

JARDIANCE- empagliflozin tablet, film coated
Praxis, LLC

JARDIANCE[®] (empagliflozin tablets), for oral use

10 OVERDOSAGE

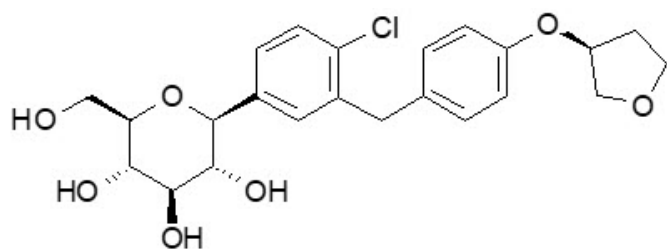
In the event of an overdose with JARDIANCE, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations. Removal of empagliflozin by hemodialysis has not been studied.

11 DESCRIPTION

JARDIANCE tablets for oral use contain empagliflozin, an inhibitor of the SGLT2.

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

Its molecular formula is C₂₃H₂₇ClO₇ and the molecular weight is 450.91. The structural formula is:



Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile, soluble in 50% acetonitrile/water, and practically insoluble in toluene.

Each film-coated tablet of JARDIANCE contains 10 mg or 25 mg of empagliflozin (free base) and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. In addition, the film coating contains the following inactive ingredients: hypromellose, polyethylene glycol, talc, titanium dioxide, and yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Empagliflozin is an inhibitor of SGLT2, the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Empagliflozin 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, increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart and downregulating sympathetic activity.

12.2 Pharmacodynamics

Urinary Glucose Excretion

In patients with type 2 diabetes mellitus, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment

period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily [see *Clinical Studies (14)*]. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume

In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology

In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

12.3 Pharmacokinetics

The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes mellitus and no clinically relevant differences were noted between the two populations. The steady-state mean plasma AUC and C_{max} were 1,870 nmol•h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4,740 nmol•h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. Empagliflozin does not appear to have time-dependent pharmacokinetic characteristics. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state.

Absorption

After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Administration of 25 mg empagliflozin after intake of a high-fat and high-calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution

The apparent steady-state volume of distribution was estimated to be 73.8 L based on a population pharmacokinetic analysis. Following administration of an oral [14 C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

Elimination

The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis.

Metabolism

No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphosphoglucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion

Following administration of an oral [14 C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Specific Populations

Pediatric Patients

The pharmacokinetics and pharmacodynamics of empagliflozin were investigated in pediatric patients aged 10 to 17 years with type 2 diabetes mellitus. Oral administration of empagliflozin at 10 mg and 25 mg resulted in exposure within the range observed in adult patients.

Effects of Age, Body Mass Index, Gender, and Race

Age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin.

Patients with Hepatic Impairment

In adult patients with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23%, 47%, and 75%, and C_{max} increased by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

Patients with Renal Impairment

In adult patients with type 2 diabetes mellitus with mild (eGFR: 60 to less than 90 mL/min/1.73 m²), moderate (eGFR: 30 to less than 60 mL/min/1.73 m²), and severe (eGFR: less than 30 mL/min/1.73 m²) renal impairment and patients on dialysis due to kidney failure, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and patients on dialysis due to kidney failure compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to patients with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Drug Interaction Studies

In vitro Assessment of Drug Interactions

Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

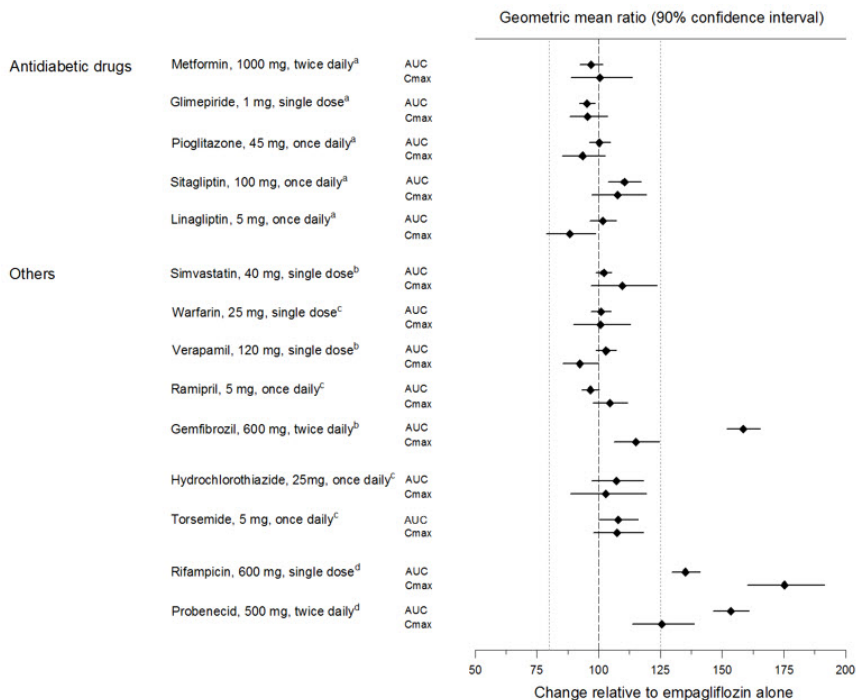
Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes mellitus (see Figure 1). In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine

without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

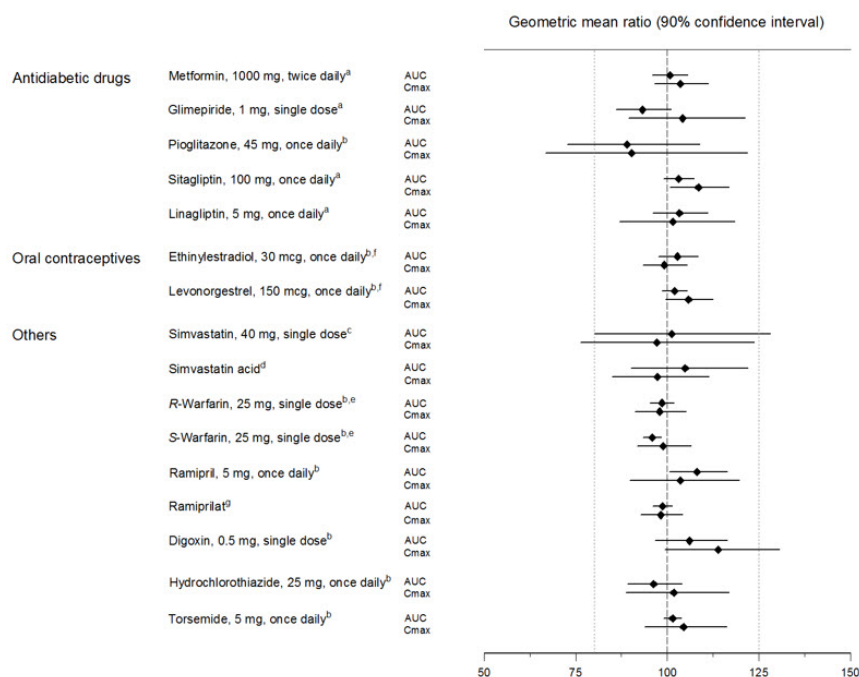
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, single dose; ^cempagliflozin, 25 mg, once daily; ^dempagliflozin, 10 mg, single dose

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



^aempagliflozin, 50 mg, once daily; ^bempagliflozin, 25 mg, once daily; ^cempagliflozin, 25 mg, single dose; ^dadministered as simvastatin; ^eadministered as warfarin racemic mixture; ^fadministered as Microgynon[®]; ^gadministered as ramipril

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1,000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1,000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Mutagenesis

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y tk⁺/mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Impairment of Fertility

Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus

JARDIANCE has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, linagliptin, and insulin. JARDIANCE has also been studied in patients with type 2 diabetes mellitus with mild or moderate renal impairment.

In adult patients with type 2 diabetes mellitus, treatment with JARDIANCE reduced hemoglobin A1c (HbA1c), compared to placebo. The reduction in HbA1c for JARDIANCE compared with placebo was observed across subgroups including sex, race, geographic region, baseline BMI and duration of disease.

Monotherapy

A total of 986 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of JARDIANCE monotherapy.

Treatment-naïve patients with inadequately controlled type 2 diabetes mellitus entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, JARDIANCE 10 mg, JARDIANCE 25 mg, or a reference comparator.

At Week 24, treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), fasting plasma glucose (FPG), and body weight compared with placebo (see Table 5 and Figure 3).

Table 5 Results at Week 24 From a Placebo-Controlled Monotherapy Trial of JARDIANCE

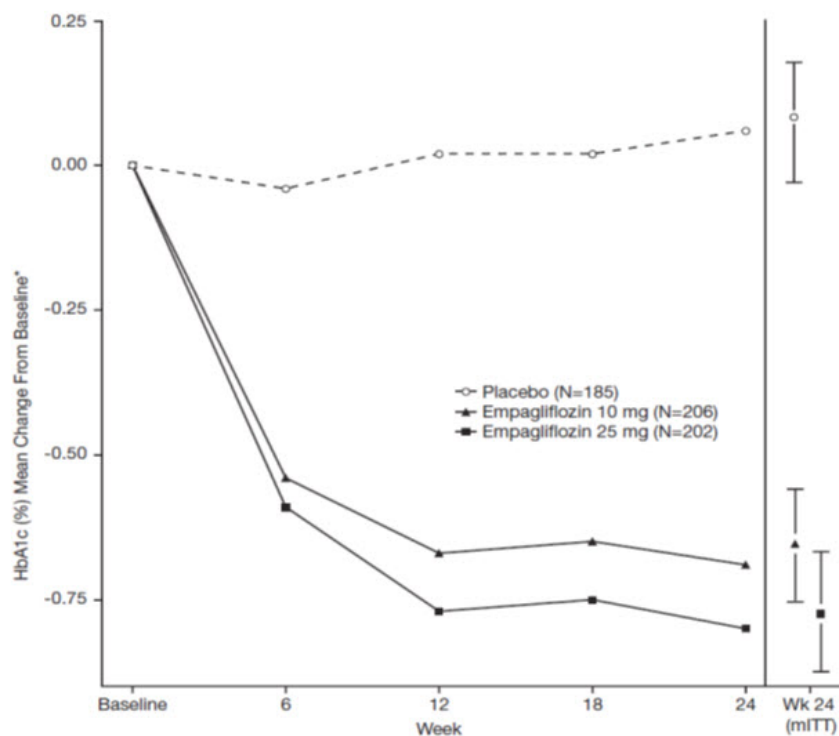
	JARDIANCE 10 mg N=224	JARDIANCE 25 mg N=224	Placebo N=228
HbA1c (%) ^a			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-0.7 ^b (-0.9, -0.6)	-0.9 ^b (-1.0, -0.7)	--
Patients [n (%)] achieving HbA1c <7%	72 (35%)	88 (44%)	25 (12%)
FPG (mg/dL) ^c			
Baseline (mean)	153	153	155
Change from baseline (adjusted mean)	-19	-25	12
Difference from placebo (adjusted mean) (95% CI)	-31 (-37, -26)	-36 (-42, -31)	--
Body Weight			
Baseline (mean) in kg	78	78	78
% change from baseline (adjusted mean)	-2.8	-3.2	-0.4
Difference from placebo (adjusted mean) (95% CI)	-2.5 ^b (-3.1, -1.9)	-2.8 ^b (-3.4, -2.2)	--

^aModified intent-to-treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 9.4%, 9.4%, and 30.7% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

^bANCOVA derived p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^cFPG (mg/dL); for JARDIANCE 10 mg, n=223, for JARDIANCE 25 mg, n=223, and for placebo, n=226

Figure 3 Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT Population) - LOCF



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, p-value=0.0231) in patients randomized to 10 mg of JARDIANCE and by -3.4 mmHg (placebo-corrected, p-value=0.0028) in patients randomized to 25 mg of JARDIANCE.

Add-On Combination Therapy with Metformin

A total of 637 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of JARDIANCE in combination with metformin.

Patients with type 2 diabetes mellitus inadequately controlled on at least 1,500 mg of metformin per day entered an open-label 2-week placebo run-in. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

At Week 24, treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 6).

Table 6 Results at Week 24 From a Placebo-Controlled Trial for JARDIANCE used in Combination with Metformin

	JARDIANCE 10 mg N=217	JARDIANCE 25 mg N=213	Placebo N=207
HbA1c (%) ^a			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	-0.1
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6 ^b (-0.7, -0.4)	-0.6 ^b (-0.8, -0.5)	--
Patients [n (%)] achieving HbA1c <7%	75 (38%)	74 (39%)	23 (13%)
FPG (mg/dL) ^c			

Baseline (mean)	155	149	156
Change from baseline (adjusted mean)	-20	-22	6
Difference from placebo + metformin (adjusted mean)	-26	-29	--
Body Weight			
Baseline mean in kg	82	82	80
% change from baseline (adjusted mean)	-2.5	-2.9	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.0 ^b (-2.6, -1.4)	-2.5 ^b (-3.1, -1.9)	--

^aModified intent-to-treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 9.7%, 14.1%, and 24.6% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

^bANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^cFPG (mg/dL); for JARDIANCE 10 mg, n=216, for JARDIANCE 25 mg, n=213, and for placebo, n=207

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-corrected, p-value <0.0001) for JARDIANCE 10 mg and -4.8 mmHg (placebo-corrected, p-value <0.0001) for JARDIANCE 25 mg.

Initial Combination Therapy with Metformin

A total of 1,364 patients with type 2 diabetes mellitus participated in a double-blind, randomized, active-controlled trial to evaluate the efficacy of JARDIANCE in combination with metformin as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes mellitus entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10.5% were randomized to one of 8 active-treatment arms: JARDIANCE 10 mg or 25 mg; metformin 1,000 mg, or 2,000 mg; JARDIANCE 10 mg in combination with 1,000 mg or 2,000 mg metformin; or JARDIANCE 25 mg in combination with 1,000 mg or 2,000 mg metformin.

At Week 24, initial therapy of JARDIANCE in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 7).

Table 7 Glycemic Parameters at 24 Weeks in a Trial Comparing JARDIANCE and Metformin to the Individual Components as Initial Therapy

	JARDIANCE 10 mg + Metformin 1,000 mg ^a N=161	JARDIANCE 10 mg + Metformin 2,000 mg ^a N=167	JARDIANCE 25 mg + Metformin 1,000 mg ^a N=165	JARDIANCE 25 mg + Metformin 2,000 mg ^a N=169	JARDIANCE 10 mg N=169	JARDIANCE 25 mg N=163	Metformin 1,000 mg ^a N=167	Metformin 2,000 mg ^a N=162
HbA1c (%)								
Baseline (mean)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
Change from baseline (adjusted mean)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.8
Comparison vs								

JARDIANCE (adjusted mean) (95% CI)	-0.6 ^b (-0.9, -0.4)	-0.7 ^b (-1.0, -0.5)	-0.6 ^c (-0.8, -0.3)	-0.7 ^c (-1.0, -0.5)	--	--	--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.8 ^b (-1.0, -0.6)	-0.3 ^b (-0.6, -0.1)	-0.8 ^c (-1.0, -0.5)	-0.3 ^c (-0.6, -0.1)	--	--	--	--

^aMetformin total daily dose, administered in two equally divided doses per day.

^bp-value ≤0.0062 (modified intent-to-treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

^cp-value ≤0.0056 (modified intent-to-treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

Add-On Combination Therapy with Metformin and Sulfonyleurea

A total of 666 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of JARDIANCE in combination with metformin plus a sulfonyleurea.

Patients with inadequately controlled type 2 diabetes mellitus on at least 1,500 mg per day of metformin and on a sulfonyleurea, entered a 2-week open-label placebo run-in. At the end of the run-in, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

Treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 8).

Table 8 Results at Week 24 from a Placebo-Controlled Trial for JARDIANCE in Combination with Metformin and Sulfonyleurea

	JARDIANCE 10 mg N=225	JARDIANCE 25 mg N=216	Placebo N=225
HbA1c (%) ^a			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	-0.8	-0.8	-0.2
Difference from placebo (adjusted mean) (95% CI)	-0.6 ^b (-0.8, -0.5)	-0.6 ^b (-0.7, -0.4)	--
Patients [n (%)] achieving HbA1c <7%	55 (26%)	65 (32%)	20 (9%)
FPG (mg/dL) ^c			
Baseline (mean)	151	156	152
Change from baseline (adjusted mean)	-23	-23	6
Difference from placebo (adjusted mean)	-29	-29	--
Body Weight			
Baseline mean in kg	77	78	76
% change from baseline (adjusted mean)	-2.9	-3.2	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.4 ^b (-3.0, -1.8)	-2.7 ^b (-3.3, -2.1)	--

^aModified intent-to-treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24,

17.8%, 16.7%, and 25.3% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

^bANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^cFPG (mg/dL); for JARDIANCE 10 mg, n=225, for JARDIANCE 25 mg, n=215, for placebo, n=224

In Combination with Linagliptin as Add-On to Metformin Therapy

A total of 686 patients with type 2 diabetes mellitus participated in a double-blind, active-controlled trial to evaluate the efficacy of JARDIANCE 10 mg or 25 mg in combination with linagliptin 5 mg compared to the individual components.

Patients with type 2 diabetes mellitus inadequately controlled on at least 1,500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10.5% were randomized 1:1:1:1 to one of 5 active-treatment arms of JARDIANCE 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg JARDIANCE as a fixed-dose combination tablet.

At Week 24, JARDIANCE 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin. Treatment with JARDIANCE/linagliptin 25 mg/5 mg or JARDIANCE/linagliptin 10 mg/5 mg daily also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference in body weight compared to JARDIANCE alone.

Active-Controlled Trial versus Glimepiride in Combination with Metformin

The efficacy of JARDIANCE was evaluated in a double-blind, glimepiride-controlled, trial in 1,545 patients with type 2 diabetes mellitus with insufficient glycemic control despite metformin therapy.

Patients with inadequate glycemic control and an HbA1c between 7% and 10% after a 2-week run-in period were randomized to glimepiride or JARDIANCE 25 mg.

At Week 52, JARDIANCE 25 mg and glimepiride lowered HbA1c and FPG (see Table 9, Figure 4). The difference in observed effect size between JARDIANCE 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dosage of glimepiride was 2.7 mg and the maximal approved dosage in the United States is 8 mg per day.

Table 9 Results at Week 52 from an Active-Controlled Trial Comparing JARDIANCE to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

	JARDIANCE 25 mg N=765	Glimepiride N=780
HbA1c (%) ^a		
Baseline (mean)	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.7
Difference from glimepiride (adjusted mean) (97.5% CI)	-0.07 ^b (-0.15, 0.01)	--
FPG (mg/dL) ^d		
Baseline (mean)	150	150
Change from baseline (adjusted mean)	-19	-9
Difference from glimepiride (adjusted mean)	-10	

Difference from glimepiride (adjusted mean)	-11	--
Body Weight		
Baseline mean in kg	82.5	83
% change from baseline (adjusted mean)	-3.9	2.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.9 ^c (-6.3, -5.5)	--

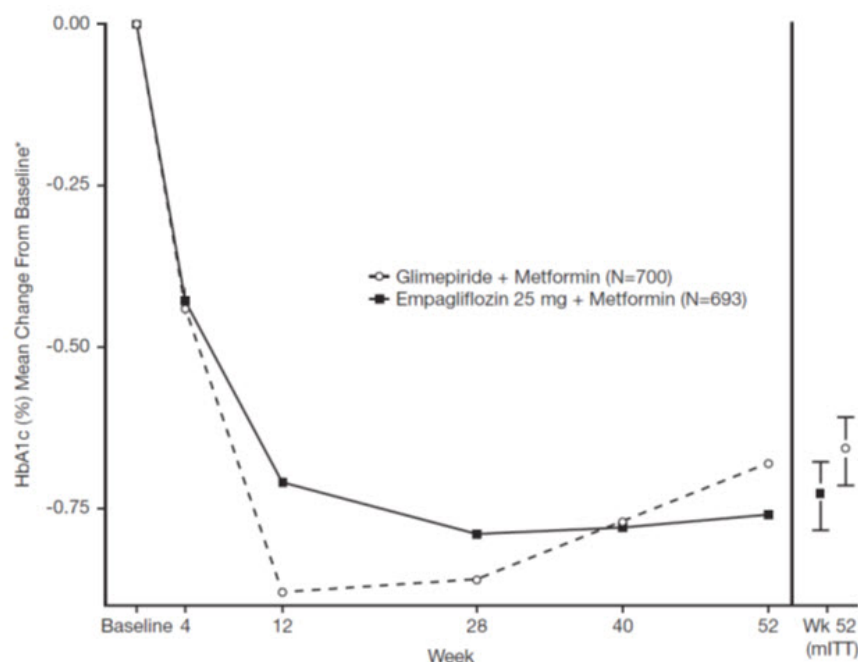
^aModified intent-to-treat population. Last observation on trial (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to JARDIANCE 25 mg and glimepiride, respectively.

^bNon-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)

^cANCOVA p-value <0.0001 (Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^dFPG (mg/dL); for JARDIANCE 25 mg, n=764, for glimepiride, n=779

Figure 4 Adjusted mean HbA1c Change at Each Time Point (Completers) and at Week 52 (mITT Population) - LOCF



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline.

At Week 52, the adjusted mean change from baseline in systolic blood pressure was -3.6 mmHg, compared to 2.2 mmHg for glimepiride. The differences between treatment groups for systolic blood pressure was statistically significant (p-value <0.0001).

At Week 104, the adjusted mean change from baseline in HbA1c was -0.75% for JARDIANCE 25 mg and -0.66% for glimepiride. The adjusted mean treatment difference was -0.09% with a 97.5% confidence interval of (-0.32%, 0.15%), excluding the pre-specified non-inferiority margin of 0.3%. The mean daily dosage of glimepiride was 2.7 mg and the maximal approved dosage in the United States is 8 mg per day. The Week 104 analysis included data with and without concomitant glycemic rescue medication, as well as off-treatment data. Missing data for patients not providing any information at the visit were imputed based on the observed off-treatment data. In this multiple imputation analysis, 13.9% of the data were imputed for JARDIANCE 25 mg and 12.9% for glimepiride.

At Week 104, JARDIANCE 25 mg daily resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.1 kg for JARDIANCE 25 mg vs. +1.3 kg for glimepiride; ANCOVA-LOCF, p-value <0.0001).

Add-On Combination Therapy with Pioglitazone with or without Metformin

A total of 498 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of JARDIANCE in combination with pioglitazone, with or without metformin.

Patients with inadequately controlled type 2 diabetes mellitus on metformin at a dose of at least 1,500 mg per day and pioglitazone at a dose of at least 30 mg per day were placed into an open-label placebo run-in for 2 weeks. Patients with inadequate glycemic control and an HbA1c between 7% and 10% after the run-in period were randomized to placebo, JARDIANCE 10 mg, or JARDIANCE 25 mg.

Treatment with JARDIANCE 10 mg or 25 mg daily resulted in statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 10).

Table 10 Results of Placebo-Controlled Trial for JARDIANCE in Combination Therapy with Pioglitazone

	JARDIANCE 10 mg N=165	JARDIANCE 25 mg N=168	Placebo N=165
HbA1c (%) ^a			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	-0.6	-0.7	-0.1
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-0.5 ^b (-0.7, -0.3)	-0.6 ^b (-0.8, -0.4)	--
Patients [n (%)] achieving HbA1c <7%	36 (24%)	48 (30%)	12 (8%)
FPG (mg/dL) ^c			
Baseline (mean)	152	152	152
Change from baseline (adjusted mean)	-17	-22	7
Difference from placebo + pioglitazone (adjusted mean) (97.5% CI)	-23 ^b (-31.8, -15.2)	-28 ^b (-36.7, -20.2)	--
Body Weight			
Baseline mean in kg	78	79	78
% change from baseline (adjusted mean)	-2.0	-1.8	0.6
Difference from placebo (adjusted mean) (95% CI)	-2.6 ^b (-3.4, -1.8)	-2.4 ^b (-3.2, -1.6)	--

^aModified intent-to-treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 10.9%, 8.3%, and 20.6% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

^bANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)

^cFPG (mg/dL); for JARDIANCE 10 mg, n=163

Add-On Combination with Insulin with or without Metformin and/or Sulfonylureas

A total of 494 patients with type 2 diabetes mellitus inadequately controlled on insulin, or insulin in combination with oral drugs participated in a double-blind, placebo-controlled trial to evaluate the efficacy of JARDIANCE as add-on therapy to insulin over 78 weeks.

Patients entered a 2-week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or sulfonylurea background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of JARDIANCE 10 mg, JARDIANCE 25 mg, or placebo. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 18 weeks of treatment. For the remaining 60 weeks, insulin could be adjusted. The mean total daily insulin dose at baseline for JARDIANCE 10 mg, 25 mg, and placebo was 45 IU, 48 IU, and 48 IU, respectively.

JARDIANCE used in combination with insulin (with or without metformin and/or sulfonylurea) provided statistically significant reductions in HbA1c and FPG compared to placebo after both 18 and 78 weeks of treatment (see Table 11). JARDIANCE 10 mg or 25 mg daily also resulted in statistically significantly greater percent body weight reduction compared to placebo.

Table 11 Results at Week 18 and 78 for a Placebo-Controlled Trial for JARDIANCE in Combination with Insulin

	18 weeks (no insulin adjustment)			78 weeks (adjustable insulin dose after 18 weeks)		
	JARDIANCE 10 mg N=169	JARDIANCE 25 mg N=155	Placebo N=170	JARDIANCE 10 mg N=169	JARDIANCE 25 mg N=155	Placebo N=170
HbA1c (%) ^a						
Baseline (mean)	8.3	8.3	8.2	8.3	8.3	8.2
Change from baseline (adjusted mean)	-0.6	-0.7	0	-0.4	-0.6	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-0.6 ^b (-0.8, -0.4)	-0.7 ^b (-0.9, -0.5)	--	-0.5 ^b (-0.7, -0.3)	-0.7 ^b (-0.9, -0.5)	--
Patients (%) achieving HbA1c <7%	18.0	19.5	5.5	12.0	17.5	6.7
FPG (mg/dL)						
Baseline (mean)	138	146	142	138	146	142
Change from baseline (adjusted mean, SE)	-17.9 (3.2)	-19.1 (3.3)	10.4 (3.1)	-10.1 (3.2)	-15.2 (3.4)	2.8 (3.2)
Difference from placebo (adjusted mean) (95% CI)	-28.2 ^b (-37.0, -19.5)	-29.5 ^b (-38.4, -20.6)	--	-12.9 ^c (-21.9, 3.9)	-17.9 ^b (-27.0, -8.8)	--

Body Weight						
Baseline mean in kg	92	95	90	92	95	90
% change from baseline (adjusted mean)	-1.8	-1.4	-0.1	-2.4	-2.4	0.7
Difference from placebo (adjusted mean) (95% CI)	-1.7 ^d (-3.0, -0.5)	-1.3 ^e (-2.5, -0.0)	--	-3.0 ^b (-4.4, -1.7)	-3.0 ^b (-4.4, -1.6)	--

^aModified intent-to-treat population. Last observation on trial (LOCF) was used to impute missing data at Week 18 and 78. At Week 18, 21.3%, 30.3%, and 21.8% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively. At Week 78, 32.5%, 38.1% and 42.4% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.

^bANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, and region; FPG: MMRM model includes baseline FPG, baseline HbA1c, treatment, region, visit and visit by treatment interaction. Body weight: MMRM model includes baseline body weight, baseline HbA1c, treatment, region, visit and visit by treatment interaction.

^cp-value=0.0049

^dp-value=0.0052

^ep-value=0.0463

Add-on Combination with MDI Insulin with or without Metformin

A total of 563 patients with type 2 diabetes mellitus inadequately controlled on multiple daily injections (MDI) of insulin (total daily dose >60 IU), alone or in combination with metformin, participated in a double-blind, placebo-controlled trial to evaluate the efficacy of JARDIANCE as add-on therapy to MDI insulin over 18 weeks.

Patients entered a 2-week placebo run-in period on MDI insulin with or without metformin background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of JARDIANCE 10 mg, JARDIANCE 25 mg, or placebo. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 18 weeks of treatment. The mean total daily insulin dose at baseline for JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo was 88.6 IU, 90.4 IU, and 89.9 IU, respectively.

JARDIANCE 10 mg or 25 mg daily used in combination with MDI insulin (with or without metformin) provided statistically significant reductions in HbA1c compared to placebo after 18 weeks of treatment (see Table 12).

Table 12 Results at Week 18 for a Placebo-Controlled Trial for JARDIANCE in Combination with Insulin and with or without Metformin

	JARDIANCE 10 mg N=186	JARDIANCE 25 mg N=189	Placebo N=188
HbA1c (%) ^a			
Baseline (mean)	8.4	8.3	8.3
Change from baseline (adjusted mean)	-0.9	-1.0	-0.5
Difference from placebo (adjusted mean) (95% CI)	-0.4 ^b (-0.6, -0.3)	-0.5 ^b (-0.7, -0.4)	--

^aModified intent-to-treat population. Last observation on trial (LOCF) was used to impute missing data at Week 18. At Week 18, 23.7%, 22.8% and 23.4% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively.
^bANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, geographical region, and background medication).

During an extension period with treatment for up to 52 weeks, insulin could be adjusted to achieve defined glucose target levels. The change from baseline in HbA1c was maintained from 18 to 52 weeks with both JARDIANCE 10 mg and 25 mg. After 52 weeks, JARDIANCE 10 mg or 25 mg daily resulted in statistically greater percent body weight reduction compared to placebo (p-value <0.0001). The mean change in body weight from baseline was -1.95 kg for JARDIANCE 10 mg, and -2.04 kg for JARDIANCE 25 mg.

Renal Impairment

A total of 738 patients with type 2 diabetes mellitus and a baseline eGFR less than 90 mL/min/1.73 m² participated in a randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy of JARDIANCE in patients with type 2 diabetes mellitus and renal impairment. The trial population comprised of 290 patients with mild renal impairment (eGFR 60 to less than 90 mL/min/1.73 m²), 374 patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m²), and 74 with severe renal impairment (eGFR less than 30 mL/min/1.73 m²). A total of 194 patients with moderate renal impairment had a baseline eGFR of 30 to less than 45 mL/min/1.73 m² and 180 patients had a baseline eGFR of 45 to less than 60 mL/min/1.73 m².

At Week 24, JARDIANCE 25 mg provided statistically significant reduction in HbA1c relative to placebo in patients with mild to moderate renal impairment (see Table 13). A statistically significant reduction relative to placebo was also observed with JARDIANCE 25 mg in patients with either mild [-0.7 (95% CI: -0.9, -0.5)] or moderate [-0.4 (95% CI: -0.6, -0.3)] renal impairment and with JARDIANCE 10 mg in patients with mild [-0.5 (95% CI: -0.7, -0.3)] renal impairment.

The glucose lowering efficacy of JARDIANCE 25 mg decreased with decreasing level of renal function in the mild to moderate range. Least square mean HbA1c changes at 24 weeks were -0.6%, -0.5%, and -0.2% for those with a baseline eGFR of 60 to less than 90 mL/min/1.73 m², 45 to less than 60 mL/min/1.73 m², and 30 to less than 45 mL/min/1.73 m², respectively [see *Dosage and Administration (2) and Use in Specific Populations (8.6)*]. For placebo, least square mean HbA1c changes at 24 weeks were 0.1%, -0.1%, and 0.2% for patients with a baseline eGFR of 60 to less than 90 mL/min/1.73 m², 45 to less than 60 mL/min/1.73 m², and 30 to less than 45 mL/min/1.73 m², respectively.

Table 13 Results at Week 24 (LOCF) of Placebo-Controlled Trial for JARDIANCE in Adults with Type 2 Diabetes Mellitus and Renal Impairment

	Mild and Moderate Impairment ^b
	JARDIANCE 25 mg
HbA1c	
Number of patients	n=284
Comparison vs placebo (adjusted mean) (95% CI)	-0.5 ^a (-0.6, -0.4)

^ap-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication)

^beGFR 30 to less than 90 mL/min/1.73 m²- Modified intent-to-treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 24.6% and 26.2% was imputed for patients randomized to JARDIANCE 25 mg and

placebo, respectively.

For patients with severe renal impairment, the analyses of changes in HbA1c and FPG showed no discernible treatment effect of JARDIANCE 25 mg compared to placebo [see *Indications and Usage (1), Dosage and Administration (2.1, 2.2) and Use in Specific Populations (8.6)*].

14.2 Glycemic Control Trial in Pediatric Patients Aged 10 to 17 Years with Type 2 Diabetes Mellitus

DINAMO(NCT03429543) was a 26-week, double-blind, randomized, placebo-controlled, parallel group trial, with a double-blind active treatment safety extension period up to 52 weeks to assess the efficacy of JARDIANCE. The trial enrolled pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus (HbA1c 6.5 to 10.5%). Patients treated with metformin (at least 1,000 mg daily or maximally tolerated dose), with or without insulin therapy, and those with a history of intolerance to metformin therapy were enrolled. Patients were randomized to 3 treatment arms (JARDIANCE 10 mg, a dipeptidyl peptidase-4 (DPP-4) inhibitor or placebo), over 26 weeks. Patients in the JARDIANCE 10 mg group who failed to achieve HbA1c <7.0% at Week 12 underwent a second randomization at Week 14 to remain on the 10 mg dose or increase to 25 mg. Patients on placebo were re-randomized at Week 26 to one of the JARDIANCE doses (10 mg or 25 mg) or a DPP-4 inhibitor.

A total of 157 patients were treated with either JARDIANCE (10 mg or 25 mg; N=52), a DPP-4 inhibitor (N=52), or placebo (N=53). Background therapies as adjunct to diet and exercise included metformin (51%), a combination of metformin and insulin (40.1%), insulin (3.2%), or none (5.7%). The mean HbA1c at baseline was 8.0% and the mean duration of type 2 diabetes mellitus was 2.1 years. The mean age was 14.5 years (range: 10-17 years) and 51.6% were aged 15 years and older. Approximately, 50% were White, 6% were Asian, 31% were Black or African American, and 38% were of Hispanic or Latino ethnicity. The mean BMI was 36.0 kg/m² and mean BMI Z-score was 3.0. Patients with an eGFR less than 60 mL/min/1.73 m² were not enrolled in the trial. Approximately 25% of the study population had microalbuminuria or macroalbuminuria.

At Week 26, treatment with JARDIANCE was superior in reducing HbA1c from baseline versus placebo (see Table 14).

Table 14 Results at Week 26 for a Placebo-Controlled Trial for JARDIANCE in Combination with Metformin and/or Insulin or as Monotherapy in Pediatric Patients Aged 10 to 17 Years with Type 2 Diabetes Mellitus^a

	JARDIANCE 10 mg and 25 mg	Placebo
HbA1c (%)^b		
Number of patients	n=52	n=53
Baseline (mean)	8.0	8.1
Change from baseline ^c	-0.2	0.7
Difference from placebo ^c (95% CI)	-0.8 ^e (-1.5, -0.2)	--
FPG (mg/dL)^{b,d}		
Number of patients	n=48	n=52
Baseline (mean)	154	159
Change from baseline ^c	-19	17
Difference from placebo ^c (95% CI)	-36 (-60.7, -10.7)	--

^aModified intent-to-treat set (All randomized and treated patients with baseline measurement).

^bMultiple imputations using placebo wash-out approach with 500 iterations for missing data. Imputed for HbA1c

(Jardiance N=5 (9.6 %), Placebo N=3 (5.7%)), for FPG (Jardiance N=4 (8.3%), Placebo N=2 (3.8%)).

^cLeast-Square Mean from Analysis of Covariance (ANCOVA) adjusted for baseline value and baseline age stratum (< 15 years vs 15 to < 18 years).

^dNot evaluated for statistical significance, not part of sequential testing procedure.

^ep-value=0.0116 (two-sided)

14.3 Cardiovascular Outcomes in Adults with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

The effect of JARDIANCE on cardiovascular (CV) risk in adult patients with type 2 diabetes mellitus and established, stable, atherosclerotic CV disease was evaluated in the EMPA-REG OUTCOME trial, a multicenter, multinational, randomized, double-blind parallel group trial. The trial compared the risk of experiencing a major adverse cardiovascular event (MACE) between JARDIANCE and placebo when these were added to and used concomitantly with standard of care treatments for diabetes mellitus and atherosclerotic CV disease. Concomitant antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, 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.

A total of 7,020 patients were treated (JARDIANCE 10 mg = 2,345; JARDIANCE 25 mg = 2,342; placebo = 2,333) and followed for a median of 3.1 years. Approximately 72% of the trial population was White, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the trial had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had diabetes mellitus for more than 10 years. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy to investigators, respectively and the mean eGFR was 74 mL/min/1.73 m². At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), and sulfonylurea (43%).

All patients had established atherosclerotic CV disease at baseline including one (82%) or more (18%) of the following: a documented history of coronary artery disease (76%), stroke (23%) or peripheral artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

The primary endpoint in EMPA-REG OUTCOME was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a CV death or a non-fatal myocardial infarction (MI) or a non-fatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg doses would be combined. 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 of MACE and superiority on MACE if non-inferiority was demonstrated. Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

JARDIANCE significantly reduced the risk of first occurrence of primary composite endpoint of CV death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI: 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of CV death in subjects randomized to empagliflozin (HR: 0.62; 95% CI: 0.49, 0.77), with no change in the risk of non-fatal myocardial infarction or non-fatal stroke (see Table 15 and Figures 5 and 6). Results for the 10 mg and 25 mg empagliflozin dosages were consistent with results for the combined dosage groups.

Table 15 Treatment Effect for the Primary Composite

Endpoint and its Components ^a

	Placebo N=2,333	JARDIANCE N=4,687	Hazard ratio vs placebo (95% CI)
Composite of CV death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence) ^b	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
Non-fatal myocardial infarction ^c	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
Non-fatal stroke ^c	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
CV death ^c	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

^aTreated set (patients who had received at least one dose of trial drug)

^bp-value for superiority (2-sided) 0.04

^cTotal number of events

Figure 5 Estimated Cumulative Incidence of First MACE

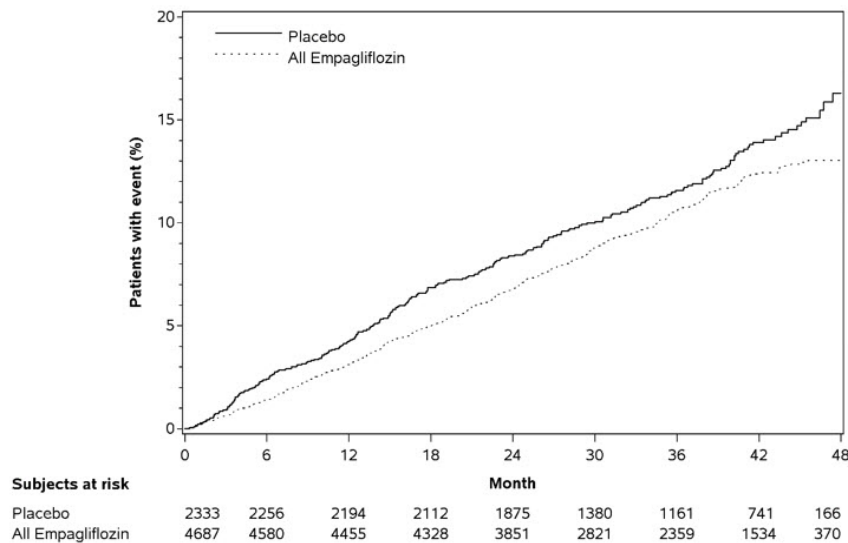
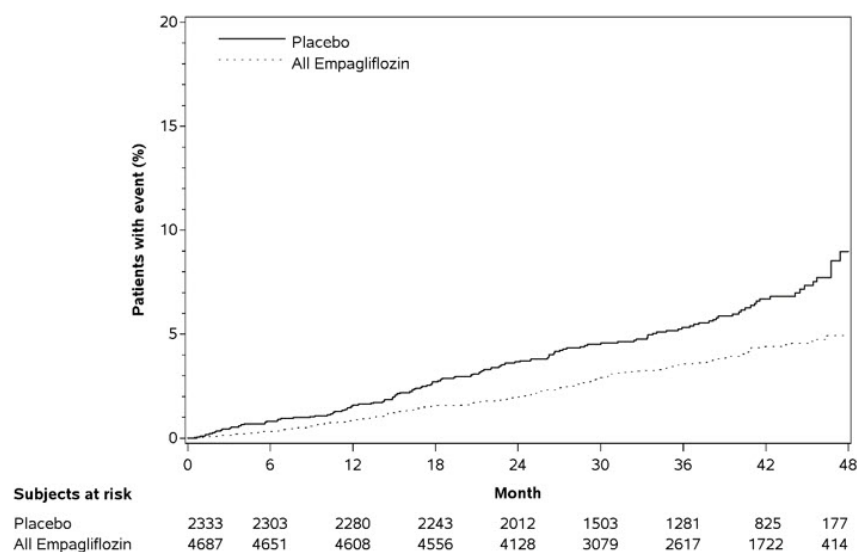


Figure 6 Estimated Cumulative Incidence of CV Death



The efficacy of JARDIANCE on CV death was generally consistent across major demographic and disease subgroups.

Vital status was obtained for 99.2% of subjects in the trial. A total of 463 deaths were recorded during the EMPA-REG OUTCOME trial. Most of these deaths were categorized as CV deaths. The non-CV deaths were only a small proportion of deaths and were balanced between the treatment groups (2.1% in patients treated with JARDIANCE, and 2.4% of patients treated with placebo).

14.4 Heart Failure Trials in Adults

EMPEROR-Reduced(NCT03057977) was a double-blind trial conducted in adults with chronic heart failure (New York Heart Association [NYHA] functional class II-IV) with left ventricular ejection fraction (LVEF) $\leq 40\%$ to evaluate the efficacy of JARDIANCE as adjunct to standard of care heart failure therapy.

Of 3,730 patients, 1,863 were randomized to JARDIANCE 10 mg and 1,867 to placebo and were followed for a median of 16 months. The mean age of the trial population was 67 years (range: 25 to 94 years) and 76% were men, 24% were women, and 27% were 75 years of age or older. Approximately 71% of the trial population were White, 18% Asian, and 7% Black or African American. At baseline, 50% of the patients had type 2 diabetes mellitus.

At randomization, 75% of patients were NYHA class II, 24% were class III, and 0.5% were class IV. The mean LVEF was 28%. At baseline, the mean eGFR was 62 mL/min/1.73 m² and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g. Approximately half of the patients (52%) had eGFR equal to or above 60 mL/min/1.73 m², 24% had eGFR 45 to less than 60 mL/min/1.73 m², 19% had eGFR 30 to less than 45 mL/min/1.73 m², and 5% had eGFR 20 to less than 30 mL/min/1.73 m².

At baseline, 88% of patients were treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI), 95% with beta-blockers, 71% with mineralocorticoid receptor antagonists (MRA), and 95% with diuretics.

The primary endpoint was the time to first event of either cardiovascular (CV) death or hospitalization for heart failure (HHF). First and recurrent HHF was assessed as a key secondary endpoint.

JARDIANCE was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalization for heart failure compared with placebo, mostly through a reduction in hospitalization for heart failure. JARDIANCE reduced the risk of first and recurrent HHF (see Table 16 and Figures 7 and 8).

Table 16 Treatment Effect for the Primary Composite Endpoint,

its Components, and Key Secondary Endpoints

	Placebo N=1,867	JARDIANCE 10 mg N=1,863	Hazard ratio vs placebo (95% CI)	p-value
	Number of Patients (%)			
CV death or HHF ^a	462 (24.7%)	361 (19.4%)	0.75 (0.65, 0.86)	<0.0001
CV death ^{a,b}	202 (10.8%)	187 (10.0%)	0.92 (0.75, 1.12)	
HHF ^a	342 (18.3%)	246 (13.2%)	0.69 (0.59, 0.81)	
	Number of Events			
First and recurrent HHF ^c	553	388	0.70 (0.58, 0.85)	0.0003

^aTime to first event

^bIncludes deaths following hospitalization

^cJoint frailty model accounting for CV death

Figure 7 Time to First Occurrence of the Primary Composite Endpoint of CV Death or Hospitalization for Heart Failure

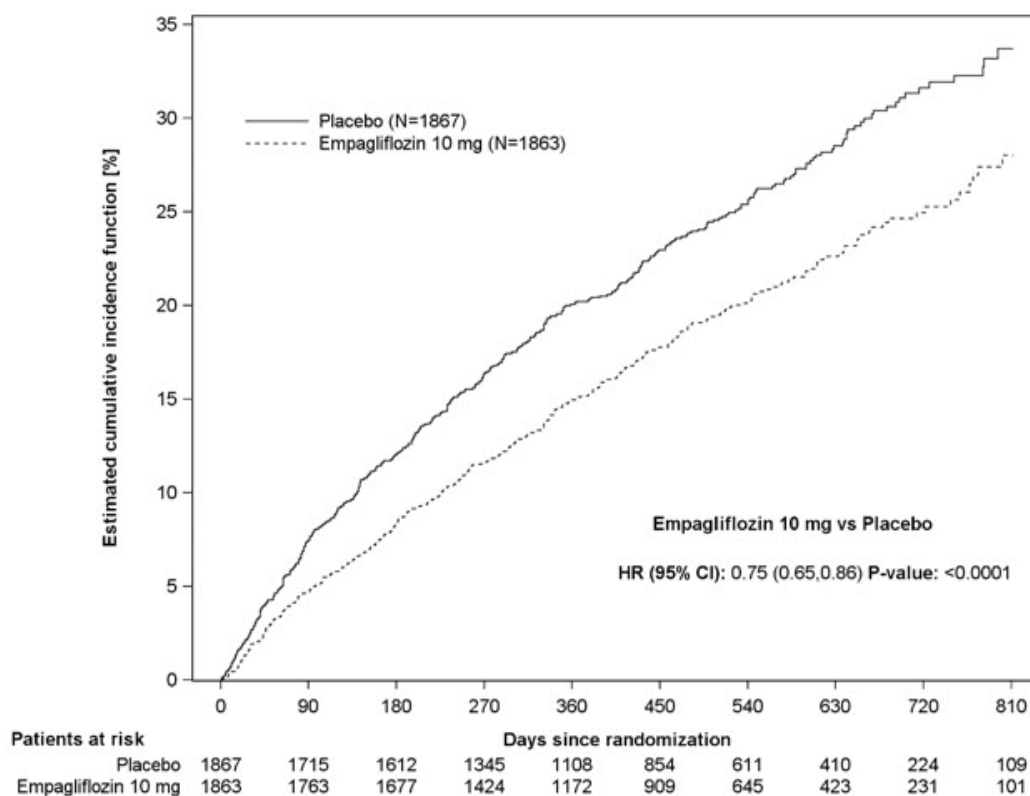
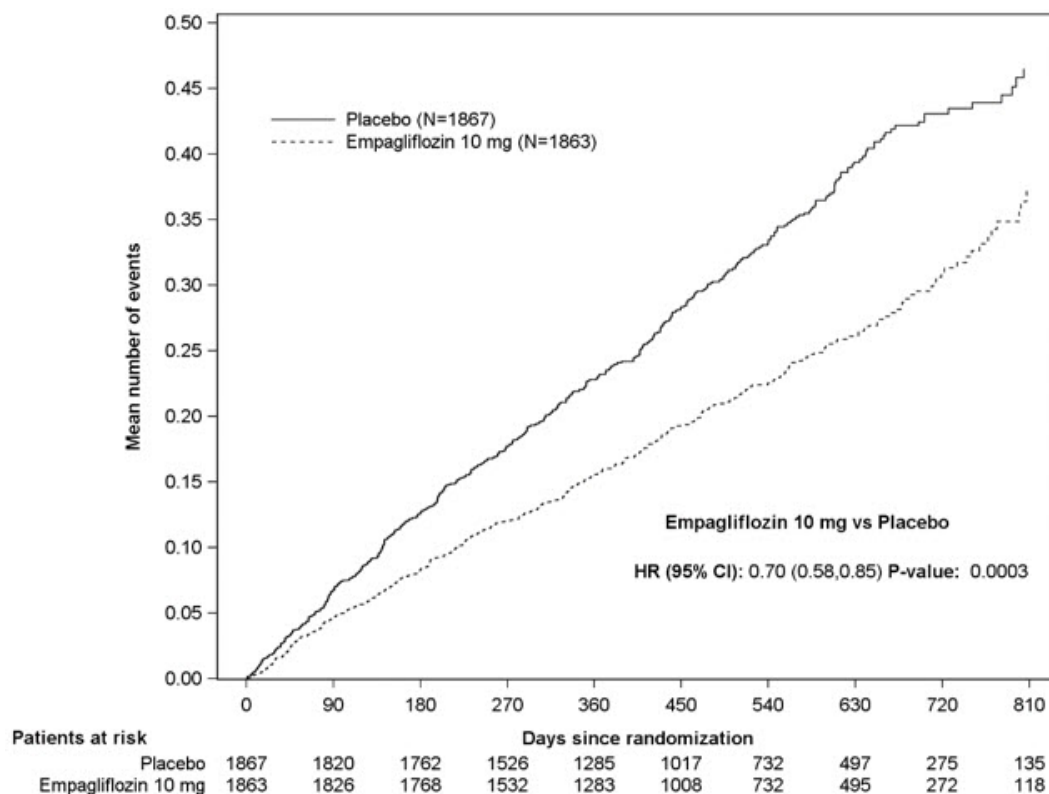
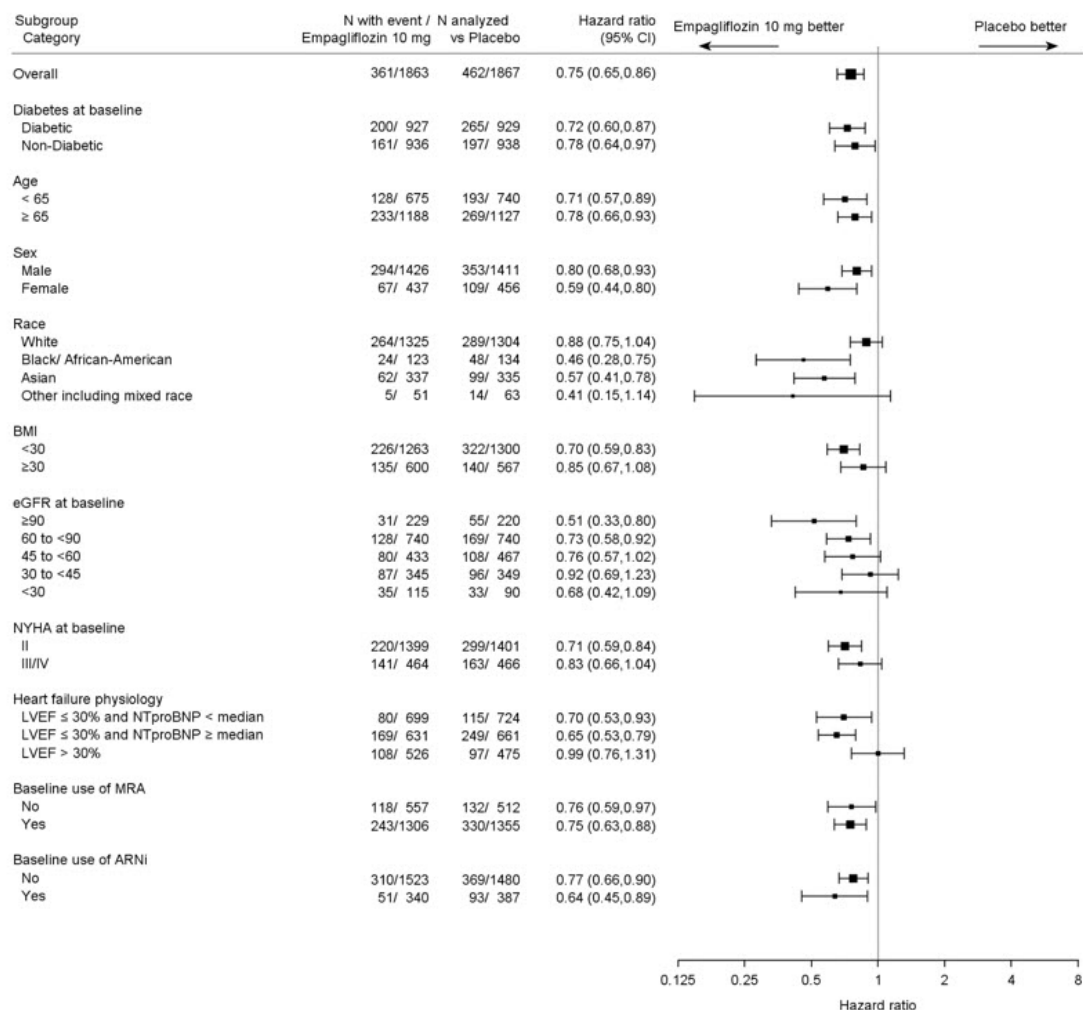


Figure 8 Time to Event of Hospitalization for Heart Failure (First and Recurrent)



The results of the primary composite were generally consistent across the pre-specified subgroups (see Figure 9).

Figure 9 Treatment Effects for the Primary Composite Endpoint (CV Death and Hospitalization for Heart Failure) Subgroup Analysis (EMPEROR-Reduced)



LVEF >30%: Includes both above and below the median NT-proBNP. To be eligible for inclusion, patients with an LVEF >30% were required to meet a higher NT-proBNP threshold than those with LVEF ≤30%, unless they additionally had a history of HHF within the past 12 months.

EMPEROR-Preserved(NCT03057951) was a double-blind trial conducted in adults with chronic heart failure NYHA Class II-IV with LVEF >40% to evaluate the efficacy of JARDIANCE as adjunct to standard of care therapy.

Of 5,988 patients, 2,997 were randomized to JARDIANCE 10 mg and 2,991 to placebo and were followed for a median of 26 months. The mean age of the trial population was 72 years (range: 22 to 100 years) and 55% were men, 45% were women, and 43% were 75 years of age or older. Approximately 76% of the trial population were White, 14% Asian, and 4% Black or African American.

At randomization, 82% of patients were NYHA class II, 18% were class III, and 0.3% were class IV. The *EMPEROR-Preserved* trial population included patients with a LVEF <50% (33.1%), with a LVEF 50 to <60% (34.4%) and a LVEF ≥60% (32.5%). At baseline, the mean eGFR was 61 mL/min/1.73 m² and the median urinary albumin to creatinine ratio (UACR) was 21 mg/g. Approximately half of the patients (50%) had eGFR equal to or above 60 mL/min/1.73 m², 26% had eGFR 45 to less than 60 mL/min/1.73 m², 19% had eGFR 30 to less than 45 mL/min/1.73 m², and 5% had eGFR 20 to less than 30 mL/min/1.73 m².

At baseline, 81% of patients were treated with ACE inhibitors, ARBs, or ARNI, 86% with beta-blockers, 38% with MRAs, and 86% with diuretics.

The primary endpoint was the time to first event of either CV death or HHF. First and recurrent HHF was assessed as a key secondary endpoint.

JARDIANCE was superior in reducing the risk of the primary composite endpoint

compared with placebo, mostly through a reduction in hospitalization for heart failure. JARDIANCE reduced the risk of first and recurrent HHF (see Table 17 and Figures 10 and 11).

Table 17 Treatment Effect for the Primary Composite Endpoint, its Components, and Key Secondary Endpoints

	Placebo N=2,991	JARDIANCE 10 mg N=2,997	Hazard ratio vs placebo (95% CI)	p-value
	Number of Patients (%)			
CV death or HHF ^a	511 (17.1%)	415 (13.8%)	0.79 (0.69, 0.90)	0.0003
CV death ^{a,b}	244 (8.2%)	219 (7.3%)	0.91 (0.76, 1.09)	
HHF ^a	352 (11.8%)	259 (8.6%)	0.71 (0.60, 0.83)	
	Number of Events			
First and recurrent HHF ^c	541	407	0.73 (0.61, 0.88)	0.0009

^aTime to first event

^bIncludes deaths following hospitalization

^cJoint frailty model accounting for CV death

Figure 10 Time to First Occurrence of the Primary Composite Endpoint of CV Death or Hospitalization for Heart Failure

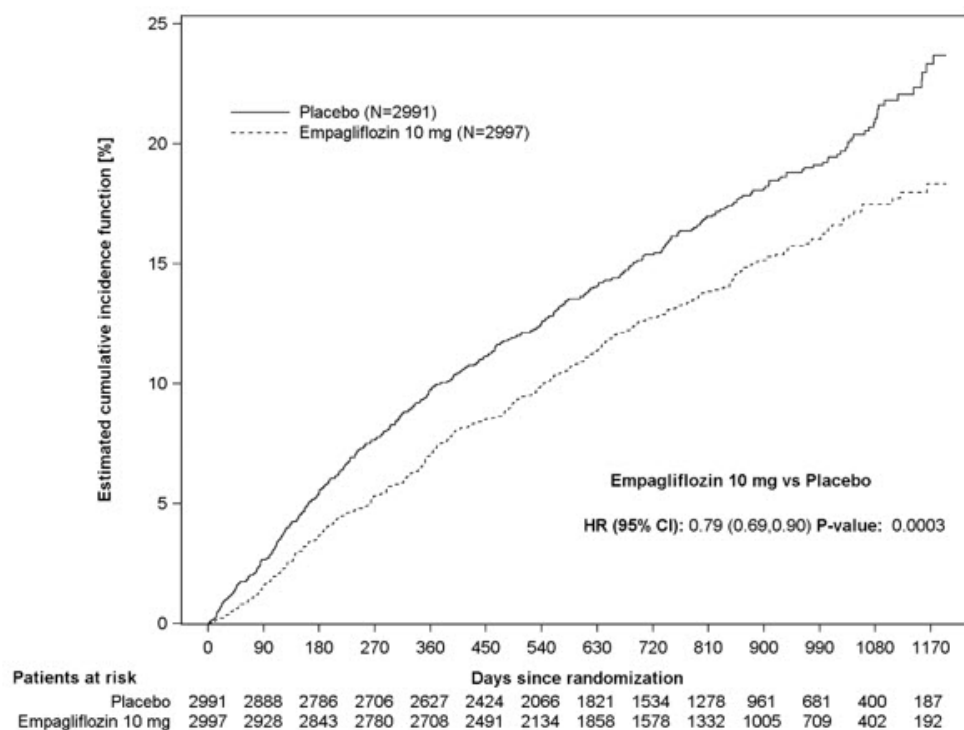
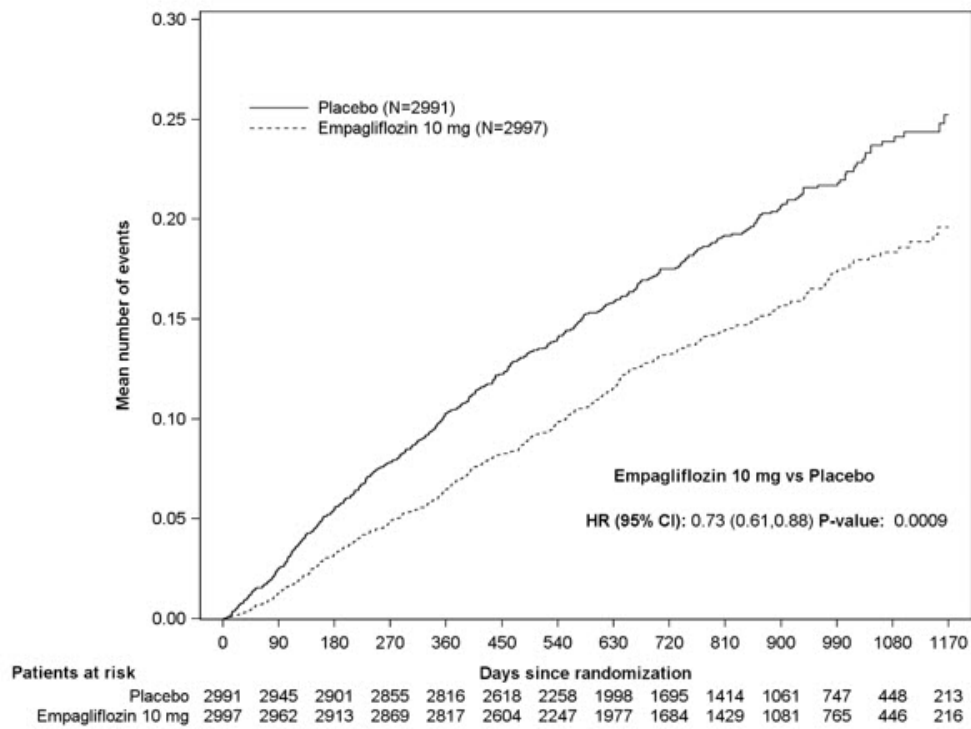
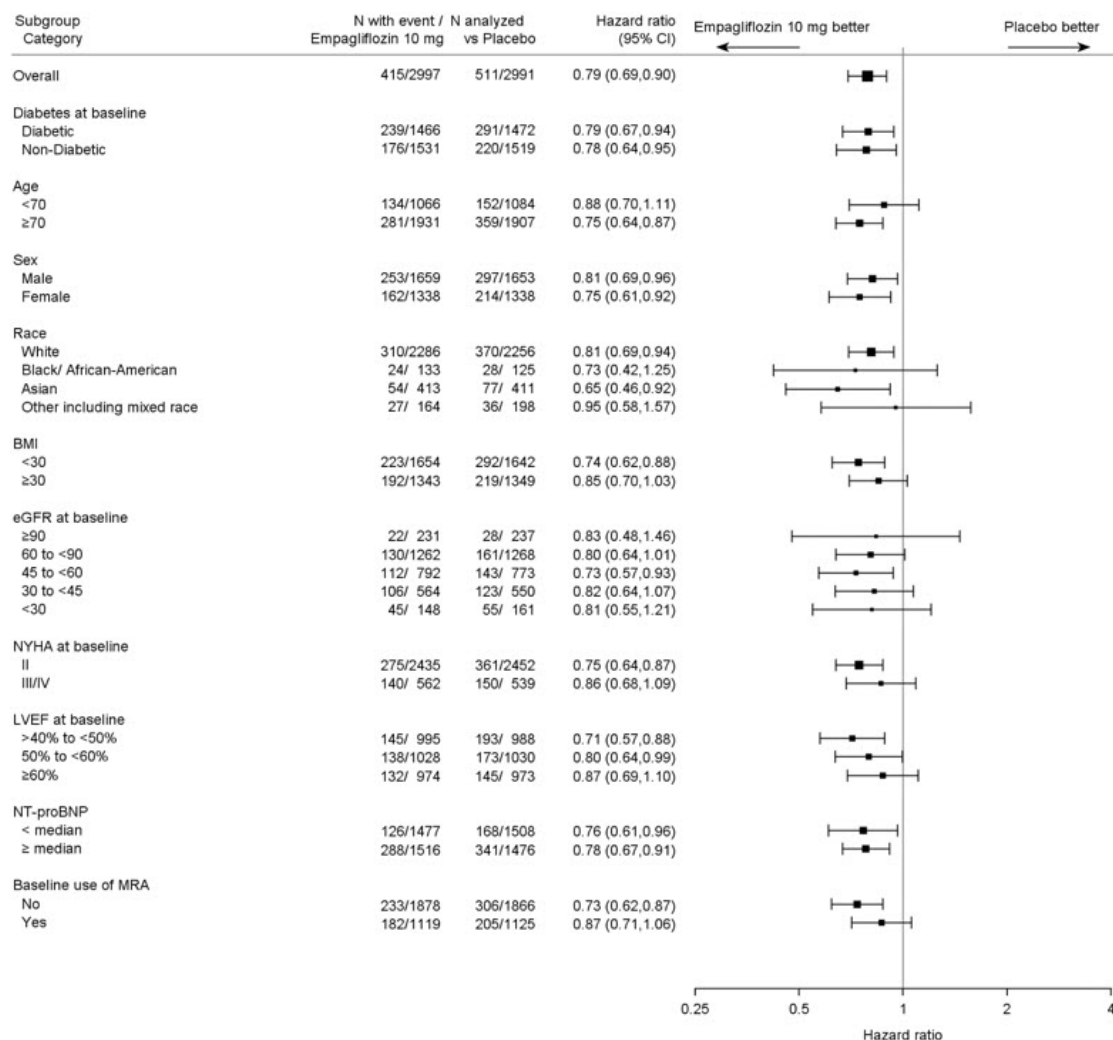


Figure 11 Time to Event of Hospitalization for Heart Failure (First and Recurrent)



The results of the primary composite endpoint were consistent across the pre-specified subgroups (see Figure 12).

Figure 12 Treatment Effects for the Primary Composite Endpoint (CV Death or Hospitalization for Heart Failure) Subgroup Analysis (EMPEROR-Preserved)



14.5 Chronic Kidney Disease Trial in Adults

EMPA-KIDNEY(NCT03594110) was a randomized, double-blind, placebo-controlled trial conducted in adults with chronic kidney disease (eGFR ≥ 20 to <45 mL/min/1.73 m²; or eGFR ≥ 45 to <90 mL/min/1.73 m² with urine albumin to creatinine ratio [UACR] ≥ 200 mg/g). The trial excluded patients with polycystic kidney disease or patients requiring intravenous immunosuppressive therapy in the preceding three months or >45 mg of prednisone (or equivalent) at the time of screening. The primary objective of the trial was to assess the effects of empagliflozin as an adjunct to standard of care therapy, including RAS-inhibitor therapy when appropriate, on time to kidney disease progression or cardiovascular death.

A total of 6,609 patients, were equally randomized to JARDIANCE 10 mg or placebo and were followed for a median of 24 months.

The mean age of the study population was 63 years (range: 18 to 94 years) and 67% were male. Approximately 58% of the study population were White, 36% Asian, and 4% Black or African American. Approximately 44% of the patients had type 2 diabetes mellitus.

At baseline, the mean eGFR was 37 mL/min/1.73 m², 21% of patients had an eGFR equal to or above 45 mL/min/1.73 m², 44% had an eGFR 30 to less than 45 mL/min/1.73 m², and 35% had an eGFR less than 30 mL/min/1.73 m². The median UACR was 329 mg/g, 20% of patients had a UACR <30 mg/g, 28% had a UACR 30 to ≤ 300 mg/g, and 52% had a UACR >300 mg/g. Approximately 1% of patients had type 1 diabetes at baseline. The most common etiologies of CKD were diabetic nephropathy/diabetic kidney disease (31%), glomerular disease (25%), hypertensive/renovascular disease (22%) and other/unknown (22%).

At baseline, 85% of patients were treated with ACE inhibitor or ARB, 64% with statins, and 34% with antiplatelet agents.

JARDIANCE was superior to placebo in reducing the risk of the primary composite endpoint of sustained $\geq 40\%$ eGFR decline, sustained eGFR < 10 mL/min/1.73 m², progression to end-stage kidney disease, or CV or renal death. The treatment effect reflected a reduction in a sustained $\geq 40\%$ eGFR decline, sustained eGFR < 10 mL/min/1.73 m², progression to end-stage kidney disease, and CV death. There were few renal deaths during the trial. JARDIANCE also reduced the risk of first and recurrent hospitalization (see Table 18 and Figure 13); information collected on the reason for hospitalization was insufficient to further characterize the benefit.

Table 18 Treatment Effect for the Primary Composite Endpoint, its Components and Key Secondary Endpoints

	Placebo N=3,305	JARDIANCE 10 mg N=3,304	Hazard ratio vs placebo (95% CI)	p-value
	Number of Patients (%)			
Composite of sustained $\geq 40\%$ eGFR decline, sustained eGFR < 10 mL/min/1.73 m ² , ESKD ^a , or CV or renal death (time to first occurrence)	558 (16.9)	432 (13.1)	0.72 (0.64, 0.82)	< 0.0001
Sustained $\geq 40\%$ eGFR decline	474 (14.3)	359 (10.9)	0.70 (0.61, 0.81)	
ESKD ^a or sustained eGFR < 10 mL/min/1.73 m ²	221 (6.7)	157 (4.8)	0.69 (0.56, 0.84)	
Renal death ^b	4 (0.1)	4 (0.1)		
CV death	69 (2.1)	59 (1.8)	0.84 (0.60, 1.19)	
	Number of Events			
First and recurrent hospitalization ^c	1,895	1,611	0.86 (0.78, 0.95)	0.0025

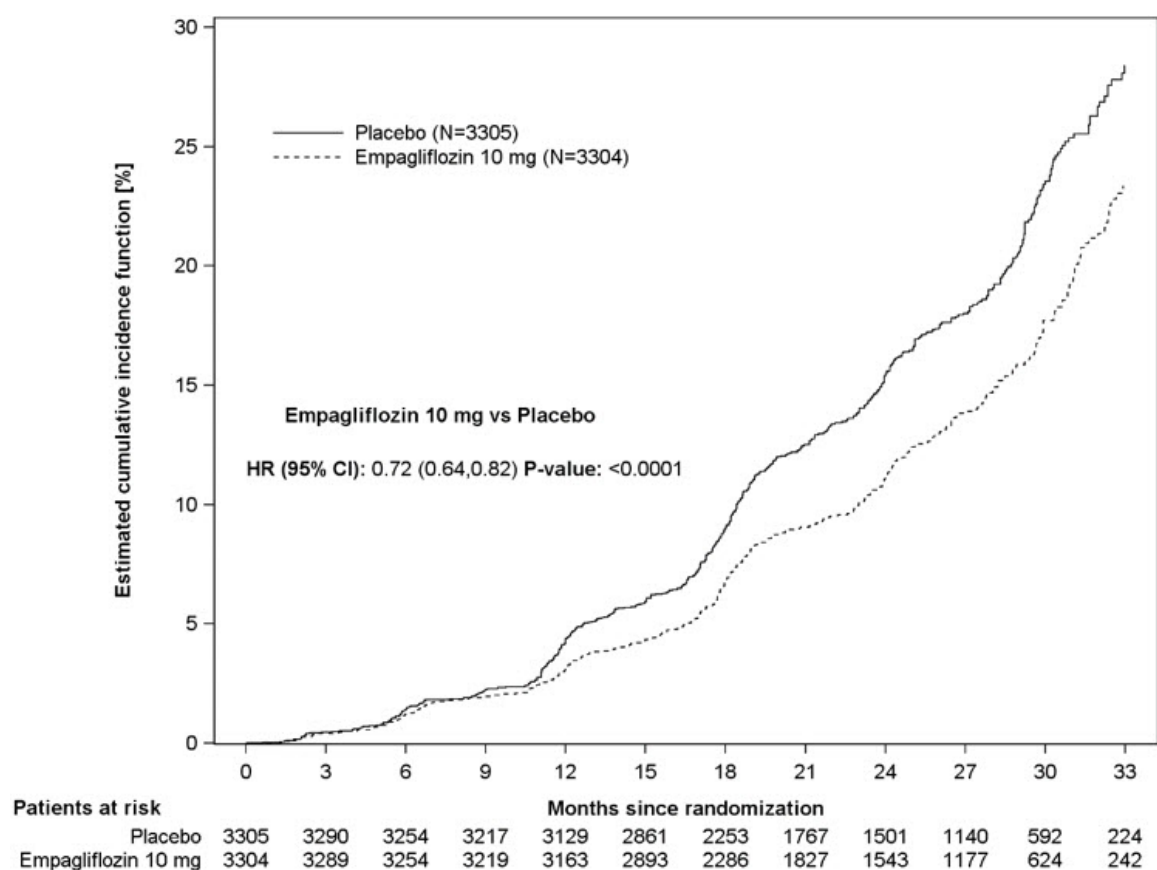
CV=Cardiovascular, eGFR=Estimated glomerular filtration rate, ESKD=End-stage kidney disease

^aESKD is defined as the initiation of maintenance dialysis or receipt of a kidney transplant.

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

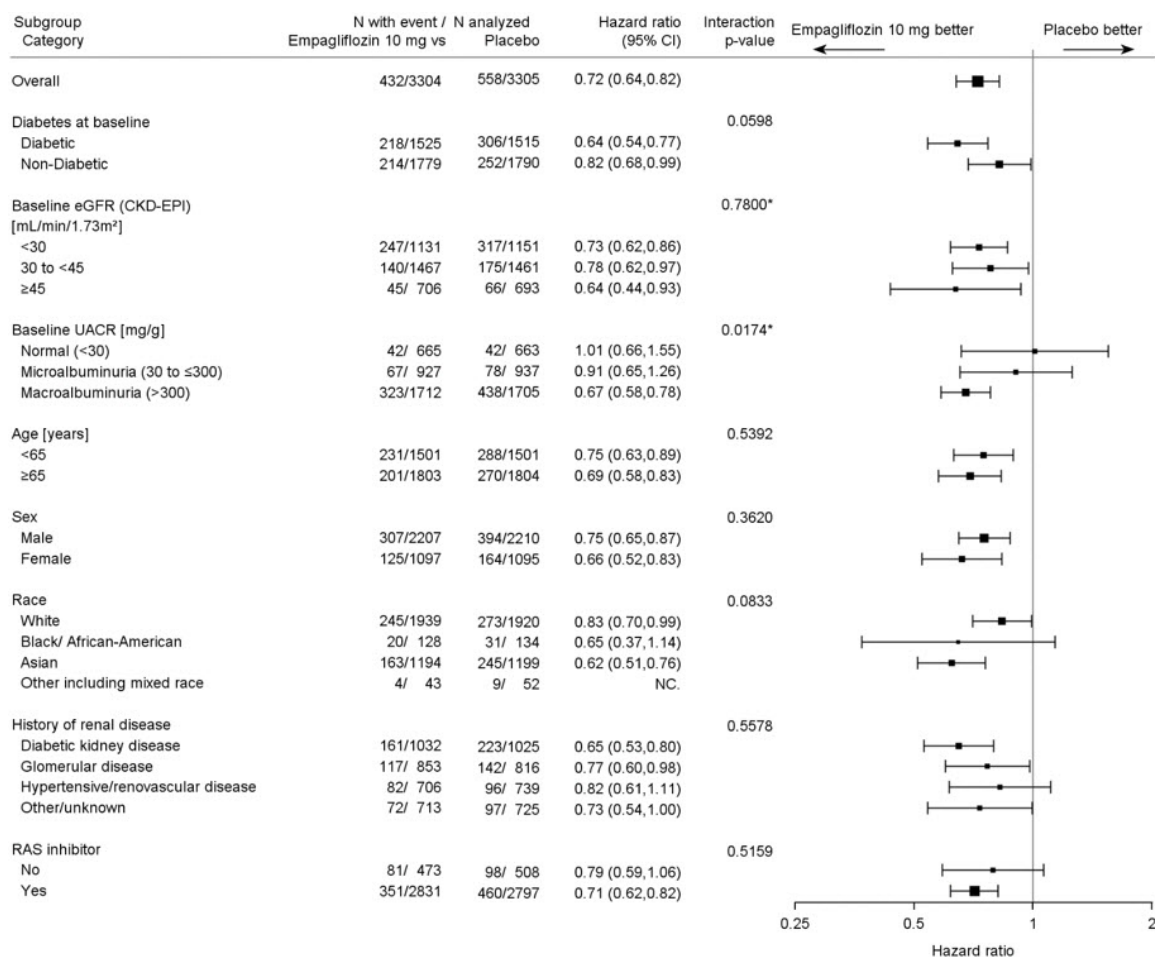
^cInformation collected on the reason for hospitalization was insufficient to further characterize the benefit.

Figure 13 Time to First Occurrence of the Primary Composite Endpoint, Sustained $\geq 40\%$ eGFR Decline, Sustained eGFR < 10 mL/min/1.73 m², ESKD or Renal Death, or CV Death



The results of the primary composite endpoint were generally consistent across the pre-specified subgroups examined, including eGFR categories, underlying cause of kidney disease, diabetes status, or background use of RAS inhibitors (see Figure 14). The treatment benefit with JARDIANCE on the primary composite endpoint was not evident in patients with very low levels of albuminuria, however there were few events in these patients.

Figure 14 Treatment Effects for the Primary Composite Endpoint (Sustained $\geq 40\%$ eGFR Decline, Sustained eGFR < 10 mL/min/1.73 m², ESKD or Renal Death, or CV Death) Subgroup Analysis (EMPA-KIDNEY)



*=Trend test

16 HOW SUPPLIED/STORAGE AND HANDLING

JARDIANCE tablets are available as follows:

10 mg tablets: pale yellow, round, biconvex, and bevel-edged film-coated tablets debossed with "S 10" on one side and the Boehringer Ingelheim company symbol on the other side.

Bottles of 30 (NDC 0597-0152-30)

Bottles of 90 (NDC 0597-0152-90)

Cartons containing 3 blister cards of 10 tablets each (3 × 10) (NDC 0597-0152-37), institutional pack.

25 mg tablets: pale yellow, oval, biconvex film-coated tablets, debossed with "S 25" on one side and the Boehringer Ingelheim company symbol on the other side.

Bottles of 30 (NDC 0597-0153-30)

Bottles of 90 (NDC 0597-0153-90)

Cartons containing 3 blister cards of 10 tablets each (3 × 10) (NDC 0597-0153-37), institutional pack.

Dispense in a well-closed container as defined in the USP.

Storage

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

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 JARDIANCE can increase their risk of life-threatening diabetic ketoacidosis and that fatal ketoacidosis has occurred. For all other patients, inform them that JARDIANCE 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 JARDIANCE and seek medical attention immediately [see *Warnings and Precautions* (5.1)] .

Volume Depletion

Inform patients that symptomatic hypotension may occur with JARDIANCE 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 maintain adequate fluid intake.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur [see *Warnings and Precautions* (5.3)] .

Hypoglycemia

Inform patients that hypoglycemia has been reported when JARDIANCE is used with insulin secretagogues or insulin. Hypoglycemia may occur in pediatric patients regardless of concomitant antidiabetic treatment. Educate patients or caregivers on the signs and symptoms of hypoglycemia [see *Warnings and Precautions* (5.4)] .

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with JARDIANCE. Counsel 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* (5.5)] .

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice [see *Warnings and Precautions* (5.6)] .

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)

Inform male patients that yeast infection of the penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice [see *Warnings and Precautions* (5.6)] .

Lower Limb Amputation

Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop [see *Warnings and Precautions* (5.7)] .

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria and

angioedema, have been reported with JARDIANCE. Advise patients to report immediately any skin reaction or angioedema, and to discontinue drug until they have consulted prescribing healthcare provider [see Warnings and Precautions (5.8)] .

Laboratory Tests

Inform patients that elevated glucose in urinalysis is expected when taking JARDIANCE [see Drug Interactions (7)] .

Pregnancy

Advise pregnant patients, and patients of reproductive potential, of the potential risk to a fetus with treatment with JARDIANCE [see Use in Specific Populations (8.1)] . Instruct patients to report pregnancies to their healthcare provider as soon as possible.

Lactation

Advise patients that breastfeeding is not recommended during treatment with JARDIANCE [see Use in Specific Populations (8.2)].

Missed Dose

Instruct patients to take JARDIANCE only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose [see Dosage and Administration (2.3)] .

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<p>MEDICATION GUIDE JARDIANCE[®] (jar DEE ans) (empagliflozin tablets) for oral use</p>
<p>What is the most important information I should know about JARDIANCE? JARDIANCE can cause serious side effects, including:</p> <ul style="list-style-type: none">• Diabetic ketoacidosis (increased ketones in your blood or urine) in people with type 1 and other ketoacidosis.JARDIANCE 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 JARDIANCE 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
- vomiting
- stomach-area (abdominal) pain
- tiredness
- trouble breathing
- ketones in your urine or blood

- **Dehydration. JARDIANCE can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension). There have been reports of sudden worsening of kidney function in people who are taking JARDIANCE.** You may be at higher risk of dehydration if you:

- take medicines to lower your blood pressure, including diuretics (water pills)
- are on low sodium (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 are sick or you cannot eat, or start to lose liquids from your body, for example from vomiting, diarrhea or being in the sun too long.

- **Vaginal yeast infection.** Symptoms of a vaginal yeast infection include:

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

- **Yeast infection of the skin around the penis (balanitis or balanoposthitis).** Swelling of an uncircumcised penis may develop that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:

- redness, itching, or swelling of the penis
- foul smelling discharge from the penis
- rash of the penis
- pain in the skin around penis

Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

What is JARDIANCE?

JARDIANCE is a prescription medicine used to:

- reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, when the heart cannot pump enough blood to the rest of your body.
- reduce the risk of further worsening of kidney disease, end-stage kidney disease (ESKD), death due to cardiovascular disease, and hospitalization in adults with chronic kidney disease.
- reduce the risk of cardiovascular death in adults with type 2 diabetes and who also have known cardiovascular disease.
- lower blood sugar (glucose) along with diet and exercise in adults and children who

are 10 years of age and older with type 2 diabetes.

JARDIANCE is not for use to lower blood sugar (glucose) in people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in blood or urine). JARDIANCE is not for use to lower blood sugar (glucose) in people with type 2 diabetes who have severe kidney problems, because it may not work. JARDIANCE is not for people with polycystic kidney disease, or who are taking or have recently received certain types of immunosuppressive therapy to treat kidney disease. JARDIANCE is not expected to work if you have these conditions. It is not known if JARDIANCE is safe and effective in children under 10 years of age.

Who should not take JARDIANCE?

Do not take JARDIANCE if you:

- are allergic to empagliflozin or any of the ingredients in JARDIANCE. See the end of this Medication Guide for a complete list of ingredients in JARDIANCE. Symptoms of a serious allergic reaction to JARDIANCE may include:
 - rash
 - raised, red areas on your skin (hives)
 - swelling of your face, lips, mouth, and throat that may cause difficulty in breathing or swallowing

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

What should I tell my healthcare provider before taking JARDIANCE?

Before taking JARDIANCE, tell your healthcare provider about all of your medical conditions, including 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 a history of amputation.
- have kidney problems.
- 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 change your diet or your dose.
- are going to have surgery. Your healthcare provider may stop your JARDIANCE before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking JARDIANCE 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).
- have ever had an allergic reaction to JARDIANCE.
- are pregnant or plan to become pregnant. JARDIANCE may harm your unborn baby. If you become pregnant while taking JARDIANCE, tell your healthcare provider as soon as possible. Talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. JARDIANCE may pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking JARDIANCE. Do not breastfeed while taking JARDIANCE.

Tell your healthcare provider about all the medicines you take,

including prescription and over-the-counter medicines, vitamins, and herbal supplements. JARDIANCE may affect the way other medicines work, and other medicines may affect how JARDIANCE 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 JARDIANCE?

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

- Take JARDIANCE by mouth 1 time in the morning each day, with or without food.
- Your healthcare provider will tell you how much JARDIANCE to take and when to take it. Your healthcare provider may change your dose if needed.
- Your healthcare provider may tell you to take JARDIANCE along with other diabetes medicines. Low blood sugar can happen more often when JARDIANCE is taken with certain other diabetes medicines. See "**What are the possible side effects of JARDIANCE?**"
- 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 two doses of JARDIANCE at the same time. Talk with your healthcare provider if you have questions about a missed dose.
- If you take too much JARDIANCE, call your healthcare provider or Poison Help line at 1-800-222-1222, or go to the nearest hospital emergency room right away.
- When taking JARDIANCE, you may have sugar in your urine, which will show up on a urine test.
- 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 do certain blood tests before you start JARDIANCE and during treatment as needed.

What are the possible side effects of JARDIANCE?

JARDIANCE may cause serious side effects, including:

- See "**What is the most important information I should know about JARDIANCE?**"
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking JARDIANCE. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
- **Low blood sugar (hypoglycemia).** In adults, if you take JARDIANCE with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. In children 10 years of age and older, the risk for low blood sugar is higher with JARDIANCE even if you do not use another medicine that can also lower blood sugar. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take JARDIANCE. Signs and symptoms of low blood sugar may include:

- | | | | |
|--------------|------------------|------------------------------|-------------|
| ◦ headache | ◦ irritability | ◦ confusion | ◦ dizziness |
| ◦ drowsiness | ◦ hunger | ◦ shaking or feeling jittery | ◦ sweating |
| ◦ weakness | ◦ fast heartbeat | | |

- **A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in people who take JARDIANCE. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may 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) |
|----------------------|------------|------------------------------|

- **Amputations. SGLT2 inhibitors may increase your risk of lower limb amputations.**

You may be at a higher risk of lower limb amputation if you:

- have a history of amputation
- have had blocked or narrowed blood vessels, usually in your leg
- have had diabetic foot infection, ulcers or sores

Call your healthcare provider right away if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Talk to your healthcare provider about proper foot care.

- **Serious allergic reactions.** If you have any symptoms of a serious allergic reaction, stop taking JARDIANCE and call your healthcare provider right away or go to the nearest hospital emergency room. See " **Who should not take JARDIANCE?**" .

The most common side effects of JARDIANCE include:

- urinary tract infections
- yeast infections in females

These are not all the possible side effects of JARDIANCE. 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 JARDIANCE?

- Store JARDIANCE at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep JARDIANCE and all medicines out of the reach of children.**

General information about the safe and effective use of JARDIANCE.

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

You can ask your pharmacist or healthcare provider for information about JARDIANCE that is written for health professionals.

What are the ingredients in JARDIANCE?

Active Ingredient: empagliflozin

Inactive Ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. In addition, the film coating contains the following inactive ingredients: hypromellose, polyethylene glycol, talc, titanium dioxide, and yellow ferric oxide.

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For more information about JARDIANCE, including current prescribing information and Medication Guide, go to **www.jardiance.com**, scan the code, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257.



This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: September 2023

PRINCIPAL DISPLAY PANEL - 10 mg Tablet Blister Card Carton

NDC 0597-0152-37

DISPENSE WITH ENCLOSED MEDICATION GUIDE

Jardiance®
(empagliflozin tablets)

10 mg

This unit dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

Rx only

30 tablets

3 blister cards. Each card contains 10 tablets.

Boehringer
Ingelheim

Lilly



PRINCIPAL DISPLAY PANEL - 25 mg Tablet Blister Card Carton

NDC 0597-0153-37

DISPENSE WITH ENCLOSED MEDICATION GUIDE

Jardiance®
(empagliflozin tablets)

25 mg

This unit dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

Rx only

30 tablets

3 blister cards. Each card contains 10 tablets.

Boehringer
Ingelheim

Lilly



JARDIANCE

empagliflozin tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:59368-379
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
EMPAGLIFLOZIN (UNII: HDC1R2M35U) (EMPAGLIFLOZIN - UNII:HDC1R2M35U)	EMPAGLIFLOZIN	10 mg

Product Characteristics

Color	yellow (pale yellow)	Score	no score
Shape	ROUND	Size	9mm
Flavor		Imprint Code	S;10
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-379-01	30 in 1 CARTON	08/01/2014	
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA204629	08/01/2014	

JARDIANCE

empagliflozin tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:59368-380
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
EMPAGLIFLOZIN (UNII: HDC1R2M35U) (EMPAGLIFLOZIN - UNII:HDC1R2M35U)	EMPAGLIFLOZIN	25 mg

Product Characteristics

Color	yellow (pale yellow)	Score	no score
Shape	OVAL	Size	11mm
Flavor		Imprint Code	S;25
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
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#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:59368-380-01	30 in 1 CARTON	08/01/2014	
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA		NDA204629	08/01/2014	

Labeler - Praxis, LLC (016329513)

Establishment			
Name	Address	ID/FEI	Business Operations
Praxis, LLC		016329513	pack(59368-379, 59368-380) , label(59368-379, 59368-380) , manufacture(59368-379, 59368-380)

Revised: 1/2023

Praxis, LLC