PROFESSIONAL INFORMATION (PI)

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

Jardiance® 10 mg
Jardiance® 25 mg

film-coated tablets

JARDIANCE IS CONTRAINDICATED FOR USE IN TYPE 1 DIABETES.
JARDIANCE IS NOT INDICATED FOR USE IN WEIGHT CONTROL PROGRAMMES.
There have been reports of metabolic acidosis, including ketoacidosis, which were serious, life threatening or fatal, in patients with diabetes mellitus taking JARDIANCE. Cases of ketoacidosis have also been reported in patients without diabetes mellitus. Patients who present with signs and symptoms including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for metabolic acidosis, even if blood glucose levels are below 11 mmol/L. JARDIANCE should be discontinued and the patient should be promptly evaluated and managed accordingly.
Predisposing factors for metabolic acidosis include insulin dose reduction, reduced caloric intake, reduced fluid intake or increased insulin requirements due to infections, illness, surgery or alcohol abuse. Caution is advised in treating these patients with JARDIANCE.
Predisposing factors for ketoacidosis include low beta-cell function reserve resulting from pancreatic disorders, e.g. history of pancreatitis or pancreatic surgery. JARDIANCE is contraindicated in these patients.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

- JARDIANCE 10 mg: Each film-coated tablet contains empagliflozin 10 mg.
- JARDIANCE 25 mg: Each film-coated tablet contains empagliflozin 25 mg.

Contains sugar (lactose): 162,5 mg lactose monohydrate per JARDIANCE 10 mg tablet and 113 mg lactose monohydrate per JARDIANCE 25 mg tablet.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

JARDIANCE 10 mg: Pale yellow, round, biconvex, bevel-edged film-coated tablets debossed on one side with the Boehringer Ingelheim company symbol and ‘S10’ on the other side.
JARDIANCE 25 mg: Pale yellow, oval, biconvex, film-coated tablets debossed on one side with the Boehringer Ingelheim company symbol and ‘S25’ on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Type 2 diabetes mellitus (T2DM)

Glycaemic control:
JARDIANCE is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

Add-on combination therapy:
In combination with glucose-lowering medicines, including metformin, a thiazolidinedione, a sulphonylurea, a DPP-4 inhibitor, or insulin, when these together with diet and exercise, do not provide adequate glycaemic control.

Prevention of cardiovascular events:
JARDIANCE is indicated in patients with type 2 diabetes mellitus and high cardiovascular risk* to reduce the risk of:
- cardiovascular death due to myocardial infarction
- cardiovascular death or hospitalisation for heart failure.

*e.g. previous myocardial infarction, multi vessel coronary artery disease, previous coronary revitalisation, single vessel coronary disease, at least 50 % narrowing of coronary artery lumen.

Heart failure (HF)
JARDIANCE is indicated in adult patients with heart failure (NYHA class II-IV) independent of left ventricular ejection fraction, with or without type 2 diabetes mellitus:
- to reduce the risk of cardiovascular death and hospitalisation for heart failure
- to slow kidney function decline.

Chronic kidney disease (CKD)
JARDIANCE is indicated in adult patients with chronic kidney disease to reduce the risk of:
- Kidney disease progression (sustained decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease or renal death) or cardiovascular death
- All-cause hospitalisation.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Assess hydration status and renal function before initiating treatment with JARDIANCE. Do not initiate treatment in patients who are volume-depleted or acidotic (see section 4.4).

Posology
Type 2 diabetes mellitus (T2DM) indications:
The recommended starting dose of JARDIANCE is 10 mg once daily.
In patients tolerating JARDIANCE 10 mg once daily who have an eGFR $\geq$30 mL/min/1,73 m^2 and requiring additional glycaemic control, the dose may be increased to 25 mg once daily.

Heart failure (HF) indication:
The recommended dose of JARDIANCE is 10 mg once daily (see section 5.1 clinical trials).

Chronic kidney disease (CKD) indication:
The recommended dose of JARDIANCE is 10 mg once daily (see section 5.1 clinical trials).

JARDIANCE can be taken with or without food.

Special populations

Patients with Renal Impairment:

Empagliflozin 10 mg can be used regardless of renal function. However, due to limited experience, it is not recommended to initiate treatment with JARDIANCE in patients on dialysis.
Glycaemic efficacy of empagliflozin is dependent on renal function and likely absent in patients with severe renal impairment. If eGFR falls below 30 mL/min/1,73 m^2 the recommended dose of empagliflozin is limited to 10 mg and additional glucose lowering treatment should be considered if needed (see section 4.4).

Patients with Hepatic Impairment:

Dose adjustment may be necessary for patients with severe hepatic impairment.

Elderly Patients:

No dosage adjustment is recommended based on age.

Combination therapy:

When JARDIANCE is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin should be considered to reduce the risk of hypoglycaemia (see sections 4.4 and 4.8).

Paediatric population:

Safety and effectiveness of JARDIANCE in children under 18 years of age have not been established.

Method of administration

Film-coated tablets for oral administration.

Missed dose

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to empagliflozin or any of the excipients of JARDIANCE (see section 6.1).
- Type 1 diabetes mellitus.
- Treatment of ketoacidosis.
- Pregnancy and lactation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

JARDIANCE should not be used in patients with type 1 diabetes.

Ketoacidosis with atypical presentation

Cases of ketoacidosis, which may be serious, life threatening or fatal, have been reported in patients with diabetes mellitus treated with JARDIANCE. Such cases require hospitalisation. The presentation of ketoacidosis is frequently atypical with

either euglycaemia or with blood glucose values mildly or moderately increased below 11 mmol/L (196 mg/dL). Although ketoacidosis is less likely to occur in patients without diabetes mellitus, cases have also been reported in these patients.
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.
Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. Treatment with JARDIANCE should be discontinued immediately in such cases and treatment instituted. Treatment, amongst others, may require fluids, carbohydrate and insulin.
The risk of developing ketoacidosis while taking JARDIANCE, is increased in patients with a reduced fluid and food intake, patients on a very low carbohydrate diet, severely dehydrated patients, insulin dose reduction in patients also requiring insulin, patients with a history of ketoacidosis or who are known to have a low beta-cell function reserve, or any pancreatic disease/disorder with or without an insulin deficiency, or patients with alcohol abuse or misusing alcohol.
A progressive increase in blood and urine ketones and a progressive increase in metabolic acidosis may be indicative of the development of ketoacidosis irrespective of blood glucose levels.
Blood and urine ketones as well as blood pH should be regularly monitored.
In clinical situations known to predispose to ketoacidosis (e.g. prolonged fasting due to an acute illness or surgery), the treatment with JARDIANCE should be temporarily discontinued. In these situations, consider monitoring of ketones, even if JARDIANCE treatment has been interrupted.
Treatment should be interrupted in patients who are hospitalised for acute serious medical illnesses.

The underlying mechanism for SGLT2 inhibition-associated ketoacidosis has not been established.
Atypical metabolic acidosis (no ketone bodies) may present in a very similar manner to ketoacidosis.

Haemoconcentration
An increase in the haematocrit of patients on treatment with JARDIANCE can be expected.

Hypoglycaemia with concomitant use with insulin and insulin secretagogues
The risk of hypoglycaemia is increased when JARDIANCE is used in combination with insulin secretagogues (e.g. sulphonylurea) or insulin (see section 4.8). Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycaemia when used in combination with JARDIANCE (see section 4.2).

Use in patients with renal impairment
Due to limited experience, it is not recommended to initiate treatment with JARDIANCE in patients on dialysis.
Glycaemic efficacy of JARDIANCE is dependent on renal function and likely absent in patients with an eGFR<30 mL/min/1,73 m^2 (see section 4.2).

Monitoring of renal function

Assessment of renal function is recommended prior to JARDIANCE initiation and periodically during treatment, i.e. at least 6-monthly.
Consider renal function when used in conjunction with metformin.

Hepatic injury
Cases of hepatic injury have been reported.

Use in patients at risk for volume depletion
Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying glycosuria may lead to intravascular volume contraction with a decrease in blood pressure. Therefore, 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 anti-hypertensive therapy and/or diuretics, and with a history of hypotension, or the elderly especially patients aged 75 years and older.

In conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended for patients receiving JARDIANCE. Temporary interruption of treatment with JARDIANCE should be considered until the fluid loss is corrected.

Complicated urinary tract infections and genital infections
SGLT2 inhibitors such as JARDIANCE have been associated with an increased risk of urinary tract infection and/or genital infection in both males and females caused by bacteria and/or fungi. Genital fungal infections appear to be more common in females. Balanoposthitis in males may result in phimosis.

Urosepsis and Pyelonephritis
Patients with a history of chronic or recurrent urinary tract infection (UTI) were more likely to experience UTI. Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with JARDIANCE (see section 4.8).
Temporary interruption of JARDIANCE should be considered in patients with complicated urinary tract infections.

Necrotising fasciitis of the perineum (Fournier's gangrene)
Cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life threatening necrotising infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalisation, multiple surgeries, and death.

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

Elderly patients

Patients aged 75 years and older are at increased risk of volume depletion, therefore, JARDIANCE should be prescribed with caution in these patients (see section 4.8).

Paediatric population
JARDIANCE is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION
Pharmacodynamic Interactions
Diuretics:
JARDIANCE may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

Effects on laboratory tests: Interference with 1,5-anhydroglucitol (1,5-AG) Assay:
Monitoring of glycaemic control cannot be done by urine glucose monitoring or with a 1,5 AG blood assay, as SGLT2 inhibitors interfere with the assay.

Pharmacokinetic Interactions
Lithium:
Concomitant use of SGLT2 inhibitors, including empagliflozin, with lithium may decrease blood lithium levels through increased renal lithium elimination. Therefore, serum lithium concentration should be monitored more frequently with empagliflozin initiation or following dose changes. Please refer the patient to the lithium prescribing doctor in order to monitor serum concentration of lithium.

In vitro assessment of medicine interactions:
JARDIANCE does not inhibit, inactivate, or induce CYP450 isoforms.

In vivo assessment of medicine interactions:
No clinically meaningful pharmacokinetic interactions were observed when empagliflozin was co-administered with other commonly used medicinal products. Empagliflozin pharmacokinetics were similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, in healthy volunteers and with or without co-administration of torasemide and hydrochlorothiazide in patients with T2DM. Increases in overall exposure (AUC) of empagliflozin were seen following co-administration with gemfibrozil (59 %), rifampicin (35 %), or probenecid (53 %). These changes were not considered to be clinically meaningful.
Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide and oral contraceptives when co-administered in healthy volunteers.

4.6 FERTILITY, PREGNANCY AND LACTATION
JARDIANCE is contraindicated in pregnancy and lactation.

Pregnancy
Animal studies showed that empagliflozin as contained in JARDIANCE crosses the placenta.

Breastfeeding

Mothers should not breastfeed their infants while taking JARDIANCE.
Animal studies have shown excretion of empagliflozin as contained in JARDIANCE, in milk of animals.
A risk to human new-borns/infants cannot be excluded.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Hypoglycaemia may impair driving and machinery use capabilities. Patients should be aware of symptoms that may herald the onset of hypoglycaemia and act appropriately.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

Adverse Reactions in Clinical Trials

Type 2 Diabetes Mellitus Indications:

A total of 15 582 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of empagliflozin, of which 10 004 patients were treated with empagliflozin, either alone or in combination with metformin, a sulphonylurea, a PPARγ agonist, DPP-4 inhibitors or insulin.
This pool includes the EMPA-REG OUTCOME study involving 7 020 patients at high cardiovascular risk (mean age 63,1 years, 9,3 % patients at least 75 years old, 28,5 % women) treated with JARDIANCE 10 mg/day (N=2 345), JARDIANCE 25 mg/day (N=2 342), or placebo (N=2 333) up to 4,5 years. The overall safety profile of empagliflozin in this study was comparable to the previously known safety profile. In the above-described trials, the frequency of AEs leading to discontinuation was similar by treatment groups for placebo, JARDIANCE 10 mg and JARDIANCE 25 mg.
The most frequent adverse drug reaction was hypoglycaemia, which depended on the type of background therapy used in the respective studies (see Table 1).

HF Indication:

The EMPEROR studies included patients with heart failure and either reduced ejection fraction (N=3 726) or preserved ejection fraction (N=5 985) treated with 10 mg empagliflozin or placebo. Approximately half of the patients had type 2 diabetes mellitus.
The most frequent adverse drug reaction was volume depletion (empagliflozin 10 mg: 11,4 %; placebo: 9,7 %).

Chronic Kidney Disease Indication:

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.
No new adverse reactions were identified in the EMPA-KIDNEY study.

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

Tabulated summary of adverse reactions

Frequency classes: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1 000, <1/100); rare (≥1/10 000, <1/1 000); very rare (<1/10 000); Not known (cannot be estimated from the available data).

Table 1 Adverse reactions reported in patients who received JARDIANCE in placebo controlled double-blind studies and adverse reactions derived from post-marketing experience.

System organ class	Adverse reaction	T2DM Indications JARDIANCE 10 mg	T2DM Indications JARDIANCE 25 mg	HF Indication JARDIANCE 10 mg
Infections and infestations	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections	Common	Common	Common
	Urinary tract infection	Common	Common	Common
	Necrotising fasciitis of the perineum (Fournier's gangrene)[3]	Not known[2]	Not known[2]	Rare
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)	Very common	Very common	Common
	Weight loss	Common	Common	Common
	Serum lipids increased	Common	Common	Common
Vascular disorders	Volume depletion[1] (hypotension and dehydration)	Uncommon	Uncommon	Very common
Gastrointestinal disorders	Thirst	Common	Common	Uncommon
	Constipation	Common	Uncommon	Common
Skin and subcutaneous tissue disorders	Pruritus	Common	Common	Common
Renal and urinary disorders	Glycosuria	Very common	Very common	Uncommon
	Increased urination	Common	Common	Uncommon
	Dysuria	Uncommon	Uncommon	Uncommon
	Ketonuria	Uncommon	Uncommon	Rare
Investigations	Increased haematocrit (haemoconcentration)	Rare	Uncommon	Uncommon
	Increased blood creatinine[1]	Uncommon	Uncommon	Uncommon
	Decreased glomerular filtration rate[1]	Uncommon	Uncommon	Uncommon

[1] see subsections below for additional information in patients with diabetes mellitus
[2] derived from post-marketing experience
[3] observed in patients with diabetes mellitus

Post-marketing experience

- Infections and infestations: Urosepsis and pyelonephritis.

- Metabolism and nutrition disorders: Ketoacidosis with atypical presentation (see section 4.4).
- Skin and subcutaneous tissue disorders: Allergic skin reactions (e.g. rash, urticaria), angioedema.
- Reproductive system and breast disorders: Phimosis has been reported with the use of SGLT2 inhibitors such as JARDIANCE.

Description of selected adverse reactions

Volume depletion:

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was similar to placebo. The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect hydration status of patients aged 75 years and older or those otherwise at risk. In patients ≥75 years of age the frequency of volume depletion events was similar for JARDIANCE 10 mg compared to placebo, but it increased with JARDIANCE 25 mg.

Blood creatinine increased and glomerular filtration rate decreased:

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was similar between JARDIANCE and placebo.
In placebo controlled, double-blind studies up to 76 weeks, initial transient increases in creatinine and initial transient decreases in estimated glomerular filtration rates have been observed. These changes were generally reversible during continuous treatment or after medicine discontinuation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

4.9 OVERDOSE

The risk and severity of adverse reactions may be increased (see section 4.8).
In the event of an overdose, symptomatic and supportive treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by haemodialysis has not been studied.
Hypoglycaemia should be monitored for, especially when other antidiabetic medication has been co-administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Category and class: A 21.2

Mechanism of action

Empagliflozin is a reversible inhibitor of SGLT2 (sodium glucose cotransporter 2) with an IC50 of 1,3 nM. It has a 5 000-fold selectivity over human SGLT1 (IC50 of 6 278 nM), responsible for glucose absorption in the gut. Furthermore, high selectivity could be shown toward other glucose transporters (GLUTs) responsible for glucose homeostasis in the different tissues.

SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible as the predominant transporter for reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes mellitus (T2DM) and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR (glomerular filtration rate). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

The mechanism of action of empagliflozin is independent of beta-cell function and insulin pathway and this contributes to a low risk of hypoglycaemia.

Urinary glucose excretion triggers calorie loss associated with body fat loss and body weight reduction.

The glycosuria observed with empagliflozin is accompanied by mild diuresis which may contribute to sustained and moderate reduction of blood pressure.

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to: increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre- and afterload of the heart, downregulating sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values which may have beneficial effects on cardiac remodelling, filling pressures and diastolic function as well as preserving kidney structure and function. Other effects such as an increase in haematocrit, a reduction in body weight and blood pressure may further contribute to the beneficial cardiac and renal effects.

Clinical Trials

Type 2 diabetes mellitus

Data from a Non-interventional Study:

In a real-world non-interventional study (EMPRISE–Europe and Asia) in adult patients with type 2 diabetes, the effectiveness and safety of empagliflozin compared with DPP-4 inhibitors was assessed. Patients initiating empagliflozin or DPP-4 inhibitors were analysed after propensity score matching to balance demographic and baseline characteristics.

Patients initiating empagliflozin had a lower risk for cardiovascular (CV) mortality, all-cause mortality, hospitalisation for heart failure, and progression to end-stage renal disease when compared with patients initiating DPP-4 inhibitors (Table 2).

These results were consistent in patients with and without a history of cardiovascular disease.

Table 2: Outcomes for empagliflozin compared with DPP-4 inhibitors

	DPP-4 inhibitor	Empagliflozin
CV mortality		
N of patients	48 900	48 900
Average years of follow up	0,75	0,59
N with events	249-252*	105-108*
Hazard ratio vs. DPP-4 inhibitor (95 % CI)		0.59 (0.42, 0.84)
All-cause mortality		
N of patients	84 405	84 405
Average years of follow up	0,74	0,66
N with events	1 177	572
Hazard ratio vs. DPP-4 inhibitor (95 % CI)		0.55 (0.48, 0.63)
Hospitalisation for heart failure		
N of patients	83 946	83 946
Average years of follow up	0,74	0,66
N with events	1 083	765
Hazard ratio vs. DPP-4 inhibitor (95 % CI)		0.70 (0.60, 0.83)
End-stage renal disease**		
N of patients	68 087	68 087
Average years of follow up	0,76	0,65
N with events	189-195*	73-85*
Hazard ratio vs. DPP-4 inhibitor (95 % CI)		0.43 (0.30, 0.63)

A longer follow-up time was generally observed in patients initiating DPP-4 inhibitors across outcomes. Differences in follow-up time were accounted for in the statistical model.

* If fewer than 5 events were observed in a country, the range of values across countries is presented to protect patient privacy

** Includes initiation of chronic dialysis and kidney transplant

These observations are consistent with the established cardiovascular outcome results for empagliflozin as previously demonstrated in the EMPA-REG OUTCOME study when compared to standard of care therapy.

Heart failure (HF)

Empagliflozin in patients with Heart Failure and Reduced Ejection Fraction:

A randomised, double-blind, placebo controlled study (EMPEROR-Reduced) was conducted in 3 730 patients with chronic heart failure (New York Heart Association [NYHA] II-IV) and reduced ejection fraction (LVEF $\leq$40 %) to evaluate the efficacy and safety of empagliflozin 10 mg once daily as adjunct to standard of care heart failure therapy. The primary endpoint was the time to adjudicated first event of either cardiovascular (CV) death or hospitalisation for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent), and eGFR (CKD-EPI)cr slope of change from baseline were included in the confirmatory testing. Heart Failure therapy at baseline included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (88,3 %), beta-blockers (94,7 %), mineralocorticoid receptor antagonists (71,3 %) and diuretics (95,0 %).

A total of 1 863 patients were randomised to empagliflozin 10 mg (placebo: 1 867) 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), 26,8 % were 75 years of age or older. 70,5 % of the study population were White, 18,0 % Asian and 6,9 % Black/African American. At randomisation, 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 %. 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. About half of the patients (51,7 %) had an eGFR of ≥60 mL/min/1,73 m^2, 24,1 % of 45 to <60 mL/min/1,73 m^2, 18,6 % of 30 to <45 mL/min/1,73 m^2 and 5,3 % 20 to <30 mL/min/1,73 m^2.
Empagliflozin was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalisation for heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent), and significantly reduced the rate of eGFR decline (see Table 3).

Table 3: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing

	Placebo	**Empagliflozin 10 mg**
N	1 867	1 863
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
eGFR (CKD-EPI)cr slope, Rate of decline (mL/min/1,73 m^2/year)	-2,28	-0,55
Treatment difference vs. placebo (99,9 % CI)***		1.73 (0.67, 2.80)
p-value		<0.0001

CV=cardiovascular, HHF=hospitalisation 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 analysed based on the randomized set.
***As pre-specified in the statistical testing procedure, a two-sided 99,9 % confidence interval was applied which corresponds to a p-value less than 0.001 for significance. eGFR slope was analysed based on the treated set.

Figure 1: Time to first event of adjudicated CV death or HHF

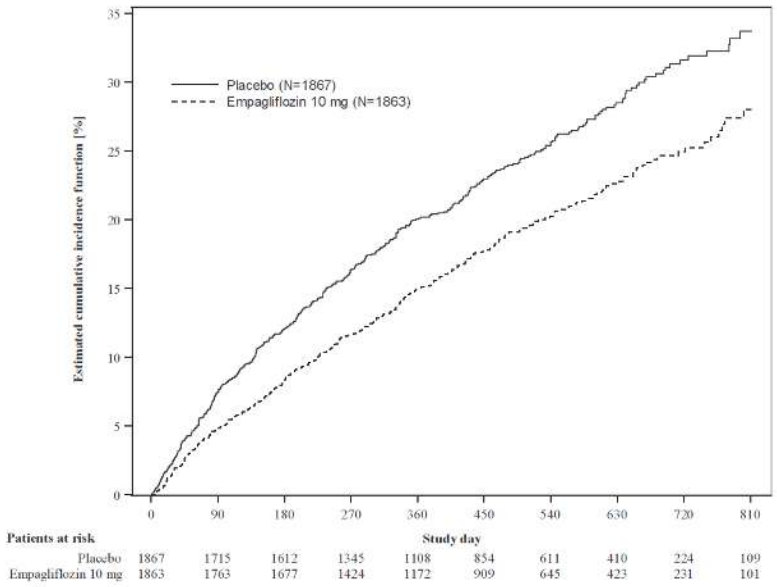
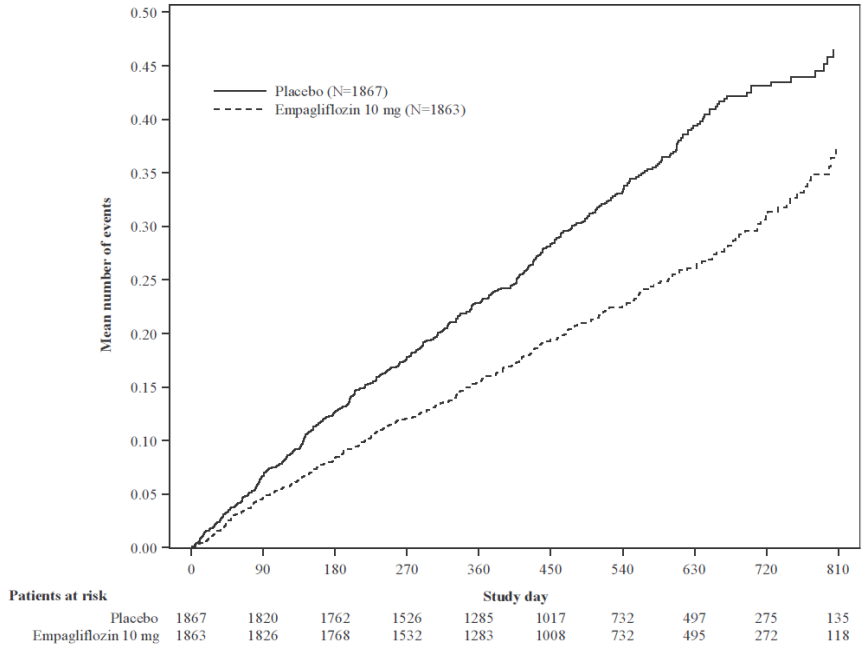
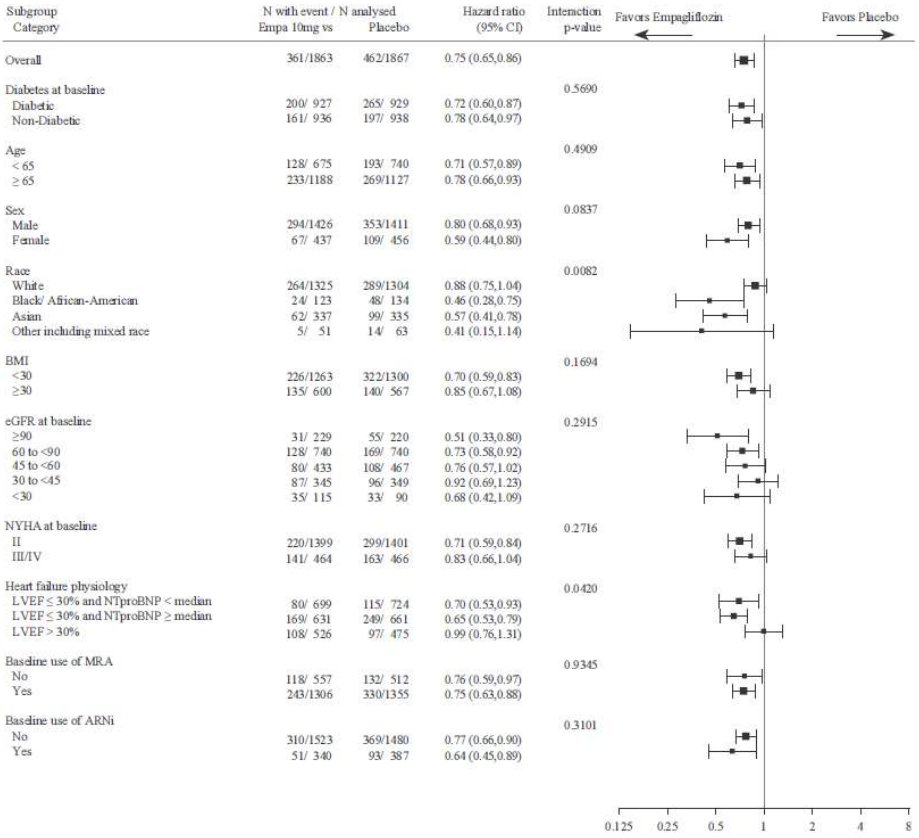


Figure 2: Time to event of adjudicated HHF



The results of the primary composite endpoint were generally consistent with a hazard ratio (HR) below 1 across the pre-specified subgroups, including heart failure patients with and without type 2 diabetes mellitus (see Figure 3).

Figure 3: Subgroup analyses for the time to the first event of adjudicated CV death or HHF

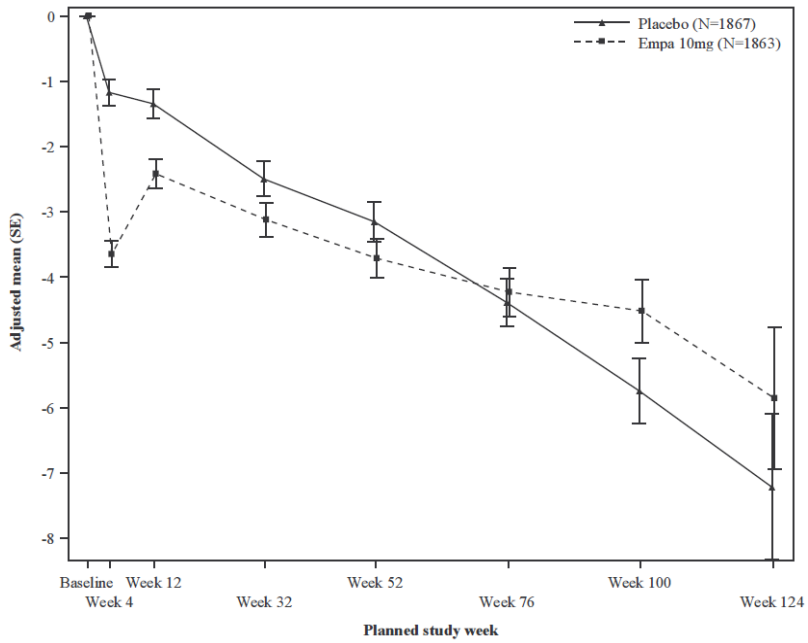


LVEF >30 %: Includes both above and below the median NTproBNP. To be eligible for inclusion, patients with an LVEF >30 % were required to meet a higher NTproBNP threshold than those with LVEF ≤30 %, unless they additionally had a history of HHF within the past 12 months.

Renal Outcome

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (see Figure 4). Treatment with empagliflozin 10 mg significantly reduced the rate of eGFR decline and the effect was consistent across all pre-specified subgroups (see Table 3). Patients treated with empagliflozin experienced an initial drop in eGFR which returned towards baseline after treatment discontinuation supporting that haemodynamic changes play a role in the acute effects of empagliflozin on eGFR.

Figure 4: Change in eGFR over time*



*eGFR (CKD-EPI) (mL/min/1,73 m^2) MMRM results over time – randomised set. The number of patients who provided data at various time points (placebo, empagliflozin): at week 4 (1 788, 1 802); at week 12 (1 729, 1 756); at week 32 (1 563, 1 614); at week 52 (1 211, 1 228); at week 76 (801, 805); at week 100 (359, 386); and at week 124 (86, 91).

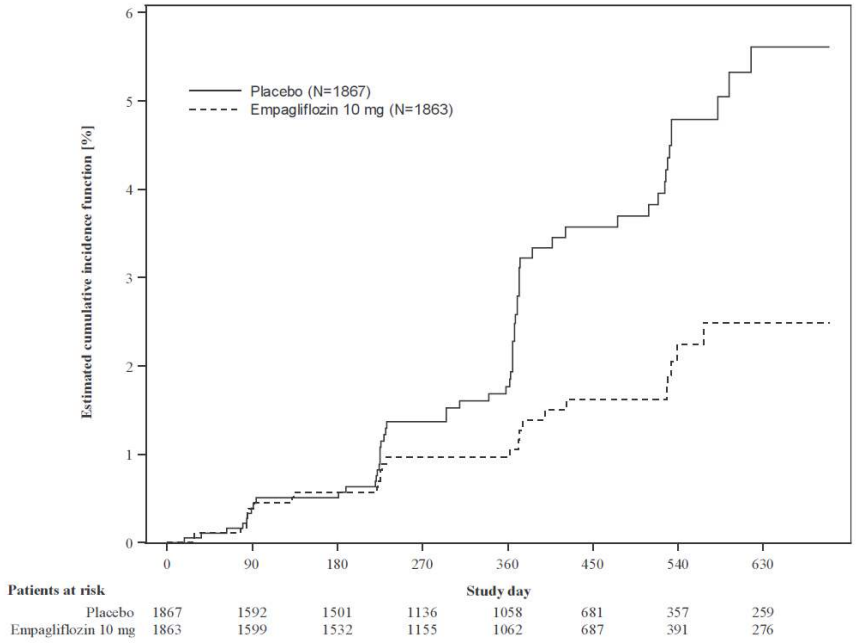
JARDIANCE reduced the risk of the renal composite endpoint defined as time to first event of chronic dialysis or renal transplant or sustained reduction in eGFR compared with placebo (Table 4 and Figure 5).

Table 4: Time to first event of composite renal endpoint and its components

	Placebo	**Empagliflozin (10 mg)**
N	1 867	1 863
Number of patients with composite renal endpoint, N (%)	58 (3,1)	30 (1,6)
HR (95 % CI)		0.50 (0.32, 0.77)
p-value (nominal)		0.0019
Sustained eGFR reduction ≥40 % as the first event, N (%)	50 (2,7)	27 (1,4)
Sustained eGFR <15 (baseline ≥30) or <10 (baseline <30) [mL/min/1,73 m^2] as the first event, N (%)	0	0
Chronic dialysis as the first event, N (%)	8 (0,4)	3 (0,2)
Renal Transplant as the first event, N (%)	0	0

Composite renal endpoint is defined as chronic dialysis or renal transplant or sustained reduction of ≥40 % eGFR (CKD-EPI)cr or sustained eGFR (CKD-EPI)cr <15 mL/min/1,73 m² (<10 mL/min/1,73 m² for patients with eGFR (CKD-EPI)cr <30 mL/min/1,73 m² at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. An eGFR (CKD-EPI)cr reduction is considered sustained, if it is determined by two or more consecutive post baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). If there is no additional measurement ≥30 days after the eGFR reduction is observed and the patient dies within 60 days of this measurement, then the eGFR reduction is also considered sustained.

Figure 5: Time to first event of composite renal endpoint



The effect of empagliflozin on heart failure symptoms at week 52 was assessed as a patient-reported outcome using the change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS), which measures average of symptom frequency and burden for swelling, fatigue, and shortness of breath and physical limitations.

There was a greater improvement in the clinical summary score from baseline in the empagliflozin group than in the placebo group at Week 52 (placebo corrected adjusted mean change from baseline 1.75, 95 % CI 0.51 to 2.99, nominal p-value=0.0058), driven by all domains included (symptom frequency, symptom burden, and physical limitations).

Empagliflozin in Patients with Heart Failure and Preserved Ejection Fraction:
A randomised, double-blind, placebo controlled study (EMPEROR-Preserved) was conducted in 5 988 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 hospitalisation for heart failure (HHF). Occurrence of adjudicated HHF (first and recurrent), and eGFR (CKD-EPI)cr slope of change from baseline were included in the confirmatory testing. Baseline therapy included ACE inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitor (80,7 %), beta-blockers (86,3 %), mineralocorticoid receptor antagonists (37,5 %) and diuretics (86,2 %).

A total of 2 997 patients were randomised to empagliflozin 10 mg (placebo: 2 991) 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 randomisation, 81,5 % of patients were NYHA class II, 18,1 % were class III and 0,3 % were class IV. The EMPEROR-Preserved study population included patients with a LVEF <50 % (33,1 %), with a LVEF 50 to <60 % (34,4 %) and a LVEF ≥60 % (32,5 %). At baseline, the mean eGFR was 60,6 mL/min/1,73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 21 mg/g. 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 was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalisation for heart failure compared with placebo. Additionally, empagliflozin significantly reduced the risk of occurrence of HHF (first and recurrent), and significantly reduced the rate of eGFR decline (see Table 5).

Table 5: Treatment effect for the primary composite endpoint, its components and the two key secondary endpoints included in the pre-specified confirmatory testing

	Placebo	Empagliflozin 10 mg
N	2 991	2 997
Time to first event of CV death or HHF, N (%)	511 (17,1)	415 (13,8)
Hazard ratio vs. placebo (95,03 % 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 (95,03 % CI)**		0.73 (0.61, 0.88)
p–value		0.0009
eGFR (CKD-EPI)cr slope, Rate of decline (mL/min/1,73 m^2/year)	−2,62	−1,25
Treatment difference vs. placebo (99,9 % CI)***		1.36 (0.86, 1.87)
p-value		<0.0001

CV=cardiovascular, HHF=hospitalisation 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 95,03 % confidence interval was applied which corresponds to a p-value less than 0.0497 for significance. CV death and HHF events were adjudicated by an independent clinical event committee and analysed based on the randomised set.

***As pre-specified in the statistical testing procedure, a two-sided 99,9 % confidence interval was applied which corresponds to a p-value less than 0.001 for significance. eGFR slope was analysed based on the treated set.

Figure 6: Time to first event of adjudicated CV death or HHF

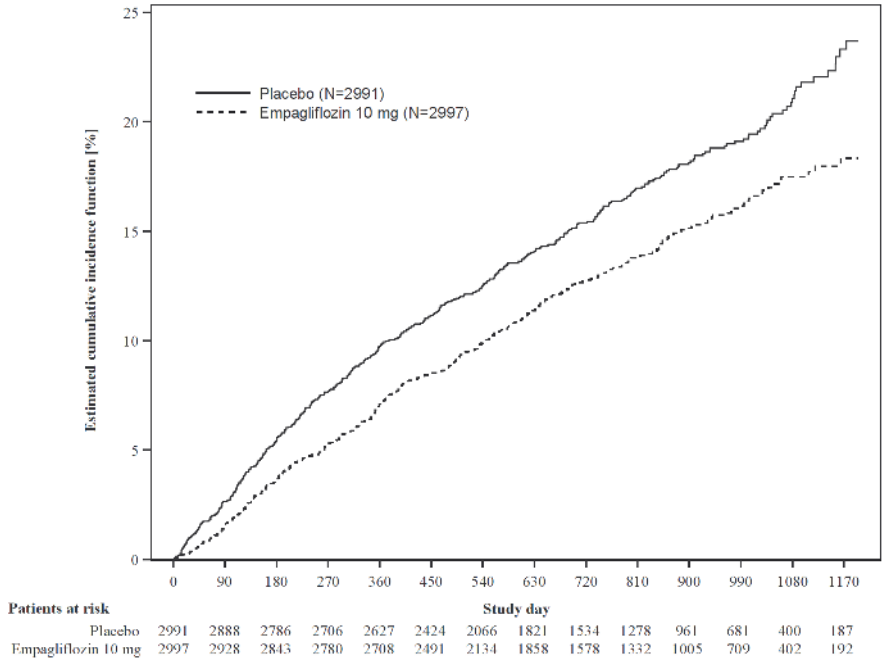
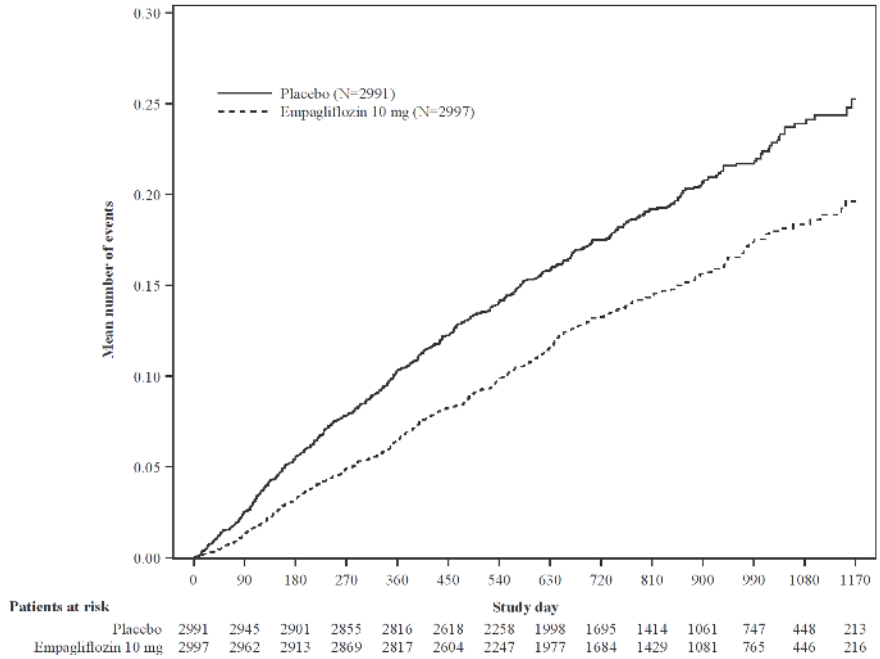
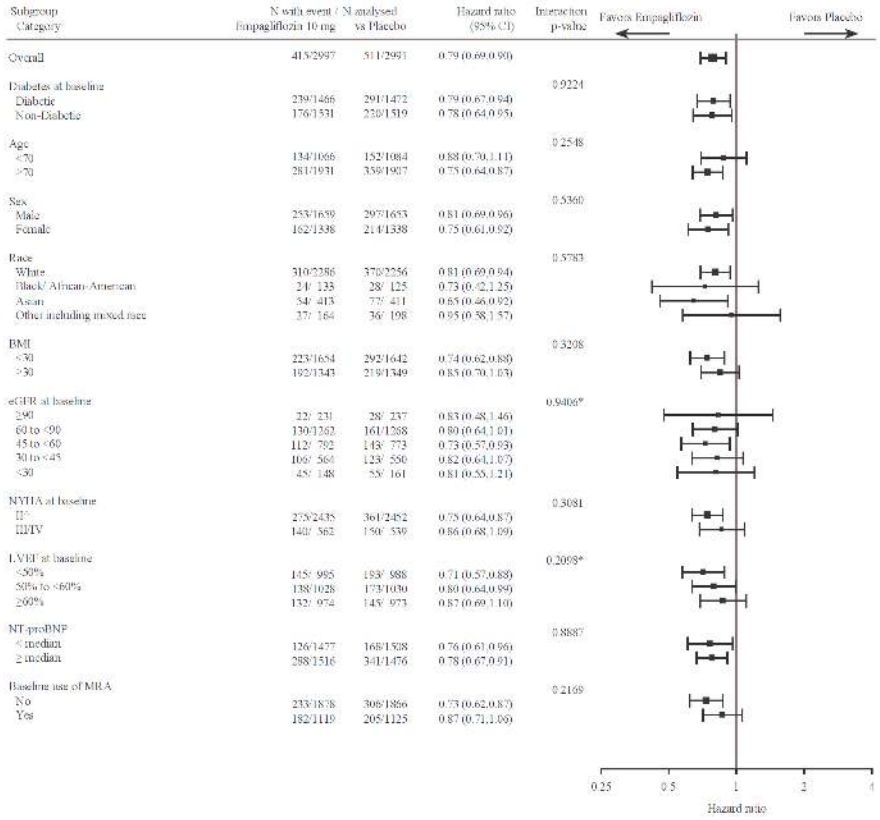


Figure 7: Time to event of adjudicated HHF



The results of the primary composite endpoint were consistent across each of the pre-specified subgroups categorized by e.g., LVEF, diabetes status or renal function down to an eGFR of 20 mL/min/1,73 m^2 (see Figure 8).

Figure 8: Subgroup analyses for the time to the first event of adjudicated CV death or HHF

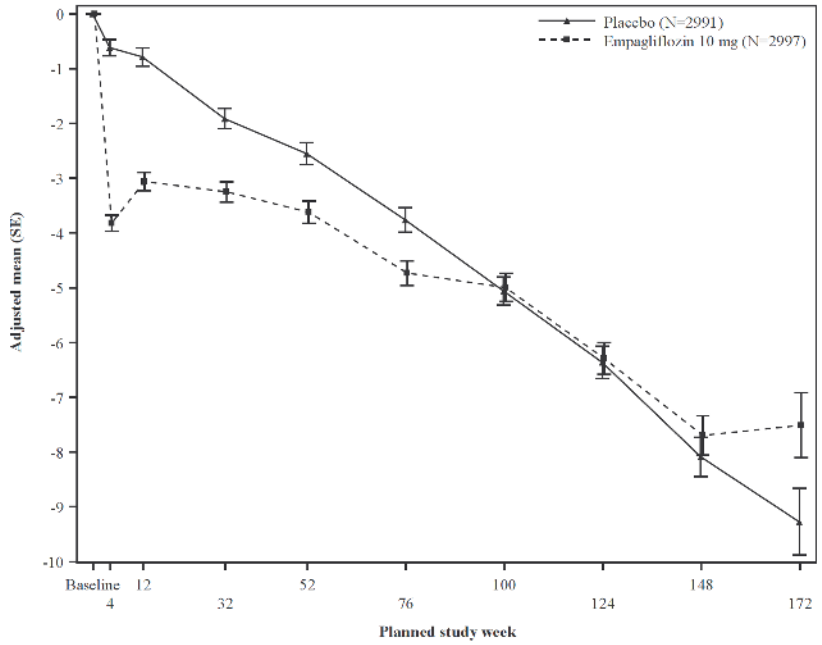


^4 patients with NYHA class I are counted in subgroup NYHA class II
*Trend test

Renal Outcome

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (see Figure 9). Treatment with empagliflozin 10 mg significantly reduced the rate of eGFR decline and the effect was consistent across all pre-specified subgroups (see Table 5). Patients treated with empagliflozin experienced an initial drop in eGFR which returned towards baseline after treatment discontinuation supporting that haemodynamic changes play a role in the acute effects of empagliflozin on eGFR.

Figure 9: Change in eGFR over time*



*eGFR (CKD-EPI) (mL/min/1,73 m^2) MMRM results over time - randomised set. The number of patients who provided data at various time points (placebo, empagliflozin): at week 4 (2 910, 2 931); at week 12 (2 820, 2 854); at week 32 (2 590, 2 629); at week 52 (2 457, 2 474); at week 76 (2 123, 2 114); at week 100 (1 548, 1 550); at week 124 (1 091, 1 122), at week 148 (695, 686), at week 172 (231, 243) and at week 196 (16, 23).

In an analysis of the composite renal endpoint (defined as time to first event of chronic dialysis or renal transplant or sustained reduction in eGFR) the hazard ratio was 0.95 (95 % CI 0.73 to 1.24, nominal p-value 0.7243).

The effect of empagliflozin on heart failure symptoms at week 52 was assessed as a patient-reported outcome using the change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS), which measures average of symptom frequency and burden for swelling, fatigue, and shortness of breath and physical limitations.

There was a greater improvement in the clinical summary score from baseline in the empagliflozin group than in the placebo group at Week 52 (placebo corrected adjusted mean change from baseline 1,32, 95 % CI 0.45 to 2.19, nominal p-value=0.0028), driven by the domains symptom frequency and symptom burden.

Empagliflozin in Patients hospitalised for Acute Heart Failure who have been Stabilised:
A randomised, double-blind, placebo controlled study (EMPULSE) was conducted in 530 patients hospitalised for acute heart failure independent of LVEF (33,0 % with de novo and 67,0 % with decompensated chronic heart failure) who have been stabilised. The study evaluated the clinical benefit and safety of empagliflozin 10 mg once daily as adjunct to standard of care therapy. Treatment was initiated in the hospital and continued for 90 days. The primary endpoint was clinical benefit, a composite of death, number of heart failure events (including hospitalisations 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) 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 %).

A total of 265 patients each were randomised to empagliflozin 10 mg or placebo and followed for a median of 98 days. The study population consisted of 66,2 % men and 33,8 % women with a mean age of 68,5 years (range: 22-98 years); 37,2 % were 75 years of age or older. 77,9 % of the study population were White, 10,8 % Asian and 10,2 % Black/African American. At randomisation, 2,6 % of patients were in NYHA class I, 35,1 % in class II, 52,6 % in class III, 9,2 % in class IV and 45,3 % of patients had T2DM. The EMPULSE study population included 66,8 % of patients with LVEF $\leq$40 %, and 31,9 % with LVEF >40 %. At baseline, 36,6 % of patients had an eGFR of $\geq$60 mL/min/1,73 m^2, 22,8 % of 45 to <60 mL/min/1,73 m^2, 25,3 % of 30 to <45 mL/min/1,73 m^2, and 8,3 % of 20 to <30 mL/min/1,73 m^2.

In the primary analysis each patient in the empagliflozin group was compared to every patient in the placebo group within each stratum (de novo or decompensated chronic HF). Pairwise comparisons were performed in a hierarchical fashion using time to death followed by number of heart failure events, time to first heart failure event and a $\geq$5 point difference in change from baseline in KCCQ-TSS determining the burden and frequency of HF symptoms. The stratified win ratio was then calculated combining the number of wins in the JARDIANCE group divided by the number of losses across strata.

Patients on empagliflozin 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 Table 6)).

Table 6: Win ratio of clinical benefit

	Placebo	**Empagliflozin 10 mg**
Number of comparisons[1] [100 %]	39 162	
Wins based on time to death [%]	4,01	7,15
Wins based on frequency of HFE[2] [%]	7,65	10,59
Wins based on time to HFE [%]	0,57	0,24
Wins based on $\geq$5 points difference in change from baseline in KCCQ-TSS[3] at day 90 [%]	27,48	35,91
Ties [%]	6,41	
Win ratio vs placebo [Empagliflozin wins/Placebo wins] (95 % CI)[4]		1.36 (1.09, 1.68)
p-value for superiority		0.0054

HFE=heart failure events, KCCQ-TSS=Kansas City Cardiomyopathy Questionnaire Total Symptom Score

[1] Pairs of patients were analysed within strata for a stratified win ratio, applying weights that are analogous to a Mantel–Haenszel approach.

[2] Frequency based on events up to the earlier of the two censoring times

[3] Based on multiple imputation with 100 iterations

[4] Variance calculated using the asymptotic normal U statistics approach

The results of the primary endpoint were generally consistent across the pre-specified subgroups, including de novo heart failure and decompensated chronic heart failure, and were independent of LVEF.
Safety data from this study was in line with previous known safety profile of empagliflozin.

Chronic kidney disease
A randomised, double-blind, placebo controlled study of empagliflozin 10 mg once daily (EMPA-KIDNEY) was conducted in 6 609 patients with chronic kidney disease (eGFR ≥20 - <45 mL/min/1,73 m²; or eGFR ≥45 - <90 mL/min/1,73 m² with an urine albumin-to-creatinine ratio [UACR] ≥200 mg/g) to assess cardio-renal outcomes as adjunct to standard of care therapy. Treatment was allowed to be continued in patients receiving dialysis. The primary endpoint was the time to first occurrence of kidney disease progression (sustained ≥40 % eGFR decline from randomisation, sustained eGFR <10 mL/min/1,73 m², end-stage kidney disease, or renal death) or CV death. All-cause hospitalisation (first and recurrent), first occurrence of hospitalisation for heart failure or CV death, and all-cause mortality were included in the confirmatory testing. Baseline therapy included an appropriate use of a RAS-inhibitor (85,2 % ACE inhibitor or angiotensin receptor blocker).
A total of 3 304 patients were randomised to empagliflozin 10 mg (placebo: 3 305) 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.
At baseline, the mean eGFR was 37,3 mL/min/1,73 m², 21,2 % patients had an eGFR of ≥45 mL/min/1,73 m², 44,3 % of 30 to <45 mL/min/1,73 m² and 34,5 % <30 mL/min/1,73 m² including 254 patients with an eGFR <20 mL/min/1,73 m². The median UACR was 329 mg/g, 20,1 % patients had an UACR <30 mg/g, 28,2 % had an UACR 30 to ≤300 mg/g and 51,7 % had an UACR >300 mg/g; 41,1 % of patients had an UACR <200 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 %).
Empagliflozin was superior in reducing the risk of the primary composite endpoint of kidney disease progression or CV death compared with placebo. In a pre-specified analysis, treatment with empagliflozin reduced the risk of end-stage kidney disease or CV death by 27 % compared with placebo (HR 0.73, 95 % CI 0.59 to 0.89, nominal p=0.0023).
Additionally, empagliflozin significantly reduced the risk of all-cause hospitalisation (first and recurrent) (see Table 7).

Table 7 Treatment effect for the primary composite and key secondary endpoints included in the pre-specified confirmatory testing and its components

	Placebo	**Empagliflozin 10 mg**
N	3 305	3 304
Time to first occurrence of kidney disease progression (sustained ≥40 % eGFR decline from randomisation, sustained eGFR <10 mL/min/1,73 m²,	558 (16,9)	432 (13,1)

end-stage kidney disease* (ESKD), or renal death) or CV death, N (%)		
Hazard ratio vs. placebo (99,83 % CI)		0.72 (0.59, 0.89)
p-value for superiority		<0.0001
Sustained ≥40 % eGFR decline from randomisation, N (%)	474 (14,3)	359 (10,9)
Hazard ratio vs. placebo (95 % CI)		0.70 (0.61, 0.81)
p-value		<0.0001
ESKD* or sustained eGFR <10 mL/min/1,73 m², N (%)	221 (6,7)	157 (4,8)
Hazard ratio vs. placebo (95 % CI)		0.69 (0.56, 0.84)
p-value		0.0003
Renal death, N (%)**	4 (0,1)	4 (0,1)
Hazard ratio vs. placebo (95 % CI)		
p-value		
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
Occurrence of all-cause hospitalisation (first and recurrent), N of events	1 895	1 611
Hazard ratio vs. placebo (99,03 % CI)		0.86 (0.75, 0.98)
p-value		0.0025
Time to first occurrence of HHF or CV death, N (%)	152 (4,6)	131 (4,0)
Hazard ratio vs. placebo (98,55 % CI)		0.84 (0.63, 1.13)
p-value		0.1530
HHF (first occurrence), N (%)	107 (3,2)	88 (2,7)
Hazard ratio vs. placebo (95 % CI)		0.80 (0.60, 1.06)
p-value		0.1263
Time to all-cause mortality N (%)	167 (5,1)	148 (4,5)
Hazard ratio vs. placebo (97,1 % CI)		0.87 (0.68, 1.11)
p-value		0.2137

CV=cardiovascular, HHF=hospitalisation for heart failure, 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 10 Time to first event of kidney disease progression or adjudicated CV death, estimated cumulative incidence function

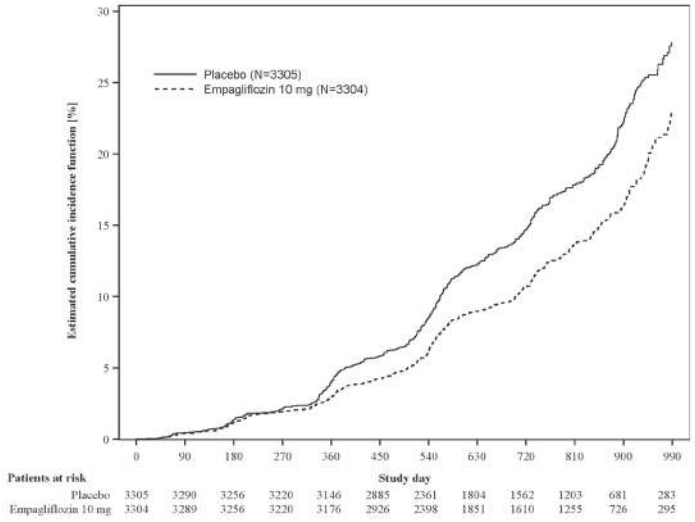
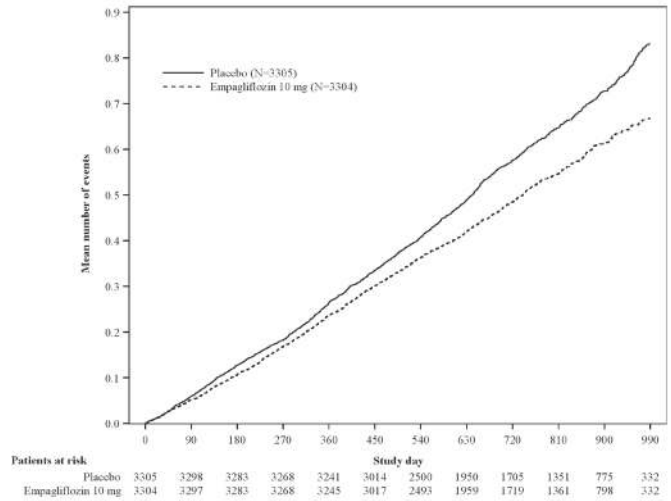


Figure 11 Occurrence of all-cause hospitalisation (first and recurrent), mean cumulative function



The results of the primary composite endpoint were generally consistent across the pre-specified subgroups, including eGFR categories, underlying cause of renal disease, diabetes status, or background use of RAS inhibitors. Treatment benefits were more clearly evident in patients with higher levels of albuminuria.
Empagliflozin slowed the annual rate of eGFR decline compared to placebo by 1,37 mL/min/1,73 m^2/year (95 % CI 1.16, 1.59), based on a pre-specified analysis of all eGFR measurements taken from the 2-month visit to the final follow-up visit. The observed effect was consistent irrespective of albuminuria, eGFR or diabetes status. These data further support the conclusion that JARDIANCE is also likely to be effective in patients with less pronounced albuminuria.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with T2DM. After oral administration, empagliflozin was 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 phase. For single doses of 10 mg and 25 mg, the terminal phase half-life is 13,1 ± 4,0 h and 10,2 ± 2,1 h, respectively. The steady-state mean plasma AUC was 4 740 nmol.h/L and C_{max} was 687 nmol/L with 25 mg empagliflozin once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetics parameters of empagliflozin were similar suggesting linear pharmacokinetics with respect to time. There were no clinically relevant differences in empagliflozin pharmacokinetics between healthy volunteers and patients with T2DM.

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

Distribution

The apparent steady-state volume of distribution was estimated to be 73,8 L, based on a population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36,8 % and plasma protein binding was 86,2 %.

Biotransformation

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 12,4 h and apparent oral clearance was 10,6 L/h based on the population pharmacokinetic analysis. The inter-subject and residual variabilities for empagliflozin oral clearance were 39,1 % and 35,8 %, respectively. With once-daily dosing, steady-state plasma concentrations of empagliflozin were reached by the fifth dose. Consistent with half-life, up to 22 % accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [^{14}C]-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.

Specific Populations

Renal Impairment:

In patients with mild (eGFR: 60 - <90 mL/min/1,73 m^2), moderate (eGFR: 30 - <60 mL/min/1,73 m^2), severe (eGFR: <30 mL/min/1,73 m^2) renal impairment and patients with kidney failure/ESKD (end-stage kidney disease) patients, AUC of empagliflozin increased by approximately 18 %, 20 %, 66 %, and 48 %, respectively, compared to subjects with normal renal function.

Hepatic Impairment:
In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased by approximately 23 %, 47 %, and 75 % and C_{max} by approximately 4 %, 23 %, and 48 %, respectively, compared to subjects with normal hepatic function. Based on pharmacokinetics, dosage adjustment may be necessary in patients with severe hepatic impairment.

Body Mass Index (BMI):
No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Gender:
No dosage adjustment is necessary based on gender.

Elderly patients:
Age did not have a clinically meaningful impact on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Paediatric:
Studies characterising the pharmacokinetics of empagliflozin in paediatric patients have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Inactive ingredients: colloidal anhydrous silica, croscarmellose sodium, hydroxypropylcellulose, hypromellose, iron oxide yellow, lactose monohydrate, macrogol, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide.
Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption should not take JARDIANCE.

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
The manufacturing and expiry dates can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store at or below 30 °C.
Keep out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER
JARDIANCE 10 mg and 25 mg film-coated tablets are packed in blister strips, consisting of colourless, transparent PVC forming foil and printed aluminium lidding foil. The blister strips are packed in printed cardboard cartons in packs of 30 tablets (3 blister strips of 10 tablets each).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION
Ingelheim Pharmaceuticals (Pty) Ltd
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus
74 Waterfall Drive
Midrand
South Africa
Tel. No.: +27 (0)11 348-2400

8 REGISTRATION NUMBERS
JARDIANCE 10 mg: 48/21.2/1380
JARDIANCE 25 mg: 48/21.2/0411

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of registration: 12 December 2017

10 DATE OF REVISION OF THE TEXT
27 March 2025

NAMIBIA Reg. No.		
JARDIANCE 10 mg	15/21.2/0158	NS2
JARDIANCE 25 mg	15/21.2/0159	

BOTSWANA Reg. No.		
JARDIANCE 10 mg	BOT1602898	S2
JARDIANCE 25 mg	BOT1602899	

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