PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**JARDIANCE®**

Empagliflozin

Tablets, 10 mg and 25 mg, Oral

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Boehringer Ingelheim (Canada) Ltd.

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Type 2 diabetes mellitus (T2DM)

Monotherapy: JARDIANCE (empagliflozin) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM for whom metformin is inappropriate due to contraindications or intolerance.

Add-on combination: JARDIANCE is indicated in adult patients with T2DM to improve glycemic control in combination with

- metformin
- metformin and a sulfonylurea
- pioglitazone (alone or with metformin)
- linagliptin and metformin
- basal or prandial insulin (alone or with metformin)

when metformin alone or the existing therapy listed above, along with diet and exercise, do not provide adequate glycemic control.

Add-on combination in patients with established cardiovascular disease: JARDIANCE is indicated as an adjunct to diet, exercise and standard care therapy to reduce the incidence of cardiovascular death in patients with T2DM and established cardiovascular disease.

Important Limitations of Use: *Use of JARDIANCE with insulin mix (regular or analogue mix) has not been studied. Therefore, JARDIANCE should not be used with insulin mix.*

Heart Failure (HF)

JARDIANCE is indicated in adults as an adjunct to standard of care therapy for the treatment of heart failure.

Limitations of Use: JARDIANCE is not recommended for the emergency treatment of acute heart failure.

Chronic kidney disease (CKD)

JARDIANCE is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease and cardiovascular and renal death in adults with chronic kidney disease.

1.1 Pediatrics

Pediatrics (<18 years of age): Safety and efficacy of JARDIANCE have not been established in patients under 18 years of age; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>*65* years of age): JARDIANCE should be used with caution in geriatric patients with type 2 diabetes mellitus. A greater increase in risk of adverse reactions in geriatric patients with type 2 diabetes mellitus treated for glycemic control, was seen with JARDIANCE in the elderly, compared to younger patients. See **4 DOSAGE AND ADMINISTRATION**, **7.1.4 Geriatrics**, and **10 CLINICAL PHARMACOLOGY**.

In the EMPEROR-Reduced study, a total of 2312 (62%) treated patients with HFrEF were 65 years of age and older. In the EMPEROR-Preserved study, a total of 4786 (80%) treated patients with HFpEF were 65 years of age and older. Safety and efficacy in both studies were similar for patients 65 years and younger and those older than 65.

The EMPA-KIDNEY study included 2089 (32%) patients 65 to <75 years of age, and 1518 (23%) patients 75 years of age and older. Efficacy was similar for patients younger than 65 years and those aged 65 and older. An increase in risk of adverse reactions was observed in the elderly, compared to younger patients in both study arms. JARDIANCE should be used with caution in geriatric CKD patients due to risks of volume depletion and hypotension.

2 CONTRAINDICATIONS

- JARDIANCE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Ketoacidosis

- Clinical trial and post-market cases of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with JARDIANCE, and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. Fatal cases of ketoacidosis have been reported in patients with T2DM taking JARDIANCE. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL). See **8 ADVERSE REACTIONS**.
- Cases of ketoacidosis have also been reported in patients without T2DM taking JARDIANCE.
- The risk of ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness. If these symptoms occur, regardless of blood glucose level, JARDIANCE treatment should be **immediately discontinued,** and patients should be assessed for ketoacidosis immediately.
- JARDIANCE should not be used for the treatment of ketoacidosis or in patients with a history of ketoacidosis.
- JARDIANCE is not indicated, and should not be used, in patients with type 1 diabetes.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- JARDIANCE may be taken at any time of the day with or without food.
- Assess renal function prior to initiation of JARDIANCE therapy and regularly thereafter. See **7**

WARNINGS AND PRECAUTIONS.

- Assess volume status and, if necessary, correct volume depletion prior to initiation of JARDIANCE therapy. See **7 WARNINGS AND PRECAUTIONS**.
- **Concomitant use with insulin or an insulin secretagogue (e.g., sulfonylurea):** When JARDIANCE is used as add-on therapy with insulin or an insulin secretagogue, a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycemia. See **7 WARNINGS AND PRECAUTIONS** and **8 ADVERSE REACTIONS**.
- **Diuretics:** JARDIANCE should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events due to volume depletion during co-administration.
- Patients hospitalized for acute heart failure (de novo or decompensated chronic heart failure) should be adequately stabilised and should receive heart failure therapies in accordance with clinical guidelines.

4.2 Recommended Dose and Dosage Adjustment

Type 2 diabetes mellitus (T2DM)

To improve glycemic control, the recommended starting dose of JARDIANCE is 10 mg taken orally, once daily. In patients tolerating JARDIANCE 10 mg once daily and who require additional glycemic control, and who have an eGFR ≥30 mL/min/1.73 m^2, the dose can be increased to 25 mg once daily.

To reduce the incidence of cardiovascular death in patients with T2DM and established cardiovascular disease the recommended dose of JARDIANCE is 10 mg taken orally once daily.

Heart Failure (HF)

The recommended dose of JARDIANCE is 10 mg taken orally once daily.

Chronic kidney disease (CKD)

The recommended dose of JARDIANCE is 10 mg taken orally once daily.

Considerations for Special Populations

Renal Impairment: The glucose-lowering efficacy of JARDIANCE is dependent on renal function and decreases with declining renal function.

If eGFR falls below 30 mL/min/1.73m^2 the recommended dose of JARDIANCE is limited to 10 mg and additional glucose lowering treatment should be considered if needed. See **7 WARNINGS AND PRECAUTIONS**.

JARDIANCE 10 mg can be used regardless of renal function. Efficacy and safety trials with JARDIANCE did not enroll adult patients with an eGFR less than 20 mL/min/1.73 m^2 or on dialysis. Due to limited experience, it is not recommended to initiate treatment with JARDIANCE in patients on dialysis. See **7 WARNINGS AND PRECAUTIONS**.

Hepatic Impairment: No dosage adjustment for JARDIANCE is necessary for patients with mild or moderate hepatic impairment. JARDIANCE exposure is increased in patients with severe hepatic impairment. See **10 CLINICAL PHARMACOLOGY**.

Experience in patients with severe hepatic impairment is limited. Therefore, JARDIANCE is not

recommended for use in this population.

Pediatrics (<18 years of age): The safety and efficacy of JARDIANCE have not been established; therefore, Health Canada has not authorized an indication for use in pediatric patients.

Geriatrics (≥65 years of age): No dose adjustment for JARDIANCE is required based on age; however renal function and risk of volume depletion should be taken into account. See **7.1.4 Geriatrics**.

4.4 Administration

JARDIANCE tablets should be taken whole and should not be cut or divided.

4.5 Missed Dose

If a dose is missed, it should be taken as soon as the patient remembers. A double dose of JARDIANCE should not be taken on the same day.

5 OVERDOSAGE

It is reasonable to employ usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. The removal of JARDIANCE by haemodialysis has not been studied.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated tablets 10 mg, or 25 mg	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, macrogol, microcrystalline cellulose, titanium dioxide, talc, and yellow ferric oxide.

Description

JARDIANCE 10 mg film-coated tablets are pale yellow, round, biconvex and bevel-edged, debossed with "S10" on one side and the Boehringer Ingelheim company symbol on the other side.

JARDIANCE 25 mg film-coated tablets are pale yellow, oval, biconvex and debossed with "S25" on one side and the Boehringer Ingelheim logo on the other.

Packaging

PVC/aluminium unit dose blisters in cartons containing: 10 x 1 blister card (physician sample for the patients); or 10 x 3 blister cards, or 10 x 9 blister cards (commercial presentation).

7 WARNINGS AND PRECAUTIONS

*Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.*

General

JARDIANCE is not indicated for use in patients with type 1 diabetes and should not be used for the treatment of ketoacidosis.

Cardiovascular

Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances: JARDIANCE is not recommended for use in patients who are volume depleted.

Due to its mechanism of action, JARDIANCE causes diuresis that may be associated with decreases in blood pressure. See **14 CLINICAL TRIALS**.

Caution should be exercised in patients for whom an empagliflozin induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on antihypertensive therapy (particularly loop diuretics), elderly patients, patients with low systolic blood pressure, or in case of intercurrent conditions that may lead to volume depletion (such as gastrointestinal illness).

Careful monitoring of volume status is recommended. Temporary interruption of JARDIANCE should be considered for patients who develop volume depletion until the depletion is corrected. See **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**, and **8 ADVERSE REACTIONS**.

Cerebrovascular Accidents

In the EMPA-REG OUTCOME trial, JARDIANCE (empagliflozin 10 mg and 25 mg treatment groups combined) was associated with a non-significant trend for a higher risk of fatal/non-fatal stroke compared to the placebo group: HR 1.18 (95% CI 0.89, 1.56). See **14 CLINICAL TRIALS**.

A causal relationship between JARDIANCE and stroke has not been established; however, caution should be observed in patients at high risk for cerebrovascular accidents.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. JARDIANCE may cause dizziness or light-headedness. Patients should be advised to take precautions and not drive or use machines until they know how the medicine affects them.

Endocrine and Metabolism

Ketoacidosis: Clinical trial and post-market cases of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus treated with JARDIANCE, or other SGLT2 inhibitors. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 13.9 mmol/L (250 mg/dL). Fatal cases of ketoacidosis have been reported in patients with diabetes mellitus taking JARDIANCE. See **8 ADVERSE REACTIONS**.

Reports of ketoacidosis, including life-threatening and fatal cases, have also been identified in post-marketing surveillance in patients with type 1 diabetes mellitus receiving SGLT2 inhibitors, including JARDIANCE. The safety and efficacy of JARDIANCE in patients with type 1 diabetes have not been established. Limited data from clinical trials suggest that ketoacidosis occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

JARDIANCE is not indicated, and should not be used, in patients with type 1 diabetes. **The diagnosis of type 2 diabetes mellitus should therefore be confirmed before initiating JARDIANCE**.

Cases of ketoacidosis have also been reported in patients without T2DM taking JARDIANCE.

Patients treated with JARDIANCE who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with JARDIANCE may be present even if blood glucose levels are less than 13.9 mmol/L (250 mg/dL).

The risk of ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue, or sleepiness.

If these symptoms occur, regardless of blood glucose level, JARDIANCE treatment should be immediately discontinued, patients should be assessed for ketoacidosis immediately, and prompt treatment should be instituted.

Treatment with JARDIANCE should be interrupted in patients who are hospitalized for major surgical procedures, serious infections, or acute serious medical illnesses. Monitoring of ketones should be performed in these patients, even after treatment with JARDIANCE has been interrupted or discontinued.

For patients who undergo scheduled surgery, consider temporarily discontinuing JARDIANCE treatment prior to surgery.

SGLT2 inhibitors have been shown to increase blood ketones in clinical trial subjects.

Before initiating JARDIANCE, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

Conditions that can precipitate ketoacidosis while taking empagliflozin include patients on a very low carbohydrate diet (as the combination may further increase ketone body production), patients with conditions that lead to restricted food intake or severe dehydration, patients with increased insulin requirement due to an acute medical illness, surgery, or alcohol abuse, patients with a low beta-cell function reserve [e.g., type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA)], pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis, or pancreatic surgery), insulin dose reduction (including insulin pump failure), and patients with a history of ketoacidosis. JARDIANCE should be used with caution in these patients. These patients should be monitored closely.

Caution should be taken when reducing the insulin dose in patients requiring insulin. See **4 DOSAGE AND ADMINISTRATION**.

JARDIANCE should not be used for the treatment of ketoacidosis or in patients with a history of ketoacidosis.

In patients treated with JARDIANCE, consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or prior to and following surgery). In these situations, monitoring of ketones should be performed, even if JARDIANCE treatment has been interrupted or discontinued. Ensure risk factors for ketoacidosis are resolved prior to restarting JARDIANCE.

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

Use with Medications Known to Cause Hypoglycemia: Insulin secretagogues and insulin are known to cause hypoglycemia. The use of JARDIANCE in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. See **8 ADVERSE REACTIONS**.

Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with JARDIANCE. See **4 DOSAGE AND ADMINISTRATION**.

Genitourinary

Genital mycotic infections: JARDIANCE increases the risk of genital mycotic infections, particularly for patients with a history of genital mycotic infections. See **8 ADVERSE REACTIONS**.

Monitor and treat as appropriate.

Urinary tract infections (including urosepsis and pyelonephritis): JARDIANCE increases the risk for urinary tract infections. See **8 ADVERSE REACTIONS**.

There have been post-marketing reports of serious urinary tract infections including urosepsis and pyelonephritis, some of them requiring hospitalization, in patients receiving SGLT2 inhibitors, including JARDIANCE. See **8.5 Post-Market Adverse Reactions**.

Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated. Temporary interruption of JARDIANCE should be considered in patients with complicated urinary tract infections.

Necrotizing fasciitis of the perineum (Fournier's gangrene): Cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including JARDIANCE. Serious outcomes have included hospitalization, multiple surgeries, and death. See **8.5 Post-Market Adverse Reactions**.

Patients treated with JARDIANCE who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, or malaise should be evaluated for necrotizing fasciitis. If suspected, JARDIANCE should be discontinued, and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Hematologic

Elevated hemoglobin and hematocrit: Mean hemoglobin and hematocrit increased in patients administered JARDIANCE, as did the frequency of patients with abnormally elevated values for hemoglobin/hematocrit. See **8 ADVERSE REACTIONS**.

JARDIANCE should be used with caution in patients with an elevated hematocrit.

Hepatic/Biliary/Pancreatic

Substantial elevations in hepatic transaminases have been reported in empagliflozin treated patients in clinical trials; however, a causal relationship with empagliflozin has not been established. Use of JARDIANCE is not recommended in patients with severe hepatic impairment. See **4 DOSAGE AND ADMINISTRATION** and **10 CLINICAL PHARMACOLOGY**.

Immune

Hypersensitivity reactions: JARDIANCE is contraindicated in patients with a history of hypersensitivity reaction to the active substance or to any of the excipients. See **2 CONTRAINDICATIONS**.

Serious hypersensitivity reactions, including rash, angioedema and urticaria, have been observed with JARDIANCE in post-marketing reports. See **8 ADVERSE REACTIONS**.

If a hypersensitivity reaction occurs, discontinue JARDIANCE; treat promptly per standard of care, and monitor until signs and symptoms resolve.

Monitoring and Laboratory Tests

Blood glucose and HbA1c: Response to JARDIANCE treatment should be monitored by periodic measurements of blood glucose and HbA1c levels.

Due to its mechanism of action, patients taking JARDIANCE will test positive for glucose in their urine. See **9.7 Drug-Laboratory Test Interactions**.

Renal function: Renal function should be assessed prior to initiation of JARDIANCE and regularly thereafter. See **7 WARNINGS AND PRECAUTIONS, Renal**.

Monitoring of renal function is recommended prior to and following initiation of any concomitant drug which might have an impact on renal function.

Reduced intravascular volume: JARDIANCE is not recommended for use in patients who are volume depleted. Before initiating JARDIANCE, assess volume status, particularly in patients at risk, as well as in case of intercurrent conditions that may lead to fluid loss (such as a gastrointestinal illness) for patients already taking JARDIANCE. See **7 WARNINGS AND PRECAUTIONS, Cardiovascular**, and **4 DOSAGE AND ADMINISTRATION**.

In these patients, careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests, including hematocrit, serum electrolytes and renal function tests) is recommended. Temporary interruption of treatment with JARDIANCE should be considered until fluid loss is corrected.

Renal

JARDIANCE causes intravascular volume contraction and increases serum creatinine and decreases eGFR in a dose dependent fashion. Renal function abnormalities can occur after initiating JARDIANCE. Patients with hypovolemia are more susceptible to these changes. See **8 ADVERSE REACTIONS**.

Renal function should be assessed prior to initiation of JARDIANCE and periodically thereafter.

The glucose-lowering benefit of JARDIANCE decreases with declining renal function and was not demonstrated to be statistically significant in subjects with eGFR less than 30 mL/min/1.73 m^2. See **14 CLINICAL TRIALS**.

Efficacy and safety trials with JARDIANCE did not enroll adult patients with an eGFR less than 20 mL/min/1.73 m^2 or on dialysis. Once enrolled, patients were not required to discontinue therapy for worsening of eGFR to less than 20 mL/min/1.73 m^2 or initiation of dialysis. Due to limited experience, it is not recommended to initiate treatment with JARDIANCE in patients on dialysis.

Safety and efficacy of JARDIANCE have not been established in CKD patients with polycystic kidney disease, or patients requiring or with a recent history (within 3 months) of intravenous

immunosuppressive therapy or greater than 45 mg of prednisone or equivalent for the treatment of kidney disease. JARDIANCE is not recommended for the treatment of CKD in these patients.

There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors. Before initiating JARDIANCE, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing JARDIANCE in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue JARDIANCE promptly and institute treatment.

7.1 Special Populations

7.1.1 Pregnant Women

JARDIANCE must not be used in pregnancy. There are limited data for the use of JARDIANCE in pregnant women. When pregnancy is detected, JARDIANCE should be discontinued. Based on results from animal studies, SGLT2 inhibitors may affect renal development and maturation. See **16 NON-CLINICAL TOXICOLOGY**.

7.1.2 Breast-feeding

JARDIANCE must not be used in nursing women. No data in humans are available on excretion of JARDIANCE into milk. Available animal data have shown excretion of empagliflozin in milk reaching levels up to 5 times higher than that in the maternal plasma. See **16 NON-CLINICAL TOXICOLOGY**.

As functional maturation of the kidneys in humans continues in the first 2 years of life, there may be a risk to the developing kidney if JARDIANCE is used during breastfeeding.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Safety and effectiveness of JARDIANCE have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): JARDIANCE should be used with caution in geriatric patients with type 2 diabetes. A total of 2721 (32%) patients treated with empagliflozin were 65 years and over, and 491 (6%) were 75 years and over in the pool of double-blind, controlled clinical safety and efficacy studies of JARDIANCE in patients with type 2 diabetes treated for glycemic control.

A greater increase in risk of adverse reactions related to urinary tract infections was seen with JARDIANCE in the elderly patients with type 2 diabetes treated for glycemic control, compared to younger patients, and increased in patients who were 75 years of age and older. A greater increase in risk of adverse reactions related to volume depletion was seen with JARDIANCE in patients ≥75 years of age. JARDIANCE is expected to have diminished antihyperglycemic efficacy in elderly patients as older patients are more likely to have impaired renal function. Therefore, JARDIANCE should be used with

caution in this population. See **1 INDICATIONS**, **4 DOSAGE AND ADMINISTRATION**, and **10 CLINICAL PHARMACOLOGY**.

In the EMPEROR-Reduced study, a total of 2312 (62%) treated patients with HFrEF were 65 years of age and older. In the EMPEROR-Preserved study, a total of 4786 (80%) treated patients with HFpEF were 65 years of age and older. Safety and efficacy in both studies were similar for patients 65 years and younger and those older than 65.

The EMPA-KIDNEY study included 2089 (32%) patients 65 to <75 years of age, and 1518 (23%) patients 75 years of age and older. Efficacy was similar for patients younger than 65 years and those aged 65 and older. An increase in risk of adverse reactions was observed in the elderly, compared to younger patients in both study arms. JARDIANCE should be used with caution in geriatric CKD patients due to risks of volume depletion and hypotension.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Type 2 diabetes mellitus (T2DM)

A total of 10 004 patients with type 2 diabetes were treated with JARDIANCE in clinical studies to evaluate the safety of JARDIANCE, alone or in combination with other antidiabetic agents.

Placebo controlled double-blinded trials of 18 to 24 weeks of exposure included 2971 patients, of which 995 were treated with placebo, 999 were treated with JARDIANCE 10 mg and 977 were treated with JARDIANCE 25 mg.

In these trials, the frequency of AEs leading to discontinuation was similar by treatment groups for placebo (5.3%) and JARDIANCE 10 mg (4.8%) and 25 mg (4.9%).

The most frequent adverse drug reaction was hypoglycemia, which depended on the type of background therapy used in the respective studies. The overall incidence of adverse events with JARDIANCE and the frequency of adverse events leading to discontinuation with JARDIANCE were similar to placebo.

Heart Failure

The EMPEROR-Reduced study included 3730 patients with heart failure and reduced ejection fraction treated with empagliflozin 10 mg or placebo. The EMPEROR-Preserved study included 5985 patients with heart failure and preserved ejection fraction treated with empagliflozin 10 mg or placebo. Approximately half of the patients had type 2 diabetes mellitus.

The most frequent adverse events (≥2% of patients receiving JARDIANCE) from the EMPEROR studies pooled data occurring at a higher incidence in the JARDIANCE arm compared to the placebo arm (≥1% higher) were hypotension (empagliflozin 10 mg: 7.5%, vs. placebo: 6.3%), and urinary tract infection (empagliflozin 10 mg: 6.3%, vs. placebo: 5.2%).

No new adverse reactions were identified in the EMPEROR heart failure studies.

The EMPULSE trial studied in-hospital initiation of JARDIANCE 10 mg in patients hospitalized for acute heart failure (de novo or decompensated chronic heart failure), irrespective of ejection fraction, once stabilized.

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

Chronic kidney disease

The EMPA-KIDNEY study included patients with chronic kidney disease (N = 6609) treated with empagliflozin 10 mg or placebo. About 44% of the patients had type 2 diabetes mellitus.

The overall safety profile of JARDIANCE was generally consistent across the studied indications.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

JARDIANCE has been evaluated in clinical trials in patients with T2DM, in patients with heart failure (HFrEF and HFpEF) and in patients with chronic kidney disease. The overall safety profile of JARDIANCE was generally consistent across the studied indications. Ketoacidosis was observed in patients with or without T2DM.

Clinical Trials in Patients with T2DM Treated for Glycemic Control

In a pooled dataset of the five 24-week placebo-controlled clinical trials and 18-week data from the placebo-controlled study as add-on to insulin therapy, adverse events regardless of causality that occurred in ≥1% of patients receiving JARDIANCE and more commonly than in patients given placebo (excluding hypoglycemia), are shown in Table 2.

Table 2: Adverse Events Reported in ≥1% of Patients with T2DM Treated with JARDIANCE and More Frequently than in Patients Treated with Placebo

System organ class Preferred term	JARDIANCE 10 mg n = 999 N (%)	JARDIANCE 25 mg n = 977 N (%)	Placebo n = 995 N (%)
Gastrointestinal disorders			
Nausea	23 (2.3)	11 (1.1)	14 (1.4)
Constipation	14 (1.4)	8 (0.8)	12 (1.2)
Toothache	10 (1.0)	3 (0.3)	5 (0.5)
Dry mouth	3 (0.3)	10 (1.0)	1 (0.1)
General disorders and administration site conditions			
Fatigue	19 (1.9)	6 (0.6)	11 (1.1)
Thirst	15 (1.5)	12 (1.2)	0 (0)
Infections and infestations			
Urinary tract infection	82 (8.2)	60 (6.1)	58 (5.8)
Upper respiratory tract infection	31 (3.1)	39 (4.0)	38 (3.8)

System organ class Preferred term	JARDIANCE 10 mg n = 999 N (%)	JARDIANCE 25 mg n = 977 N (%)	Placebo n = 995 N (%)
Vaginal infection[1]	6 (1.4)	4 (1.0)	2 (0.4)
Bronchitis	13 (1.3)	9 (0.9)	10 (1.0)
Gastroenteritis	13 (1.3)	10 (1.0)	9 (0.9)
Sinusitis	11 (1.1)	9 (0.9)	7 (0.7)
Vulvovaginal candidiasis[1]	5 (1.1)	3 (0.7)	0 (0)
Vulvovaginal mycotic infection[1]	4 (0.9)	7 (1.7)	0 (0)
Influenza	9 (0.9)	12 (1.2)	11 (1.1)
Vulvitis[1]	0 (0)	5 (1.2)	0 (0)
Investigations			
Weight decreased	5 (0.5)	14 (1.4)	2 (0.2)
Metabolism and nutrition disorders			
Hypoglycemia	78 (7.8)	79 (8.1)	61 (6.1)
Dyslipidemia	39 (3.9)	28 (2.9)	34 (3.4)
Hyperlipidemia	8 (0.8)	12 (1.2)	8 (0.8)
Musculoskeletal and connective tissue disorders			
Arthralgia	24 (2.4)	22 (2.3)	22 (2.2)
Muscle spasms	9 (0.9)	10 (1.0)	7 (0.7)
Renal and urinary disorders			
Pollakiuria	19 (1.9)	15 (1.5)	5 (0.5)
Polyuria	14 (1.4)	10 (1.0)	1 (0.1)
Reproductive system and breast disorders			
Balanoposthitis[2]	7 (1.3)	1 (0.2)	0 (0)
Vulvovaginal pruritus[1]	11 (2.5)	8 (1.9)	3 (0.6)
Respiratory, thoracic and mediastinal disorders			
Cough	14 (1.4)	12 (1.2)	11 (1.1)

[1]Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), JARDIANCE 10 mg (N=443), JARDIANCE 25 mg (N=420).
[2]Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), JARDIANCE 10 mg (N=556), JARDIANCE 25 mg (N=557).

Table 3: Serious and/or Unexpected Adverse Event Reported at a Higher Frequency than Placebo during JARDIANCE Treatment in the EMPA-REG OUTCOME Trial

MedDRA System organ class/ Preferred term (PT)	**JARDIANCE 10 mg N=2345 n (%)**	**JARDIANCE 25 mg N=2342 n (%)**	**Placebo N=2333 n (%)**
Skin and subcutaneous tissue disorders			
Rash	43 (1.8)	53 (2.3)	34 (1.5)
Musculoskeletal and connective tissue disorders			
Osteoporosis[a]	25 (1.1)	16 (0.7)	13(0.6)
Infections and infestations			
Urosepsis	6 (0.3)	11 (0.5)	3 (0.1)
Pyelonephritis	3 (0.1)	10 (0.4)	4 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Pancreatic neoplasm malignant[a,b]	6 (0.3)	6 (0.3)	2 (0.1)
Hepatobiliary disorders			
Hepatomegaly	5 (0.2)	4 (0.2)	2 (0.1)
Vascular disorders			
Deep vein thrombosis	3 (0.1)	10 (0.4)	5 (0.2)
Metabolism and nutrition disorders			
Diabetic ketoacidosis[a]	3 (0.1)	1 (0.04)	1 (0.04)

a) Based on grouping of terms
b) Up until trial completion

Description of Selected Adverse Reactions in T2DM Patients Being Treated for Glycemic Control

Hypoglycemia: The frequency of hypoglycemia depended on the type of background therapy used in each study (see Table 4). The incidence of hypoglycemia is increased when JARDIANCE was administered with insulin or a sulfonylurea. See **7 WARNINGS AND PRECAUTIONS**.

Table 4: Incidence of Overall[a] and Severe[b] Hypoglycemia in Placebo-Controlled Clinical Studies

Monotherapy (24 weeks)			
	Placebo (n=229)	**JARDIANCE 10 mg (n=224)**	**JARDIANCE 25 mg (n=223)**
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
Background with Metformin (24 weeks)			
	Placebo + Metformin (n=206)	**JARDIANCE 10 mg + Metformin (n=217)**	**JARDIANCE 25 mg + Metformin (n=214)**
Overall (%)	0.5	1.8	1.4

Severe (%)	0	0	0
Background with Metformin + Sulfonylurea (24 weeks)			
	Placebo (n=225)	**JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)**	**JARDIANCE 25 mg + Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
Background with Pioglitazone +/- Metformin (24 weeks)			
	Placebo (n=165)	**JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)**	**JARDIANCE 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In combination with MDI Insulin (18 weeks)			
	Placebo (n=53)	**JARDIANCE 10 mg (n=58)**	**JARDIANCE 25 mg (n=52)**
Overall (%)	30.2	41.4	40.4
Severe (%)	0	1.7	0
In combination with MDI Insulin + Metformin (18 weeks)			
	Placebo (n=135)	**JARDIANCE 10 mg (n=128)**	**JARDIANCE 25 mg (n=137)**
Overall (%)	40	39.1	41.6
Severe (%)	0.7	0	0.7
Patients with high CV risk (EMPA-REG OUTCOME)			
	Placebo (n=2333)	**JARDIANCE 10 mg (n=2345)**	**JARDIANCE 25 mg (n=2342)**
Overall (%)	27.9	28.0	27.6
Severe (%)	1.5	1.4	1.3
In Combination with metformin and linagliptin (24 weeks)			
	Placebo (n=110)	**JARDIANCE 10 mg (n=112)**	**JARDIANCE 25 mg (n=110)**
Overall (%)	0.9	0.0	2.7
Severe (%)	0.0	0.0	0.9

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 3.89 mmol/L
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose

Genital Mycotic Infections: In a pooled dataset of the five 24-week placebo-controlled clinical trials and 18-week data from the placebo-controlled study as add-on to insulin therapy, the frequency of vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for JARDIANCE 10 mg (4.1%) and JARDIANCE 25 mg (3.7%) compared to placebo (0.9%). Patients with a prior history of genital infections were more likely to experience a genital infection event.

Genital infection events were reported more frequently in female patients (5.4%, 6.4% and 1.5%, for JARDIANCE 10 mg, 25 mg, or placebo, respectively) than in male patients (3.1%, 1.6% and 0.4%, for JARDIANCE 10 mg, 25 mg, or placebo, respectively). Discontinuation from study due to genital infection occurred in 0.2% of patients treated with either JARDIANCE 10 or 25 mg and 0% of placebo treated patients.

In the EMPA-REG OUTCOME trial, genital infection events were reported more frequently in patients treated with JARDIANCE than placebo, and more frequently in female patients (9.2%, 10.8% and 2.6%, for JARDIANCE 10 mg, 25 mg, or placebo, respectively) than in male patients (5.4%, 4.6% and 1.5%, for JARDIANCE 10 mg, 25 mg, or placebo, respectively).

Phimosis occurred more frequently in patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 25 mg (0.1%) than placebo (0%) in the pooled 24-week placebo-controlled trials. In the subgroup of male patients in the EMPA-REG OUTCOME trial, phimosis was reported at an incidence of 0.3% in the empagliflozin 10 mg group, 0.8% in the empagliflozin 25 mg group, and 0.2% in the placebo group.

Increased Urination: In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) were reported by 3.4%, 3.2% and 1.0% of patients treated with JARDIANCE 10 mg, 25 mg and placebo, respectively. Nocturia was reported by 0.3%, 0.8%, and 0.4% of patients treated with JARDIANCE 10 mg, 25 mg, and placebo respectively.

Urinary Tract Infections: In a pooled dataset of the five 24-week placebo-controlled clinical trials and 18-week data from the placebo-controlled study as add-on to insulin therapy, the frequency of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) occurred in 9.3%, 7.6%, and 7.6% of patients treated with JARDIANCE 10 mg, 25 mg, and placebo, respectively. Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection.

Urinary tract infection events were reported more frequently in female patients (18.3% and 15.5% for JARDIANCE 10 mg and 25 mg respectively, 12.5% for placebo) than in male patients (2.2% and 1.6% for JARDIANCE 10 mg and 25 mg respectively, 3.1% for placebo). The incidence of pyelonephritis and urosepsis with JARDIANCE was <0.1% and similar to placebo.

In elderly patients the incidence of urinary tract infections with JARDIANCE compared to placebo was greater than in younger patients. See **7 WARNINGS AND PRECAUTIONS**.

In the EMPA-REG OUTCOME trial, the incidence of urosepsis was greater in the empagliflozin groups than in the placebo group (0.3% for empagliflozin 10 mg, 0.5% for empagliflozin 25 mg, and 0.1% for placebo).

Volume Depletion and hypotension: Adverse reactions related to volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) were reported for 0.5%, 0.3%, and 0.3% of patients treated with JARDIANCE 10 mg, 25 mg and placebo, respectively.

The incidence of volume depletion was increased in patients ≥75 years of age, with adverse events reported for 2.3%, 4.4%, and 2.1% of patients treated with JARDIANCE 10 mg, 25 mg, and placebo, respectively.

Blood creatinine increased and glomerular filtration rate decreased: In placebo-controlled, double-blind studies up to 76 weeks, increases in creatinine (mean change from baseline after 12 weeks: empagliflozin 10 mg 0.02 mg/dL, empagliflozin 25 mg 0.01 mg/dL) and decreases in estimated glomerular filtration rates (mean change from baseline after 12 weeks: empagliflozin 10 mg -1.34 mL/min/1.73m^2, empagliflozin 25 mg -1.37 mL/min/1.73m^2) have been observed. These changes were reversible in some patients during continuous treatment or after drug discontinuation. See **7 WARNINGS AND PRECAUTIONS**.

In the EMPA-REG OUTCOME trial, the decrease in eGFR was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes. See **14 CLINICAL TRIALS**.

Patients with renal impairment: JARDIANCE was compared to placebo as add-on to pre-existing antidiabetic therapy over 52 weeks in 741 patients with type 2 diabetes and renal impairment. See **14 CLINICAL TRIALS**.

The adverse reactions related to renal impairment, volume depletion and urinary tract and genital infections increased with worsening renal function. See **7 WARNINGS AND PRECAUTIONS**.

Use of JARDIANCE was associated with increases in serum creatinine and decreases in eGFR, and patients with moderate renal impairment at baseline (eGFR 30 to <60 mL/min/1.73m^2), displayed larger mean changes. In patients with moderate renal impairment, decreases in eGFR at Week 24 were -3.2 mL/min/1.73m^2 versus 0.2 mL/min/1.73m^2, for empagliflozin 25 mg and placebo, respectively, compared to the pooled 24 week clinical trial population, where eGFR decreased -1.4 mL/min/1.73m^2 and -0.3 mL/min/1.73m^2, for empagliflozin 25 mg and placebo, respectively.

Ketoacidosis: Cases of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes treated with JARDIANCE, or other SGLT2 inhibitors. Fatal cases of ketoacidosis have been reported in patients treated with JARDIANCE. JARDIANCE is not indicated, and should not be used, in patients with type 1 diabetes. In some cases, the presentation of the condition was atypical, with blood glucose levels only moderately elevated (<13.9 mmol/L (250 mg/dL)). See **7 WARNINGS AND PRECAUTIONS**.

In the EMPA-REG OUTCOME trial, serious adverse events of ketoacidosis occurred at a rate of 0.05/100 pt. yrs in the empagliflozin 10 mg group and 0.02/100 pt. yrs in the empagliflozin 25 mg group. One patient (0.02/100 pt. yrs with a non-serious ketoacidosis event was reported in the placebo group.

Cases of ketoacidosis have also been reported in patients without T2DM taking JARDIANCE.

Clinical Trial in Patients with Chronic Kidney Disease (EMPA-KIDNEY)

The EMPA-KIDNEY study included patients with chronic kidney disease (N = 6 609) treated with 10 mg empagliflozin or placebo. About 44% of the patients had type 2 diabetes mellitus. The most frequent adverse events in the EMPA-KIDNEY study while on treatment were gout (empagliflozin 7.0% vs placebo 8.0%), and acute kidney injury (empagliflozin 2.8% vs placebo 3.5%) which were more frequently reported in patients on placebo. The occurrence of lower limb amputations up to the final follow-up visit was reported in 28 (0.8%) patients in

empagliflozin group and 19 (0.6%) patients in placebo, respectively, with toe amputation most commonly reported in both groups.

8.3 Less Common Clinical Trial Adverse Reactions (<1%)[a]

Infections and infestations: Balanitis, balanitis candida, candiduria, genital candidiasis, genital infection, genital infection fungal, genitourinary tract infection, penile infection, pyelonephritis, scrotal abscess, urinary tract infection bacterial, urogenital infection fungal, urosepsis, vaginitis bacterial, vulvovaginitis.

Investigations: Blood glucose decreased, blood creatinine increased, glomerular filtration rate decreased, hematocrit increased.

Metabolism and nutrition disorders: Dehydration, hypovolemia.

Renal and urinary disorders: Nocturia, oliguria, renal impairment, renal failure acute, dysuria.

Skin and subcutaneous disorders: Pruritus.

Vascular disorders: Hypotension, orthostatic hypotension.

[a]Adverse drug reactions (ADRs) were identified based on a comprehensive assessment of biological plausibility, mechanism of action, dose dependence in incidence rate, time of onset, seriousness, and consistency of findings across pivotal Phase 3 clinical studies.

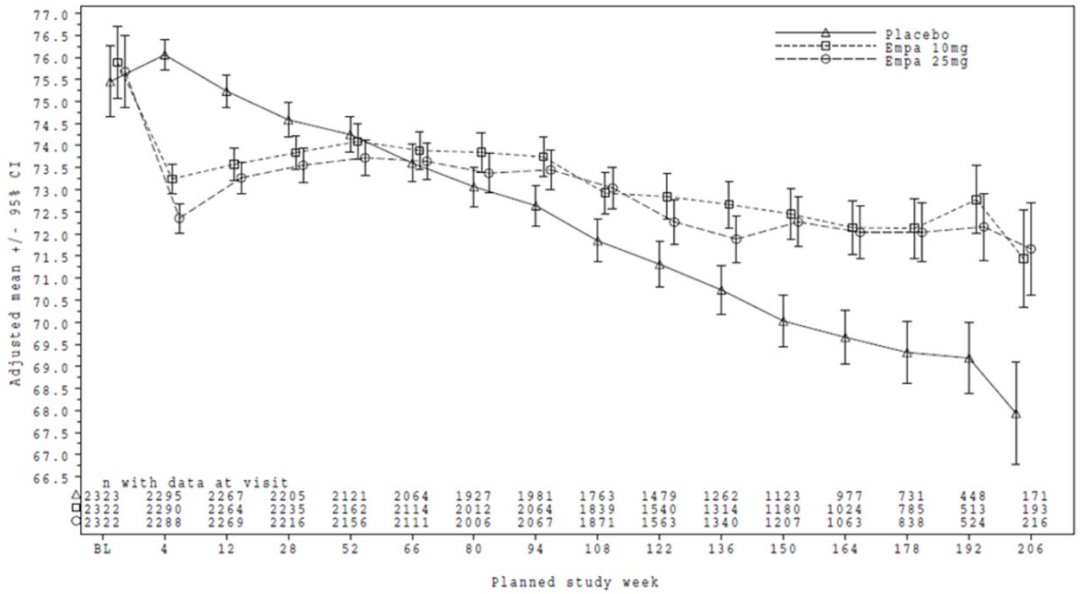
8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Increases in serum creatinine and decreases in eGFR: In a pool of four-placebo-controlled trials, the mean change from baseline for eGFR (mL/min/1.73 m^2) at week 24 was -0.55, -1.41 and - 0.32, for JARDIANCE 10 mg, 25 mg and placebo respectively. The mean change from baseline for creatinine (µmol/L) was 0.66, 1.28 and 0.35 for JARDIANCE 10 mg, 25 mg and placebo, respectively.

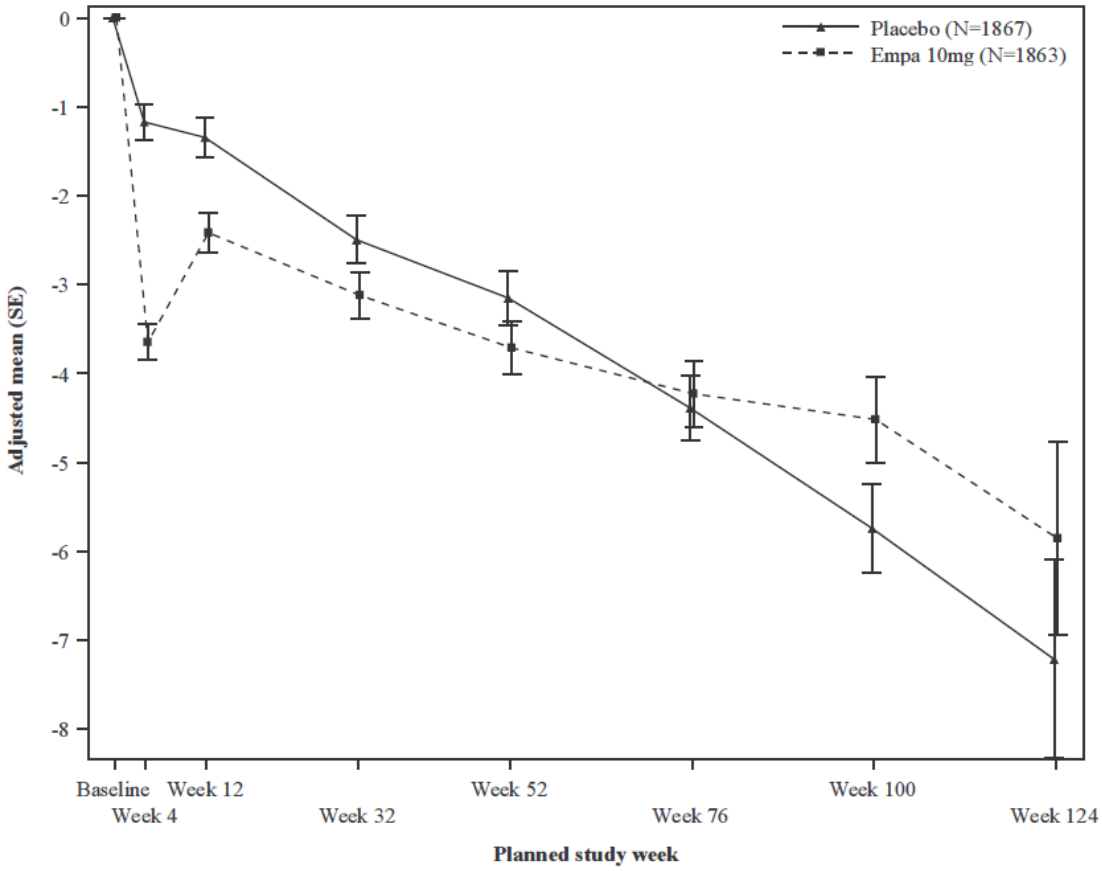
In the EMPA-REG OUTCOME trial, mean eGFR in the JARDIANCE 10 mg and 25 mg groups showed an initial decrease, and then stabilized, whereas mean eGFR in the placebo group showed a progressive decline (see Figure 1).

Figure 1: Time profile plot adjusted mean eGFR, individual empagliflozin doses vs placebo in the EMPA-REG OUTCOME trial



During treatment in the EMPEROR-Reduced trial, the JARDIANCE group had an initial decrease in eGFR at Week 4, which partially recovered at Week 12. Thereafter, a slower decline of eGFR was observed in the JARDIANCE group compared to the placebo group (see Figure 2).

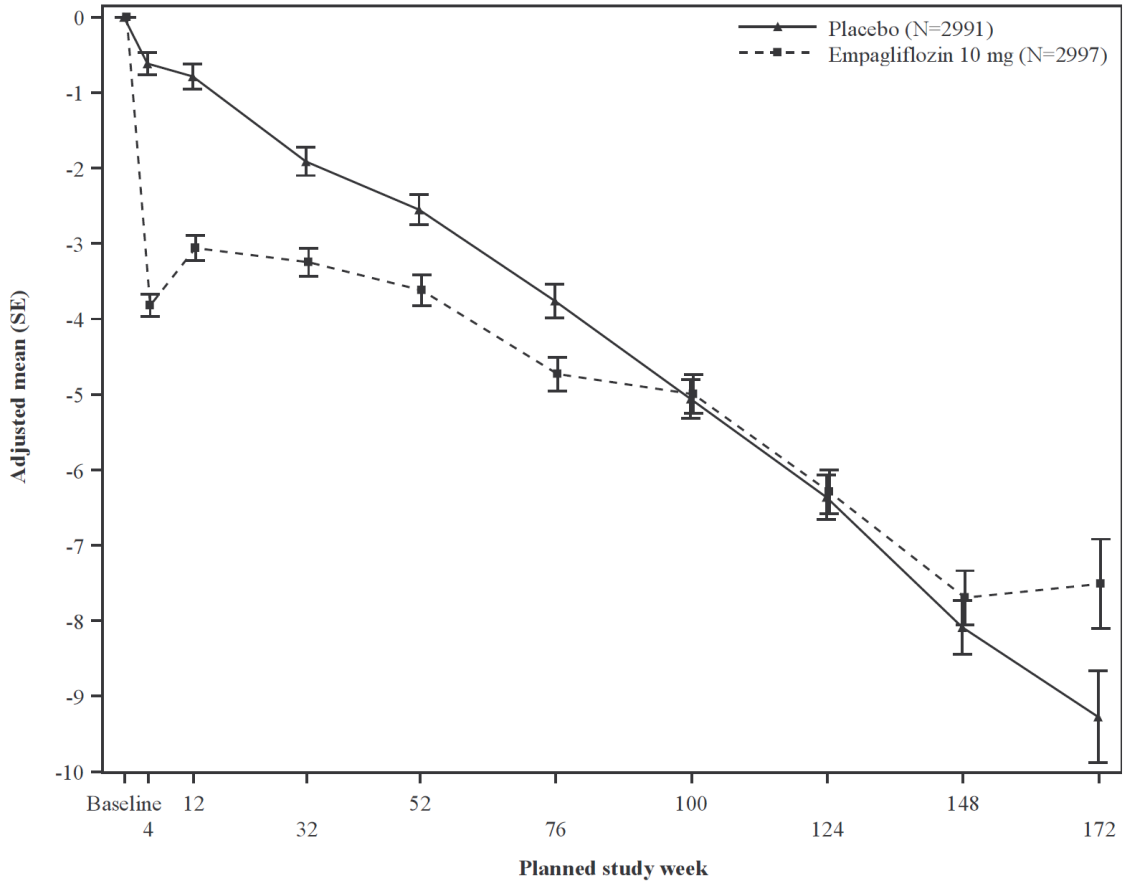
Figure 2: Change in eGFR over time* in the EMPEROR-Reduced trial



*eGFR (CKD-EPI) (mL/min/1.73m^2) MMRM results over time - treated set. The number of patients who provided data at various time points (placebo, empagliflozin): at week 4 (1788, 1802); at week 12 (1729, 1756); at week 32 (1563, 1614); at week 52 (1211, 1228); at week 76 (801, 805); at week 100 (359, 386); and at week 124 (86, 91).

During treatment in the EMPEROR-Preserved trial, the JARDIANCE group had an initial decrease in eGFR at Week 4, which partially recovered at Week 12. Thereafter, a slower decline of eGFR was observed in the JARDIANCE group compared to the placebo group (see Figure 3).

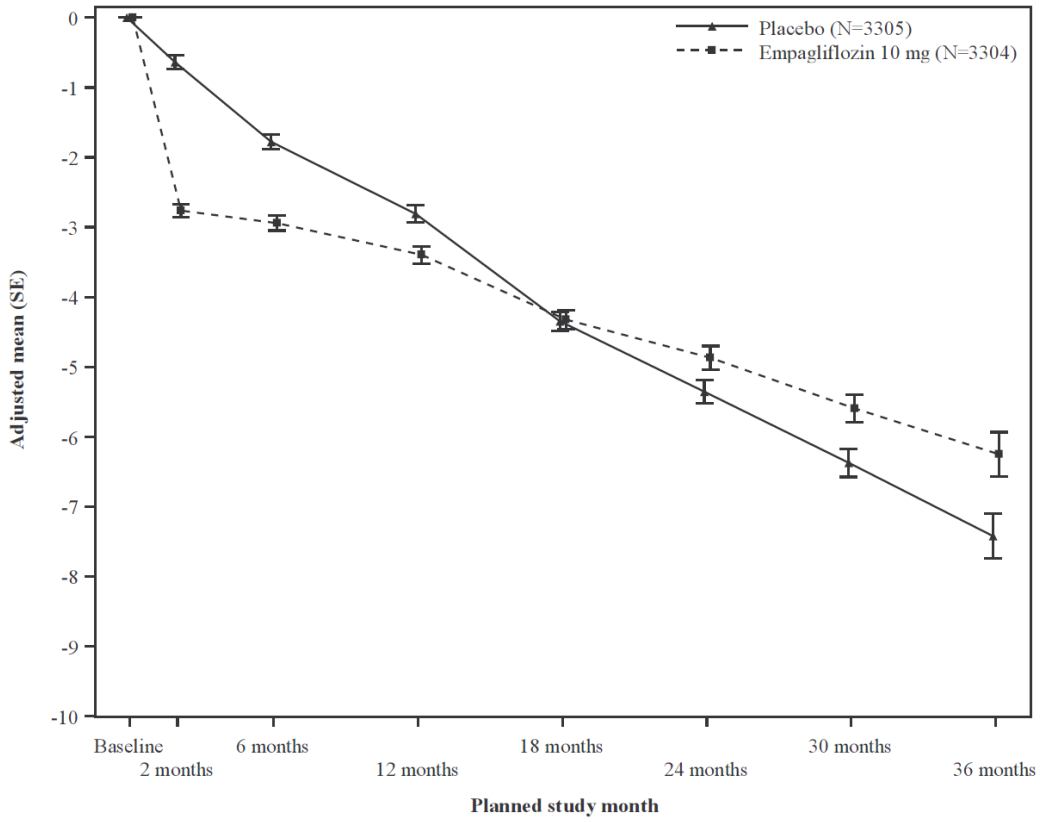
Figure 3: Change in eGFR over time* EMPEROR-Preserved



*eGFR (CKD-EPI) (mL/min/1.73m^2) MMRM results over time - randomized set. The number of patients who provided data at various time points (placebo, empagliflozin): at week 4 (2910, 2931); at week 12 (2820, 2854); at week 32 (2590, 2629); at week 52 (2457, 2474); at week 76 (2123, 2114); at week 100 (1548, 1550); at week 124 (1091, 1122), at week 148 (695, 686), at week 172 (231, 243).

In the EMPA-KIDNEY study, there was an initial decrease in eGFR at 2 months in the JARDIANCE group, the adjusted mean change from baseline (mixed model with repeated measurements [MMRM] results) -2.76 mL/min/1.73 m^2 (95% CI -2.95, -2.58) compared to -0.64 (95% CI -0.82, -0.45) in the placebo group. After the initial drop, a slower decline of eGFR was observed for JARDIANCE compared with placebo.

Figure 4: Change in eGFR over time* EMPA-KIDNEY



*eGFR (CKD-EPI) (mL/min/1.73m^2) MMRM results over time - randomized set. The number of patients who provided data at scheduled time points (placebo, empagliflozin): Baseline (3184, 3190), 2 months (2911, 2875), 6 months (2861, 2809), 12 months (2821, 2820), 18 months (2621, 2605), 24 months (1723, 1752), 30 months (1204, 1239), 36 months (293, 298).

Electrolytes: The following statistically significant changes from baseline in serum electrolytes were observed during JARDIANCE treatment in the EMPA-REG OUTCOME trial (see Table 5).

Table 5: Placebo-Adjusted Mean Changes from Baseline in Electrolytes at Week 12 in EMPA-REG OUTCOME trial

Analyte [normal range, unit]	Baseline, mean (SE)	Placebo-corrected change from baseline at Week 12, mean (95% CI)	p-value
Sodium [135 – 145 mmol/L]			
JARDIANCE 10 mg	141.04 (0.06)	0.46 (0.32, 0.60)	<0.0001
JARDIANCE 25 mg	141.12 (0.07)	0.55 (0.41, 0.69)	<0.0001
Potassium [3.5 – 5.0 mmol/L]			
JARDIANCE 10 mg	4.54 (0.01)	−0.02 (−0.04, 0.00)	0.1034
JARDIANCE 25 mg	4.54 (0.01)	−0.03 (−0.05, 0.00)	0.0370
Magnesium [0.75 – 0.95 mmol/L]			
JARDIANCE 10 mg	0.77 (0.00)	0.07 (0.07, 0.08)	<0.0001
JARDIANCE 25 mg	0.78 (0.00)	0.08 (0.08, 0.08)	<0.0001
Bicarbonate [24 – 30 mmol/L]			
JARDIANCE 10 mg	25.72 (0.07)	−0.35 (−0.50, −0.19)	<0.0001
JARDIANCE 25 mg	25.76 (0.07)	−0.48 (−0.64, −0.33)	<0.0001
Phosphate [0.80 – 1.50 mmol/L]			
JARDIANCE 10 mg	1.16 (0.00)	0.06 (0.05, 0.07)	<0.0001
JARDIANCE 25 mg	1.16 (0.00)	0.07 (0.06, 0.08)	<0.0001

SE = standard error
ANCOVA for Week 12 includes baseline electrolyte and baseline HbA_{1c} as linear covariates and baseline eGFR category, baseline BMI category, geographical region, and treatment as fixed effects.

The following shifts from normal range at baseline to below or above the normal range at worst value on treatment were reported in the treated set in EMPA-REG OUTCOME trial:

- Increases in serum sodium above the upper limit of normal occurred more frequently in patients receiving JARDIANCE than in those receiving placebo (6.8%, 6.7%, and 4.4% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).
- Decreases in serum potassium below the lower limit of normal occurred slightly more frequently in patients receiving JARDIANCE than in those receiving placebo (4.8%, 4.4%, and 3.9% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).
- Decreases in serum magnesium below the lower limit of normal occurred more frequently in patients receiving placebo (13.8%, 11.7%, and 35.0% for JARDIANCE 10 mg, 25 mg, and placebo, respectively), whilst increases in serum magnesium above the upper limit of normal occurred more frequently in patients receiving JARDIANCE than in those receiving placebo (2.0%, 2.7%, and 0.8% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).
- Decreases of serum bicarbonate below the lower limit of normal occurred more frequently in patients receiving JARDIANCE than in those receiving placebo (43.0%, 44.2%, and 34.7% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

- Increases of serum phosphate above the upper limit of normal occurred more frequently in patients receiving JARDIANCE than in those receiving placebo (11.8%, 12.6% and 9.7% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

Elevations of serum phosphate above the normal range occurred more frequently in patients receiving empagliflozin than in those receiving placebo (1.5%, 1.9% and 0.4% for JARDIANCE 10 mg, 25 mg, and placebo, respectively) in a pool of four placebo-controlled trials.

Low density lipoprotein Cholesterol (LDL-C): In a pool of four placebo-controlled studies, LDL-C increases with JARDIANCE were observed. Placebo-corrected mean changes from baseline in LDL-C were 2.3 mg/dL (3.5%) for JARDIANCE 10 mg and 3.3 mg/dL (4.6%) for JARDIANCE 25 mg.

Uric Acid: In the EMPA-REG OUTCOME trial, statistically significant reductions in uric acid were observed at most time points during empagliflozin treatment. At week 12, the placebo-adjusted mean change from baseline was -0.36 mg/dL in both the empagliflozin 10 mg and 25 mg treatment groups ($p<0.0001$).

Hematocrit: In a pool of four placebo-controlled studies, hematocrit increases with JARDIANCE were observed. Mean changes from baseline in hematocrit were 2.3%, 2.6% and -0.8% for JARDIANCE 10 mg, 25 mg and placebo respectively. Elevations of hematocrit or hemoglobin above the normal ranges occurred more frequently in patients receiving empagliflozin than in those receiving placebo (2.5%, 3.2% and 0.5% for JARDIANCE 10 mg, 25 mg, and placebo, respectively).

In the EMPA-REG OUTCOME trial, statistically significant ($p<0.0001$) differences from placebo in mean change from baseline in hematocrit were observed from week 12 to week 206, inclusive (2.21% in the empagliflozin 10 mg group and 2.56% in the empagliflozin 25 mg group at week 12).

8.5 Post-Market Adverse Reactions

The following additional adverse reactions have been identified during post-approval use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatic/Biliary/Pancreatic: Acute pancreatitis

Infections and Infestations: Necrotizing fasciitis of the perineum (Fournier´s gangrene)

Metabolism: Ketoacidosis

Skin and Subcutaneous Tissue Disorders: Allergic skin reactions (e.g., rash, angioedema and urticaria)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro assessment of interactions

In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. The relative contribution of each isoform to empagliflozin clearance has not been determined.

Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1. The effect of UGT induction 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, JARDIANCE 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. JARDIANCE does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations therefore, no effect of JARDIANCE is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

9.3 Drug-Behavioural Interactions

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

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be alerted to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural hypotension, and to the risk of hypoglycemia when JARDIANCE is used in combination with insulin or an insulin secretagogue.

9.4 Drug-Drug Interactions

The drugs listed in the table below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Effects of other co-administered drugs on JARDIANCE

In clinical studies, JARDIANCE pharmacokinetics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin (CYP2C9 substrate), verapamil (P-gp inhibitor), ramipril, and simvastatin (CYP3A4, OATP1B1, OATP1B3 substrate) in healthy volunteers (see Table 6). Torasemide and hydrochlorothiazide had no clinically relevant effect on the pharmacokinetics of JARDIANCE in T2DM patients.

JARDIANCE overall exposure (AUC) increased by 59%, 35% and 53%, when co-administered with gemfibrozil (CYP2C8 and OATP1B1 inhibitor), rifampicin (OATP1B1 and 1B3 inhibitor) and probenecid (UGT, OAT3 inhibitor) respectively and were not considered clinically relevant. In subjects with normal renal function, co-administration of JARDIANCE with probenecid resulted in a 30% decrease in the fraction of JARDIANCE excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

The pharmacokinetic parameters of empagliflozin and linagliptin in patients administered empagliflozin and linagliptin in a fixed dose combination were not studied. The lack of pharmacokinetic interaction between linagliptin and empagliflozin was demonstrated in a drug-drug interaction study with linagliptin 5 mg and empagliflozin 50 mg.

Table 6: Effect of Other Co-Administered Drugs on Pharmacokinetics of JARDIANCE

Co-administered drug	Source of Evidence	Dose of co-administered drug	Dose of JARDIANCE	Geometric Mean ratio (Ratio with/without co-administered drug) No effect=1.0		Clinical comment
				AUC (90% CI)	C_{max} (90% CI)	
Metformin	CT	1000 mg, bid, 5 days	50 mg, qd, 5 days	0.97 (0.92; 1.02)	1.00 (0.89; 1.14)	No dose adjustment of JARDIANCE required
Glimepiride	CT	1 mg, single dose	50 mg, qd, 6 days	0.95 (0.92; 0.99)	0.96 (0.88; 1.03)	No dose adjustment of JARDIANCE required
Pioglitazone	CT	45 mg, qd, 7 days	50 mg, qd, 7 days	1.00 (0.96; 1.05)	0.93 (0.85; 1.03)	No dose adjustment of JARDIANCE required
Warfarin	CT	25 mg, single dose	25 mg, qd, 7 days	1.01 (0.97; 1.05)	1.01 (0.90; 1.13)	No dose adjustment of JARDIANCE required
Sitagliptin	CT	100 mg, qd, 5 days	50 mg, qd, 5 days	1.10 (1.04; 1.17)	1.08 (0.97; 1.19)	No dose adjustment of JARDIANCE required
Linagliptin	CT	5 mg, qd, 7 days	50 mg, qd, 7 days	1.02 (0.97; 1.07)	0.88 (0.79; 0.99)	No dose adjustment of JARDIANCE required
Hydrochloro-thiazide	CT	25 mg, qd, 5 days	25 mg, qd, 5 days	1.07 (0.97; 1.18)	1.03 (0.89; 1.19)	No dose adjustment of JARDIANCE required
Torasemide	CT	5 mg, qd, 5 days	25 mg, qd, 5 days	1.08 (1.00; 1.16)	1.08 (0.98; 1.18)	No dose adjustment of JARDIANCE required
Verapamil	CT	120 mg, single dose	25 mg, single dose	1.03 (0.99; 1.07)	0.92 (0.85; 1.00)	No dose adjustment of JARDIANCE required
Ramipril	CT	5 mg, qd, 5 days	25 mg, qd, 5 days	0.97 (0.93; 1.00)	1.04 (0.98; 1.12)	No dose adjustment of JARDIANCE required
Gemfibrozil	CT	600 mg, bid, 5 days	25 mg, single dose	1.59 (1.52; 1.66)	1.15 (1.06; 1.25)	No dose adjustment of JARDIANCE required
Simvastatin	CT	40 mg, single dose	25 mg, single dose	1.02 (0.99; 1.05)	1.09 (0.97; 1.24)	No dose adjustment of JARDIANCE required
Rifampicin	CT	600 mg, single dose	10 mg, single dose	1.35 (1.30; 1.41)	1.75 (1.60; 1.92)	No dose adjustment of JARDIANCE required
Probenecid	CT	500 mg, bid, 4 days	10 mg, single dose	1.53 (1.46; 1.61)	1.26 (1.14; 1.39)	No dose adjustment of JARDIANCE required

For single dose, AUC is $AUC_{0-\infty}$; for multiple dose, AUC is $AUC_{\tau,ss}$
Legend: CT = Clinical Trial

Effects of JARDIANCE on other co-administered drugs

In clinical studies, JARDIANCE had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin (CYP2C9 substrate), digoxin (P-gp substrate), ramipril, simvastatin (CYP3A4, OATP1B1, OATP1B3 substrate), and oral contraceptives ethinyl estradiol and norgestrel (CYP3A4 substrate) when co-administered in healthy volunteers. JARDIANCE had no clinically relevant effect on the pharmacokinetics of torasemide and hydrochlorothiazide in patients with T2DM (see Table 7).

Table 7: Effect of JARDINACE on Pharmacokinetics of Other Co-Administered Drugs Co-administered drug

Co-administered drug	Source of Evidence	Dose of co-administered drug	Dose of JARDIANCE	Geometric Mean ratio (Ratio with/without co-administered drug) No effect=1.0		Clinical comment
				AUC (90% CI)	C_{max} (90% CI)	
Metformin	CT	1000 mg, bid, 5 days	50 mg, qd, 5 days	1.01 (0.96; 1.06)	1.04 (0.97; 1.11)	No dose adjustment required for metformin
Glimepiride	CT	1 mg, single dose	50 mg, qd, 6 days	0.93 (0.86; 1.01)	1.04 (0.89; 1.21)	No dose adjustment required for glimepiride
Pioglitazone	CT	45 mg, qd, 7 days	50 mg, qd, 7 days	1.58 (1.48; 1.69)	1.88 (1.66; 2.12)	No dose adjustment required for pioglitazone
	CT	45 mg, qd, 7 days	10 mg, qd, 9d	0.90 (0.78; 1.04)	0.88 (0.74; 1.04)	
	CT	45 mg, qd, 7 days	25 mg, qd, 9d	0.89 (0.73; 1.09)	0.90 (0.67; 1.22)	
	CT	45 mg, qd, 7 days	50 mg, qd, 9d	0.91 (0.77; 1.07)	0.90 (0.71; 1.14)	
Warfarin (R-warfarin)	CT	25 mg, single dose	25 mg, qd, 7 days	0.98 (0.95; 1.02)	0.98 (0.91; 1.05)	No dose adjustment required for warfarin
(S-warfarin)	CT			0.96 (0.93; 0.98)	0.99 (0.92; 1.06)	
Sitagliptin	CT	100 mg, qd, 5 days	50 mg, qd, 5 days	1.03 (0.99; 1.07)	1.08 (1.01; 1.17)	No dose adjustment required for sitagliptin
Linagliptin	CT	5 mg, qd, 7 days	50 mg, qd, 7 days	1.03 (0.96; 1.11)	1.01 (0.87; 1.19)	No dose adjustment required for linagliptin
Digoxin	CT	0.5 mg, single	25 mg, qd,	1.06	1.14	No dose adjustment required for digoxin

Co-administered drug	Source of Evidence	Dose of co-administered drug	Dose of JARDIANCE	Geometric Mean ratio (Ratio with/without co-administered drug) No effect=1.0			Clinical comment
				AUC (90% CI)		C_{max} (90% CI)	
		dose	8 days	(0.97; 1.16)		(0.99; 1.31)	
Microgynon® tablet	CT	Ethinyl-estradiol, 30 µg, qd, 7 days	25 mg, qd, 7 days	1.03 (0.98; 1.08)		0.99 (0.93; 1.05)	No dose adjustment required for oral contraceptives
	CT	Levonor-gestrel 150 µg, qd, 7 days		1.02 (0.99; 1.05)		1.06 (0.99; 1.13)	
Hydrochloro-thiazide	CT	25 mg, qd, 5 days	25 mg, qd, 5 days	0.96 (0.89; 1.04)		1.02 (0.89; 1.17)	No dose adjustment required for hydrochlorothiazide
Torasemide	CT	5 mg, qd, 5 days	25 mg, qd, 5 days	1.01 (0.99; 1.04)		1.04 (0.94; 1.16)	No dose adjustment required for torasemide
	CT			M1 meta-bolite	1.04 (1.00; 1.09)	1.03 (0.94; 1.12)	
	CT			M3 meta-bolite	1.03 (0.96; 1.11)	1.02 (0.98; 1.07)	
Ramipril	CT	5 mg, qd, 5 days	25 mg, qd, 5 days	1.08 (1.01; 1.16)		1.04 (0.90; 1.20)	No dose adjustment required for ramipril
	CT			Rami-prilat	0.99 (0.96; 1.01)	0.98 (0.93; 1.04)	
Simvastatin	CT	40 mg, single dose	25 mg, single dose	1.01 (0.80; 1.28)		0.97 (0.76; 1.24)	No dose adjustment required for simvastatin
	CT			Simv-astatin acid	1.05 (0.90; 1.22)	0.97 (0.85; 1.11)	

For single dose, AUC is $AUC_{0-\infty}$; for multiple dose, AUC is $AUC_{\tau,ss}$
Legend:CT = Clinical Trial

Pharmacodynamic interactions

Diuretics: JARDIANCE may add to the diuretic effect of loop diuretics and may increase the risk of dehydration and hypotension. Caution is recommended when JARDIANCE is co-administered with diuretics; particularly loop diuretics. See **4 DOSAGE AND ADMINISTRATION** and **7 WARNINGS AND PRECAUTIONS**.

Pharmacokinetic Interactions

Lithium: Concomitant use of JARDIANCE or other SGLT2 inhibitors with lithium may decrease blood lithium levels through increased renal lithium elimination. Therefore, serum lithium concentration should be monitored more frequently with JARDIANCE initiation or following dose changes or following discontinuation. Patient should be referred to the lithium prescribing doctor to monitor serum lithium concentration so as to maintain clinical supervision as required during treatment.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Due to its mechanism of action, patients taking JARDIANCE will test positive for glucose in their urine. Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sodium-glucose co-transporter 2 (SGLT2) is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. SGLT2 is selectively expressed in the kidney. Empagliflozin is an inhibitor of SGLT2. In patients with type 2 diabetes mellitus (T2DM), by inhibiting SGLT2, empagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal reabsorption of filtered glucose and lowering the renal threshold for glucose, and thereby increasing urinary glucose excretion. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Empagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Empagliflozin acts independently of insulin secretion and insulin action.

Urinary glucose excretion (glucuresis) induced by empagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by empagliflozin is also associated with mild diuresis and transient natriuresis.

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 pre- and afterload of the heart, improving cardiac remodelling, improving diastolic function, and reducing left ventricular wall stress as evidenced by lower NT-proBNP values. Some of these mechanisms may preserve kidney

function and structure.

Secondary effects of SGLT2 inhibition with empagliflozin also include an increase in hematocrit.

The cardiovascular and renal benefits of empagliflozin are not solely dependent on the blood glucose lowering effect and are not limited to patients with diabetes.

10.2 Pharmacodynamics

Urinary Glucose Excretion: In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of JARDIANCE 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 JARDIANCE once daily.

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 treatment.

Cardiac Electrophysiology: In a randomized, double-blind, 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 recommended dose), moxifloxacin, and placebo. The empagliflozin 25 mg and 200 mg treatments were not observed to affect the QTc interval, the QRS duration, the PR interval, or heart rate.

10.3 Pharmacokinetics

Table 8: Summary of JARDIANCE Pharmacokinetic Parameters in T2DM Patients

Single dose mean	$C_{max,ss}$ (nmol/L) mean (% CV)	$T_{max,ss}$ (h) (% CV)	$t_{½}$ (h)	$AUC_{0-\infty\tau,ss}$ (nmol•h/L) (% CV)	CL/F_{ss} (mL/min) (% CV)	Vd
25 mg qd	687 (18.4)	1.5 (49.9)	--	4740 (21.2)	203 (21.4)	--
10 mg qd	259 (24.8)	1.72 (42.5)	--	1870 (15.9)	202 (15.9)	--

Absorption: After oral administration in patients with T2DM, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median T_{max} 1.5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal elimination phase. The steady state mean plasma AUC and C_{max} were 1870 nmol•h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol•h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Population pharmacokinetic analysis results suggested that empagliflozin exposure (AUC) in T2DM patients is approximately 33% higher for doses less than 400 mg compared to healthy volunteers.

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 [14C]-empagliflozin solution to

healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%, mainly to albumin. Protein binding is independent of plasma empagliflozin concentration. There were no relevant changes in protein binding of empagliflozin due to renal or hepatic impairment.

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'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Elimination: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4h and apparent oral clearance was 10.6 L/h based on the population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

Dose Proportionality, Accumulation and Steady-state Pharmacokinetics

Systemic exposure of multiple dose empagliflozin in male and female diabetic patients increased in a dose-proportional manner between the doses of 2.5 mg to 100 mg qd for both AUC and C_{max}. The single-dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time.

With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with half-life, up to 23% accumulation with respect to plasma AUC, was observed at steady state.

Special Populations and Conditions

- **Pediatrics (<18 years of age):** Studies characterizing the pharmacokinetics of empagliflozin in pediatric patients have not been performed.
- **Geriatrics (≥65 years of age):** Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. The changes in AUCτ,ss were decreased by 8.06% for patients 35 years of age and increased by 6.43%, and 10.1% for patients 65 and 75 years of age, respectively, compared to patients with an age of 50 years and assuming normal renal function (eGFR 100 mL/min/1.73 m^2).
- **Sex:** Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. AUCτ,ss in females was 12.8% higher compared to males.
- **Genetic Polymorphism:** The influence of UGT1A9 and other UGT genetic polymorphisms on the pharmacokinetics of JARDIANCE have not been evaluated.
- **Ethnic Origin:** Based on the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asian patients with a BMI of 25 kg/m^2 compared to non-Asian patients with a BMI of 25 kg/m^2. These changes are not considered clinically meaningful.
- **Hepatic Insufficiency:** In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively, compared to subjects

with normal hepatic function. Experience in patients with severe hepatic impairment is limited.

- **Renal Insufficiency:** In patients with mild (eGFR: 60 - <90 mL/min/1.73m^2), moderate (eGFR: 30 - <60 mL/min/1.73m^2), severe (eGFR: <30 mL/min/1.73m^2) renal impairment and patients with kidney failure/ESRD patients, 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 subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects 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.
- **Obesity:** BMI had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis. The changes in AUCτ,ss were increased by 7.48% for patients with BMI of 20 kg/m^2 and decreased by 5.82%, 10.4%, and 17.3% for patients with BMI of 30, 35 and 40 kg/m^2, respectively, compared to patients with a BMI of 25 kg/m^2.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-30°C). Do not flush medicines down the toilet or sink. Bring unused and expired prescription drugs, over-the-counter medications and natural health products to your local pharmacist for proper disposal.

12 SPECIAL HANDLING INSTRUCTIONS

Store in a safe place and out of the reach of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

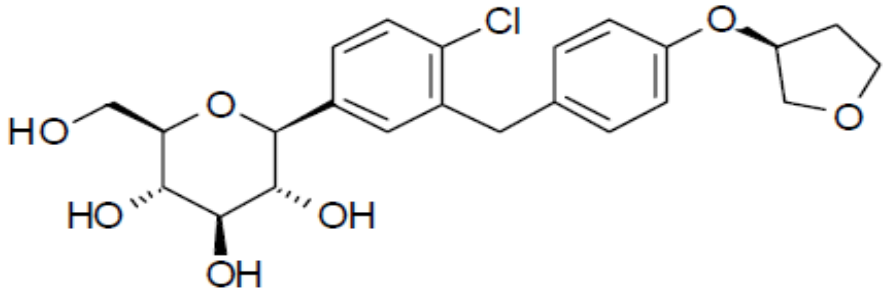
Drug Substance

Proper name: Empagliflozin

Chemical name: (1S)-1,5-anhydro-1-(4-chloro-3-{4-[(3S)-tetrahydrofuran-3yloxy]benzyl}phenyl)-D-glucitol

Molecular formula and molecular mass: $C_{23}H_{27}ClO_7$; 450.91 g/mol

Structural formula:



Physicochemical properties: Empagliflozin is a white to yellowish, not hygroscopic solid powder, very slightly soluble in water (0.28 mg/mL), sparingly soluble in methanol (33.4 mg/mL), slightly soluble in ethanol (8.0 mg/mL), slightly soluble in acetonitrile (2.6 mg/mL), slightly soluble in 50% methanol in water (6.4 mg/mL), soluble in 50% acetonitrile in water (68 mg/mL), and practically insoluble in toluene (<0.001 mg/mL).

Solubility data of empagliflozin in aqueous media at room temperature:
Water (pH 8.6) 0.28 mg/mL;
0.1N HCl (pH 1.1) 0.30 mg/mL;
McIlvaine buffer pH 4.0 (pH 4.1) 0.21 mg/mL;
McIlvaine buffer pH 7.4 (pH 7.5) 0.14 mg/mL.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Type 2 diabetes mellitus (T2DM)

Table 9: Summary of patient demographics for clinical trials in patients with T2DM

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number) randomized/ treated	Mean age (Range)	Sex (%M/F)
Monotherapy					
1245.20	Randomized, multicentre, double-blind, active and placebo-controlled parallel group	Empagliflozin 10 mg or 25 mg vs placebo or vs. Sitagliptin 100 mg Tablets, orally, once daily Run-in: 2 weeks placebo open-label Randomized treatment: 24 weeks Extension: up to 76 weeks Follow-up: 1 week	Total: 986/986 Empagliflozin: 10 mg: 224/224 25 mg: 224/224 Placebo: 228/228 Sitagliptin: 223/223	Empagliflozin: 10 mg: 56.2 (11.6) 25 mg: 53.8 (11.6) Placebo: 54.6 (10.9) Sitagliptin: 55.1 (9.9)	Empagliflozin: 10 mg: 63/37 25 mg: 65/35 Placebo: 54/46 Sitagliptin: 63/37
Add-on Combination Therapy with Metformin					
1245.23	Randomized, multicentre, double-blind, placebo-controlled, parallel group	Empagliflozin 10 mg, 25 mg, placebo tablets, Tablets, orally, once daily Run-in: 2 weeks placebo open-label Randomized Treatment: 24 weeks Extension: up to 76 weeks Follow-up: 1 week	Total: 707/706 Empagliflozin: 10 mg: 217/217 25 mg: 214/213 Placebo: 207/207	Empagliflozin: 10 mg: 55.5 (9.9) 25 mg: 55.6 (10.2) Placebo: 56.0 (9.7)	Empagliflozin: 10 mg: 58/42 25 mg: 56/44 Placebo: 56/44
1245.28	Randomized, multicentre, double blind, active-controlled, parallel-group	Empagliflozin 25 mg Glimepiride (Amaryl®):1 to 4 mg Placebo (run-in period) tablets, oral, once	Total: 1549/1545 (until interim database lock)		

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number) randomized/ treated	Mean age (Range)	Sex (%M/F)
		daily Run-in: 2 weeks Treatment: 104 weeks Extension: 104 weeks Follow-up: 4 weeks	Empagliflozin: 25 mg: 769/765 Glimepiride 1 to 4 mg: 780/780	Empagliflozin: 25 mg: 56.2 (10.3) Glimepiride: 55.7 (10.4)	Empagliflozin: 25 mg: 56/43 Glimepiride: 54/46
Add-on Combination Therapy with Metformin and a Sulfonylurea					
1245.23+	Randomized, multicentre, double-blind, placebo-controlled, parallel group	Empagliflozin 10 mg, 25 mg, placebo tablets, orally, once daily Run-in: 2 weeks placebo open-label Randomized treatment: 24 weeks Extension: up to 76 weeks Follow-up: 1 week	Total: 669/666 Empagliflozin: 10 mg: 226/225 25 mg: 218/216 Placebo: 225/225	Empagliflozin: 10 mg: 57.0 (9.2) 25 mg: 57.4 (9.3) Placebo: 56.9 (9.2)	Empagliflozin: 10 mg: 50/50 25 mg: 53/47 Placebo: 50/50
Add-on Combination Therapy with Pioglitazone					
1245.19	Randomized, multicentre, double-blind, placebo-controlled parallel group	Empagliflozin 10mg or 25 mg vs placebo Tablets, orally, once daily Run-in: 2 weeks placebo open-label Randomized treatment: 24 weeks Extension: up to 76 weeks Follow-up: 1 week	Total 499/498 patients Empagliflozin 10 mg: 165/165 25 mg: 168/168 Placebo: 166/165	Empagliflozin: 10 mg: 54.7 (9.9) 25 mg: 54.2 (8.9) Placebo: 54.6 (10.5)	Empagliflozin: 10 mg: 50/50 25 mg: 50/50 Placebo: 44/56
Add-on Combination Therapy with MDI of Basal and Prandial Insulin (with or without Metformin)					
1245.49	Randomized, multicentre, double-blind, placebo-controlled, parallel group	E 10mg, 25 mg Placebo tablets, oral, once daily Randomized treatment: 52 weeks Week 1-18 &41-52 -	Total: 566/563 Empagliflozin: 10 mg: 187/186 25 mg: 190/189 Placebo: 189/188	Empagliflozin: 10 mg: 56.7 (8.7) 25 mg: 58.0 (9.4) Placebo: 55.3 (10.1)	Empagliflozin: 10 mg: 52/48 25 mg: 44/56 Placebo: 40/60

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number) randomized/ treated	Mean age (Range)	Sex (%M/F)
		stable insulin dose Week 19-40, treat-to-target insulin dose			
Patients With Type 2 Diabetes and Established Cardiovascular Disease					
1245.25	Randomized, multicentre, double-blind, placebo-controlled	E 10mg, 25 mg Placebo tablets, oral, once daily + standard of care treatment: event-driven follow up: about 3 years	Total: 7028/7020 Empagliflozin: 10 mg: 2347/2345 25 mg: 2344/2342 Placebo: 2337/2333	Empagliflozin: 10 mg: 63.0 (8.6) 25 mg: 63.2 (8.6) Placebo: 63.2 (8.8)	Empagliflozin: 10 mg: 70/30 25 mg: 72/28 Placebo: 72/28
Patients with T2DM Inadequately Controlled on Linagliptin and Metformin (GLYXAMBI)					
1275.9	Randomized, multicenter, double-dummy, double-blind, placebo-controlled parallel group	GLYXAMBI 10/5 + metformin GLYXAMBI 25/5 + metformin Lina 5 + metformin Tablets, orally, once daily treatment: 24-week	n = 109 n = 110 n = 108	54.3 (9.6) 55.4 (9.9) 55.9 (9.7)	61/39 65/35 56/44

JARDIANCE (empagliflozin) was studied as monotherapy and in combination with other antidiabetic medications, including metformin, metformin and sulfonylurea, pioglitazone, linagliptin or basal or prandial insulin (with or without metformin) (see Table 9). JARDIANCE was also studied in patients with type 2 diabetes and cardiovascular disease and in patients with different degrees of renal impairment.

Treatment with JARDIANCE as monotherapy and in combination with metformin, glimepiride, pioglitazone, linagliptin, or basal and prandial insulin (with or without metformin) produced clinically relevant and statistically significant improvements in mean change from baseline at Week 24 in HbA1c, fasting plasma glucose (FPG), blood pressure and 2-hour post-prandial glucose (where measured), compared to placebo or control. In the double-blind placebo-controlled extension of these studies, reductions of HbA1c and body weight were sustained up to Week 76. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, baseline BMI and patients with high baseline HbA1c >10%.

Monotherapy (Study 1245.20)

The efficacy and safety of JARDIANCE as monotherapy was evaluated in a double-blind, placebo- and active-controlled study of 24 weeks duration in treatment-naïve patients. As shown in Table 10, statistically significant reductions (p<0.0001) in HbA1c and body weight relative to placebo were observed with JARDIANCE 10 mg and 25 mg at Week 24. Statistically significant changes from baseline in systolic blood pressure (SBP, mmHg) of -2.9, -3.7, and -0.3 were observed for JARDIANCE 10 mg, 25 mg, and placebo, respectively.

Table 10: Results at Week 24 (LOCF) in a Placebo-Controlled Study of JARDIANCE Monotherapy in Patients with Type 2 Diabetes

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg	Sitagliptin[a]
N	228	224	224	223
HbA1c (%)				
Baseline (mean)	7.91	7.87	7.86	7.85
Change from baseline[1]	0.08	-0.66	-0.78	-0.66
Difference from placebo[1] (97.5% CI)		-0.74* (-0.90, -0.57)	-0.85* (-1.01, -0.69)	-0.73 (-0.88, -0.59)[2]
N	208	204	202	200
Patients[3] (%) achieving HbA1c <7%	15.4	39.3	46.0	41.7
N	228	224	224	223
Body Weight (kg)				
Baseline (mean)	78.23	78.35	77.80	79.31
Change from baseline[1]	-0.33	-2.26	-2.48	0.18
Difference from placebo[1] (97.5% CI)		-1.93* (-2.48, -1.38)	-2.15* (-2.70,-1.60)	0.52 (-0.04, 1.00)[2]

[a] Sitagliptin 100 mg per day
[1] mean adjusted for baseline value
[2] 95% CI
[3] The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.
*<0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 6 and resulted in significant reductions in HbA1c with JARDIANCE 10 mg and 25 mg vs placebo (-0.5% and -0.55% respectively; p<0.0001) which were sustained over time.

Add-on Therapy with Metformin (Study 1245.23)

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of JARDIANCE in patients not sufficiently treated with metformin. As shown in Table 11, statistically significant (p<0.0001) reductions in HbA1c, FPG and body weight relative to placebo were observed with JARDIANCE 10 mg and 25 mg at Week 24.

Table 11: Results of a 24-Week (LOCF) Placebo-Controlled Study of JARDIANCE in Add-on Combination with Metformin

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
N	207	217	213
HbA1c (%)			
Baseline (mean)	7.90	7.94	7.86
Change from baseline[1]	-0.13	-0.70	-0.77
Difference from placebo[1] (97.5% CI)		-0.57* (-0.72, -0.42)	-0.64* (-0.79, -0.48)
N	184	199	191
Patients[2] (%) achieving HbA1c <7%	16.4	40.6	40.8
N	207	216	213
FPG (mmol/L)			
Baseline (mean)	8.66	8.58	8.29
Change from baseline[1]	0.35	-1.11	-1.24
Difference from placebo[1] (95% CI)		-1.47 (-1.74, -1.20)	-1.59 (-1.86, -1.32)
N	207	217	213
Body Weight (kg)			
Baseline (mean)	79.73	81.59	82.21
Change from baseline[1]	-0.45	-2.08	-2.46
Difference from placebo[1](97.5% CI)		-1.63* (-2.17, -1.08)	-2.01* (-2.56, -1.46)

[1] mean adjusted for baseline value

[2] The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.

*p-value <0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 6 and resulted in significant reductions in HbA1c with JARDIANCE 10 mg and 25 mg vs placebo (-0.46% and -0.51% respectively; p<0.0001) which were sustained over time.

Add-on Therapy with Metformin - Active-Controlled Study versus Glimepiride (Study 1245.28)

In a study comparing the efficacy and safety of JARDIANCE 25 mg versus glimepiride (4 mg) in patients with inadequate glycemic control on metformin alone, as shown in Table 12, JARDIANCE daily resulted in a statistically significant (p<0.0001) reduction in HbA1c, FPG and body weight at Week 104. Systolic blood pressure (SBP, mmHg) change from baseline was -3.1, and 2.5 for JARDIANCE 25 mg, and glimepiride respectively.

Treatment with JARDIANCE resulted in statistically significantly lower proportion of patients with hypoglycemic events compared to glimepiride (2.5% for JARDIANCE 25 mg, 24.2% for glimepiride, p<0.0001).

Table 12: Results at 104-Week (LOCF) in an Active-Controlled Study Comparing JARDIANCE to Glimepiride as Add-on to Metformin

Efficacy Parameter	**JARDIANCE 25 mg**	**Glimepiride**
N	765	780
HbA1c (%)		
Baseline (mean)	7.92	7.92
Change from baseline[1]	-0.66	-0.55
Difference from glimepiride[1] (97.5% CI)	-0.11*(-0.20, -0.01)	
N	690	715
Patients[2] (%) achieving HbA1c <7%	37.5	32.6
N	764	779
FPG (mmol/L)		
Baseline (mean)	8.33	8.32
Change from baseline[1]	-0.85	-0.17
Difference from glimepiride[1] (95% CI)	-0.69 (-0.86, -0.52)	
N	765	780
Body Weight (kg)		
Baseline (mean)	82.52	83.03
Change from baseline[1]	-3.12	1.34
Difference from glimepiride[1] (97.5% CI)	-4.46** (-4.87, -4.05)	

[1] mean adjusted for baseline value

[2] The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.

[*] p<0.0001 for non-inferiority, p<0.0153 for superiority

[**] p-value <0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 4 and resulted in reductions in HbA1c with JARDIANCE 25 mg and glimepiride vs baseline (-0.41% and -0.43% respectively) which were sustained over time.

Add-on Therapy with Metformin and Sulfonylurea (Study 1245.23+)

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of JARDIANCE in patients not sufficiently treated with a combination of metformin and a sulphonylurea. As shown in Table 13, treatment with JARDIANCE resulted in statistically significant ($p<0.0001$) reductions in HbA1c and body weight, and clinically meaningful reductions in FPG compared to placebo at Week 24.

Table 13: Results of a 24-Week (LOCF) Placebo-Controlled Study of JARDIANCE as Add-on Therapy to Metformin with a Sulfonylurea

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
N	225	225	216
HbA1c (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline[1]	-0.17	-0.82	-0.77
Difference from placebo[1] (97.5% CI)		-0.64* (-0.79, -0.49)	-0.59* (-0.74, -0.44)
N	216	209	202
Patients[2] (%) achieving HbA1c <7%	11.1	31.1	34.3
N	224	225	215
FPG (mmol/L)			
Baseline (mean)	8.42	8.38	8.68
Change from baseline[1]	0.31	-1.29	-1.29
Difference from placebo[1] (95% CI)		-1.60 (-1.90, -1.30)	-1.60 (-1.90, -1.29)
N	225	225	216
Body Weight (kg)			
Baseline (mean)	76.23	77.08	77.50
Change from baseline[1]	-0.39	-2.16	-2.39
Difference from placebo[1](97.5% CI)		-1.76* (-2.25, -1.28)	-1.99* (-2.48, -1.50)

[1] mean adjusted for baseline value

[2] The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.

*p-value <0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 6 and resulted in significant reductions in HbA1c with JARDIANCE 10 mg and 25 mg vs placebo (-0.58% and -0.6% respectively; p<0.0001) which were sustained over time.

Add-on Therapy with Pioglitazone (with or without Metformin, Study 1245.19)

The efficacy and safety of JARDIANCE were evaluated in a double-blind, placebo-controlled study of 24 weeks duration in patients not sufficiently treated with a combination of metformin and pioglitazone or pioglitazone alone. As shown in Table 14, JARDIANCE in combination with pioglitazone (mean dose ≥30 mg) with or without metformin resulted in statistically significant (p<0.0001) reductions in HbA1c, fasting plasma glucose, and body weight compared to placebo at Week 24.

Table 14: Results of a 24-Week (LOCF) Placebo-Controlled Study of JARDIANCE as Add-on to Pioglitazone

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
N	165	165	168
HbA1c (%)			
Baseline (mean)	8.16	8.07	8.06
Change from baseline[1]	-0.11	-0.59	-0.72
Difference from placebo[1] (97.5% CI)		-0.48* (-0.69, -0.27)	-0.61* (-0.82, -0.40)
N	155	151	160
Patients[2] (%) achieving HbA1c <7%	9.7	27.9	31.5
N	165	163	168
FPG (mmol/L)			
Baseline (mean)	8.43	8.44	8.43
Change from baseline[1]	0.37	-0.94	-1.23
Difference from placebo[1] (97.5% CI)		-1.32 (-1.72, -0.91)	-1.61 (-2.01, -1.21)
N	165	165	168
Body Weight (kg)			
Baseline (mean)	78.1	77.97	78.93
Change from baseline[1]	0.34	-1.62	-1.47
Difference from placebo[1] (97.5% CI)		-1.95* (-2.64, -1.27)	-1.81* (-2.49, -1.13)

[1] mean adjusted for baseline value

[2] The HbA1c responder analyses were performed on FAS with a noncompleters considered failure (NCF) imputation approach by determining the percentage of patients that fulfil responder criteria.

*p-value <0.0001

The first measurement of HbA1c after initiation of the treatment period occurred at week 6 and resulted in significant reductions in HbA1c with JARDIANCE 10 mg and 25 mg vs placebo (-0.4% and -0.51% respectively; p<0.0001) which were sustained over time.

Patients with T2DM Inadequately Controlled on Linagliptin and Metformin (Study 1275.9)

Following a 16-week open-label period with metformin (≥1500 mg/day) and linagliptin 5 mg, patients with T2DM who did not achieve adequate glycemic control were randomized (1:1:1) to receive 24-week double-blind treatment with either metformin + GLYXAMBI 10/5 (empagliflozin 10 mg + linagliptin 5 mg), metformin + GLYXAMBI 25/5 (empagliflozin 25 mg + linagliptin 5 mg) or metformin + linagliptin 5 mg (background therapy). The study was not designed to evaluate the efficacy of GLYXAMBI 25/5 in patients with T2DM inadequately controlled with GLYXAMBI 10/5.

Approximately 15% of randomized patients were aged ≥65 years (2% aged ≥75 years). Approximately 58% were White, 27% were Asian and 9% were Black. The mean body mass index (BMI) was 30.2 kg/m^2. Approximately 62% of patients had been diagnosed with T2DM for longer than 5 years, and approximately 7% for less than or equal to 1 year.

The primary endpoint of the study was the difference in change from baseline HbA1c at week 24. Key secondary endpoints were change from baseline fasting plasma glucose (FPG) and body weight, at week 24. Metformin + GLYXAMBI 10/5 and metformin + GLYXAMBI 25/5 each provided statistically significant improvements in HbA1c, FPG and body weight after 24 weeks of treatment compared to metformin + linagliptin 5 mg (see Table 15).

The proportion of patients with a baseline HbA1c ≥7.0% who achieved a target HbA1c of <7% at week 24 was 37.0% in the metformin + GLYXAMBI 10/5 group, 32.7% in the metformin + GLYXAMBI 25/5, and 17.0% in the metformin + linagliptin 5 mg group.

Table 15: Efficacy Parameters in the Clinical Study Comparing GLYXAMBI + Metformin to Linagliptin + Metformin in Patients with T2DM Inadequately Controlled on Linagliptin + Metformin (Study 1275.9)

	GLYXAMBI 10/5 + Metformin	**GLYXAMBI 25/5 + Metformin**	**Lina 5 + Metformin**
Efficacy Parameter			
HbA1c (%) - 24 weeks[2]			
N[1]	109	110	106
Baseline (mean)	7.97	7.97	7.96
Change from baseline (adjusted mean)	-0.65	-0.56	0.14
Difference from Lina 5 + Metformin (adjusted mean) (95% CI)	-0.79 (-1.02, -0.55) p<0.001	-0.70 (-0.93, -0.46) p<0.001	
FPG (mmol/L) – 24 weeks[2]			
N[1]	109	109	106

	GLYXAMBI 10/5 + Metformin	GLYXAMBI 25/5 + Metformin	Lina 5 + Metformin
Efficacy Parameter			
HbA1c (%) - 24 weeks[2]			
N[1]	109	110	106
Baseline (mean)	9.32	9.44	9.04
Change from baseline (adjusted mean)	-1.46	-1.75	0.34
Difference from Lina 5 + Metformin (adjusted mean) (95% CI)	-1.80 (-2.31, -1.28) p<0.01	-2.09 (-2.61, -1.57) p<0.01	
Body Weight (kg) – 24 weeks[2]			
N[1]	109	110	106
Baseline (mean) in kg	88.4	84.4	82.3
Change from baseline (adjusted mean)	-3.1	-2.5	-0.3
Difference from Lina 5 + Metformin (adjusted mean) (95% CI)	-2.8 (-3.5, -2.1) p<0.01	-2.2 (-2.9, -1.5) p<0.01	

Abbreviations: GLYXAMBI 10/5 = empagliflozin 10 mg + linagliptin 5 mg; GLYXAMBI 25/5 = empagliflozin 25 mg + linagliptin 5 mg; Lina 5 = linagliptin 5 mg

[1]N = Full Analysis Set (FAS): treated patients with a pre-randomization baseline and at least one on-treatment HbA1c assessment

[2]MMRM (mixed model repeated measures) model on FAS (observed case) includes baseline HbA1c, baseline eGFR (modification of diet in renal disease), geographical region, visit treatment, and treatment by visit interaction. For FPG, baseline FPG is also included. For weight, baseline weight is also included.

Add-on Therapy with MDI of Basal and Prandial Insulin (with or without Metformin) (Study 1245.49)

The efficacy and safety of JARDIANCE as add on to multiple daily injections of basal and prandial insulin with or without metformin were evaluated at Week 18 and Week 52 in a randomized, double-blind, placebo-controlled study of empagliflozin 10 mg and 25 mg. From Week 1 to Week 18, patients were to maintain a stable insulin dose. From Week 19 to 40, treat-to-target insulin dose adjustments were to be made as needed in order to achieve glucose treat-to-target values (pre-prandial 5.5 mmol/L and post-prandial 7.8 mmol/L). From Week 41 to Week 52, patients were to maintain a stable insulin dose, and adjustments were to be made for safety reasons only. Insulin mix, regular and/or analogue mix, have not been studied.

The primary endpoint was the change from baseline in HbA1c after 18 weeks of treatment, analyzed on the full analysis set (FAS-18). As shown in Table 16, statistically significant reduction in HbA1c relative to placebo was observed with JARDIANCE 10 mg and 25 mg at Week 18.

Table 16: Results of 18-Week Placebo-Controlled Study-FAS (LOCF-18) of JARDIANCE in Combination with Insulin alone or with Metformin

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
All patients, N	188	186	189
Insulin only, N (%)	53 (28.2)	58 (31.2)	52 (27.5)
HbA1c (%)			
Baseline[2] (mean) (SE)	8.44 (0.10)	8.32 (0.10)	8.31 (0.11)
Change from baseline[1] mean (SE) (at Week 18)	-0.33 (0.10)	-0.79 (0.10)	-0.96 (0.10)
Difference from placebo[1] 97.5% confidence interval	--	-0.46 (-0.78, -0.14)	-0.62 (-0.95, -0.29)
p-value	--	0.0016	<0.0001
Insulin + metformin, N (%)	135 (71.8)	128 (68.8)	137 (72.5)
HbA1c (%)			
Baseline[2] (mean) (SE)	8.29 (0.06)	8.42 (0.06)	8.29 (0.06)
Change from baseline[1] mean (SE) (at Week 18)	-0.58 (0.06)	-0.99 (0.06)	-1.03 (0.06)
Difference from placebo[1] 97.5% confidence interval	--	-0.41 (-0.61, -0.21)	-0.45 (-0.65, -0.25)
p-value	--	<0.0001	<0.0001

During the first 18 weeks of treatment, the background insulin dose was not to be changed.
SE= standard error
[1] adjusted mean for baseline HbA1c, eGFR and geographical region
[2] Model included baseline HbA1c (p<0.0001) as a linear covariate, baseline eGFR (MDRD) (p=0.7812), treatment (p<0.0001), baseline background medication (p=0.0541), and treatment by baseline background medication interaction (p=0.3254) as fixed effects.

Blood pressure

The effects of JARDIANCE on blood pressure were evaluated in a double-blind, placebo-controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic and up to 2 antihypertensive therapies. Treatment with JARDIANCE once daily resulted in statistically significant reduction in 24-hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring (see Table 17).

Treatment with JARDIANCE also provided reductions in seated SBP (change from baseline of -0.67 mmHg for placebo -4.60 mmHg for empagliflozin 10 mg and -5.47 mmHg for empagliflozin 25 mg) and seated DBP (change from baseline of -1.13 mmHg for placebo and -3.06 mmHg for empagliflozin 10 mg and -3.02 mmHg for empagliflozin 25 mg) at week 12.

Table 17: 24-Hour Ambulatory Blood Pressure Results at 12-week (LOCF) in a placebo-controlled study of JARDIANCE in patients with type 2 diabetes and uncontrolled blood pressure[#] (Full Analysis Set)

Efficacy Parameter	Placebo	JARDIANCE 10 mg	JARDIANCE 25 mg
N	271	276	276
24-hour SBP at week 12			
Baseline (mean)	131.72	131.34	131.18
Change from baseline[1]	0.48	-2.95	-3.68
Difference from placebo[1] (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24-hour DBP at week 12			
Baseline (mean)	75.16	75.13	74.64
Change from baseline[1]	0.32	-1.04	-1.40
Difference from placebo[1] (95% CI)		-1.36** (-2.15, -0.56)	-1.72* (-2.51, -0.93)

[a] completer analysis
Patients with mean seated SBP 130 to 159 mmHg and DBP 80 to 99 mmHg at screening
[1] mean adjusted for baseline value
*p-value <0.0001
**p-value=0.0008

Use in Patients with Type 2 Diabetes and Established Cardiovascular Disease (EMPA-REG OUTCOME; study 1245.25)

The EMPA-REG OUTCOME study is a multi-centre, multi-national, randomized, double-blind, placebo-controlled, parallel-group, event-driven trial, investigating the effect of JARDIANCE as adjunct to standard care therapy in reducing cardiovascular events in patients with type 2 diabetes and one or more of the following established cardiovascular diseases: coronary artery disease, peripheral artery disease, history of myocardial infarction (MI), and history of stroke.

The study was conducted in patients with an eGFR ≥30 mL/min/1.73m^2.

The primary endpoint was the time to first event in the composite of CV death, nonfatal MI, or nonfatal stroke (Major Adverse Cardiovascular Events [MACE-3]). The key secondary composite outcome was MACE-4 (i.e., MACE-3 plus hospitalization for unstable angina). Additional pre-specified, adjudicated endpoints included CV death, fatal/nonfatal myocardial infarction, fatal/non-fatal stroke, hospitalization for heart failure, and all-cause mortality. Patients without events were considered censored at the end of their individual observation periods.

A total of 7020 patients were treated (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) for a median duration of 2.6 years and followed for a median of 3.1 years. Baseline demographic and other characteristics, including background medications for diabetes and cardiovascular disease, were balanced across the treatment groups.

The population was 72.4% Caucasian, 21.6% Asian, and 5.1% Black. The mean age was 63 years (9.3% patients at least 75 years old) and 71.5% were male.

At randomisation, 75.6% of patients had coronary artery disease (including 46.6% with a history of myocardial infarction), 23.3% had a history of stroke, and 20.8% had peripheral artery disease. In total, 80.3% of patients had only 1 of these 3 factors reported at baseline, while 17.3% had 2 of the 3 factors and 1.6% had all 3 high-risk factors. A history of heart failure was reported for 10% of the patients.

At baseline, approximately 81% of patients were being treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 89% with anticoagulants, and 81% with lipid-lowering medication. Approximately 74% of patients were being treated with metformin at baseline, 48% with insulin, and 43% with sulphonylurea.

Mean HbA1C was 8.1% at baseline.

At baseline 52.2% of patients had an eGFR of 60-90 mL/min/1.73 m^2, 17.8% had an eGFR of 45-60 mL/min/1.73 m^2 and 7.7% had eGFR of 30-45 mL/min/1.73 m^2.

Mean systolic BP was 135 mmHg, diastolic BP 77 mmHg, LDL 2.22 mmol/L, and HDL 1.14 mmol/L at baseline.

Primary MACE Composite Endpoint: The primary analysis of MACE-3 was based on the treated set (TS), considering all events up to individual trial completion. According to hierarchical testing for non-inferiority and superiority, the pooled empagliflozin 10 and 25 mg treatment group (all empagliflozin) was found to be:

- Non-inferior to placebo, since the upper bound of the 95.02% CI was below 1.3, and
- Superior to placebo, since the upper bound of the 95.02% CI was also below 1.0

Table 18: Cox regression for time to first 3-point MACE, all JARDIANCE vs. placebo – TS

	Placebo	All JARDIANCE
Analysed patients, N (100%)	2333	4687
Patients with event, N (%)	282 (12.1)	490 (10.5)
Incidence rate per 1000 years at risk	43.9	37.4
Hazard ratio vs. placebo	--	0.86
(95.02% CI) [1]		(0.74, 0.99)
(95% CI)		(0.74, 0.99)
p−value for HR≥1.3 (1-sided)		<0.0001
p−value for HR≥1.0 (1-sided)		0.0191
p−value (2-sided)		0.0382

[1] Based on the reduced alpha level of 0.0249 resulting from the interim analysis

The treatment effect reflected a significant reduction in cardiovascular death with no significant change in non-fatal MI, or non-fatal stroke.

Results for the MACE-4 composite endpoint, including hospitalization for unstable angina, were non-inferior, but not superior, to placebo.

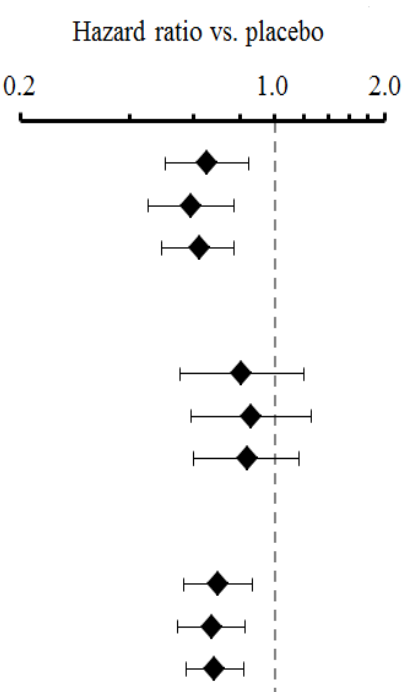
Other Adjudicated Cardiovascular Endpoints

Mortality Endpoints

JARDIANCE decreased all-cause mortality which was driven by a reduction in cardiovascular death. There was no statistically significant difference between JARDIANCE and placebo in non-cardiovascular mortality.

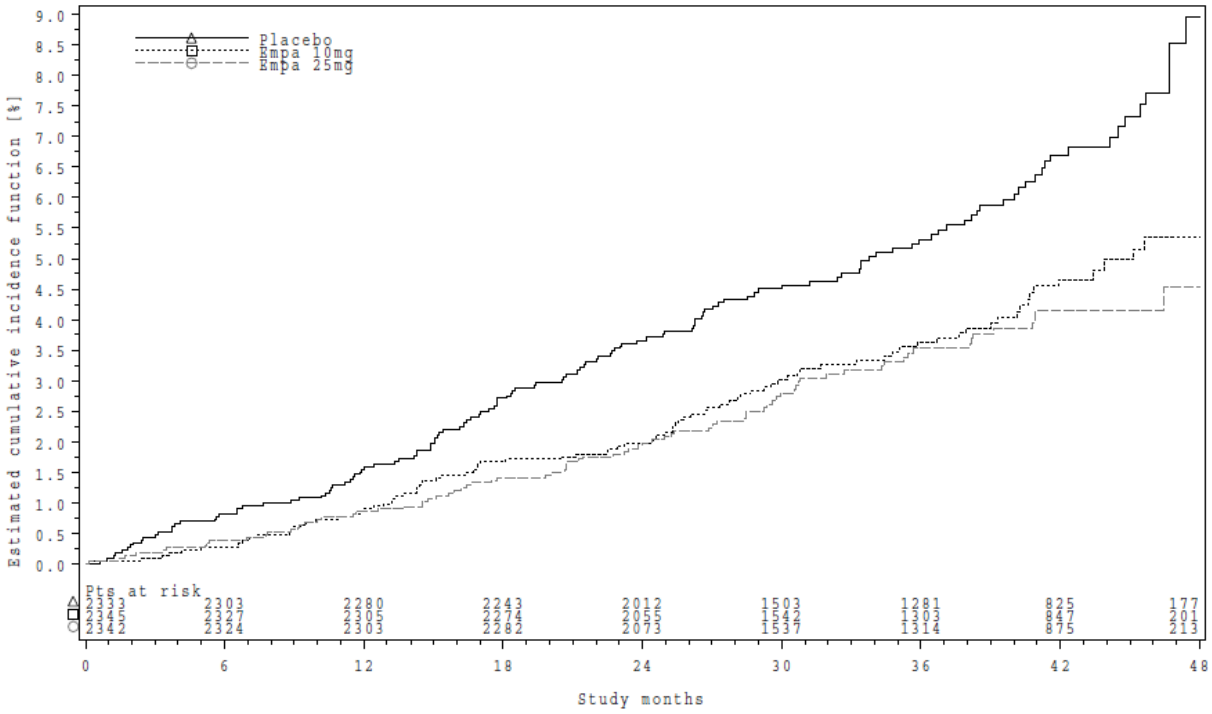
Table 19: Summary of endpoints of death – TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
CV death						
Placebo	137 (5.9)	20.2	--	--	--	--
Empa 10 mg	90 (3.8)	13.0	0.65	0.50	0.85	0.0016
Empa 25 mg	82 (3.5)	11.8	0.59	0.45	0.77	0.0001
All empa	172 (3.7)	12.4	0.62	0.49	0.77	<0.0001
Non-CV death						
Placebo	57 (2.4)	8.4	--	--	--	--
Empa 10 mg	47 (2.0)	6.8	0.81	0.55	1.20	0.2909
Empa 25 mg	50 (2.1)	7.2	0.86	0.59	1.26	0.4400
All empa	97 (2.1)	7.0	0.84	0.60	1.16	0.2852
All-cause mortality						
Placebo	194 (8.3)	28.6	--	--	--	--
Empa 10 mg	137 (5.8)	19.8	0.70	0.56	0.87	0.0013
Empa 25 mg	132 (5.6)	19.0	0.67	0.54	0.83	0.0003
All empa	269 (5.7)	19.4	0.68	0.57	0.82	<0.0001



For the graph: the diamond indicates the HR and the bars 95% CIs for the HR of empagliflozin vs. placebo

Figure 5: Estimated incidence function for time to CV death, individual empagliflozin doses vs placebo – treated set



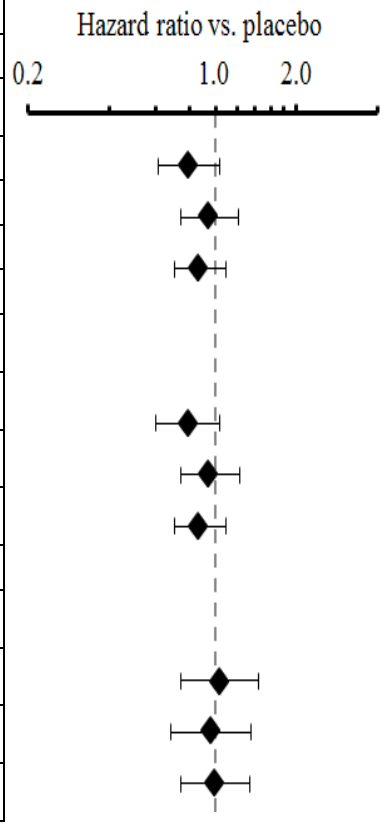
In this trial, there were 1819 patients with eGFR below 60 mL/min/1.73 m^2. The cardiovascular death findings in this subgroup were consistent with the overall findings. The efficacy and safety of JARDIANCE have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis.

Myocardial Infarction (MI) and Hospitalization for Unstable Angina

No statistically significant difference was observed between JARDIANCE and placebo for fatal/non-fatal MI, non-fatal MI, or hospitalization for unstable angina.

Table 20: Summary of MI-related endpoints – TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
MI (fatal/non-fatal)						
Placebo	126 (5.4)	19.3	--	--	--	--
Empa 10 mg	101 (4.3)	15.2	0.79	0.61	1.03	0.0852
Empa 25 mg	122 (5.2)	18.3	0.95	0.74	1.22	0.7141
All empa	223 (4.8)	16.8	0.87	0.70	1.09	0.2302
Non-fatal MI						
Placebo	121 (5.2)	18.5	--	--	--	--
Empa 10 mg	96 (4.1)	14.4	0.79	0.60	1.03	0.0769
Empa 25 mg	117 (5.0)	17.6	0.95	0.74	1.23	0.7114
All empa	213 (4.5)	16.0	0.87	0.70	1.09	0.2189
Hospitalization for unstable angina						
Placebo	66 (2.8)	10.0	--	--	--	--
Empa 10 mg	69 (2.9)	10.4	1.03	0.74	1.45	0.8509
Empa 25 mg	64 (2.7)	9.5	0.96	0.68	1.35	0.7981
All empa	133 (2.8)	10.0	0.99	0.74	1.34	0.9706

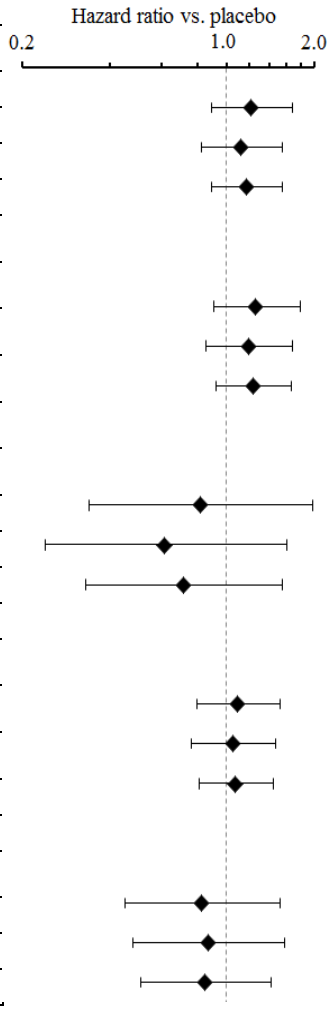


Stroke

For the endpoints fatal/non-fatal stroke and non-fatal stroke, non-significant unfavourable trends were observed in the empagliflozin groups. Much of this imbalance was driven by events that occurred off-treatment (more than 90 days after stop of treatment). For transient ischemic attacks, a non-significant favourable trend was observed. The majority of the stroke events were ischemic (149 of 164 for empagliflozin, 62 of 69 for placebo).

Table 21: Summary of cerebrovascular disease-related endpoints – TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
Stroke (fatal/non-fatal)						
Placebo	69 (3.0)	10.5	--	--	--	--
Empa 10 mg	85 (3.6)	12.7	1.22	0.89	1.68	0.2119
Empa 25 mg	79 (3.4)	11.8	1.13	0.82	1.56	0.4594
All empa	164 (3.5)	12.3	1.18	0.89	1.56	0.2567
Non-fatal stroke						
Placebo	60 (2.6)	9.1	--	--	--	--
Empa 10 mg	77 (3.3)	11.5	1.27	0.91	1.79	0.1593
Empa 25 mg	73 (3.1)	10.9	1.20	0.85	1.69	0.2954
All empa	150 (3.2)	11.2	1.24	0.92	1.67	0.1638
Fatal stroke						
Placebo	11 (0.5)	1.6	--	--	--	--
Empa 10 mg	9 (0.4)	1.3	0.82	0.34	1.98	0.6572
Empa 25 mg	7 (0.3)	1.0	0.62	0.24	1.61	0.3275
All empa	16 (0.3)	1.2	0.72	0.33	1.55	0.4015
Treatment-emergent stroke (fatal/non-fatal)*						
Placebo	66 (2.8)	11.1	--	--	--	--
Empa 10 mg	74 (3.2)	12.0	1.10	0.79	1.53	0.5773
Empa 25 mg	72 (3.1)	11.6	1.06	0.76	1.48	0.7229
All empa	146 (3.1)	11.8	1.08	0.81	1.45	0.6014
Transient ischemic attack (TIA)						
Placebo	23 (1.0)	3.5	--	--	--	--
Empa 10 mg	19 (0.8)	2.8	0.83	0.45	1.53	0.5603
Empa 25 mg	20 (0.9)	2.9	0.87	0.48	1.58	0.6357
All empa	39 (0.8)	2.9	0.85	0.51	1.42	0.5368



*Including all events up to 90 days after stop of treatment

Reductions in risk of heart failure requiring hospitalization or death from heart failure

JARDIANCE significantly reduced the risk of heart failure requiring hospitalization and heart failure requiring hospitalization or death from heart failure compared with placebo.

Table 22: Summary of heart failure-related endpoints – TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
Heart failure requiring hospitalization						
Placebo	95 (4.1)	14.5	--	--	--	--
Empa 10 mg	60 (2.6)	8.9	0.62	0.45	0.86	0.0044
Empa 25 mg	66 (2.8)	9.8	0.68	0.50	0.93	0.0166
All empa	126 (2.7)	9.4	0.65	0.50	0.85	0.0017
Heart failure requiring hospitalization or death from heart failure						
Placebo	104 (4.5)	15.8	--	--	--	--
Empa 10 mg	62 (2.6)	9.2	0.59	0.43	0.81	0.0010
Empa 25 mg	67 (2.9)	9.9	0.63	0.46	0.86	0.0034
All empa	129 (2.8)	9.6	0.61	0.47	0.79	0.0002

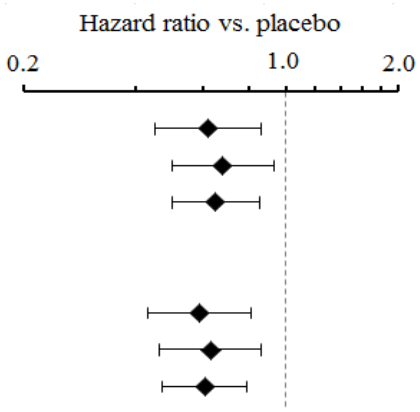
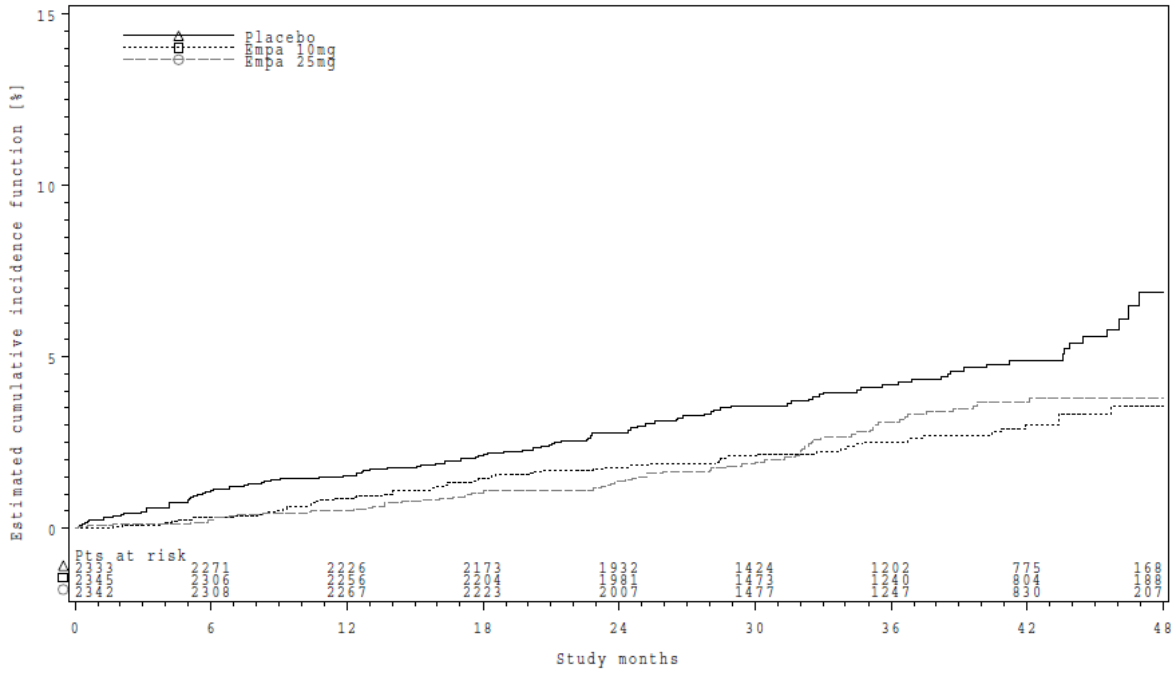


Figure 6: Estimated cumulative incidence function for time to first hospitalization for heart failure (HF) or death from worsening of heart failure, individual empagliflozin vs placebo – treated set



Other

Use in Patients with Type 2 Diabetes and Renal Impairment (Study 1245.36)

The efficacy and safety of JARDIANCE as add-on to antidiabetic therapy were evaluated in patients with type 2 diabetes and different degrees of renal impairment. A total of 738 patients with a baseline eGFR less than 90 mL/min/1.73 m^2 participated in a 52-week randomized, double-blind, placebo-controlled, parallel-group study.

In patients with mild renal impairment, treatment with JARDIANCE 10 mg and 25 mg led to statistically significant reduction of HbA1c at Week 24 compared to placebo. Although the 10 mg dose is the recommended starting dose of JARDIANCE, this dose was only studied in patients with mild renal impairment. For patients with type 2 diabetes with moderate or severe renal impairment, the 25 mg dose of JARDIANCE was used. The glucose lowering efficacy of JARDIANCE 25 mg decreased with decreasing renal function (see Table 23). In patients with severe renal impairment, JARDIANCE 25 mg did not reduce HbA1c at Week 24 and more adverse events were noted.

Table 23: Results at 24-Week (LOCF) in a Placebo-Controlled Study of Jardiance in Renally Impaired Type 2 Diabetes Patients (Full Analysis Set)

Efficacy Parameter	Placebo	JARDIANCE		Placebo	JARDIANCE 25 mg	Placebo	JARDIANCE 25 mg
		10 mg	25 mg				
	Mild (eGFR ≥60 to <90 mL/min/1.73m²)			Moderate 3A (eGFR ≥45 to <60 mL/min/1.73m²		Moderate 3B (eGFR ≥30 to <45 mL/min/1.73m²)	
N (%)	95 (12.9)	98 (13.3)	97 (13.1)	89 (12.1)	91 (12.3)	98 (13.3)	96 (13.0)
HbA1c (%)							
Baseline (mean)	8.09	8.02	7.96	8.08	8.12	8.01	7.95
Change from baseline[1]	0.06	-0.46	-0.63	-0.09	-0.54	0.17	-0.21
Difference from placebo[1] (95% CI)		-0.52* (-0.72, -0.32)	-0.68* (-0.88,-0.49)		-0.46* (-0.66, -0.27)		-0.39* (-0.58, -0.19)

[1] mean adjusted for baseline value

* p<0.0001

Heart Failure

Table 24: Summary of patient demographics for clinical trials in patients with Heart Failure

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number) randomized / treated	Mean age (Range)	Sex (%M/F)
1245.121 EMPEROR-Reduced	randomized, double-blind, placebo-controlled study	Empagliflozin 10 mg vs placebo + standard of care Tablets, orally, once daily treatment: event-driven follow up: about 15.7 months	Total: 3730/3726 Empagliflozin: 10 mg: 1863/1863 Placebo: 1867/1863	66.8 years (range: 25-94 years),	76.1% M/ 23.9% F
1245.110 EMPEROR-Preserved	randomized, double-blind, placebo-controlled study	Empagliflozin 10 mg vs placebo + standard of care Tablets, orally, once daily treatment: event-driven follow up: about 26.2 months	Total: 5988/5985 Empagliflozin: 10 mg: 2997/2996 Placebo: 2991/2989	71.9 years (range: 22-100 years),	55.3 % M/ 44.7 % F
1245.204 EMPULSE	randomized, double-blind, placebo-controlled study	Empagliflozin 10 mg vs placebo + standard of care Tablets, orally, once daily treatment: 90 days after clinical stability.	Total: 530/524 Empagliflozin: 10 mg: 265/260 Placebo: 265/264	68.5 years (range: 22-98 years)	66% M/ 34% F

JARDIANCE was studied in a randomized, double-blind, placebo-controlled study (EMPEROR-Reduced) in patients with chronic heart failure and reduced ejection fraction (LVEF ≤40 %) as adjunct to standard of care and in a randomized, double-blind, placebo-controlled study (EMPEROR-Preserved) in patients with chronic heart failure and preserved ejection fraction (LVEF >40 %) as adjunct to standard of care.

JARDIANCE was studied in a randomized, double-blind, placebo-controlled, parallel-group trial (EMPULSE) in patients hospitalized for acute heart failure (de novo or decompensated chronic heart failure) regardless of ejection fraction, after initial stabilisation.

Use in Patients with chronic heart failure and reduced ejection fraction (LVEF ≤40 %) (*EMPEROR-Reduced*; study 1245.121)

A randomized, double-blind, placebo-controlled study (EMPEROR-Reduced) was conducted in 3730 patients with chronic heart failure and reduced ejection fraction (LVEF ≤40 %) to evaluate the efficacy and safety of JARDIANCE 10 mg once daily as adjunct to standard of care heart failure therapy.

A total of 1863 patients were randomized to JARDIANCE 10 mg (placebo: 1867 patients) and followed for a median of 15.7 months. The study population consisted of 76.1% men and 23.9% women with a mean age of 66.8 years (range: 25-94 years); 62% of randomized patients with HFrEF were 65 years of age and older, 26.8% were 75 years of age or older.

Of the study population 70.5% were White, 18.0% Asian and 6.9% Black/African American.

Heart Failure therapy at baseline included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (88.3%), 19.5% of patients were receiving an angiotensin receptor-neprilysin inhibitor, beta blockers (94.7%), diuretics (95.0%) and mineralocorticoid receptor antagonists (71.3%). 31.4% of patients had an implanted cardiac defibrillator and 11.8% of patients had cardiac resynchronization therapy.

At randomization, 75.1% of patients were NYHA class II, 24.4% were class III and 0.5% were class IV. The mean LVEF was 27.5%, with 73.2% of patients having an LVEF ≤30%. Approximately half of patients (49.8%) had diabetes.

The study enrolled patients with eGFR equal to or above 20 mL/min/1.73 m^2. At baseline, the mean eGFR was 62.0 mL/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g (2.49 mg/mmol). About half of the patients (51.7%) had an eGFR of ≥60 mL/min/1.73 m^2, 24.1% had an eGFR of 45 to <60 mL/min/1.73 m^2, 18.6% had an eGFR of 30 to <45 mL/min/1.73 m^2 and 5.3% had an eGFR 20 to <30 mL/min/1.73 m^2.

The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalization for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent) was included in the confirmatory testing.

JARDIANCE was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalization for heart failure compared with placebo. Additionally, JARDIANCE significantly reduced the risk of occurrence of HHF (first and recurrent), see (Table 25 and Figure 7).

Table 25: Treatment effect for the primary composite endpoint, its components and the key secondary endpoint included in the pre-specified confirmatory testing

	Placebo	**JARDIANCE 10 mg**
N	1867	1863
Time to first event of CV death or HHF, N (%)	462 (24.7)	361 (19.4)
Hazard ratio vs. placebo (95.04% CI)**		0.75 (0.65, 0.86)
p−value for superiority		<0.0001
CV Death, N (%)*	202 (10.8)	187 (10.0)
Hazard ratio vs. placebo (95% CI)		0.92 (0.75, 1.12)

p-value		0.4113
HHF (first occurrence), N (%)*	342 (18.3)	246 (13.2)
Hazard ratio vs. placebo (95% CI)		0.69 (0.59, 0.81)
p−value		<0.0001
HHF (first and recurrent), N of events	553	388
Hazard ratio vs. placebo (95.04% CI)**		0.70 (0.58, 0.85)
p−value		0.0003

CV = cardiovascular, HHF = hospitalization for heart failure,
*not controlled for type 1 error
**Due to an interim analysis, a two-sided 95.04% confidence interval was applied which corresponds to a p-value less than 0.0496 for significance. CV death and HHF events were adjudicated by an independent clinical event committee and analyzed based on the randomized set.

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

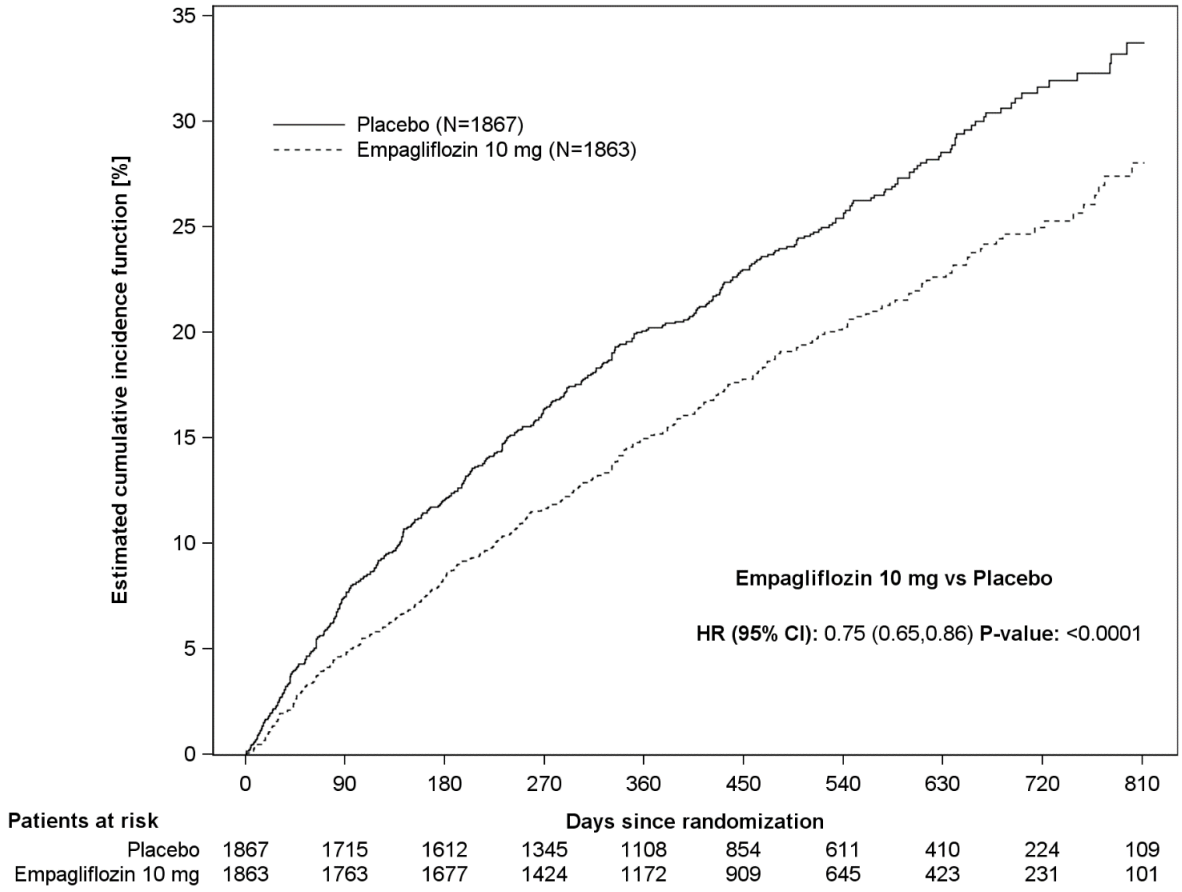
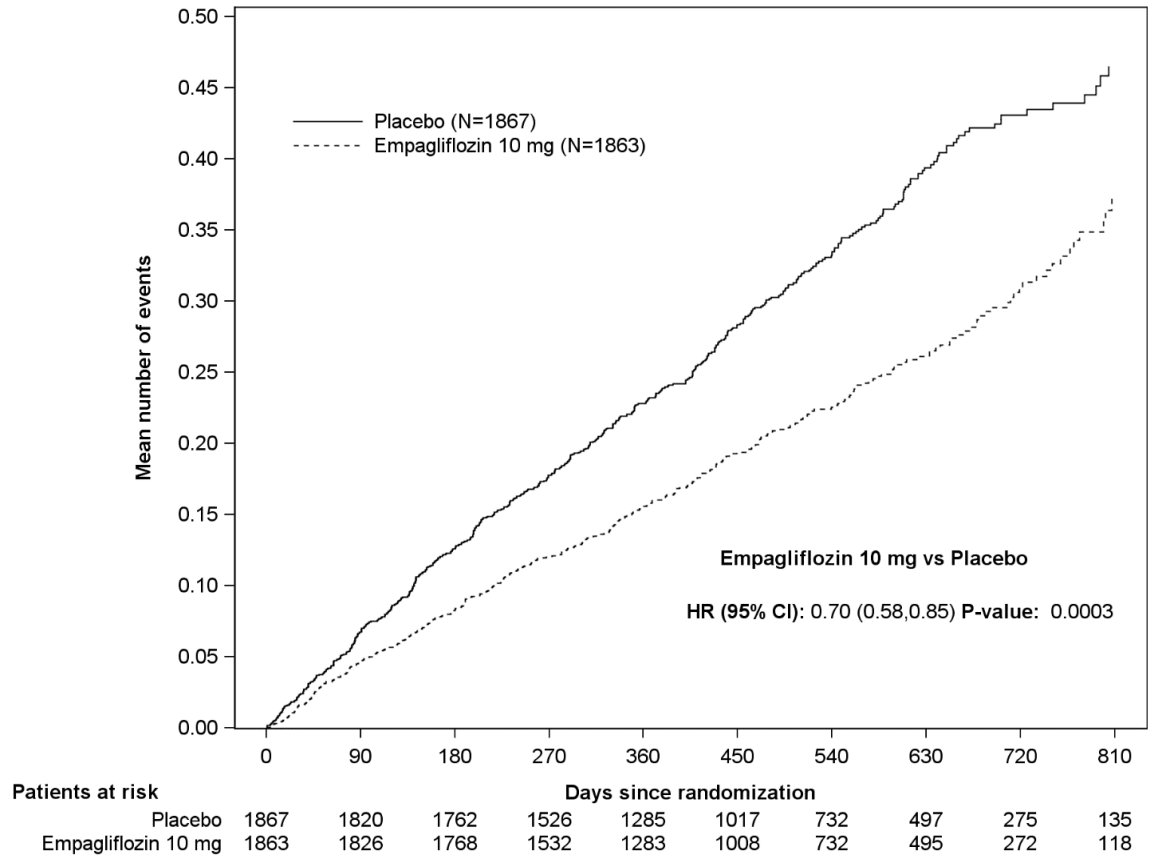
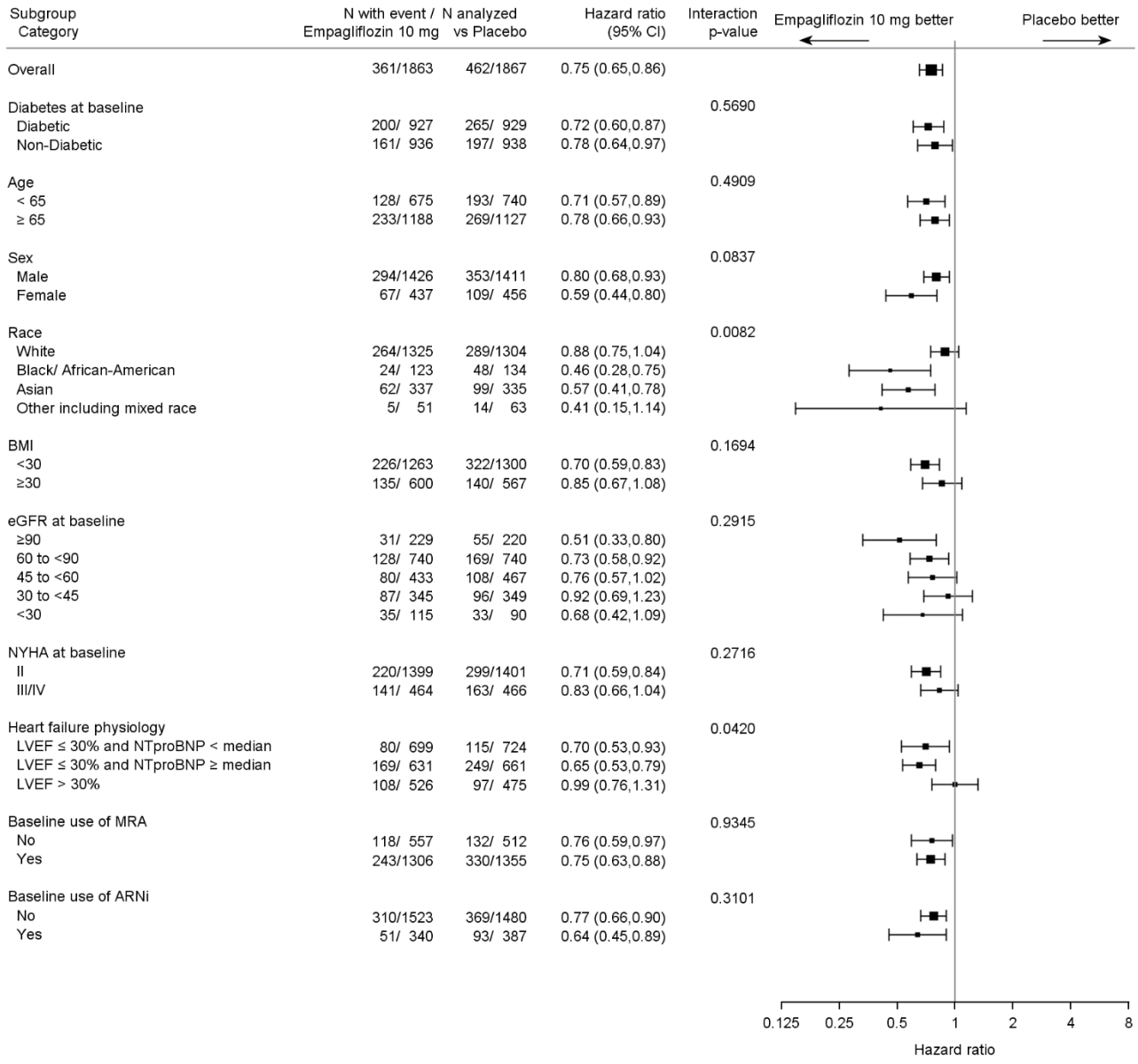


Figure 8: Occurrence of adjudicated HHF (first and recurrent), mean cumulative function



The results of the primary composite endpoint were generally consistent across the pre-specified subgroups, including heart failure patients with and without type 2 diabetes mellitus (Figure 9).

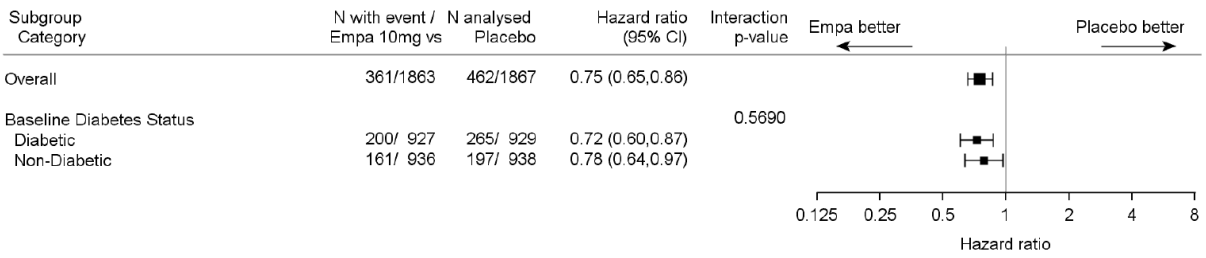
Figure 9: Treatment Effects for the Primary Composite Endpoint (Cardiovascular Death and Hospitalization for Heart Failure) Subgroup Analysis (EMPEROR-Reduced)



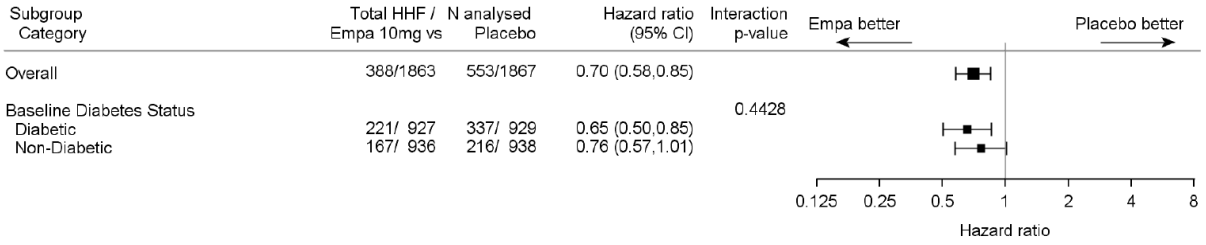
LVEF >30%: Includes both above and below the median NTproBNP. To be eligible for inclusion, patients with an LVEF >30% were required to meet a higher NTproBNP threshold than those with LVEF ≤30%, unless they additionally had a history of HHF within the past 12 months.

Figure 10: Primary and key secondary endpoint by baseline T2DM status in patients with HFrEF

Time to the first CV death or HHF, Cox regression, randomized set



HHF (first and recurrent), joint frailty model, randomized set



Use in Patients with chronic heart failure and preserved ejection fraction (LVEF >40 %) (*EMPEROR-Preserved*; study 1245.110)

A randomized, double-blind, placebo-controlled study (EMPEROR-Preserved) was conducted in 5988 patients with chronic heart failure (NYHA II-IV) and preserved ejection fraction (LVEF >40%) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care therapy.

The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalization for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent), and eGFR $(CKD\text{-}EPI)_{cr}$ slope of change from baseline were included in the confirmatory testing. Baseline therapy included angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB)/angiotensin receptor-neprilysin inhibitor (ARNi) (80.7%), beta blockers (86.3%), mineralocorticoid receptor antagonists (37.5%) and diuretics (86.2%).

A total of 2997 patients were randomized to empagliflozin 10 mg (placebo: 2991) and followed for a median of 26.2 months. The study population consisted of 55.3% men and 44.7% women with a mean age of 71.9 years (range: 22-100 years), 43.0% were 75 years of age or older. 75.9% of the study population were White, 13.8% Asian and 4.3% Black/African American. At randomization, 81.5% of patients were NYHA class II, 18.1% were NYHA class III and 0.3% were NYHA class IV.

The mean LVEF was 54.3%; LVEF <50% (33.1%), LVEF 50 to <60% (34.4%) and LVEF ≥60% (32.5%). The main cause of HF was ischemic (35.4%), hypertensive (36.5%), idiopathic (9.2%), and valvular heart disease (5.9%). Patients with prior diagnosis of cardiomyopathy based on infiltrative diseases (e.g., amyloidosis) were excluded. Approximately half of patients (49.1%) had diabetes (48.9% T2DM).

At baseline, the mean eGFR was 60.6 mL/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 2.4 mg/mmol. About half of the patients (50.1%) had an eGFR of ≥60 mL/min/1.73 m^2, 26.1% of 45 to <60 mL/min/1.73 m^2, 18.6% of 30 to <45 mL/min/1.73 m^2 and 4.9% 20 to <30 mL/min/1.73 m^2.

Empagliflozin significantly reduced the risk of the primary composite endpoint of cardiovascular death or hospitalization for heart failure compared with placebo (HR 0.79; 95.03%CI 0.69 to 0.90, p= 0.0003). The separation of the estimated cumulative incidence of CV death or first HHF between empagliflozin and placebo started shortly after randomisation and was maintained throughout the trial. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent) (see Table 26 and Figures 11 and 12).

Table 26: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing in EMPEROR-Preserved

	Placebo	**JARDIANCE 10 mg**
N	2991	2997
Time to first event of CV death or HHF, N (%)	511 (17.1)	415 (13.8)
Hazard ratio vs. placebo (95.04% CI)**		0.79 (0.69, 0.90)
p−value for superiority		0.0003
CV Death, N (%)*	244 (8.2)	219 (7.3)
Hazard ratio vs. placebo (95% CI)		0.91 (0.76, 1.09)
p-value		0.2951
HHF (first occurrence), N (%)*	352 (11.8)	259 (8.6)
Hazard ratio vs. placebo (95% CI)		0.71 (0.60, 0.83)
p−value		<0.0001
HHF (first and recurrent), N of events	541	407
Hazard ratio vs. placebo (95.04% CI)**		0.73 (0.61, 0.88)
p−value		0.0009

CV = cardiovascular, HHF = hospitalization for heart failure, eGFR = Estimated glomerular filtration rate, CKD EPI = Chronic kidney disease epidemiology collaboration equation

*not controlled for type 1 error

**Due to an interim analysis, a two-sided 95.04% confidence interval was applied which corresponds to a p-value less than 0.0496 for significance. CV death and HHF events were adjudicated by an independent clinical event committee and analyzed based on the randomized set.

Figure 11: Time to first event of adjudicated CV death or Hospitalization for Heart Failure (EMPEROR-Preserved)

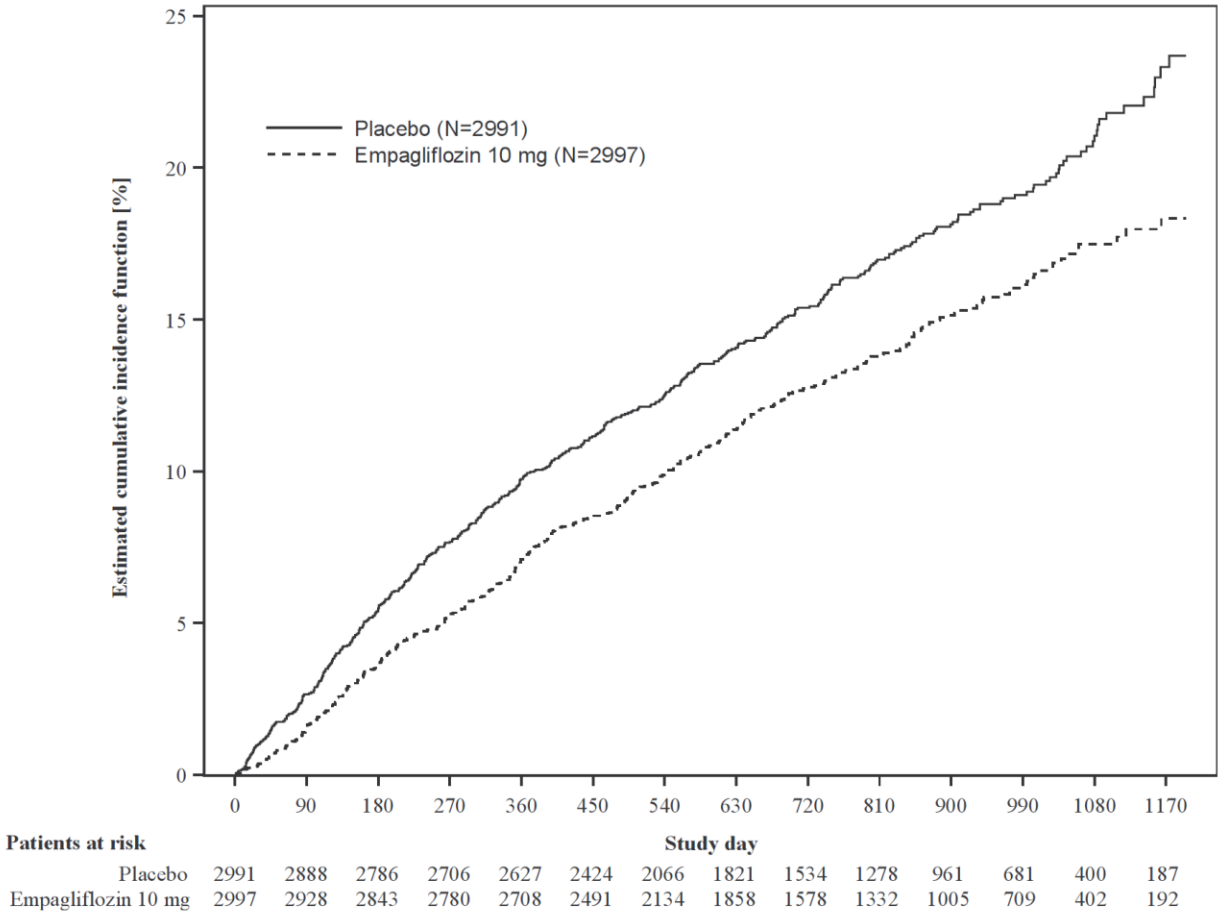
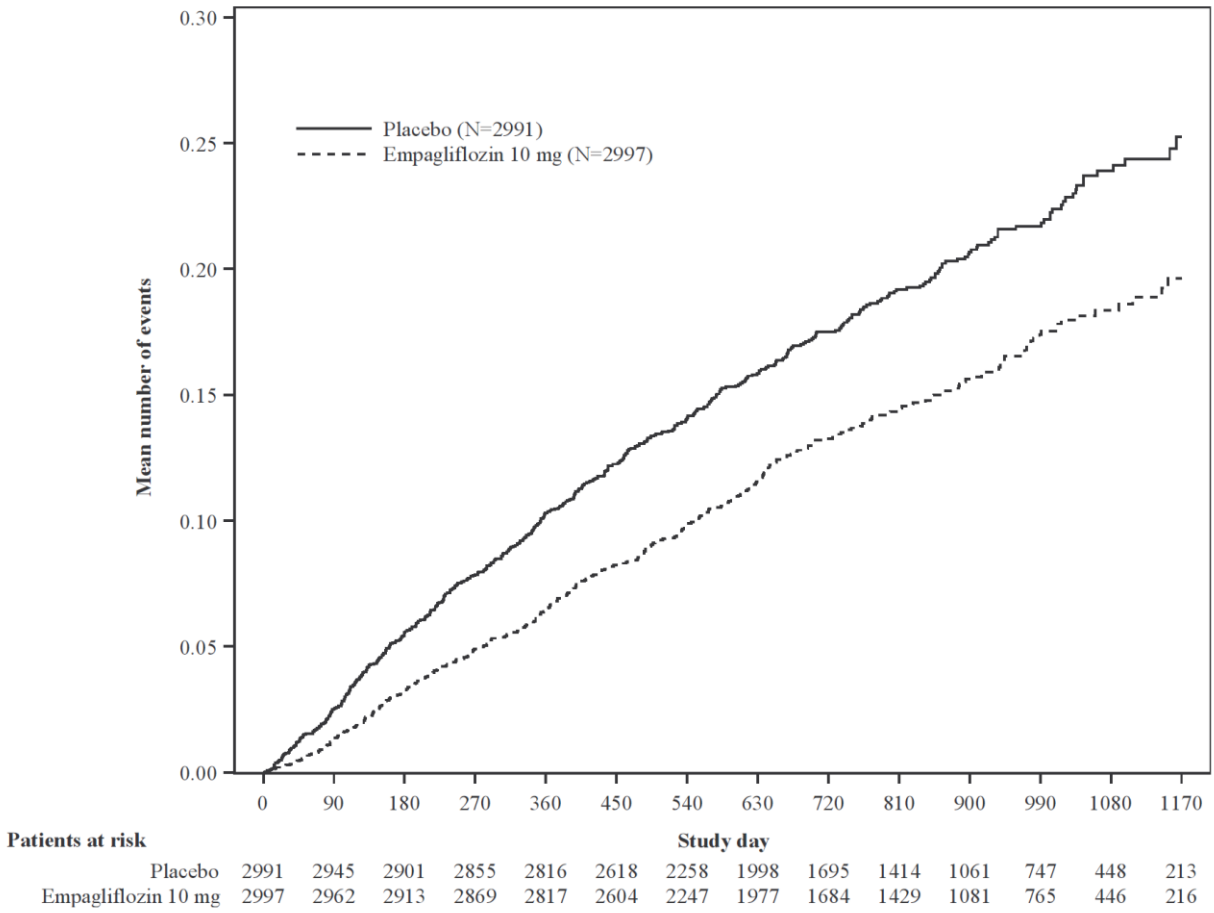
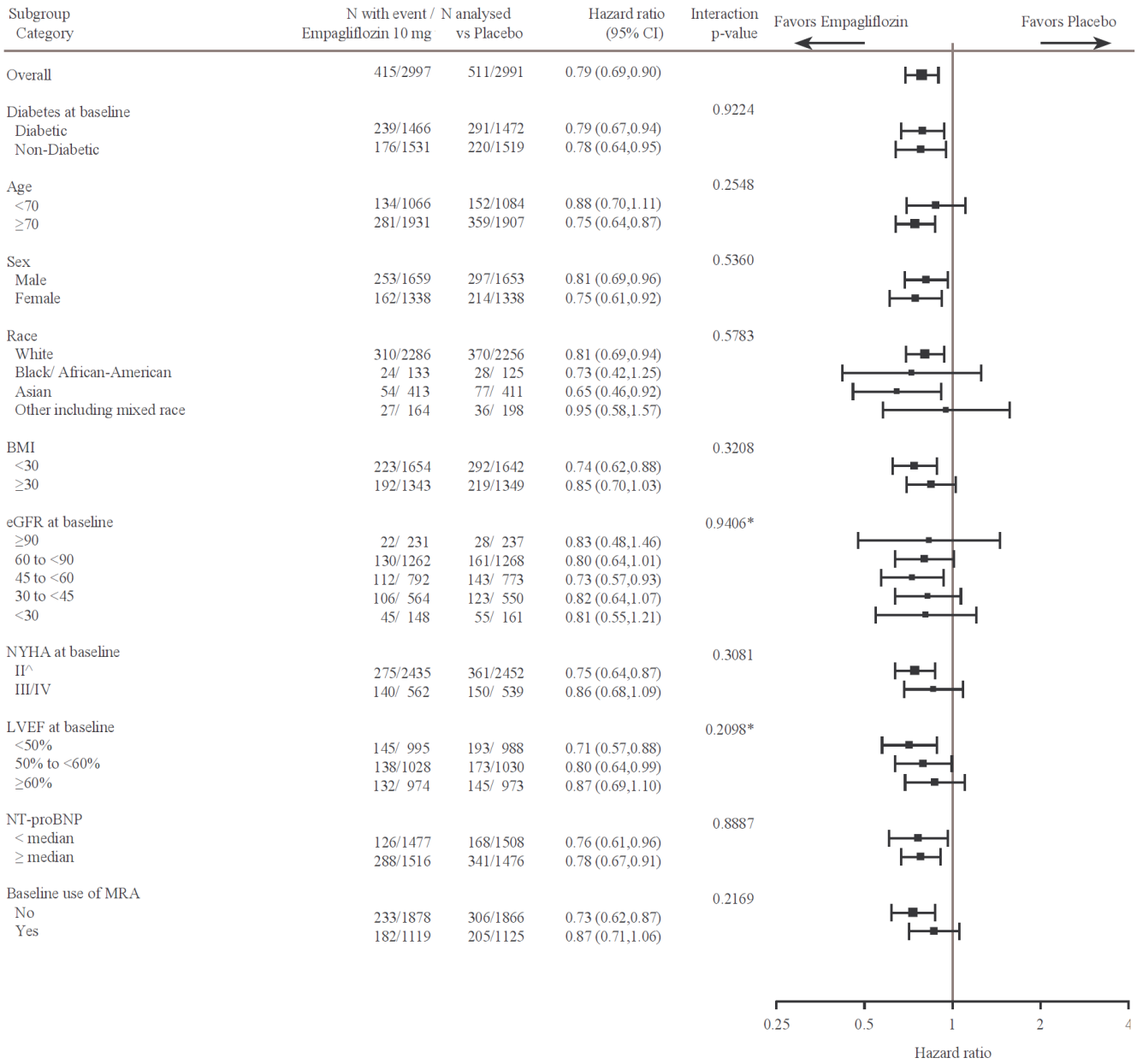


Figure 12: Time to event of adjudicated HHF (first and recurrent, EMPEROR-Preserved)



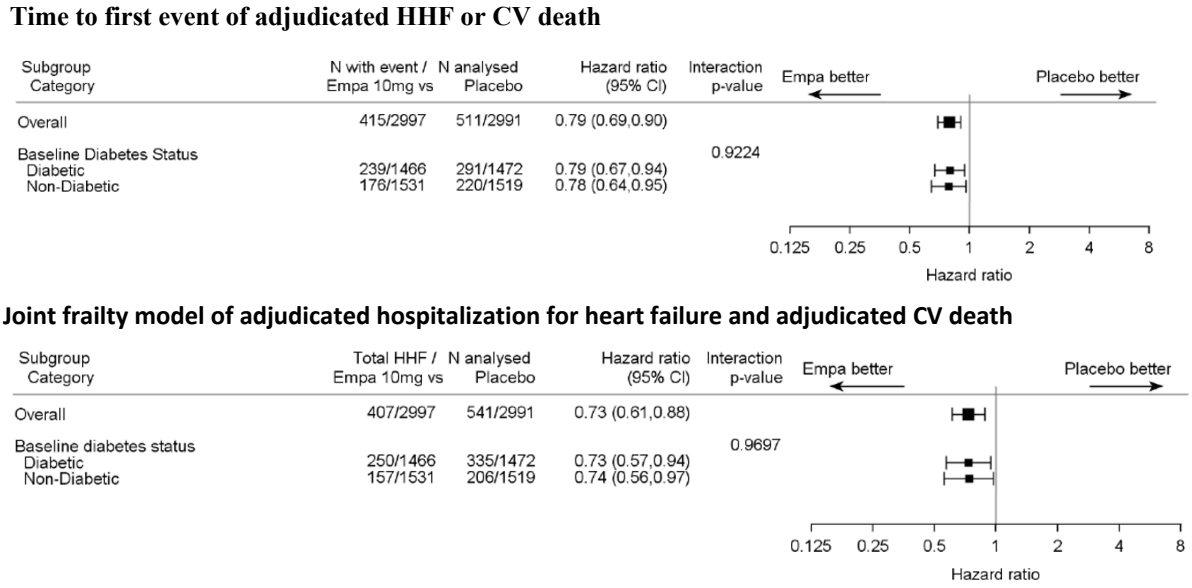
The results of the primary composite endpoint were consistent across each of the pre-specified subgroups (see Figure 13).

Figure 13: Treatment Effects for the Primary Composite Endpoint (Cardiovascular Death and Hospitalization for Heart Failure) Subgroup Analysis (EMPEROR-Preserved)



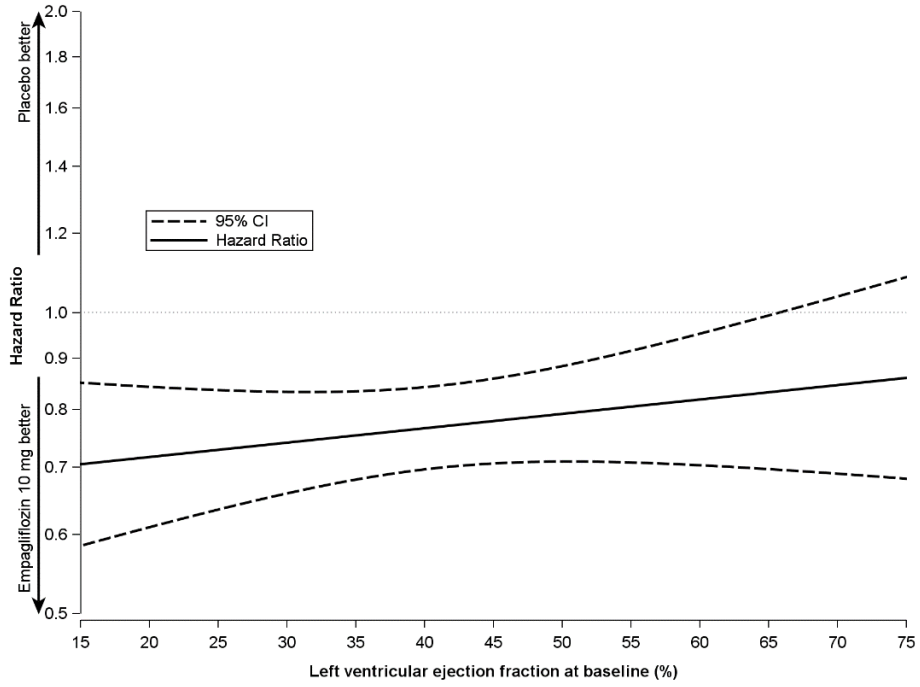
^4 patients with NYHA class I are counted in subgroup NYHA class II
*trend test

Figure 14: Primary and key secondary endpoints by baseline T2DM status in patients from EMPEROR-Preserved)



In a pooled analysis of the relationship between LVEF and primary composite endpoint in EMPEROR-Reduced and EMPEROR-Preserved, a consistent beneficial treatment effect of JARDIANCE was observed in patients across the LVEF spectrum (see Figure 15).

Figure 15: Treatment Effect for the Primary Composite Endpoint (Cardiovascular Death or Hospitalization for Heart Failure) by baseline LVEF in EMPEROR-Reduced and EMPEROR-Preserved



Use in patients hospitalized for acute heart failure who have been stabilised (EMPULSE, 1245-0204)

A randomized, double-blind, placebo-controlled study (EMPULSE) was conducted in 530 patients hospitalized for acute heart failure (33% with de novo and 67% with decompensated chronic heart failure) irrespective of LVEF who have been stabilised. The index hospitalization was primarily triggered by intravascular volume overload. Patients with recent acute coronary syndrome, myocardial infarction or transient ischemic attack were excluded.

The study evaluated the clinical benefit and safety of JARDIANCE 10 mg once daily as adjunct to standard of care therapy for heart failure. Treatment was initiated in the hospital once stabilisation was confirmed and continued for 90 days. The primary endpoint was a hierarchical composite of death, number of heart failure events (including hospitalizations for heart failure, urgent heart failure visits and unplanned outpatient visits), time to first heart failure event, and change from baseline in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS), which determines self-reported burden and frequency of heart failure symptoms, after 90 days of treatment assessed by the win ratio. Baseline therapy included angiotensin-converting-enzyme (ACE) inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (70.0%), beta blockers (79.4%), and diuretics (90.6%). According to the clinical trial protocol JARDIANCE was added as adjunct to standard therapy for heart failure with or without reduced ejection fraction and did not replace any other treatment indicated to manage heart failure.

Participants were equally randomized to JARDIANCE 10 mg or placebo and followed for a median of 98 days. The study population consisted of 66% men and 34% women with a mean age of 68.5 years (range: 22-98 years); 37% were 75 years of age or older; 78% of the study population were White, 11% Asian and 10% Black/African American.

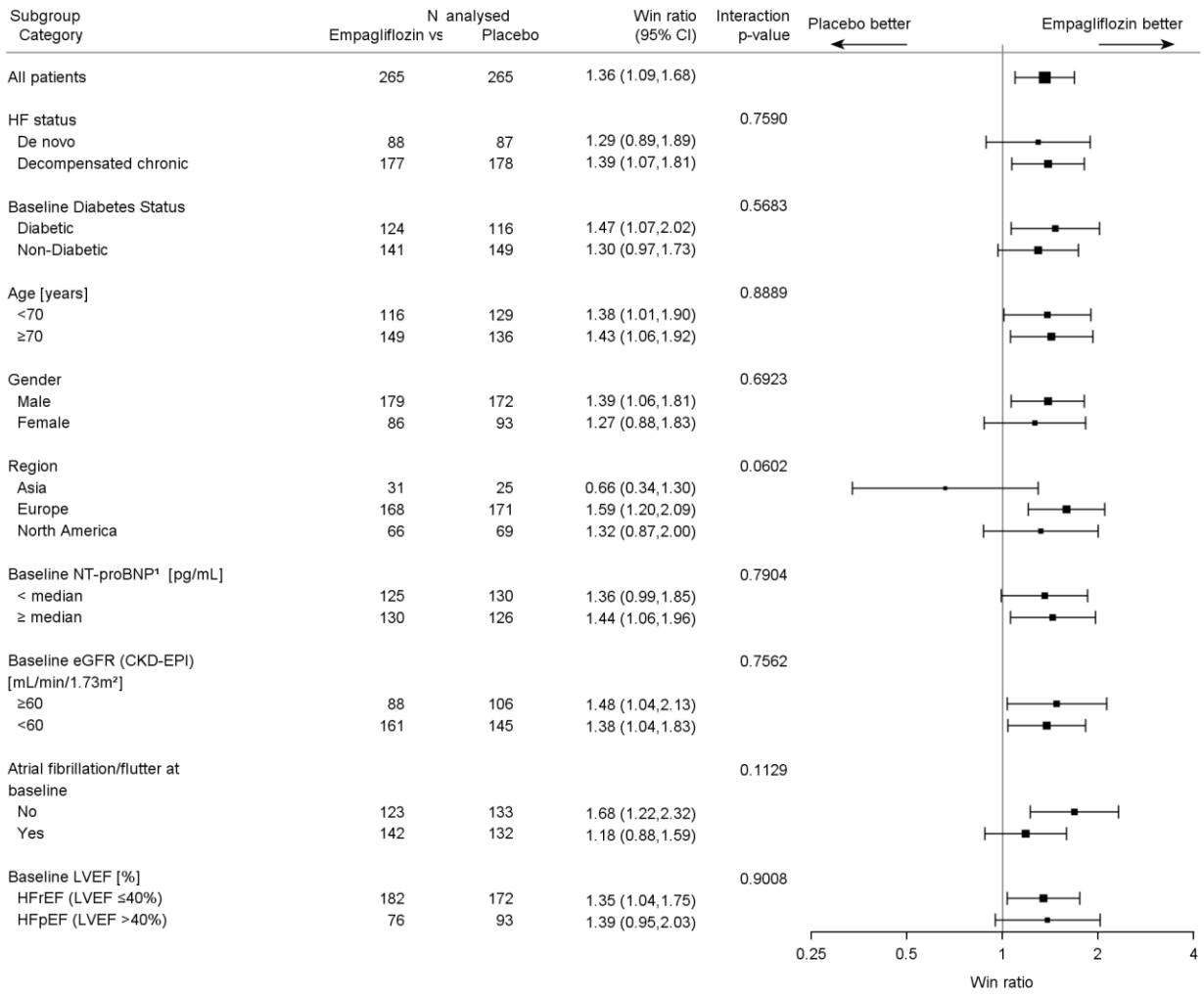
At randomization, 3% of patients were in NYHA class I, 35% in class II, 53% in class III, 9% in class IV and 45% of patients had T2DM. The EMPULSE study population included 67% of patients with LVEF ≤40%, and 32% with LVEF >40%. At baseline, 37% of patients had an eGFR of ≥60 ml/min/1.73 m^2, 23% of 45 to <60 ml/min/1.73 m^2, 25% of 30 to <45 ml/min/1.73 m^2, and 10% of <30 ml/min/1.73 m^2.

In the primary analysis, each patient in the JARDIANCE group was compared to every patient in the placebo group within each stratum (de novo or decompensated chronic heart failure). Pairwise comparisons were performed in a hierarchical fashion and stopped when the winning treatment could be determined in each pair for time to death, followed by number of heart failure events, time to first heart failure event, and finally a ≥5 point between-participant difference in change from baseline in KCCQ-TSS. The stratified win ratio was then calculated by combining the number of wins in the JARDIANCE group divided by the number of losses across strata.

Overall, participants taking JARDIANCE were 36% more likely to experience a clinical benefit compared to placebo (win ratio 1.36, 95% CI 1.09, 1.68; p = 0.0054; see Figure 16). The majority of the benefit was observed in the KCCQ-TSS endpoint.

The benefits were generally consistent across the pre-specified subgroups, including de novo heart failure and decompensated chronic heart failure, and were independent of LVEF.

Figure 16: Primary efficacy endpoint: win ratio of clinical benefit, overall and by subgroup (EMPULSE)



Chronic Kidney Disease

Table 27: Summary of patient demographics for clinical trials in patients with Chronic Kidney Disease

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number) randomized	Mean age (Range)	Sex (%M/F)
1245.137 EMPA-KIDNEY Study	randomized, double-blind, placebo-controlled study	Empagliflozin 10 mg vs placebo + standard of care Tablets, orally, once daily treatment: event-driven follow up: about 24.3 months	Total: 6609 Empagliflozin: 10 mg: 3304 Placebo: 3305	63.3 years (Range: 18-94 years)	66.8% M/ 33.2% F

Use in Patients with chronic kidney disease (EMPA-KIDNEY Study)

A randomized, double-blind, placebo-controlled study of JARDIANCE 10 mg once daily (EMPA-KIDNEY) was conducted in patients (N= 6609) with chronic kidney disease (eGFR ≥20 -to <45 mL/min/1.73m^2; or eGFR ≥45 -to <90 mL/min/1.73m^2 with UACR ≥200 mg/g) to assess cardio-renal outcomes as adjunct to standard of care therapy. Patients with polycystic kidney disease, or patients requiring or with a recent history (within 3 months) of intravenous immunosuppressive therapy or greater than 45 mg of prednisone or equivalent were excluded from the study.

The primary endpoint was the time to first occurrence of kidney disease progression (sustained ≥40% eGFR decline from randomization, sustained eGFR <10 mL/min/1.73m², end-stage kidney disease, or renal death) or CV death. Key secondary endpoints assessed were all-cause hospitalization (first and recurrent), first occurrence of hospitalization for heart failure or CV death, and all-cause mortality. Baseline therapy included an appropriate use of a RAS-inhibitor (85.2% ACE inhibitor or angiotensin receptor blocker).

A total of 3304 patients were randomized to JARDIANCE 10 mg once daily (placebo: 3305) and followed for a median of 24.3 months. The study population consisted of 66.8% men and 33.2% women with a mean age of 63.3 years (range: 18-94 years), 23.0% were 75 years of age or older. 58.4% of the study population were White, 36.2% Asian and 4.0% Black/African American. Approximately 44.4% (N= 2936) of the patients had type 2 diabetes mellitus.

At baseline, the mean eGFR was 37.3 mL/min/1.73 m^2, 21.2% patients had an eGFR of ≥45 mL/min/1.73 m^2, 44.3% of 30 to <45 mL/min/1.73 m^2 and 34.5% <30 mL/min/1.73 m^2 including 254 patients with an eGFR <20 mL/min/1.73 m^2. The median UACR was 329 mg/g, 20.1% patients had an UACR <30 mg/g, 28.2% had an UACR 30 to ≤300mg/g and 51.7% had an UACR >300 mg/g. Primary causes of chronic kidney disease were diabetic nephropathy/diabetic kidney disease (31%), glomerular disease (25%), hypertensive/renovascular disease (22%) and other/unknown (22%).

JARDIANCE was superior in reducing the risk of the primary composite endpoint of sustained ≥40% eGFR decline, sustained eGFR <10 mL/min/1.73m², ESKD, renal death or CV death compared with placebo. Additionally, JARDIANCE significantly reduced the risk of all-cause hospitalization, first and recurrent.

Table 28: Treatment effect for the primary composite endpoint, its components, and key secondary endpoint

	Placebo	Empagliflozin 10 mg
N	3305	3304
Time to first occurrence of composite of sustained ≥40% eGFR decline, sustained eGFR <10 mL/min/1.73m², ESKD*, renal death or CV death, N (%)	558 (16.9)	432 (13.1)
Hazard ratio vs. placebo (95% CI)		0.72 (0.64, 0.82)
p−value for superiority		<0.0001
Sustained ≥40% eGFR decline from randomization, N (%)	474 (14.3)	359 (10.9)
Hazard ratio vs. placebo (95% CI)		0.70 (0.61, 0.81)
p-value		<0.0001
Sustained eGFR <10 mL/min/1.73m², N (%)	167 (5.1)	116 (3.5)
Hazard ratio vs. placebo (95% CI)		0.69 (0.54, 0.87)
p-value		0.0021
ESKD*, N (%)	158 (4.8)	108 (3.3)
Hazard ratio vs. placebo (95% CI)		0.67 (0.52, 0.85)
p-value		0.0012
Renal death, N (%)**	4 (0.1)	4 (0.1)
CV Death, N (%)	69 (2.1)	59 (1.8)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.19)
p-value		0.3366
All-cause hospitalizations (first and recurrent), N of events	1895	1611
Hazard ratio vs. placebo (95% CI)		0.86 (0.78, 0.95)
p-value		0.0025

CV = cardiovascular, eGFR = Estimated glomerular filtration rate

* End-stage kidney disease (ESKD) is defined as the initiation of maintenance dialysis or receipt of a kidney transplant.

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

Figure 17: Time to First Occurrence of the Primary Composite Endpoint, Sustained ≥40% eGFR Decline from Randomization, Sustained eGFR <10 mL/min/1.73 m^2, ESKD or Renal Death, or CV Death

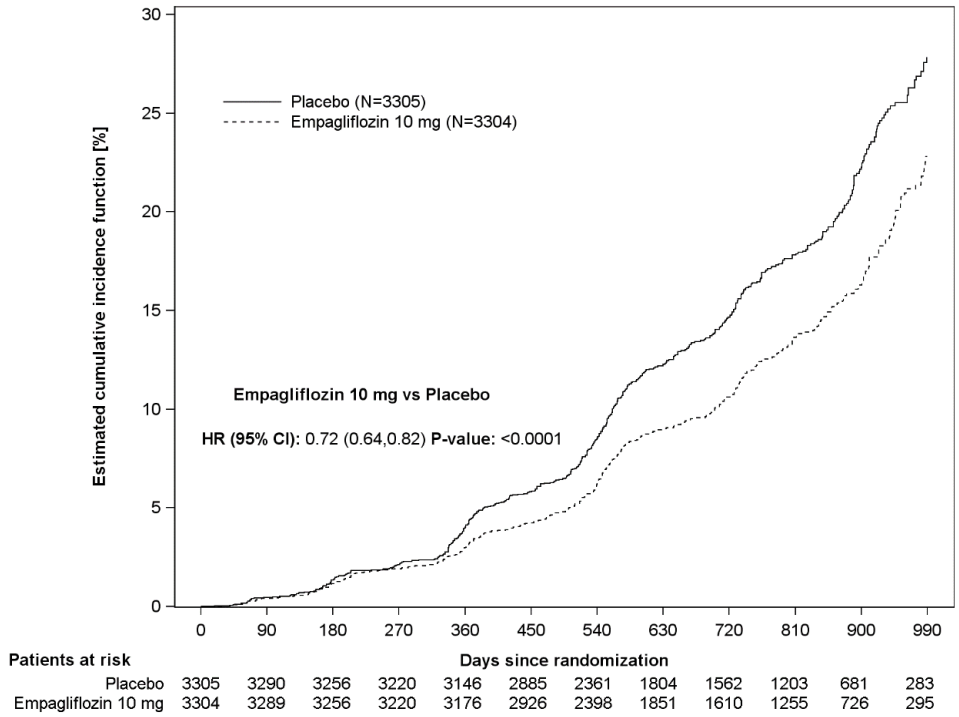
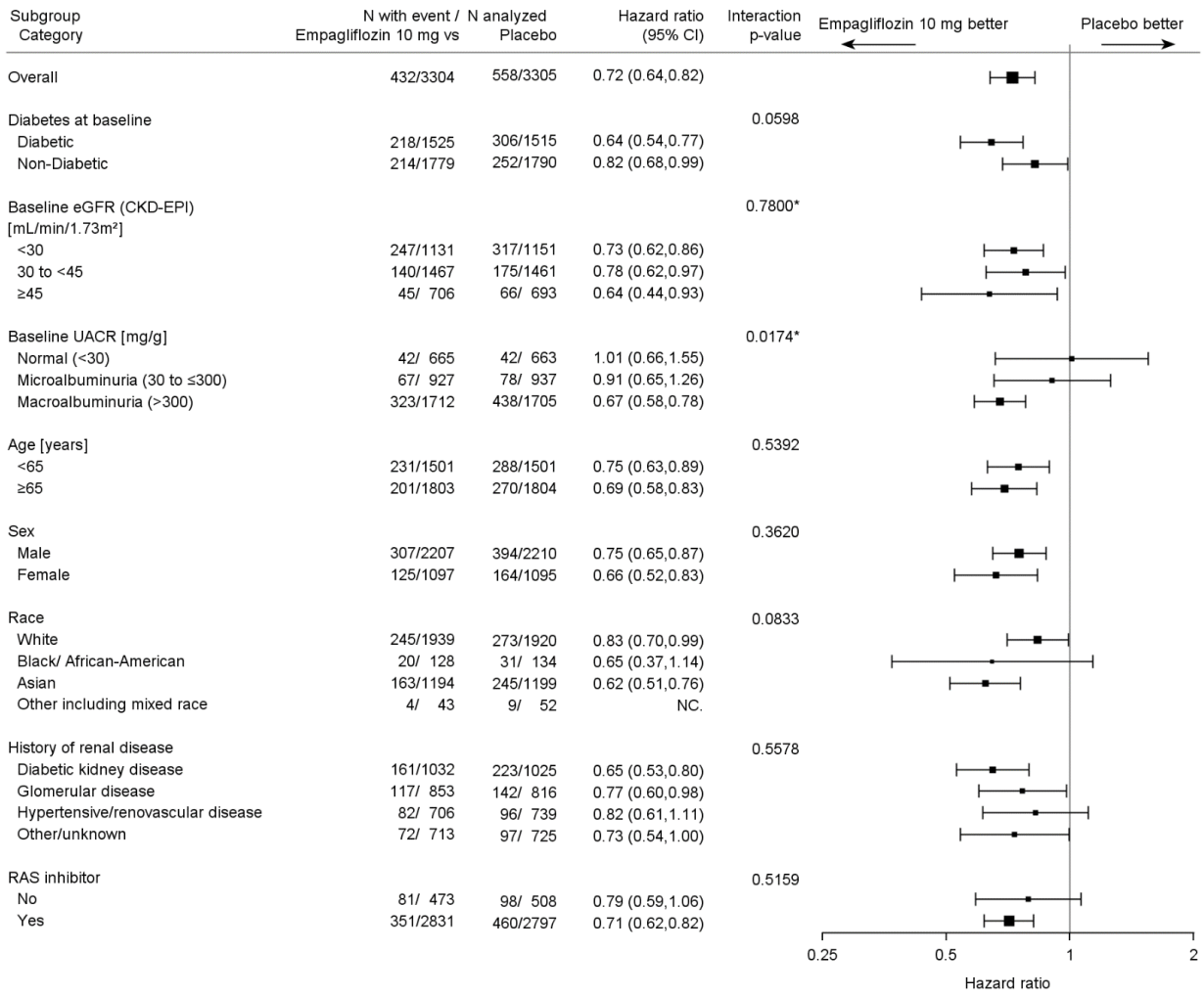


Figure 18: Treatment Effects for the Primary Composite Endpoint (Sustained ≥40% eGFR Decline, Sustained eGFR <10 mL/min/1.73 m^2, ESKD, Renal Death, or CV Death) Subgroup Analysis



The results of the primary composite endpoint were generally consistent across the pre-specified subgroups examined, including eGFR categories, underlying cause of renal disease, diabetes status, or background use of RAS inhibitors. The treatment benefits with JARDIANCE were more clearly evident in patients with high levels of albuminuria than patients with low levels of albuminuria.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute toxicity: Empagliflozin demonstrated low acute toxicity. The single lethal oral dose of empagliflozin was greater than 2000 mg/kg in mice and rats.

Sub-chronic and chronic toxicity: Repeat-dose oral toxicity studies were conducted in mice, rats and monkeys for up to 13, 26, and 52 weeks, respectively. Signs of toxicity were generally observed at exposures greater than or equal to 10 times the human exposure (AUC) at the maximum recommended dose of 25 mg. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and included decreased body weight and body fat, increased food consumption, diarrhea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism, gluconeogenesis and electrolyte imbalances, urinary changes such as polyuria and glycosuria. Increases in liver weight, elevated hepatic enzyme activities (e.g., AST and ALT) and hepatocellular vacuolation were observed in mice, rats and dogs. These changes in the liver may be related to gluconeogenesis and/or mobilization of lipid for energy production. The main target organ of empagliflozin toxicity was the kidney. Microscopic changes in the kidney were observed across species and included tubular karyomegaly, single cell necrosis, cystic hyperplasia and hypertrophy (mouse), renal mineralization and cortical tubular vacuolation (rat), and tubular nephropathy and interstitial nephritis (dog).

In a 2-year study in mice, mortality associated with urinary tract lesions was dose-dependently increased for males given empagliflozin at oral doses of ≥100 mg/kg/day (≥4 times the clinical dose of 25 mg based on AUC comparisons).

Carcinogenicity: The carcinogenic potential of empagliflozin was evaluated in 2-year studies in mice and rats. Empagliflozin did not increase the incidence of tumors in female rats up to the highest dose of 700 mg/kg/day (up to 72 times the clinical dose of 25 mg based on AUC comparisons). In male rats, treatment-related benign vascular proliferative lesions (hemangiomas) of the mesenteric lymph node were observed at 700 mg/kg/day (approximately 42 times the clinical dose of 25 mg based on AUC comparisons), but not at 300 mg/kg/day which corresponds to approximately 26 times the clinical exposure from 25 mg dose. These tumors are common in rats and the incidence (18%) was within literature historical control (0-26%). No vascular lesions were seen in the mouse and dog. Empagliflozin did not increase the incidence of tumors in female mice at doses up to 1000 mg/kg/day (up to, approximately 62 times the clinical dose of 25 mg based on AUC comparisons). Renal tumors were observed in male mice at 1000 mg/kg/day (approximately 45 times the clinical dose of 25 mg based on AUC comparisons), but not at 300 mg/kg/day which corresponds to approximately 11 times the clinical exposure from a 25 mg dose. The mode of action for these tumors may be dependent on the natural predisposition of the male mouse to renal pathology which is exacerbated by a male mouse kidney-specific cytotoxic oxidative metabolite. Therefore, the renal tumors found in mice may not be relevant to patients given clinical doses of empagliflozin.

Genotoxicity: Empagliflozin was not genotoxic in the Ames bacterial mutagenesis test, the L5178/tk+/- mouse lymphoma assay, or the *in vivo* rat micronucleus test.

Reproductive and Developmental Toxicology: In a study of fertility and early embryonic development in rats, empagliflozin had no effects on mating and fertility in males or females or early embryonic development up to the highest dose of 700 mg/kg/day (approximately 50 times the clinical dose of 25 mg based on AUC comparisons). Empagliflozin administered during the period of organogenesis was not

teratogenic at doses up to 300 mg/kg/day in the rat or rabbit, which corresponds to approximately 48 times or 128 times the clinical dose of 25 mg based on AUC comparisons, respectively. Doses of empagliflozin causing maternal toxicity in the rat also caused the malformation of bent limb bones at exposures approximately 155 times the clinical exposure from a 25 mg dose. Maternally toxic doses in the rabbit also caused increased embryofetal loss at doses approximately 139 times the clinical dose of 25 mg based on AUC comparisons.

In a pre- and postnatal toxicity study in rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at 10, 30 and 100 mg/kg/day, and pups were indirectly exposed in utero and throughout lactation. There was no evidence of maternal toxicity up to the high dose of 100 mg/kg/day; however, a reduction in F1 pup body weight gains, mainly during lactation, was observed at doses of ≥30 mg/kg/day (≥4 times the clinical dose of 25 mg based on AUC comparisons). The F1 male pups also had learning and memory deficits at 100 mg/kg (approximately 16 times the clinical dose of 25 mg based on AUC comparisons) on postnatal day (PND) 22, but not on PND 62. These neurobehavioral effects were likely to be secondary to the retarded growth rates of the F1 male pups. The NOAEL for F1 neonatal toxicity was 10 mg/kg/day (approximately 1.4 times the clinical dose of 25 mg based on AUC comparisons).

Special Toxicity: Empagliflozin demonstrated good *in vitro* potency towards inhibition of human (IC50 of 1.3 nM) and rat (IC50 of 1.7 nM) renal SGLT2 transporters. The three major human metabolites of empagliflozin, all glucuronides, exhibited very weak activity toward the SGLT2 transporter *in vitro*, with IC50 values ranging from 860 – 1435 nM. Oral doses of empagliflozin increased urinary glucose excretion in diabetic rodents and normoglycemic dogs. This triggered the lowering of blood glucose in diabetic rodents after single oral dosing, as well as after chronic treatment.

Juvenile Toxicity: In a juvenile toxicity study, empagliflozin was administered directly to young rats from post-natal day 21 until postnatal day 90 at oral doses of 1, 10, 30 and 100 mg/kg/day. Increases in kidney weights were observed in males at ≥ 10 mg/kg/day (≥ 0.7 times the clinical dose of 25 mg based on AUC comparisons) and in females at ≥ 30 mg/kg/day (≥ 4 times the clinical dose of 25 mg based on AUC comparisons). Minimal to mild renal tubular and pelvic dilation was seen at 100 mg/kg/day, which approximates 11-times the clinical dose of 25 mg based on AUC comparisons. These findings were absent after a 13-week, drug-free recovery period.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Jardiance®

Empagliflozin Tablets

Read this carefully before you start taking **JARDIANCE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **JARDIANCE**.

Serious Warnings and Precautions

- **Ketoacidosis** can happen while you are taking JARDIANCE. It is a serious and life-threatening condition, which may need urgent hospital care. In ketoacidosis the body produces high levels of blood acids called ketones. Some cases of ketoacidosis have led to death. Ketoacidosis can happen to patients with diabetes with normal or high blood sugar levels because the body does not have enough insulin. Cases of ketoacidosis have also been reported in patients without diabetes.
- **Seek medical help right away and stop taking JARDIANCE immediately if you have any of the ketoacidosis symptoms**. Do this even if your blood sugar levels are normal. The symptoms of ketoacidosis are: difficulty breathing, nausea, vomiting, stomach pain, and loss of appetite. Confusion, feeling thirsty, feeling unusually tired or sleepy, along with a sweet or metallic taste in the mouth or sweet-smelling breath can be noticed. You may have a different odour to your urine or sweat.
- **Do not use** JARDIANCE if you have:
  - ketoacidosis or a history of ketoacidosis;
  - type 1 diabetes.

What is JARDIANCE used for?

JARDIANCE is used:

- along with diet and exercise to improve blood sugar levels in adults with type 2 diabetes. It can be used alone, or with other blood sugar lowering medications.
- to reduce the risk of death due to cardiovascular problems in adults with type 2 diabetes and cardiovascular disease (heart and blood vessel problems).
- along with standard of care, to treat heart failure in adults.
- in adults with chronic kidney disease to reduce the risk of kidney disease progression, or death due to problems with your kidneys, heart or blood vessels.

How does JARDIANCE work?

JARDIANCE belongs to a class of medicines called sodium-glucose co-transporter 2 (SGLT2) inhibitors. If you have too much sugar in your blood, JARDIANCE removes excess sugar from the body through the urine. This reduces the amount of sugar in the blood. JARDIANCE can also affect other organs and functions in your body (e.g., blood vessels, the heart and kidneys) to provide cardiovascular and kidney benefits. JARDIANCE helps protect your heart from getting weaker and improves your symptoms if you have heart failure. JARDIANCE also helps protect your kidneys from losing their function.

What are the ingredients in JARDIANCE?

Medicinal ingredient: Empagliflozin.

Non-medicinal ingredients: Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, macrogol, microcrystalline cellulose, titanium dioxide, talc, and yellow ferric oxide.

JARDIANCE comes in the following dosage forms:

Tablets: 10 mg and 25 mg of empagliflozin.

Do not use JARDIANCE if:

- you are allergic to empagliflozin or any of the other ingredients in JARDIANCE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take JARDIANCE. Talk about any health conditions or problems you may have, including if you:

- have type 1 diabetes (your body does not produce any insulin). JARDIANCE should not be used if you have type 1 diabetes;
- have ketoacidosis or a history of ketoacidosis (increased level of ketones in the blood). JARDIANCE should not be used in patients with ketoacidosis;
- have an increased chance of developing ketoacidosis, including if you:
  - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
  - are on a very low carbohydrate diet;
  - have been fasting for a while;
  - are eating less, or there is a change in your diet;
  - drink a lot of alcohol;
  - have or have had problems with your pancreas. This includes pancreatitis (inflammation of the pancreas) or surgery on your pancreas;
  - are going to have surgery and after your surgery;
  - are hospitalized for a major surgery, serious infection, or serious medical illnesses;
  - have an acute illness;
  - have sudden reduction in insulin dose;
  - have a history of ketoacidosis.
- are 65 years of age or older and being treated for your blood sugar levels;
- have kidney problems or are on dialysis;
- have liver problems;
- have low blood pressure;
- are taking a medicine for high blood pressure or taking a water pill (used to remove excess water from the body);
- are taking medicines to lower your blood sugar such as glyburide, gliclazide, glimepiride (sulfonylureas), or insulin. Taking JARDIANCE with any of these medicines can increase the risk of having low blood sugar (hypoglycemia);
- have intolerance to some milk sugars. JARDIANCE tablets contain the milk sugar lactose;
- have a history of infections in the genital area;
- have a history of urinary tract infections.

Other warnings you should know about:

Taking JARDIANCE can cause the following:

- **Increased urination:** This is common in patients with high blood sugar (glucose).
- **Urinary tract infections:** This can include urosepsis and pyelonephritis. Your healthcare professional will monitor your health for any signs of an infection. If a urinary tract infection is suspected, they may temporarily stop your treatment with JARDIANCE.
- **Yeast infections of the penis or vagina:** This is more likely if you have had a yeast infection in the past.
- **Fournier's gangrene:** This is a rare, but serious and potentially life-threatening infection affecting the soft tissue around the groin that may lead to hospitalization, surgery, and even death in both men and women. If you notice any signs of Fournier's gangrene, stop taking JARDIANCE and tell your healthcare professional right away.
- **Serious allergic reactions:** The signs can include swelling of tissue under the skin, rashes, and itchiness. If you notice any signs of an allergic reaction, stop taking JARDIANCE and tell your healthcare professional right away.
- **Kidney problems:** This may happen shortly after you start taking JARDIANCE. This can affect how your kidneys are working. Your healthcare professional will assess your kidney function before and during your treatment.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

Pregnancy: JARDIANCE should not be used if you are pregnant or planning to become pregnant. It is not known if JARDIANCE can harm your unborn baby. Talk with your healthcare professional about the best way to control your blood sugar while you are pregnant. If you become pregnant while taking JARDIANCE, stop your treatment and tell your healthcare professional.

Breastfeeding: JARDIANCE should not be used if you are breastfeeding. It is not known if JARDIANCE will pass into your breastmilk. Talk to your healthcare professional if you are planning to breastfeed.

Monitoring and testing: Your healthcare professional will monitor your health before and during your treatment with JARDIANCE. This can include performing physical examinations and blood tests. This will help them to evaluate:

- your blood glucose levels;
- your hemoglobin (a protein in red blood cells that carries oxygen) levels;
- your kidneys, especially if you are prescribed another medication;
- your fluid volume, especially if you are at a higher risk of volume depletion or have a condition that may lead to fluid loss (e.g., gastrointestinal problems). If fluid loss is detected your healthcare professional may stop your treatment until this is resolved;
- the amount of red blood cells in your blood (hematocrit).

JARDIANCE will cause your urine to test positive for sugar (glucose).

Driving and using machines: JARDIANCE can cause dizziness and light-headedness. Before you drive or do tasks that require special attention, wait until you know how you respond to JARDIANCE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with JARDIANCE:

- medicines used for diabetes, especially sulfonylurea medications such as glyburide, gliclazide, glimepiride (sulfonylureas), or insulin;
- medicines used to increase the amount of water released in your urine known as diuretics;
- lithium, because JARDIANCE can lower the amount of lithium in your blood.

How to take JARDIANCE:

You should take JARDIANCE:

- once daily;
- at any time of the day;
- by mouth;
- with or without food.

Swallow the tablet whole. Do NOT cut or divide tablets.

Usual dose:

Patient with Type 2 Diabetes:

- **To control your blood sugar:** the usual adult starting dose is 10 mg once daily. Your healthcare professional may increase your dose to 25 mg once daily, if needed.

- **To reduce the risk of cardiovascular death:** the usual adult dose is 10 mg once daily.

Patients with Heart Failure or Chronic Kidney Disease:
The usual adult dose is 10 mg once daily.

Overdose:

If you think you, or a person you are caring for, have taken too much JARDIANCE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of this medication, follow the instructions below to ensure that you do not take a double dose of JARDIANCE:

- If it is 12 hours or more until your next dose, take the missed dose as soon as you remember. Then take your next dose at the usual time.
- If it is less than 12 hours until your next dose, skip the missed dose. Then take your next dose at the usual time.

What are possible side effects from using JARDIANCE?

These are not all the possible side effects you may have when taking JARDIANCE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of JARDIANCE may include:

- unusual thirst;
- passing more urine than usual or needing to pass more often;
- itching;
- rash or hives;
- straining or pain when emptying the bladder;
- constipation;
- weight decrease.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Hypoglycemia (low blood sugar): shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood.		✓	
COMMON			
Urinary tract infection (infection in the urinary system including kidneys, ureters, bladder and urethra): pain or burning sensation when urinating, pain in the pelvis, mid-back pain, increased need to urinate, blood in urine, strong smelling urine, or cloudy urine.		✓	
Vaginal yeast infection (a genital infection): severe itching, burning, soreness, irritation, or a whitish-gray cottage cheese-like discharge.	✓		
Yeast infection of the penis (a genital infection): red, swollen, itchy head of penis, thick lumpy discharge under foreskin, unpleasant odour, difficulty retracting foreskin, or pain passing urine or during sex.	✓		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Volume depletion (loss of fluids from the body, dehydration): dry or sticky mouth, headache, dizziness, shock, low blood pressure, thirsty, or urinating less often than normal.			✓
Allergic skin reactions: rash, hives, or swelling of your lips, face, throat, or tongue that may cause difficulty in breathing or swallowing.			✓
UNCOMMON			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying to sitting to standing up).		✓	
Kidney problems: any change in the amount, frequency or colour (pale or dark) of urine, nausea, vomiting, fever, swelling of extremities, fatigue, thirst, dry skin, irritability, dark urine, blood in the urine, rash, weight gain (from retaining fluid), loss of appetite, abnormal blood test results, or mental status changes (drowsiness, confusion, coma).		✓	
Urosepsis (severe infection of the blood that spreads from urinary tract throughout body): fever, high or very low body temperature, chills, rapid breathing, rapid heartbeat, pain with urination, difficulty urinating, little to no urine, dizziness, low blood pressure or palpitations.			✓
Acute kidney infection: painful, urgent or frequent urination, lower back (flank) pain, fever or chills, cloudy or foul-smelling urine or sweat, blood in your urine,			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, thirst, unusual fatigue, sleepiness or tiredness, a sweet or metallic taste in the mouth, or sweet-smelling breath.			
RARE			
Ketoacidosis (high levels of ketones, a type of acid, in urine or blood): rapid weight loss, feeling sick or being sick, difficulty breathing or fast and deep breathing, feeling very thirsty, vomiting, stomach pain, nausea, loss of appetite, confusion, fatigue, feeling unusually tired or sleepy, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.			✓
UNKNOWN FREQUENCY			
Fournier's gangrene (a serious infection affecting soft tissue): fever, feeling weak, tiredness, uncomfortable tenderness, redness, or swelling in and around the genitals or anus.			✓
Pancreatitis (inflammation of the pancreas): upper abdominal pain, severe stomach pain that lasts and gets worse when you lie down; nausea, vomiting, fever, rapid heartbeat, or tenderness when touching the abdomen.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store JARDIANCE tablets at room temperature (15°C to 30°C).
- If there are any leftover, unused or expired tablets, bring them to your local pharmacist for proper disposal. Do not flush the medication down the toilet or sink.
- Keep out of reach and sight of children.

If you want more information about JARDIANCE:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's, Boehringer Ingelheim (Canada) Ltd., website (https://www.boehringer-ingelheim.ca), or by calling 1-800-263-5103, extension 84633.

The information in this leaflet is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd., Burlington, ON, Canada L7L 5H4, co-promoted with Eli Lilly Canada Inc. Box 73, Toronto, ON, Canada M5X 1B1.

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