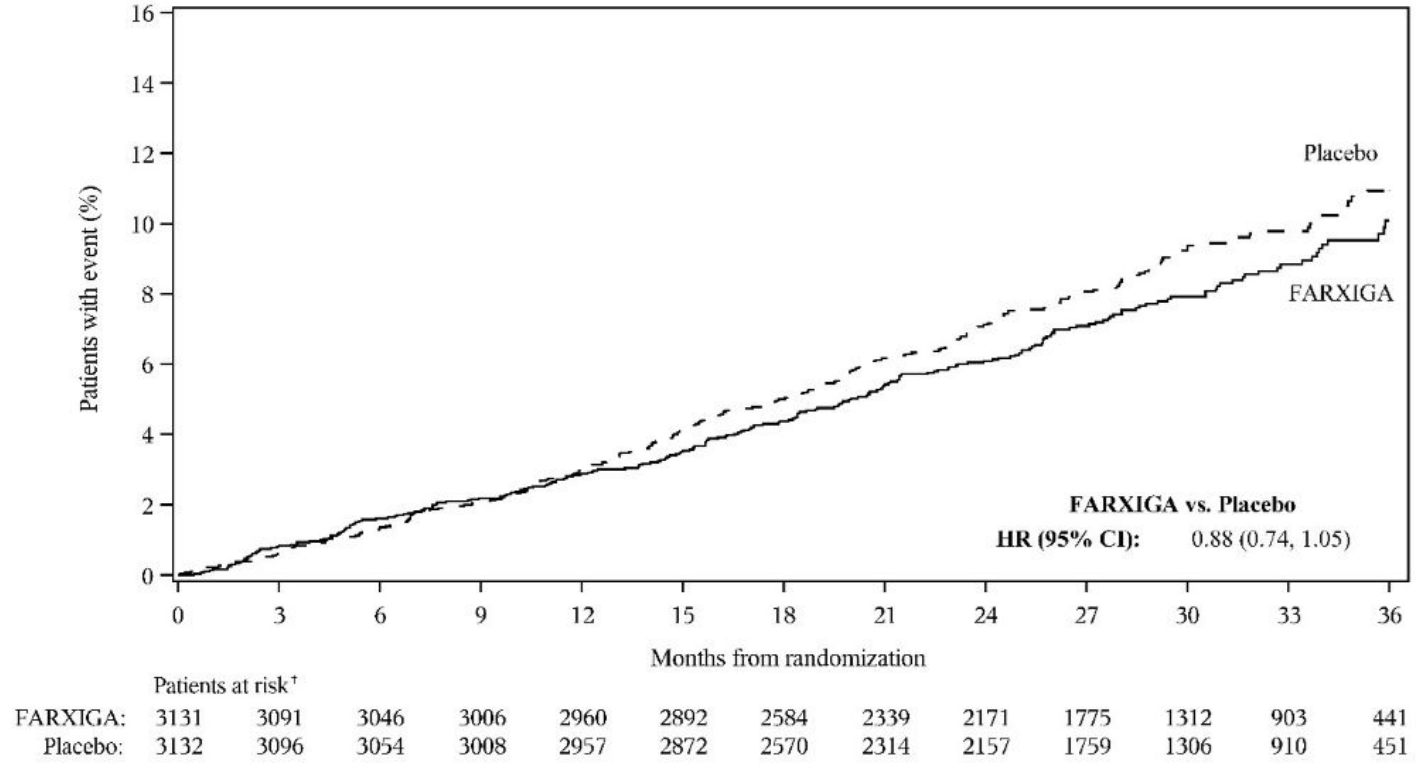
A) DAPA-HF Trial



Patients at risk†

FARXIGA:	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo:	2371	2330	2279	2230	2091	1636	1219	664	234

B) DELIVER Trial



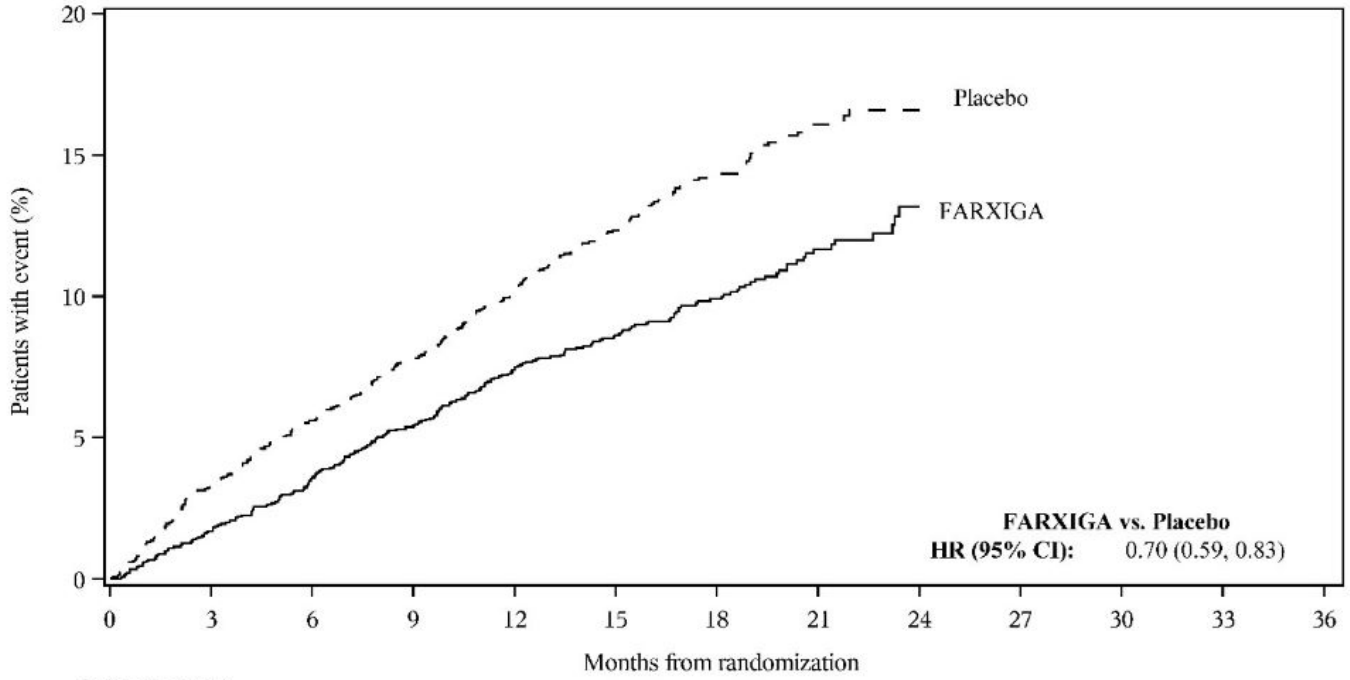
* In DAPA-HF, the CV death component of the primary endpoint included death of undetermined cause. In DELIVER, the CV death component of the primary endpoint excluded death of undetermined cause.

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

HR=Hazard ratio, CI=Confidence interval, CV=Cardiovascular.

Figure 9: Time to the First Occurrence of Hospitalization for Heart Failure or Urgent Heart Failure Visit

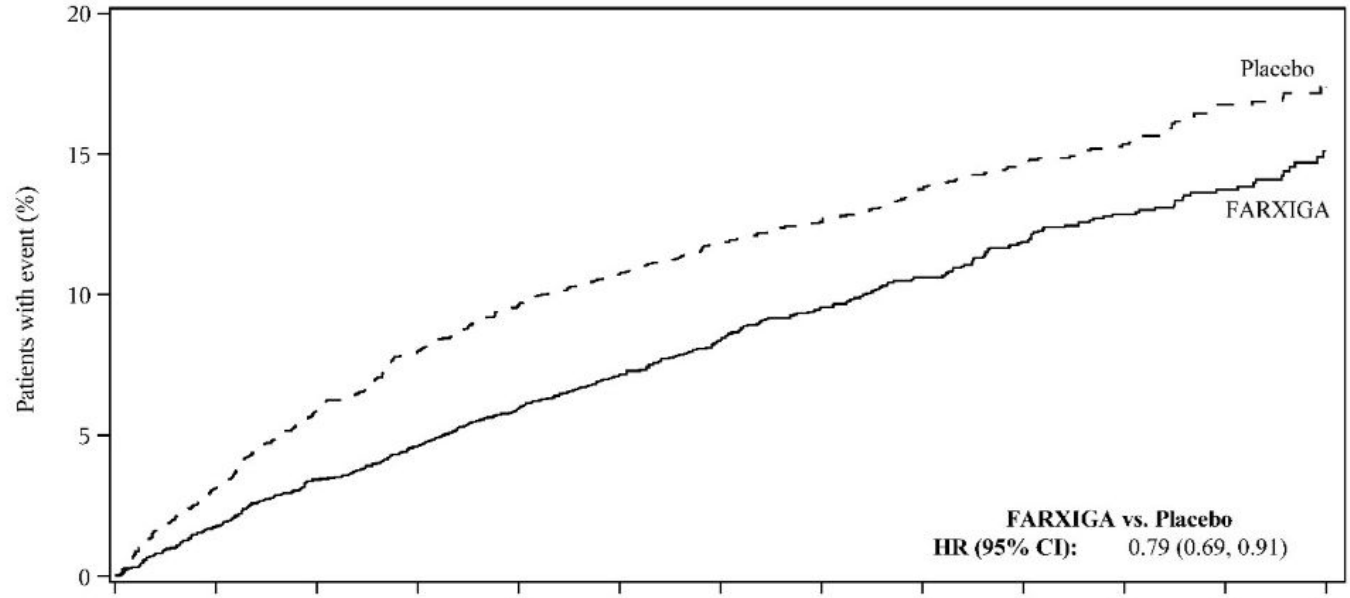
A) DAPA-HF Trial



Patients at risk*

FARXIGA:	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo:	2371	2258	2163	2075	1917	1478	1096	593	210

B) DELIVER Trial



Patients at risk*

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

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

HR=Hazard ratio, CI=Confidence interval.

In DAPA-HF, FARXIGA reduced the total number of hospitalizations for heart failure (first

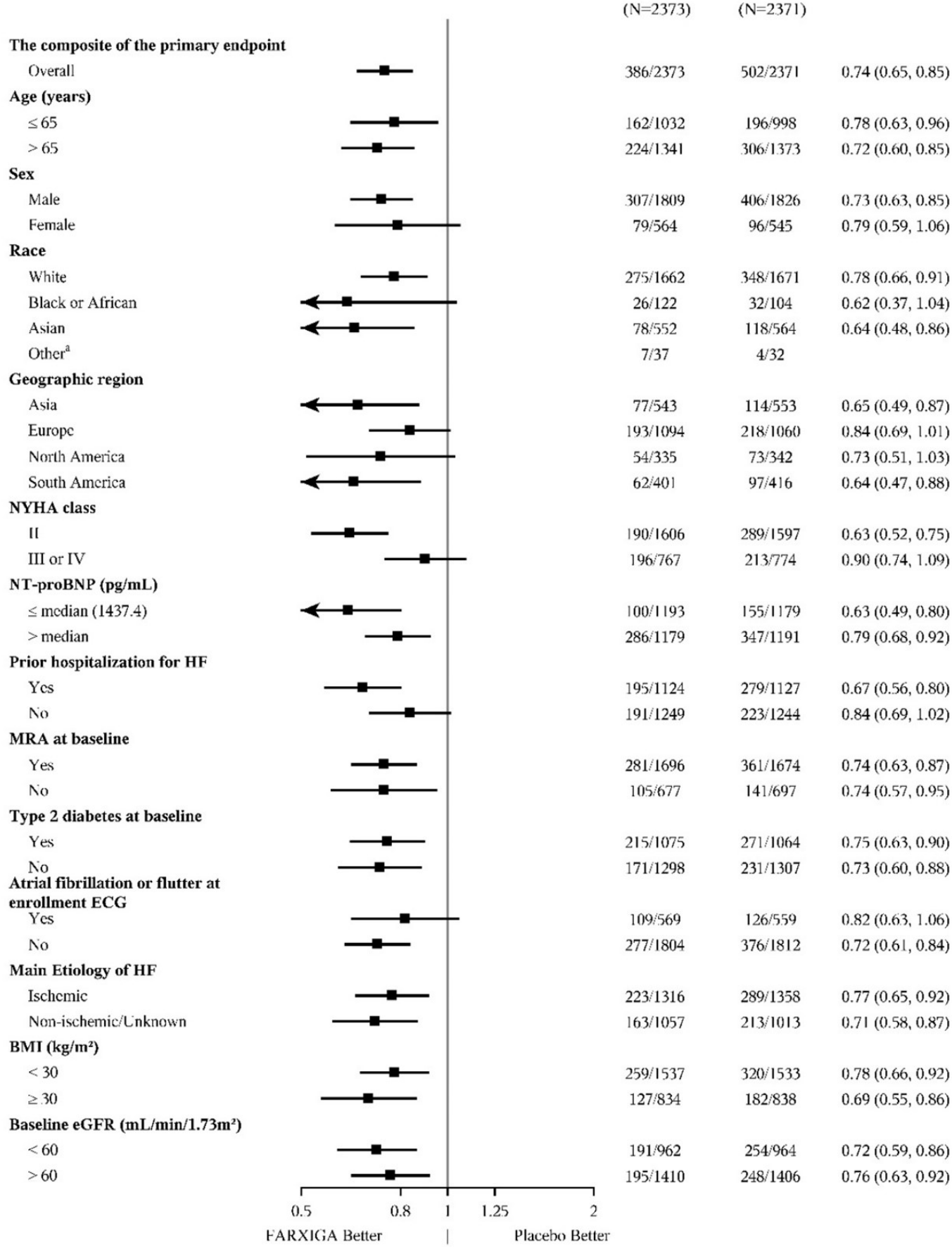
and recurrent) events and CV death, with 567 and 742 total events in the FARXIGA-treated vs placebo group [Rate Ratio 0.75 (95% CI 0.65, 0.88); p=0.0002].

In DELIVER, FARXIGA reduced the total number of heart failure events (first and recurrent hospitalization for heart failure or urgent heart failure visit) and CV death, with 815 and 1057 total events in the FARXIGA treated vs placebo group [Rate Ratio 0.77 (95% CI 0.67, 0.89); p=0.0003].

In both trials, the results of the primary composite endpoint were consistent across the subgroups examined (see Figure 10).

Figure 10: Treatment Effects for Primary Composite Endpoint (CV Death and Heart Failure Events) Subgroup Analysis

A) DAPA-HF Trial


Characteristics
HR (95% CI)
n/N#
FARXIGA (N=2373)
Placebo (N=2371)
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)
NT-proBNP (pg/mL)
≤ median (1437.4) 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/1.73m²)
< 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.

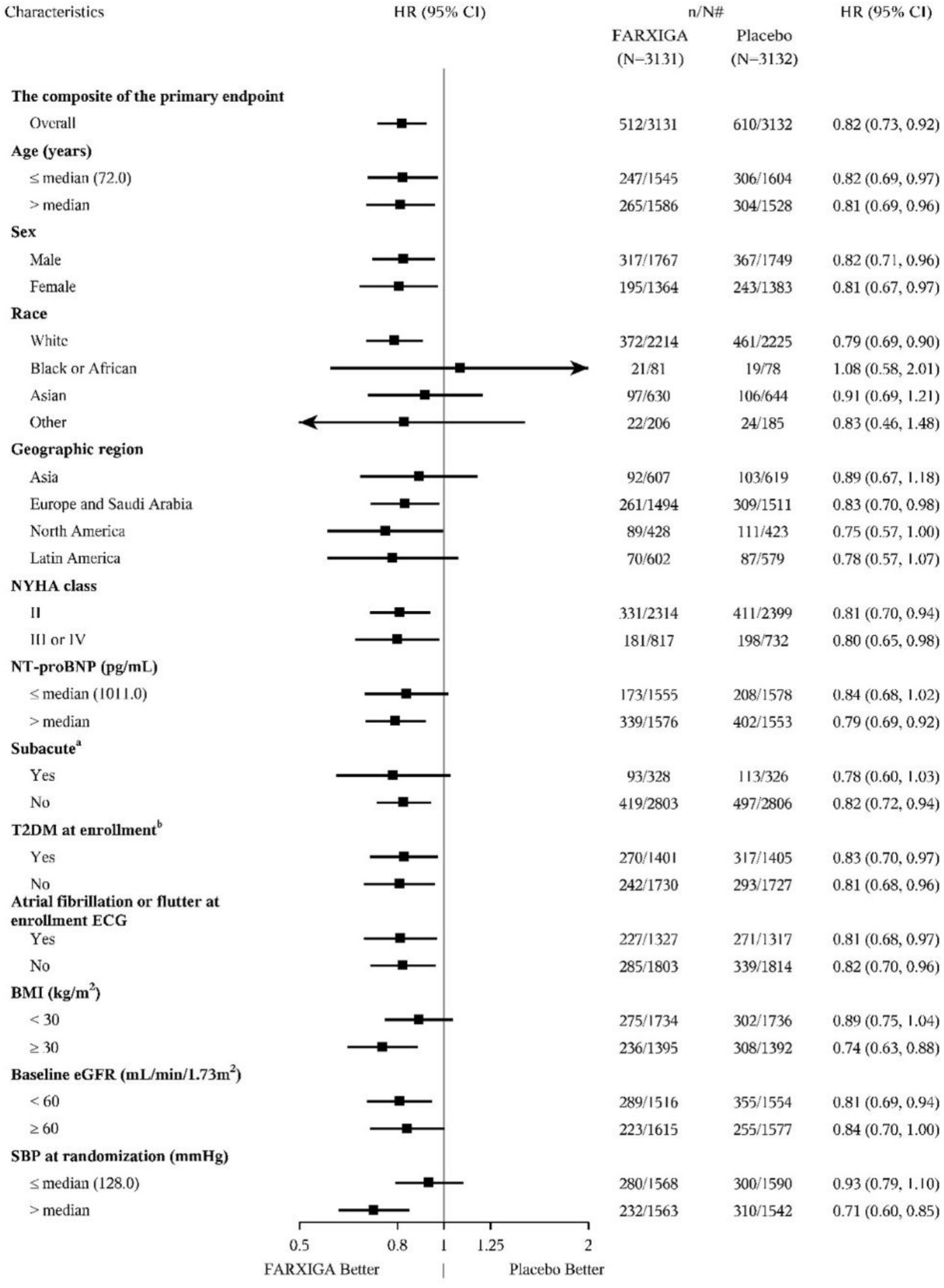
n/N# Number of subjects with event/number of subjects in the subgroup.

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.

B) DELIVER Trial


Characteristics
HR (95% CI)
n/N#
FARXIGA (N=3131)
Placebo (N=3132)
HR (95% CI)
The composite of the primary endpoint
Overall 512/3131 610/3132 0.82 (0.73, 0.92)
Age (years)
≤ median (72.0) 247/1545 306/1604 0.82 (0.69, 0.97)
> median 265/1586 304/1528 0.81 (0.69, 0.96)
Sex
Male 317/1767 367/1749 0.82 (0.71, 0.96)
Female 195/1364 243/1383 0.81 (0.67, 0.97)
Race
White 372/2214 461/2225 0.79 (0.69, 0.90)
Black or African 21/81 19/78 1.08 (0.58, 2.01)
Asian 97/630 106/644 0.91 (0.69, 1.21)
Other 22/206 24/185 0.83 (0.46, 1.48)
Geographic region
Asia 92/607 103/619 0.89 (0.67, 1.18)
Europe and Saudi Arabia 261/1494 309/1511 0.83 (0.70, 0.98)
North America 89/428 111/423 0.75 (0.57, 1.00)
Latin America 70/602 87/579 0.78 (0.57, 1.07)
NYHA class
II 331/2314 411/2399 0.81 (0.70, 0.94)
III or IV 181/817 198/732 0.80 (0.65, 0.98)
NT-proBNP (pg/mL)
≤ median (1011.0) 173/1555 208/1578 0.84 (0.68, 1.02)
> median 339/1576 402/1553 0.79 (0.69, 0.92)
Subacute[a]
Yes 93/328 113/326 0.78 (0.60, 1.03)
No 419/2803 497/2806 0.82 (0.72, 0.94)
T2DM at enrollment[b]
Yes 270/1401 317/1405 0.83 (0.70, 0.97)
No 242/1730 293/1727 0.81 (0.68, 0.96)
Atrial fibrillation or flutter at enrollment ECG
Yes 227/1327 271/1317 0.81 (0.68, 0.97)
No 285/1803 339/1814 0.82 (0.70, 0.96)
BMI (kg/m2)
< 30 275/1734 302/1736 0.89 (0.75, 1.04)
≥ 30 236/1395 308/1392 0.74 (0.63, 0.88)
Baseline eGFR (mL/min/1.73m2)
< 60 289/1516 355/1554 0.81 (0.69, 0.94)
≥ 60 223/1615 255/1577 0.84 (0.70, 1.00)
SBP at randomization (mmHg)
≤ median (128.0) 280/1568 300/1590 0.93 (0.79, 1.10)
> median 232/1563 310/1542 0.71 (0.60, 0.85)
0.5
0.8
1
1.25
2
FARXIGA Better
Placebo Better

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

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

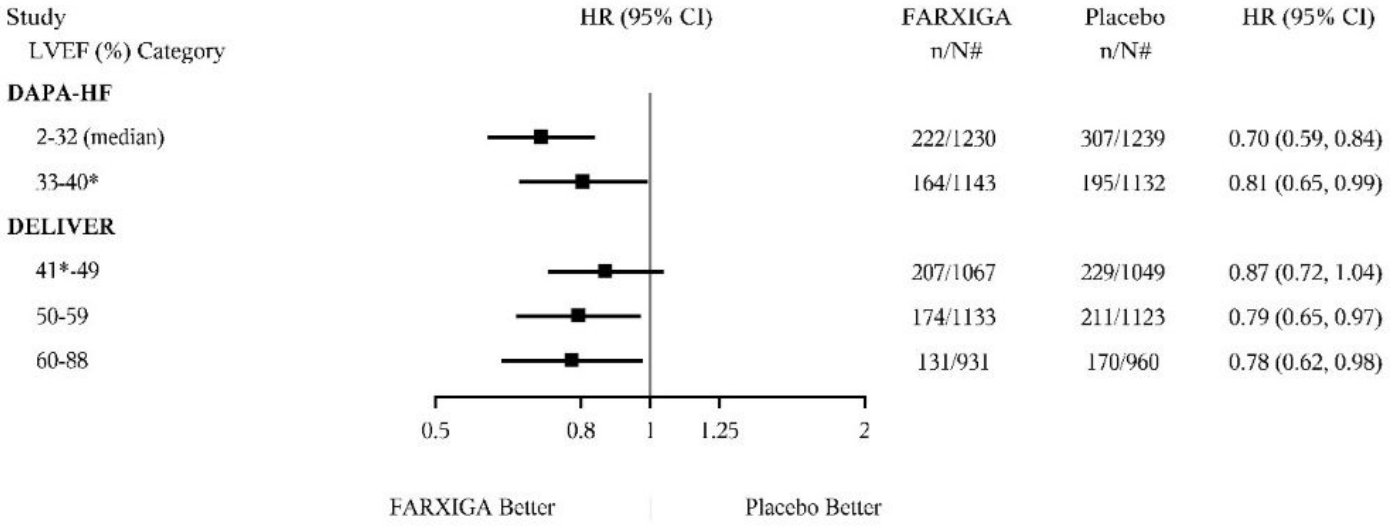
n/N# Number of subjects with event/number of subjects in the subgroup.

NT-proBNP = N-terminal pro b-type natriuretic peptide, HF = Heart failure, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, BMI = body mass index, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus.

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.

The treatment effect of FARXIGA on the composite endpoint of CV death, hospitalization for heart failure or urgent heart failure was consistent across the LVEF range as evaluated in DAPA-HF and DELIVER trials (Figure 11).

Figure 11: Treatment Effects for Primary Composite Endpoint (CV Death and Heart Failure Events) by LVEF (DAPA-HF and DELIVER Trials)



* 1 patient in DAPA-HF trial had LVEF >40. 4 patients in DELIVER trial had LVEF ≤40.

In DAPA-HF trial, the 5% and 95% percentiles of LVEF were 20 and 40 respectively. In DELIVER trial, the 5% and 95% percentiles of LVEF were 42 and 70, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

FARXIGA (dapagliflozin) tablets have markings on both sides and are available in the strengths and packages listed

5 mg: yellow, biconvex,round, “5” engraved on one side and “1427” engraved on the

other side

NDC: 70518-4614-00

NDC: 70518-4614-01

OUTER PACKAGING: 50 in 1 BOX

PACKAGING: 1 in 1 POUCH

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

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Remedy Repack, Inc.

625 Kolter Dr. Suite #4 Indiana, PA 1-724-465-8762

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Diabetic Ketoacidosis in Patients with Type 1 Diabetes Mellitus and Other Ketoacidosis

In patients with type 1 diabetes mellitus, inform them that using FARXIGA can increase their risk of life-threatening diabetic ketoacidosis. For all other patients, inform them that FARXIGA can cause potentially fatal ketoacidosis and that type 2 diabetes mellitus and pancreatic disorders (e.g., history of pancreatitis or pancreatic surgery) are risk factors.

Educate all patients on precipitating factors (such as insulin dose reduction or missed insulin doses, infection, reduced caloric intake, ketogenic diet, surgery, dehydration, and alcohol abuse) and symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing). Inform patients that blood glucose may be normal even in the presence of ketoacidosis.

Advise patients that they may be asked to monitor ketones. If symptoms of ketoacidosis occur, instruct patients to discontinue FARXIGA and seek medical attention immediately *[see Warnings and Precautions (5.1)]* .

Volume Depletion

Inform patients that symptomatic hypotension may occur with FARXIGA and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.2)]* . Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Genitourinary Infections, including Urosepsis, Pyelonephritis, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene), and Genital Mycotic Infections

Counsel patients that genitourinary infections may occur when taking FARXIGA and may become serious. Educate patients on the symptoms and advise them to seek medical advice if symptoms occur. Specifically, advise patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.3)]* .

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Inform patients that the incidence of hypoglycemia may increase when FARXIGA is added to an insulin secretagogue (e.g., sulfonylurea) and/or insulin. Educate patients on the signs and symptoms of hypoglycemia *[see Warnings and Precautions (5.4)]* .

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions (e.g., urticaria, anaphylactic reactions, and angioedema) have been reported with FARXIGA. Advise patients to immediately report any signs or symptoms suggesting allergic reaction or angioedema, and to take no more of the drug until they have consulted prescribing physicians.

Pregnancy

Advise pregnant patients of the potential risk to a fetus with treatment with FARXIGA. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant *[see Use in Specific Populations (8.1)]* .

Lactation

Advise patients that use of FARXIGA is not recommended while breastfeeding *[see Use in Specific Populations (8.2)].*

Laboratory Tests

Due to its mechanism of action, patients taking FARXIGA will test positive for glucose in their urine.

Missed Dose

Instruct patients to take FARXIGA only as prescribed. If a dose is missed, it should be taken as soon as possible. Advise patients not to double their next dose *[see Dosage and Administration (2.5)]* .

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625 Kolter Drive, Indiana, PA 15701

(724) 465-8762

MEDICATION GUIDE
FARXIGA ®[FAR-SEE-GUH]
(dapagliflozin)
tablets, for oral use

What is the most important information I should know about FARXIGA?

FARXIGA can cause serious side effects, including:

Diabetic ketoacidosis (increased ketones in your blood or urine) in people with type 1 diabetes and other ketoacidosis. FARXIGA can cause ketoacidosis that can be life-threatening and may lead to death. Ketoacidosis is a serious condition which needs to be treated in a hospital. People with type 1 diabetes have a high risk of getting ketoacidosis. People with type 2 diabetes or pancreas problems also have an increased risk of getting ketoacidosis. Ketoacidosis can also happen in people who: are sick, cannot eat or drink as usual, skip meals, are on a diet high in fat and low in carbohydrates (ketogenic diet),

take less than the usual amount of insulin or miss insulin doses, drink too much alcohol, have a loss of too much fluid from the body (volume depletion), or who have surgery. Ketoacidosis can happen even if your blood sugar is less than 250 mg/dL. Your healthcare provider may ask you to periodically check ketones in your urine or blood. Stop taking FARXIGA and call your healthcare provider or get medical help right away if you get any of the following. If possible, check for ketones in your urine or blood, even if your blood sugar is less than 250 mg/dL.

nausea

tiredness

vomiting

trouble breathing

stomach area (abdominal) pain

ketones in your urine or blood

Dehydration. FARXIGA can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). There have been reports of sudden kidney injury in people with Type 2 diabetes who are taking FARXIGA. You may be at a higher risk of dehydration if you:

take medicines to lower your blood pressure, including water pills (diuretics)
are on a low salt diet
have kidney problems
are 65 years of age or older

Talk to your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. Call your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you cannot eat or you start to lose liquids from your body, for example from vomiting, diarrhea, or being in the sun too long.
Genital and urinary tract infections.FARXIGA can cause serious infections in your genital area or urinary tract that could require hospitalization. A rare but serious bacterial infection called necrotizing fasciitis can cause damage to the tissue under the skin in the area between and around the anus and genitals (perineum).This infection may require hospitalization, multiple surgeries, and could lead to death. Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:

pain or tenderness

swelling

redness of skin (erythema)

Also tell your healthcare provider if you have any of these signs or symptoms of urinary tract infections or yeast infections:

Urinary tract infection:

burning feeling when you urinate

need to urinate often or right away
pain in the lower part of your stomach (pelvis)
blood in your urine

You may also have a fever, back pain, nausea, or vomiting.

Vaginal yeast infection:

vaginal odor
white or yellowish vaginal discharge (may be lumpy or look like cottage cheese)
vaginal itching

Yeast infection of the skin around the penis (balanitis or balanoposthitis):If you are uncircumcised, swelling may make it difficult to pull back the skin around the tip of your penis. Other symptoms include:

redness, itching, or swelling of the penis

rash on the penis

bad smelling discharge from the penis

pain in the skin around the penis

Talk to your healthcare provider about what to do if you get symptoms of a yeast infection. They may suggest you use an over-the-counter antifungal medicine. Contact your healthcare provider right away if your symptoms do not improve after using an over-the-counter antifungal medicine.

What is FARXIGA?

FARXIGA is a prescription medicine used:

to reduce the risk of further worsening of your kidney disease, end-stage kidney disease (ESKD), death due to cardiovascular disease, and hospitalization for heart failure in adults with chronic kidney disease.
to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure, when the heart cannot pump enough blood to the rest of your body.
to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes who also have known cardiovascular disease or multiple cardiovascular risk factors.
along with diet and exercise to improve blood sugar (glucose) control in adults and children who are 10 years of age and older with type 2 diabetes.

FARXIGA is not for use to improve blood sugar (glucose) control in people with type 1 diabetes.
FARXIGA is not for use to improve blood sugar (glucose) control in people with type 2 diabetes who have moderate to severe kidney problems, because it may not work.
FARXIGA is not for people with certain genetic forms of polycystic kidney disease, or who are taking or have recently received immunosuppressive therapy to treat kidney disease. FARXIGA is not expected to work if you have these conditions.
It is not known if FARXIGA is safe and effective to lower blood sugar (glucose) in children younger than 10 years of age with type 2 diabetes.

It is not known if FARXIGA is safe and effective for treatment of heart failure or chronic kidney disease in children younger than 18 years of age.

Who should not take FARXIGA?

Do not take FARXIGA if you:

are allergic to dapagliflozin or any of the ingredients in FARXIGA. See the end of this Medication Guide for a list of ingredients in FARXIGA. Symptoms of a seriousallergic reaction to FARXIGA may include:

rash
raised red patches on your skin (hives)
swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

If you have any of these symptoms, stop taking FARXIGA and contact your healthcare provider or go to the nearest hospital emergency room right away.

What should I tell my healthcare provider before taking FARXIGA?

Before you take FARXIGA, tell your healthcare provider if you:

have type 1 diabetes or have had diabetic ketoacidosis.
have a decrease in your insulin dose.
have a serious infection.
have a history of infection of the vagina or penis.
have liver problems.
have a history of urinary tract infections or problems with urination.
are on a low sodium (salt) diet. Your healthcare provider may ask you to change your diet.
are going to have surgery. Your healthcare provider may stop your FARXIGA before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking FARXIGA and when to start it again.
are eating less or there is a change in your diet.
are dehydrated.
have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
drink alcohol very often or drink a lot of alcohol in the short term (“binge” drinking).
are pregnant or plan to become pregnant. FARXIGA may harm your unborn baby. If you become pregnant while taking FARXIGA, your healthcare provider may switch you to a different medicine to control your blood sugar. Talk to your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
are breastfeeding or plan to breastfeed. It is not known if FARXIGA passes into your breast milk. You should not breastfeed if you take FARXIGA.

Tell your healthcare provider about all the medicines you take,including prescription and over-the-counter medicines, vitamins, and herbal supplements.

FARXIGA may affect the way other medicines work, and other medicines may affect how FARXIGA works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take FARXIGA?

Take FARXIGA exactly as your healthcare provider tells you to take it.

Take FARXIGA by mouth 1 time each day, with or without food.
Your healthcare provider will tell you how much FARXIGA to take and when to take it.
Your healthcare provider may change your dose if needed.
If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take 2 doses of FARXIGA at the same time. Talk with your healthcare provider if you have questions about a missed dose.
If you take too much FARXIGA, call your healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest emergency room right away.
If you have diabetes:

When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your healthcare provider right away if you have any of these conditions and follow your healthcare provider's instructions.
Your healthcare provider may tell you to take FARXIGA along with other diabetes medicines. Low blood sugar can happen more often when FARXIGA is taken with certain other diabetes medicines. See " What are the possible side effects of FARXIGA?"

FARXIGA will cause your urine to test positive for glucose.
Your healthcare provider may do certain blood tests before you start FARXIGA and during treatment as needed. Your healthcare provider may change your dose of FARXIGA based on the results of your blood tests.

What are the possible side effects of FARXIGA?

FARXIGA may cause serious side effects, including:

See "What is the most important information I should know about FARXIGA?".

Low blood sugar (hypoglycemia) in patients with diabetes mellitus.If you take FARXIGA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take FARXIGA. Signs and symptoms of low blood sugar may include:

headache

drowsiness

weakness

confusion

dizziness

sweating

hunger

fast heartbeat

irritability

shaking or feeling jittery

Serious allergic reaction.If you have any symptoms of a serious allergic reaction, stop taking FARXIGA and call your healthcare provider right away or go to the nearest

hospital emergency room. See “ Who should not take FARXIGA?”. Your healthcare provider may give you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.

The most common side effects of FARXIGA include:

vaginal yeast infections and yeast infections of the penis
stuffy or runny nose and sore throat
changes in urination, including urgent need to urinate more often, in larger amounts, or at night

These are not all the possible side effects of FARXIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FARXIGA?

Store FARXIGA at room temperature between 68°F and 77°F (20°C and 25°C).

General information about the safe and effective use of FARXIGA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FARXIGA for a condition for which it is not prescribed. Do not give FARXIGA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about FARXIGA. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about FARXIGA that is written for healthcare professionals.

For more information about FARXIGA, go to www.farxiga.com or call 1-800-236-9933.

What are the ingredients in FARXIGA?

Active ingredient:dapagliflozin.

Inactive ingredients:anhydrous lactose, crospovidone, magnesium stearate, microcrystalline cellulose, and silicon dioxide. The film coating contains: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and yellow iron oxide.

FARXIGA is a registered trademark of the AstraZeneca group of companies.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised 06/2026

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625 Kolter Drive, Indiana, PA 15701

(724) 465-8762

DRUG: FARXIGA

GENERIC: DAPAGLIFLOZIN

DOSAGE: TABLET, FILM COATED

ADMINSTRATION: ORAL

NDC: 70518-4614-0

NDC: 70518-4614-1

COLOR: yellow

SHAPE: ROUND

SCORE: No score

SIZE: 7 mm

IMPRINT: 5;1427

PACKAGING: 1 in 1 POUCH

OUTER PACKAGING: 50 in 1 BOX

ACTIVE INGREDIENT(S):

- DAPAGLIFLOZIN PROPANEDIOL 5mg in 1

INACTIVE INGREDIENT(S):

- MICROCRYSTALLINE CELLULOSE
- anhydrous lactose
- CROSPOVIDONE, UNSPECIFIED
- silicon dioxide
- magnesium stearate

Farxiga Tablet
dapagliflozin

MFG NDC: 00310-6205-30
MFG: AstraZeneca, Wilmington, DE 19850

Usual Dosage: See Insert

Keep this and all medication out o the reach of children
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [See USP]

5 mg

QTY: 50 Per Box
NDC #: **70518-4614-00**
LOT #:
Expires:
Round YELLOW 5;1427

remedy repack

RX ONLY

Repackaged By: RemedyRepack Inc.,
Indiana, PA 15701, 724.465.8762

Farxiga Tablet
dapagliflozin

MFG NDC: 00310-6205-30
MFG: AstraZeneca, Wilmington, DE 19850

Usual Dosage: See Insert

Keep this and all medication out o the reach of children
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [See USP]

5 mg

QTY: 1 Tablet
NDC #: **70518-4614-01**
LOT #:
Expires:
Round YELLOW 5;1427

remedy repack

RX ONLY

Repackaged By: RemedyRepack Inc.,
Indiana, PA 15701, 724.465.8762

FARXIGA

dapagliflozin tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70518-4614(NDC:0310-6205)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DAPAGLIFLOZIN PROPANEDIOL (UNII: 887K2391VH) (DAPAGLIFLOZIN - UNII:1ULL0QJ8UC)	DAPAGLIFLOZIN	5 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CROSPOVIDONE, UNSPECIFIED (UNII: 2S7830E561)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	yellow	**Score**	no score
Shape	ROUND (biconvex)	**Size**	7mm
Flavor		**Imprint Code**	5;1427
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70518-4614-0	50 in 1 BOX	04/23/2026	
1	NDC:70518-4614-1	1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA202293	04/23/2026	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 9/2026 REMEDYREPACK INC.