1. NAME OF THE MEDICINAL PRODUCT

EMFLODIAZ 10 (Empagliflozin Film-Coated Tablets 10mg)
EMFLODIAZ 25 (Empagliflozin Film-Coated Tablets 25mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg or 25 mg empagliflozin.
Excipient with known effect:
Each tablet contains lactose monohydrate of 44.4 mg (10 mg Empagliflozin) or 111.0 mg (25 mg Empagliflozin)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

3.1 Product description
EMFLODIAZ 10 mg: Pale Yellow, round, biconvex film coated tablet debossed with '10' on one side and plain on other side

EMFLODIAZ 25 mg: Pale Yellow, oval, biconvex film coated tablets, debossed with '25' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
TYPE 2 DIABETES MELLITUS

Glycaemic control

Empagliflozin Tablets is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:

Monotherapy
When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy*
In combination with other glucose–lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

Prevention of cardiovascular death

Empagliflozin Tablets is indicated in patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death (see section 5, Clinical efficacy and safety).

To prevent cardiovascular deaths, Empagliflozin Tablets should be used in conjunction with other measures to reduce cardiovascular risk in line with the current standard of care.

HEART FAILURE

Empagliflozin Tablets is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV).

CHRONIC KIDNEY DISEASE
Empagliflozin Tablets is indicated in adults for the treatment of chronic kidney disease.

** Emflodiaz product is not recommended to use in combination with linagliptin.*

4.2 Posology and method of administration
POSOLOGY
Type 2 diabetes mellitus
The recommended starting dose is 10 mg empagliflozin once daily for monotherapy and add-on combination therapy* with other glucose-lowering medicinal products. In patients tolerating empagliflozin 10 mg once daily and need tighter glycaemic control, the dose can be increased to 25 mg once daily. The maximum daily dose is 25 mg (see below and section 4.4).

Heart failure
The recommended dose is 10 mg empagliflozin once daily.

Chronic kidney disease
The recommended dose is 10 mg empagliflozin once daily.

All indications
When empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

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

Special populations
Patients with renal impairment:
Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73 m^2.
In patients with type 2 diabetes mellitus, the glucose lowering efficacy of empagliflozin is reduced in patients with an eGFR <45 ml/min/1.73 m^2 and likely absent in patients with an eGFR <30 ml/min/1.73 m^2. Therefore, if eGFR falls below 45 ml/min/1.73 m2, additional glucose lowering treatment should be considered if needed (see sections 4.4, 4.8, 5.1 and 5.2).

Type 2 diabetes mellitus:
The glucose lowering efficacy of empagliflozin declines with decreasing renal function (see section 5.1 Table 9). Empagliflozin is contraindicated in patient with severe renal impairment (eGFR < 30 ml/min/1.73m^2), end-stage renal disease or patients on dialysis (see section 4.3). No dosage adjustment for empagliflozin is necessary in patient with mild to moderate renal impairment.

More intensive monitoring of glycaemic and renal biomarker and signs and symptoms of renal dysfunction is recommended if empagliflozin is used in patients with an eGFR < 60 ml/ min/1.73m^2, especially if the eGFR is < 45 ml/min/1.73m^2.

Empagliflozin Tablets should be discontinued if the eGFR fall to a level < 30 ml/min/1.73 m^2 (see section 4.3, 4.4, 4.8 and 5.1).

Heart failure:
For treatment of heart failure in patients with or without type 2 diabetes mellitus, empagliflozin 10 mg is not recommended for use in patients with eGFR < 20 ml/min/1.73 m^2 (see section 4.4). There are insufficient data to support use in these patients.

Patients with hepatic impairment:
No dose adjustment is required for patients with hepatic impairment. Empagliflozin exposure is increased in patients with severe hepatic impairment. Therapeutic experience in patients with severe hepatic impairment is limited and therefore not recommended for use in this population (see section 5.2).

Elderly patients:
No dose adjustment is recommended based on age. In patients 75 years and older, an increased risk for volume depletion should be taken into account (see sections 4.4 and 4.8).

Paediatric population:
The safety and efficacy of empagliflozin in children and adolescents has not yet been established. No data are available.

Method of administration
The tablets can be taken with or without food, swallowed whole with water.

** Emflodiaz product is not recommended to use in combination with linagliptin.*

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warning and precautions for use

General
Empagliflozin Tablets should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Ketoacidosis
Cases of ketoacidosis, a serious life-threatening condition requiring urgent hospitalisation, have been reported in patients with diabetes mellitus treated with empagliflozin, including fatal cases. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/l (250 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. If ketoacidosis is suspected, Empagliflozin Tablets should be discontinued, patients should be evaluated and prompt treatment should be instituted.

Patients who may be at higher risk of ketoacidosis while taking Empagliflozin Tablets include patients with a very low carbohydrate diet (as the combination may further increase ketone body production), patients with an acute illness, pancreatic disorders suggesting insulin deficiency (e.g. type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction (including insulin pump failure), alcohol abuse, severe dehydration and patient with a history of ketoacidosis. Empagliflozin Tablets should be used with caution in these patients. When reducing the insulin dose (see section 4.2), caution should be taken. In patients treated with Empagliflozin Tablets, consider monitoring for ketoacidosis and temporarily discontinuing Empagliflozin Tablets in clinical situations known to predispose to ketoacidosis (e.g. prolong fasting due to acute illness or surgery). In these situations, consider monitoring of ketones, even if Empagliflozin Tablets treatment has been interrupted.

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, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death.
Patients treated with Empagliflozin Tablets who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotizing fasciitis. If suspected, Empagliflozin Tablets should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Use in patients with renal impairment
Due to limited experience, it is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 ml/min/1.73 m^2.
The glucose lowering efficacy of empagliflozin is dependent on renal function, and is reduced in patients with an eGFR <45 ml/min/1.73 m^2 and is likely absent in patients with an eGFR <30 ml/min/1.73 m^2 (see section 4.2, 5.1 and 5.2).

Monitoring of renal function
Assessment of renal function is recommended as follows:
- Prior to empagliflozin initiation and periodically during treatment, i.e. at least yearly (see sections 4.2, 4.8, 5.1 and 5.2).
- Prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.

Hepatic injury
Cases of hepatic injury have been reported with empagliflozin in clinical trials. A causal relationship between empagliflozin and hepatic injury has not been established.

Elderly patients
The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients aged 75 years and older may be at an increased risk of volume depletion. A higher number of these patients treated with empagliflozin had adverse reactions related to volume depletion as compared to placebo (see section 4.8). Therefore, special attention should be given to their volume intake in case of co-administered medicinal products which may lead to volume depletion (e.g. diuretics, ACE inhibitors).

Use in patients at risk for volume depletion
Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying glucosuria may lead to a modest decrease in blood pressure (see section 5.1). 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 with a history of hypotension or patients aged 75 years and older.

In case of 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 empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected.

<u>Complicated urinary tract infections</u>
Cases of complicated urinary tract infections including pyelonephritis or urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

<u>Lower limb amputations</u>
An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine prevention foot-care.

Urine laboratory assessments
Due to its mechanism of action, patients taking Empagliflozin Tablets will test positive for glucose in their urine.

Excipients
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.
Each tablet contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium free'

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics
Empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Insulin and insulin secretagogues
Insulin and insulin secretagogues, such as sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin (see sections 4.2 and 4.8).

Interference with 1, 5-anhydroglucitol (1, 5-AG) Assay
Monitoring glycaemic control with 1, 5-AG assay is not recommended as measurements of 1, 5-AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycaemic control.

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.

Effects of other medicinal products on empagliflozin
In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by uridine 5'-diphosphoglucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).
Co-administration of empagliflozin with probenecid, an inhibitor of UGT enzymes and OAT3, resulted in a 26% increase in peak empagliflozin plasma concentrations (C_{max}) and a 53% increase in area under the concentration-time curve (AUC). These changes were not considered to be clinically meaningful.
The effect of UGT induction on empagliflozin has not been studied. Co-medication with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy.
An interaction study with gemfibrozil, an in vitro inhibitor of OAT3 and OATP1B1/1B3 transporters, showed that empagliflozin C_{max} increased by 15% and AUC increased by 59% following co-administration. These changes were not considered to be clinically meaningful.
Inhibition of OATP1B1/1B3 transporters by co-administration with rifampicin resulted in a 75% increase in C_{max} and a 35% increase in AUC of empagliflozin. These changes were not considered to be clinically meaningful.
Empagliflozin exposure was similar with and without co-administration with verapamil, a P-gp inhibitor,

indicating that inhibition of P-gp does not have any clinically relevant effect on empagliflozin.
Interaction studies suggested that the pharmacokinetics of empagliflozin were not influenced by co-administration with metformin, glimepiride, pioglitazone, sitagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide.

Effects of empagliflozin on other medicinal products
Based on in vitro studies, empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Drug-drug interactions involving the major CYP450 isoforms or UGT with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin does not inhibit P-gp at therapeutic doses. Based on in vitro studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Co-administration of digoxin, a P-gp substrate, with empagliflozin resulted in a 6% increase in AUC and 14% increase in Cmax of digoxin. These changes were not considered to be clinically meaningful.

Empagliflozin does not inhibit human uptake transporters such as OAT3, OATP1B1, and OATP1B3 in vitro at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

Interaction studies conducted in healthy volunteers suggest that empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, simvastatin, warfarin, ramipiril, digoxin, diuretics and oral contraceptives.

4.6 Fertility, pregnancy and lactation
Pregnancy
There are no data from the use of empagliflozin in pregnant women. Animal studies show that empagliflozin crosses the placenta during late gestation to a very limited extent but do not indicate direct or indirect harmful effects with respect to early embryonic development. However, animal studies have shown adverse effects on postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Empagliflozin Tablets during early pregnancy. Empagliflozin Tablets is not recommended during the second and third trimester of pregnancy.

Breast-feeding
No data in humans are available on excretion of empagliflozin into milk. Available toxicological data in animals have shown excretion of empagliflozin in milk. A risk to the newborns/infants cannot be excluded. Empagliflozin Tablets should not be used during breast-feeding.

Fertility
No studies on the effect on human fertility have been conducted for Empagliflozin Tablets. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effect on ability to drive and use machines
Empagliflozin Tablets has minor influence on the ability to drive and use machines. Patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Empagliflozin Tablets is used in combination with a sulphonylurea and/or insulin.

4.8 Undesirable effects
Summary of the safety profile

Type 2 diabetes mellitus

A total of 15,582 patients with type 2 diabetes were included in clinical studies to evaluate the safety of empagliflozin, of which 10,004 patients received empagliflozin, either alone or in combination with metformin, a sulphonylurea, pioglitazone, DPP-4 inhibitors* or insulin.

** Emflodiaz product is not recommended to use in combination with linagliptin.*

In 6 placebo-controlled trials of 18 to 24 weeks duration, 3,534 patients were included of which 1,183 were treated with placebo and 2,351 with empagliflozin. The overall incidence of adverse events in patients treated with empagliflozin was similar to placebo. The most frequently reported adverse reaction was hypoglycaemia when used with sulphonylurea or insulin (see description of selected adverse reactions).

Heart failure

The EMPEROR studies included patients with heart failure and either reduced ejection fraction (N = 3726) or preserved ejection fraction (N = 5985) 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
The EMPA-KIDNEY study included patients with chronic kidney disease (N = 6609) 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 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 overall safety profile of Empagliflozin Tablets was generally consistent across the studied indications.

Tabulated list of adverse reactions
Adverse reactions classified by system organ class and MedDRA preferred terms reported in patients who received empagliflozin in placebo-controlled studies are presented in the table below (Table 1).

The adverse reactions are listed by absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), or very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 1: Adverse reactions reported in placebo-controlled studies

System organ class	Very common	Common	Uncommon	Rare
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infectiona Urinary tract infection (including pyelonephritis and urosepsis)[a]		Necrotizing fasciitis of the perineum (Fournier´s gangrene)[*]
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[a]	Thirst	Ketoacidosis[*]	
Gastrointestinal		Constipation		

disorders				
Skin and subcutaneous tissue disorders		Pruritus (generalised), Allergic skin reactions (rash, urticaria)	Angioedema	
Vascular disorders	Volume depletion[a]			
Renal and urinary disorders		Increased urination[a]	Dysuria	
Investigations		Serum lipids increased[a]	Blood creatinine increased/ Glomerular filtration rate decreased[a], Haematocrit increased[a]	

[a]see subsections below for additional information
*see section 4.4

Description of selected adverse reactions

Hypoglycaemia
The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as monotherapy, add-on to metformin, add-on to pioglitazone with or without metformin and as adjunct to standard care therapy and for the combination of empaglilfozin with metformin in drug–naïve patients compared to those treated with empagliflozin and metformin as individual components. An increased frequency was noted when given as add-on to metformin and a sulphonylurea (empagliflozin 10 mg: 16.1%, empagliflozin 25 mg: 11.5%, placebo: 8.4%), and as add-on to basal insulin with or without metformin and with or without a sulphonylurea (empagliflozin 10 mg: 19.5%, empagliflozin 25 mg: 28.4%, placebo: 20.6% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg and 25mg: 36.1%,, placebo 35.3% over the 78-week trial) and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 39.8%, empagliflozin 25 mg: 41.3%, placebo: 37.2% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 51.1%, empagliflozin 25 mg: 57.7%, placebo: 58% over the 52-week trial).

In the EMPEROR heart failure studies, similar frequency of hypoglycaemia was noted when used add- on to sulphonylurea or insulin (empagliflozin 10 mg: 6.5%, placebo: 6.7%).

Major hypoglycaemia (event requiring assistance)
No increase in major hypoglycaemia was observed with empagliflozin compared to placebo as monotherapy, add-on to metformin, add-on to metformin and a sulphonylurea, add-on to pioglitazone with or without metformin, , as adjunct to standard care therapy and for the combination of empaglilfozin with metformin in drug–naïve patients compared to those treated with empagliflozin and metformin as individual components. An increased frequency was noted when given as add-on to basal insulin with or without metformin and with or without a sulphonylurea (empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo: 0% during initial 18 weeks treatment
when insulin could not be adjusted; empagliflozin 10 mg: 0%, empagliflozin 25 mg: 1.3%, placebo 0% over the 78-week trial) and add-on to MDI insulin with or without metformin (empagliflozin 10 mg: 0.5%, empagliflozin 25 mg: 0.5%, placebo: 0.5% during initial 18 weeks treatment when insulin could not be adjusted; empagliflozin 10 mg: 1.6%, empagliflozin 25 mg: 0.5%, placebo: 1.6% over the 52-week trial).

In the EMPEROR heart failure studies, major hypoglycaemia was observed at similar frequencies in

patients with diabetes mellitus when treated with empagliflozin and placebo as add-on to sulphonylurea or insulin (empagliflozin 10 mg: 2.2%, placebo: 1.9%).

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection
Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently in patients treated with empagliflozin (empagliflozin 10 mg: 4.0%, empagliflozin 25 mg: 3.9%) compared to placebo (1.0%). These infections were reported more frequently in females treated with empagliflozin compared to placebo, and the difference in frequency was less pronounced in males. The genital tract infections were mild or moderate in intensity.

In the EMPEROR heart failure studies, the frequency of these infections was more pronounced in patients with diabetes mellitus (empagliflozin 10 mg: 2.3%; placebo: 0.8%) than in patients without diabetes mellitus (empagliflozin 10 mg: 1.7%; placebo: 0.7%) when treated with empagliflozin compared to placebo.

Increased urination
Increased urination (including the predefined terms pollakiuria, polyuria, and nocturia) was observed at higher frequencies in patients treated with empagliflozin (empagliflozin 10 mg: 3.5%, empagliflozin 25 mg: 3.3%) compared to placebo (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was similar for placebo and empagliflozin (<1%).
In the EMPEROR heart failure studies, increased urination was observed at similar frequencies in patients treated with empagliflozin and placebo (empagliflozin 10 mg: 0.9%, placebo 0.5%).

Urinary tract infection
The overall frequency of urinary tract infection reported as adverse event was similar in patients treated with empagliflozin 25 mg and placebo (7.0% and 7.2%) and higher in empagliflozin 10 mg (8.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin in patients with a history of chronic or recurrent urinary tract infections. The intensity (mild, moderate, severe) of urinary tract infection was similar in patients treated with empagliflozin and placebo. Urinary tract infection was reported more frequently in females treated with empagliflozin compared to placebo; there was no difference in males.

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 in patients treated with empagliflozin (empagliflozin 10 mg: 0.6%, empagliflozin 25 mg: 0.4%) and placebo (0.3%). The frequency of volume depletion events was increased in patients 75 years and older treated with empagliflozin 10 mg (2.3%) or empagliflozin 25 mg (4.3%) compared to placebo (2.1%).

Blood creatinine increased/ Glomerular filtration rate decreased
The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was similar between empagliflozin and placebo (blood creatinine increased: empagliflozin 10 mg 0.6%, empagliflozin 25 mg 0.1%, placebo 0.5%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.3%).

In placebo-controlled, double-blind studies up to 76 weeks, initial transient 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 initial transient 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 generally reversible during continuous treatment or after drug discontinuation (see section Clinical Trials Figure 6 for the eGFR course in the EMPA-REGOUTCOME study).

Serum lipids increased

Mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 4.9% and 5.7% versus 3.5%; HDL-cholesterol 3.3% and 3.6% versus 0.4 %; LDL-cholesterol 9.5% and 10.0% versus 7.5%; triglycerides 9.2% and 9.9% versus 10.5%.

Haematocrit increased
Mean changes from baseline in haematocrit were 3.4% and 3.6% for empagliflozin 10 mg and 25 mg, respectively, compared to 0.1% for placebo. In the EMPA-REG Outcome study, haematocrit values returned towards baseline values after a follow-up period of 30 days after treatment stop.

4.9 Overdose
Symptoms
In controlled clinical studies single doses of up to 800 mg empagliflozin (equivalent to 32 times the highest recommended daily dose) in healthy volunteers and multiple daily doses of up to 100 mg empagliflozin (equivalent to 4 times the highest recommended daily dose) in patients with type 2 diabetes did not show any toxicity. Empagliflozin increased urine glucose excretion leading to an increase in urine volume. The observed increase in urine volume was not dose-dependent and is not clinically meaningful.

Therapy
In the event of an overdose, treatment should be initiated as appropriate to the patient's clinical status. The removal of empagliflozin by haemodialysis has not been studied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Drugs used in diabetes, Sodium-glucose co-transporter 2 (SGLT2). ATC code: A10BK03.

Mechanism of action
Empagliflozin is a reversible, highly potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. 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 the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed.

Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. Inhibition of SGLT2 in patients with type 2 diabetes and hyperglycaemia leads to excess glucose excretion in the urine.

In patients with type 2 diabetes, urinary glucose excretion increased immediately following the first dose of empagliflozin and is continuous over the 24-hour dosing interval. Increased urinary glucose excretion was maintained at the end of the 4-week treatment period, averaging approximately 78 g/day. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

Empagliflozin improves both fasting and post-prandial plasma glucose levels. The mechanism of action of empagliflozin is independent of beta cell function and insulin pathway and this contributes to a low risk of hypoglycaemia. Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-β (HOMA-β) was noted. In addition, urinary glucose excretion triggers calorie loss,

associated with body fat loss and body weight reduction. The glucosuria 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 of sympathetic activity and reducing left ventricular wall stress as evidenced by lower NT-proBNP values and beneficial effects on cardiac remodeling, filling pressures and diastolic function. Other effects such as an increase in haematocrit, a reduction in body weight and blood pressure may further contribute to the beneficial effects observed independent of left ventricular ejection fraction (LVEF).

Clinical efficacy and safety
Type 2 diabetes mellitus

A total of 17331 patients with type 2 diabetes were treated in 15 double-blind, placebo- and active-controlled clinical studies, of which 4603 patients received empagliflozin 10 mg and 5567 received empagliflozin 25 mg. Six studies had a treatment duration of 24 weeks; in extensions of applicable studies, and other trials, patients were exposed to empagliflozin for up to 102 weeks.

Treatment with empagliflozin (10 mg and 25 mg) as monotherapy and in combination with metformin, pioglitazone, sulphonylurea, DPP-4 inhibitors*, and insulin lead to clinically relevant improvements in HbA1c, fasting plasma glucose (FPG), body weight, and systolic and diastolic blood pressure (SBP and DBP, respectively). Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA1c goal of less than 7% and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. There was a clinically meaningful improvement in HbA1c in all subgroups of gender, race, geographic region, time since diagnosis of T2DM, body mass index, insulin resistance based on HOMA-IR, and beta cell function based on HOMA-β. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Clinically meaningful HbA1c reduction was seen for patients with eGFR >30 mL/min/1.73 m² (See section 4.2, Patients with renal impairment). In patients aged 75 years and older, reduced efficacy of empagliflozin was observed.

* *Emflodiaz product is not recommended to use in combination with linagliptin.*

Monotherapy
The efficacy and safety of empagliflozin as monotherapy was evaluated in a double-blind, placebo- and active-controlled study of 24 weeks duration in treatment-naïve patients. Treatment with empagliflozin resulted in a statistically significant ($p<0.0001$) reduction in HbA1c compared to placebo (Table 2) and a clinically meaningful decrease in FPG.

In a pre-specified analysis of patients (N=201) with a baseline HbA1c ≥8.5%, treatment resulted in a reduction in HbA1c from baseline of -1.44% for empagliflozin 10 mg, -1.43% for empagliflozin 25 mg, -1.04% for sitagliptin, and an increase of 0.01% for placebo.

In the double-blind placebo-controlled extension of this study, reductions of HbA1c, body weight and blood pressure were sustained up to Week 76.

Table 2: Efficacy results of a 24-week placebo-controlled study of empagliflozin as monotherapy[a]

	Placebo	Empagliflozin		Sitagliptin
		10mg	25mg	100mg
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 placebo1 (97.5% CI)		-0.74* (-0.90, -0.57)	-0.85* (-1.01, -0.69)	-0.73 (-0.88, -0.59)
N	208	204	202	200
Patient (%) achieving HbA1c <7% with baseline HbA1c ≥ 7%[2]	12.0	35.3	43.6	37.5
N	228	224	224	223
Body Weight (kg)				
Baseline (mean)	78.2	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)[3]
N	228	224	224	223
SBP (mmHg)[4]				
Baseline (mean)	130.	133.0	129.9	132.5
Change from baseline[1]	-0.3	-2.9	-3.7	0.5
Difference from placebo[1] (97.5% CI)		-2.6* (-5.2, -0.0)	-3.4* (-6.0, - 0.9)	0.8 (-1.4, 3.1)[3]

[a]Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy
[1]Mean adjusted for baseline value
[2]Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
[3]95% CI
[4]LOCF, values after antihypertensive rescue censored
*P-value <0.0001

Combination therapy

Empagliflozin as add on to metformin, sulphonylurea, pioglitazone
Empagliflozin as add-on to metformin, metformin and a sulphonylurea, or pioglitazone with or without metformin resulted in statistically significant (p<0.0001) reductions in HbA1c and body weight compared to placebo (Table 3). In addition it resulted in a clinically meaningful reduction in FPG, systolic and diastolic blood pressure compared to placebo.
In the double-blind placebo-controlled extension of these studies, reduction of HbA1c, body weight and blood pressure were sustained up to Week 76.

Table 3: Efficacy results of 24-week placebo-controlled studies

Add-on to metformin therapy			
	Placebo	Empagliflozin	
		10mg	25mg
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 (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	12.5	37.7	38.7
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)
N	207	217	213
SBP (mmHg)[2]			
Baseline (mean)	128.6	129.6	130.0
Change from baseline[1]	-0.4	-4.5	-5.2
Difference from placebo[1] (95% CI)		-4.1* (-6.2, -2.1)	-4.8* (-6.9, -2.7)
Add-on to metformin and a sulphonylurea therapy			
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 (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	9.3	26.3	32.2
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)
N	225	225	216
SBP (mmHg)[2]			
Baseline (mean)	128.8	128.7	129.3
Change from baseline[1]	-1.4	-4.1	-3.5
Difference from placebo[1] (95% CI)		-2.7 (-4.6, -0.8)	-2.1 (-4.0, -0.2)
Add-on to pioglitazone +/- metformin therapy			
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 (%) achieving HbA1c <7% with baseline HbA1c ≥ 7%[2]	7.7	24	30
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)
N	165	165	168
SBP (mmHg)[3]			
Baseline (mean)	125.7	126.5	126
Change from baseline[1]	0.7	-3.1	-4.0
Difference from placebo[1] (95% CI)		-3.9 (-6.23, -1.50)	-4.7 (-7.08, -2.37)

[a]Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy
[1]Mean adjusted for baseline value
[2]Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure
[3]LOCF, values after antihypertensive rescue censored
*P-value <0.0001

In combination with metformin in drug-naïve patients
A factorial design study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in drug-naïve patients. Treatment with empagliflozin in combination with metformin (5mg and 500mg; 5mg and 1000mg; 12.5mg and 500mg and 12.5mg and 1000mg given twice daily) provided statistically significant improvement in HbA1c (Table 4) and led to greater reductions in FPG (compared to the individual components) and body weight (compared to metformin).

Table 4: Efficacy results at 24 week comparing empagliflozin in combination with metformin to the individual components[a]

	Empagliflozin 10 mg[b]			Empagliflozin 25 mg[b]			Metformin[c]	
	+ Met 1000 mg[c]	+ Met 2000 mg[c]	No Met	+ Met 1000 mg[c]	+ Met 2000 mg[c]	No Met	1000 mg	2000 mg
N	161	167	169	165	169	163	167	162
HbA1c (%)								
Baseline	8.68	8.65	8.62	8.84	8.66	8.86	8.69	8.55
Change from baseline[1]	-1.98	-2.07	-1.35	-1.93	-2.08	-1.36	-1.18	-1.75
Comparison vs. empa (95% CI) [1]	-0.63* (-0.86, -0.40)	-0.72* (-0.96, -0.49)		-0.57* (-0.81, -0.34)	-0.72* (-0.95, -0.48)			
Comparison vs. met (95% CI) [1]	-0.79* (-1.03, -0.56)	-0.33* (-0.56, -0.09)		-0.75* (-0.98 -0.51)	-0.33* (-0.56, -0.10)			

Met = metformin; empa = empagliflozin
[1]Mean adjusted for baseline value
[a]Analyses were performed on the full analysis set (FAS) using an observed cases (OC) approach
[b]Given in two equally divided doses per day when given together with metformin
[c]Given in two equally divided doses per day
*p≤0.0062 for HbA1c

Empagliflozin 24 months data, as add on to metformin in comparison to glimepiride
In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (up to 4 mg per day) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA1c (Table 5), and a clinically meaningful reduction in FPG, compared to glimepiride. Empagliflozin daily resulted in a statistically significant reduction in body weight, systolic and diastolic blood pressure and a statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin, 24.2% for glimepiride, p<0.0001).

Table 5: Efficacy results at 104 weeks in an active controlled study comparing empagliflozin to glimepiride as add on to metformin[a]

	Empagliflozin 25 mg	Glimepiride[b]
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 (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	33.6	30.9
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)	
N	765	780
SBP (mmHg) [2]		
Baseline (mean)	133.4	133.5
Change from baseline[1]	-3.1	2.5
Difference from glimepiride[1] (97.5% CI)	-5.6** (-7.0, -4.2)	

[a] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

[b] Up to 4mg glimepiride

[1] Mean adjusted for baseline value

[2] LOCF, values after antihypertensive rescue censored

*P-value <0.0001 for non-inferiority, and p-value = 0.0153 for superiority

**P-value < 0.0001

Add-on to insulin therapy

Empagliflozin as add on to multiple daily insulin
The efficacy and safety of empagliflozin as add-on to multiple daily insulin with or without concomitant metformin therapy was evaluated in a double-blind, placebo-controlled trial of 52 weeks duration. During the initial 18 weeks and the last 12 weeks, the insulin dose was kept stable, but was adjusted to achieve pre-prandial glucose levels <100 mg/dl [5.5 mmol/l], and post-prandial glucose levels <140 mg/dl [7.8 mmol/l] between Weeks 19 and 40.
At Week 18, empagliflozin provided statistically significant improvement in HbA1c compared with placebo (Table 6).
At Week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared with placebo and a reduction in FPG and body weight.

Table 6: Efficacy results at 18 and 52 weeks in a placebo-controlled study of empagliflozin as add on to multiple daily doses of insulin with or without metformin

	Placebo	Empagliflozin	
		10mg	25mg
N	188	186	189
HbA1c (%) at week 18			
Baseline (mean)	8.33	8.39	8.29
Change from baseline[1]	-0.50	-0.94	-1.02
Difference from placebo[1] (97.5% CI)		-0.44* (-0.61, -0.27)	-0.52* (-0.69, -0.35)
N	115	119	118
HbA1c (%) at week 52[2]			
Baseline (mean)	8.25	8.40	8.37
Change from baseline[1]	-0.81	-1.18	-1.27
Difference from placebo[1] (97.5% CI)		-0.38*** (-0.62, -0.13)	-0.46* (-0.70, -0.22)

N	113	118	118
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7% at week 52	26.5	39.8	45.8
N	115	118	117
Insulin dose (IU/day) at week 52[2]			
Baseline (mean)	89.94	88.57	90.38
Change from baseline[1]	10.16	1.33	-1.06
Difference from placebo[1] (97.5% CI)		-8.83[#] (-15.69, -1.97)	-11.22[**] (-18.09, -4.36)
N	115	119	118
Body Weight (kg) at week 52[2]			
Baseline (mean)	96.34	96.47	95.37
Change from baseline[1]	0.44	-1.95	-2.04
Difference from placebo[1] (97.5% CI)		-2.39[*] (-3.54, -1.24)	-2.48[*] (-3.63, -1.33)

1 Mean adjusted for baseline value

2 Week 19-40: treat-to-target regimen for insulin dose adjustment to achieve pre-defined glucose target levels (pre-prandial <100 mg/dl (5.5 mmol/l), post-prandial <140 mg/dl (7.8 mmol/l)

* p-value <0.0001

** p-value = 0.0003

*** p-value = 0.0005

p-value = 0.0040

Empagliflozin as add on to basal insulin

The efficacy and safety of empagliflozin as add on to basal insulin with or without metformin and/or a sulphonylurea was evaluated in a double-blind, placebo-controlled trial of 78 weeks duration. During the initial 18 weeks the insulin dose was kept stable, but was adjusted to achieve a FPG <110 mg/dl in the following 60 weeks.

At week 18, empagliflozin provided statistically significant improvement in HbA1c (Table 7).

At 78 weeks, empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared to placebo. Furthermore, empagliflozin resulted in a reduction in FPG, body weight, and blood pressure.

Table 7: Efficacy results at 18 and 78 weeks in a placebo-controlled study of empagliflozin as add on to basal insulin with or without metformin or a sulphonylurea[a]

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
N	125	132	117
HbA1c (%) at week 18			
Baseline (mean)	8.10	8.26	8.34
Change from baseline[1]	-0.01	-0.57	-0.71
Difference from placebo[1] (97.5% CI)		-0.56* (-0.78, -0.33)	-0.70* (-0.93, -0.47)
N	112	127	110
HbA1c (%) at week 78			
Baseline (mean)	8.09	8.27	8.29
Change from baseline[1]	-0.02	-0.48	-0.64
Difference from placebo[1] (97.5% CI)		-0.46* (-0.73, -0.19)	-0.62* (-0.90, -0.34)
N	112	127	110
Basal insulin dose (IU/day) at week 78			
Baseline (mean)	47.84	45.13	48.43
Change from baseline[1]	5.45	-1.21	-0.47
Difference from placebo[1] (97.5% CI)		-6.66** (-11.56, -1.77)	-5.92** (-11.00, -0.85)

[a] Full analysis set (FAS) - Completers using last observation carried forward (LOCF) prior to glycaemic rescue therapy

[1] mean adjusted for baseline value

* p-value <0.0001

** p-value <0.025

Patients with renal impairment, 52 week placebo controlled data

The efficacy and safety of empagliflozin as add on to antidiabetic therapy was evaluated in patients with mild to moderate renal impairment in a double-blind, placebo-controlled study for 52 weeks. Treatment with empagliflozin led to a statistically significant reduction of HbA1c (Table 8) and clinically meaningful improvement in FPG, body weight and blood pressure compared to placebo at Week 24. The improvement in HbA1c, FPG, body weight, and blood pressure was sustained up to 52 weeks.

Table 8: Results at 24 weeks (LOCF) in a placebo-controlled study of empagliflozin in renally impaired type 2 diabetes patients[a]

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Placebo	Empagliflozin 25 mg
	eGFR ≥60 to <90 ml/min/1.73 m²			eGFR ≥30 to <60 ml/min/1.73 m²	
N	95	98	97	187	187
HbA1c (%)					
Baseline (mean)	8.09	8.02	7.96	8.04	8.03
Change from baseline[1]	0.06	-0.46	-0.63	0.05	-0.37

Difference from placebo[1] (95% CI)		-0.52* (-0.72, -0.32)	-0.68* (-0.88, -0.49)		-0.42* (-0.56, -0.28)
N	89	94	91	178	175
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%[2]	6.7	17.0	24.2	7.9	12.0
N	95	98	97	187	187
FPG (mg/dl) [mmol/l] [2]					
Baseline (mean)	144.8 [8.04]	146.0 [8.10]	148.4 [8.24]	153.4 [7.98]	134.0 [7.92]
Change from baseline[1]	5.7 [0.31]	-13.9 [-0.77]	-18.1 [-1.00]	10.2 [0.56]	-9.3 [-0.51]
Difference from placebo[1] (95% CI)		-19.6 (-29.2, -9.9) [-1.09 (-1.62, -0.55)]	-23.8 (-33.5, -14.0) [-1.32 (-1.86, -0.78)]		-19.4* (-27.2, -11.6) [-11.08 (-1.51, -0.64)]
N	95	98	97	187	187
Body Weight (kg) [2]					
Baseline (mean)	86.00	92.05	88.06	82.49	83.22
Change from baseline[1]	-0.33	-1.76	-2.33	-0.08	-0.98
Difference from placebo[1] (95% CI)		-1.43 (-2.09, -0.77)	-2.00 (-2.66, -1.34)		-0.91 (-1.41, -0.41)
N	95	98	97	187	187
SBP (mmHg) [2]					
Baseline (mean)	134.69	137.37	133.68	136.38	136.64
Change from baseline[1]	0.65	-2.92	-4.47	0.40	-3.88
Difference from Placebo[1] (95% CI)		-3.57 (-6.86, -0.29)	-5.12 (-8.41, -1.82)		-4.28 (-6.88, -1.68)

[a] Full analysis set (FAS) using last observation carried forward (LOCF) prior to glycaemic rescue therapy

[1] Mean adjusted for baseline value

[2] Not evaluated for statistical significance as a result of the sequential confirmatory testing procedure

* $p<0.0001$

Fasting plasma glucose

In four placebo-controlled studies, treatment with empagliflozin as monotherapy or add-on therapy to metformin, pioglitazone, or metformin plus a sulphonylurea resulted in mean changes from baseline in FPG of -20.5 mg/dl [-1.14 mmol/l] for empagliflozin 10 mg and -23.2 mg/dl [-1.29 mmol/l] for empagliflozin 25 mg compared to placebo (7.4 mg/dl [0.41 mmol/l]). This effect was observed after 24 weeks and maintained for 76 weeks.

2-hour post-prandial glucose

Treatment with empagliflozin as add-on to metformin or metformin and a sulphonylurea resulted in a clinically meaningful reduction of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add- on to metformin: placebo +5.9 mg/dl, empagliflozin 10 mg: -46.0 mg/dl, empagliflozin 25 mg: -44.6

mg/dl, add-on to metformin and a sulphonylurea: placebo -2.3 mg/dl, empagliflozin 10 mg: -35.7 mg/dl, empagliflozin 25 mg: -36.6 mg/dl).

Patients with high baseline HbA1c >10%
In a pre-specified pooled analysis of three phase 3 studies, treatment with open-label empagliflozin 25 mg in patients with severe hyperglycaemia (N=184, mean baseline HbA1c 11.15%) resulted in a clinically meaningful reduction in HbA1c from baseline of 3.27% at week 24; no placebo or empagliflozin 10 mg arms were included in these studies.

Body weight
In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin resulted in body weight reduction (-0.24 kg for placebo, -2.04 kg for empagliflozin 10 mg and -2.26 kg for empagliflozin 25 mg) at week 24 that was maintained up to week 52 (-0.16 kg for placebo, -1.96 kg for empagliflozin 10 mg and -2.25 kg for empagliflozin 25 mg).

Blood pressure
The efficacy and safety of empagliflozin was 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 empagliflozin once daily resulted in statistically significant improvement in HbA1c, and 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring (Table 9). Treatment with empagliflozin provided reductions in seated SBP and DBP.

Table 9: Efficacy results at 12 weeks in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressure[a]

	Placebo	Empagliflozin	
		10mg	25mg
N	271	276	276
HbA1c (%) at week 12[1]			
Baseline (mean)	7.90	7.87	7.92
Change from baseline[2]	0.03	-0.59	-0.62
Difference from placebo[2] (95% CI)		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
24 hour SBP at week 12[3]			
Baseline (mean)	131.72	131.34	131.18
Change from baseline[4]	0.48	-2.95	-3.68
Difference from placebo[4] (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24 hour DBP at week 12[3]			
Baseline (mean)	75.16	75.13	74.64
Change from baseline[5]	0.32	-1.04	-1.40
Difference from placebo[5] (95% CI)		-1.36** (-2.15, -0.56)	-1.72* (-2.51, -0.93)

[a] Full analysis set (FAS)

1 LOCF, values after taking antidiabetic rescue therapy censored

2 Mean adjusted for baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products

3 LOCF, values after taking antidiabetic rescue therapy or changing antihypertensive rescue therapy censored

[4] Mean adjusted for baseline SBP, baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products

[5] Mean adjusted for baseline DBP, baseline HbA1c, baseline eGFR, geographical region and number of antihypertensive medicinal products

* p-value <0.0001

** p-value <0.001

In a pre-specified pooled analysis of 4 placebo-controlled studies, treatment with empagliflozin resulted in a reduction in systolic blood pressure (empagliflozin 10 mg: -3.9 mmHg; empagliflozin 25 mg: -4.3 mmHg) compared with placebo (-0.5 mmHg) and in diastolic blood pressure (empagliflozin 10 mg: -1.8 mmHg; empagliflozin 25 mg: -2.0 mmHg) compared with placebo (-0.5 mmHg) at week 24 that were maintained up to week 52.

Cardiovascular outcome

The EMPA-REG OUTCOME study is a multi-centre, multi-national, randomised, double-blind, placebo-controlled trial investigating the effect of Empagliflozin as adjunct to standard care therapy in reducing cardiovascular events in patients with type 2 diabetes and one or more cardiovascular risk factors, including coronary artery disease, peripheral artery disease, history of myocardial infarction (MI), or history of stroke. The primary endpoint was the time to first event in the composite of CV death, nonfatal MI, or non-fatal stroke [(Major Adverse Cardiovascular Events (MACE-3)]. Additional pre-specified endpoints addressing clinically relevant outcomes tested in an exploratory manner included CV death, the composite of heart failure requiring hospitalisation or CV death, all-cause mortality and the composite of new or worsening nephropathy.

A total of 7,020 patients were treated with Empagliflozin Tablets (empagliflozin 10 mg: 2,345, empagliflozin 25 mg: 2,342, placebo: 2,333) and followed for a median of 3.1 years. The population was 72.4% Caucasian, 21.6% Asian, and 5.1% Black. The mean age was 63 years and 71.5% were male. 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.

About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73 m^2, 17.8% of 45-60 ml/min/1.73 m^2 and 7.7% of 30-45 ml/min/1.73 m^2. Mean systolic BP was 136 mmHg, diastolic BP 76 mmHg, LDL 86 mg/dL, HDL 44 mg/dL, and urinary albumin to creatinine ratio (UACR) 175 mg/g at baseline.

<u>Reductions in risk of CV death and all-cause mortality</u>

Empagliflozin Tablets was superior in reducing the primary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke compared to placebo. The treatment effect reflected a significant reduction in cardiovascular death with no significant change in non-fatal MI, or non-fatal stroke (Table 10 and Figure 1).

Empagliflozin Tablets also improved overall survival (Table 10 and Figure 2), which was driven by a reduction in cardiovascular death with Empagliflozin Tablets. There was no statistically significant difference between empagliflozin and placebo in non-cardiovascular mortality.

Table 10: Treatment effect for the primary composite endpoint, its components and mortality (Treated Set*)

	Placebo	Empagliflozin (10 and 25 mg, pooled)
N	2333	4687
Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke N (%)	282 (12.1)	490 (10.5)

Hazard ratio vs. placebo (95.02% CI)**		0.86 (0.74, 0.99)
p−value for superiority		0.0382
CV Death N (%)	137 (5.9)	172 (3.7)
Hazard ratio vs. placebo (95% CI)		0.62 (0.49, 0.77)
p-value		<0.0001
Non-fatal MI N (%)	121 (5.2)	213 (4.5)
Hazard ratio vs. placebo (95% CI)		0.87 (0.70, 1.09)
p−value		0.2189
Non-fatal stroke N (%)	60 (2.6)	150 (3.2)
Hazard ratio vs. placebo (95% CI)		1.24 (0.92, 1.67)
p−value		0.1638
All-cause mortality N (%)	194 (8.3)	269 (5.7)
Hazard ratio vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		<0.0001
Non-CV mortality N (%)	57 (2.4)	97 (2.1)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.16)

* i.e. patients who had received at least one dose of study drug

** Since data from the trial were included in an interim analysis, a two-sided 95.02% confidence interval applied which corresponds to a p-value of less than 0.0498 for significance.

Figure 1: Time to occurrence of CV death

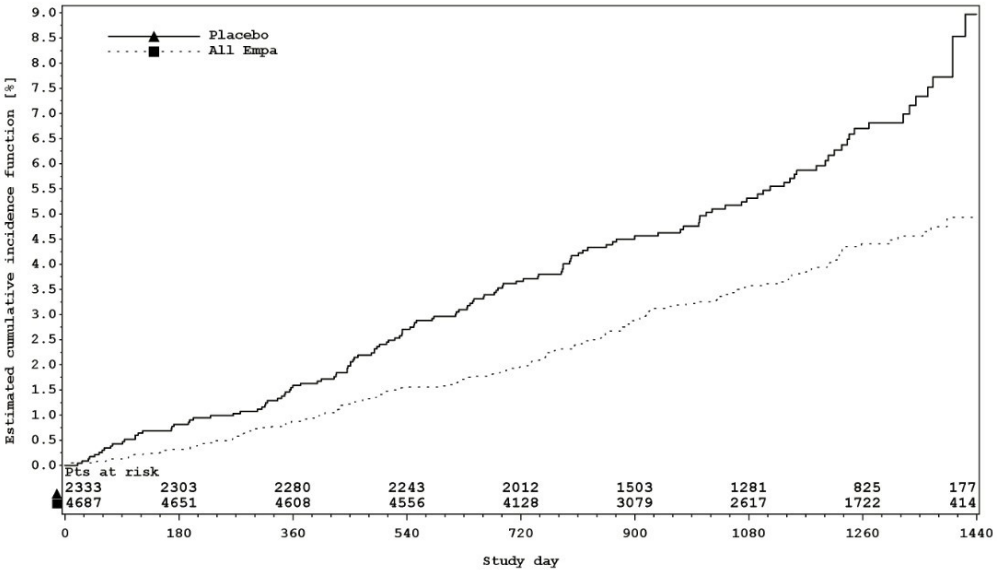
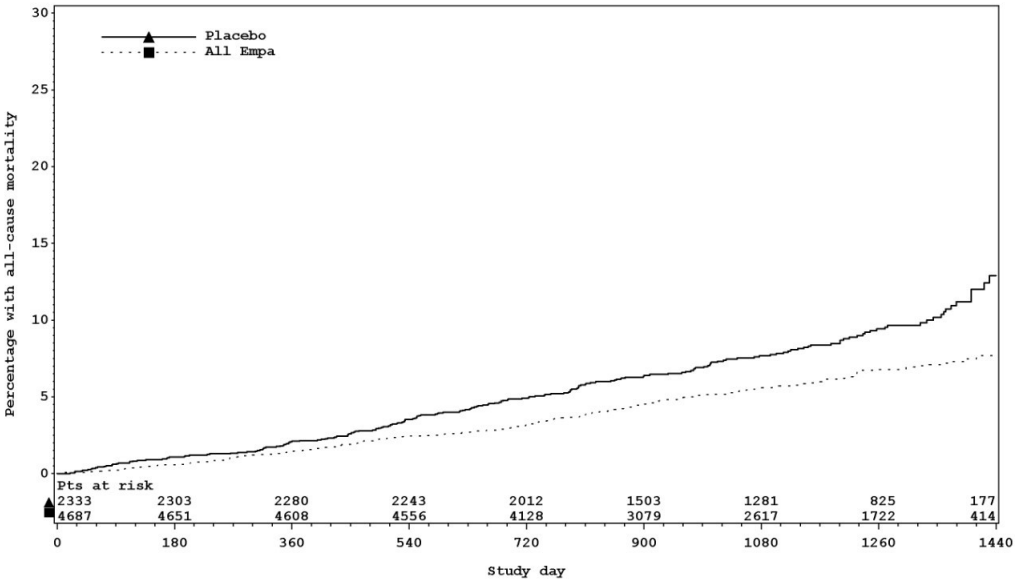


Figure 2: Time to occurrence of all-cause mortality*



*Kaplan-Meier estimate of time to all cause-mortality, pooled empagliflozin vs. placebo –treated set

Reductions in risk of heart failure requiring hospitalization or CV death

Empagliflozin significantly reduced the risk of hospitalization for heart failure and cardiovascular death or hospitalization for heart failure compared with placebo (Table 11 and Figure 3).

Table 11: Treatment effect for hospitalization for heart failure or cardiovascular death (excluding fatal stroke) (Treated Set*)

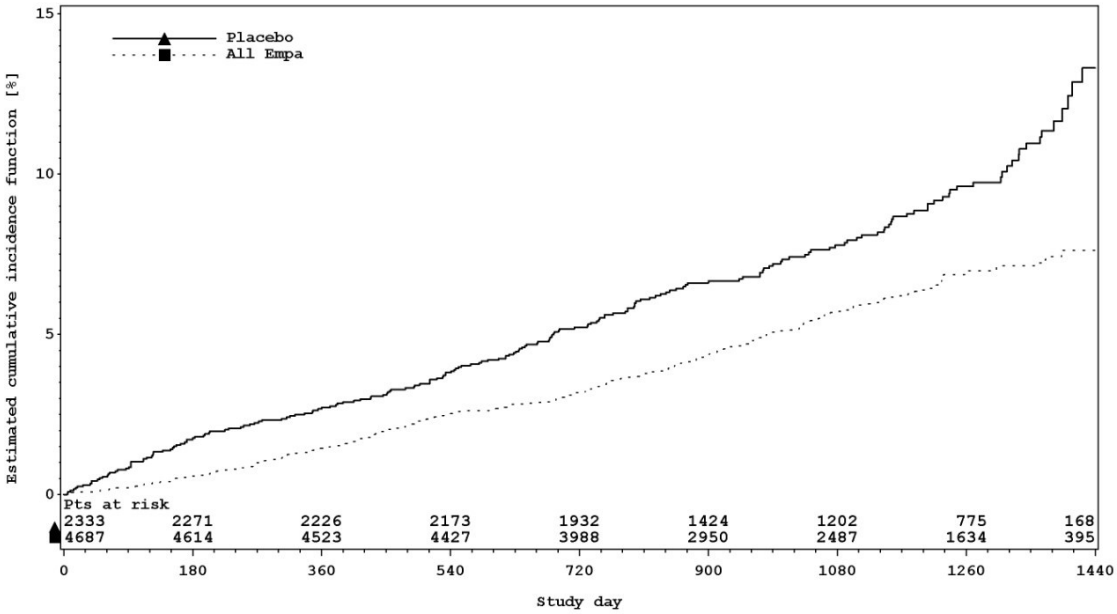
	Placebo	Empagliflozin** (10 and 25 mg, pooled)
N	2333	4687
Heart failure requiring hospitalisation or CV death (excluding fatal stroke) N (%)***	198 (8.5)	265 (5.7)
HR (95% CI)		0.66 (0.55, 0.79)
p−value		<0.0001
Heart failure requiring hospitalization N (%)	95 (4.1)	126 (2.7)
HR (95% CI)		0.65 (0.50, 0.85)
p−value		0.0017
CV death (excluding fatal stroke) N (%)	126 (5.4)	156 (3.3)
HR (95% CI)		0.61 (0.48, 0.77)
p−value		<0.0001

*i.e. patients who had received at least one dose of study drug

**empagliflozin 10 mg and 25 mg showed consistent results

*** time to first event

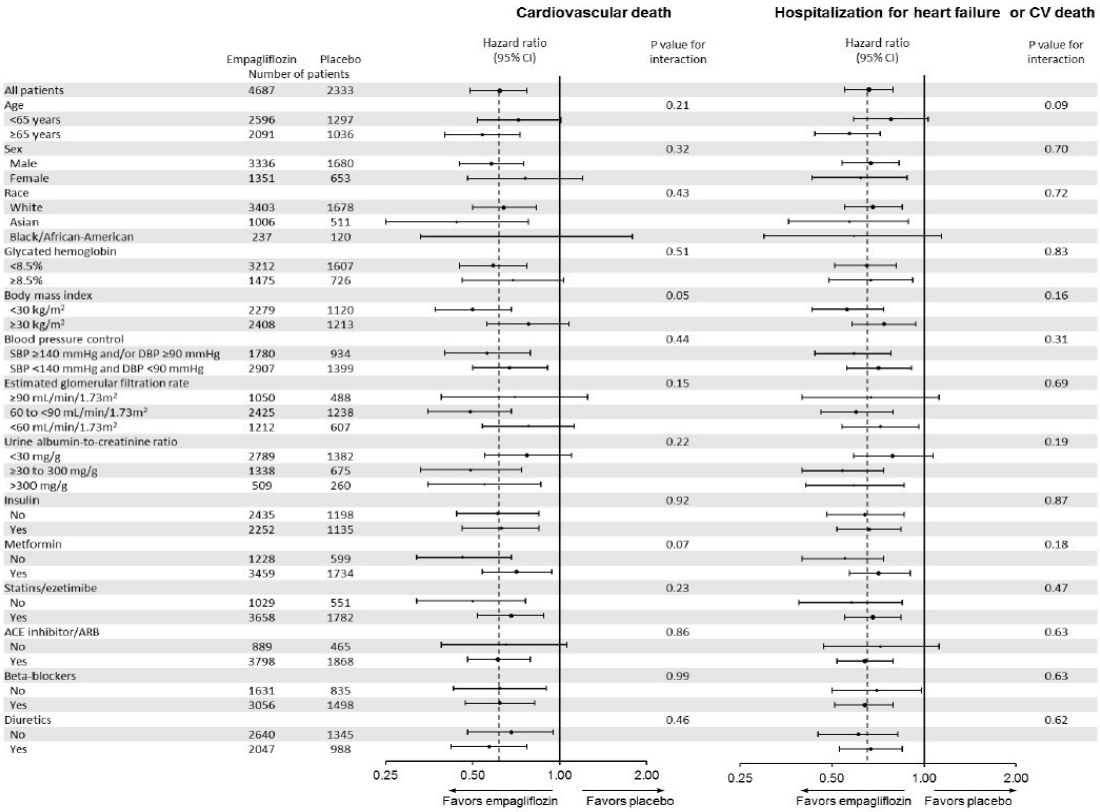
Figure 3: time to first occurrence of first heart failure hospitalization or CV death*



*Estimated cumulative incidence function for time to first occurrence of first heart failure hospitalization or CV death, pooled empagliflozin vs placebo – treated set

The cardiovascular benefits of Empagliflozin Tablets observed were consistent across the subgroups depicted in Figure 4.

Figure 4: subgroup analyses for CV death and hospitalization for heart failure or CV death*.**



* Hospitalization for heart failure or CV death excludes fatal stroke

**p-value is for test of homogeneity of treatment group difference among subgroups (test for group by covariate interaction) with no adjustment for multiple tests and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Diabetic kidney disease

In the EMPA-REG OUTCOME study population, the risk of new or worsening nephropathy [defined as onset of macroalbuminuria, doubling of serum creatinine, and initiation of renal replacement therapy (i.e. hemodialysis)] was significantly reduced in empagliflozin group compared to placebo (Table 12 and Figure 4).

Empagliflozin Tablets compared with placebo showed a significantly higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria (HR 1.82, 95% CI 1.40, 2.37).

Table 12: Time to first new or worsening of nephropathy (Treated Set*)

	Placebo	Empagliflozin (10 and 25 mg, pooled)
N	2061	4124
New or worsening nephropathy N (%)	388 (18.8)	525 (12.7)
HR (95% CI)		0.61 (0.53, 0.70)
p−value		<0.0001
N	2323	4645
Doubling of serum creatinine level**N (%)	60 (2.6)	70 (1.5)
HR (95% CI)		0.56 (0.39, 0.79)
p−value		0.0009
N	2033	4091
New onset of macroalbuminuria*** N (%)	330 (16.2)	459 (11.2)
HR (95% CI)		0.62 (0.54, 0.72)
p−value		<0.0001
N	2333	4687
Initiation of continuous renal replacement therapy N (%)	14 (0.6)	13 (0.3)
HR (95% CI)		0.45 (0.21, 0.97)
p−value		0.0409
N	2333	4687
Death due to renal disease N (%)****	0	3 (0.1)

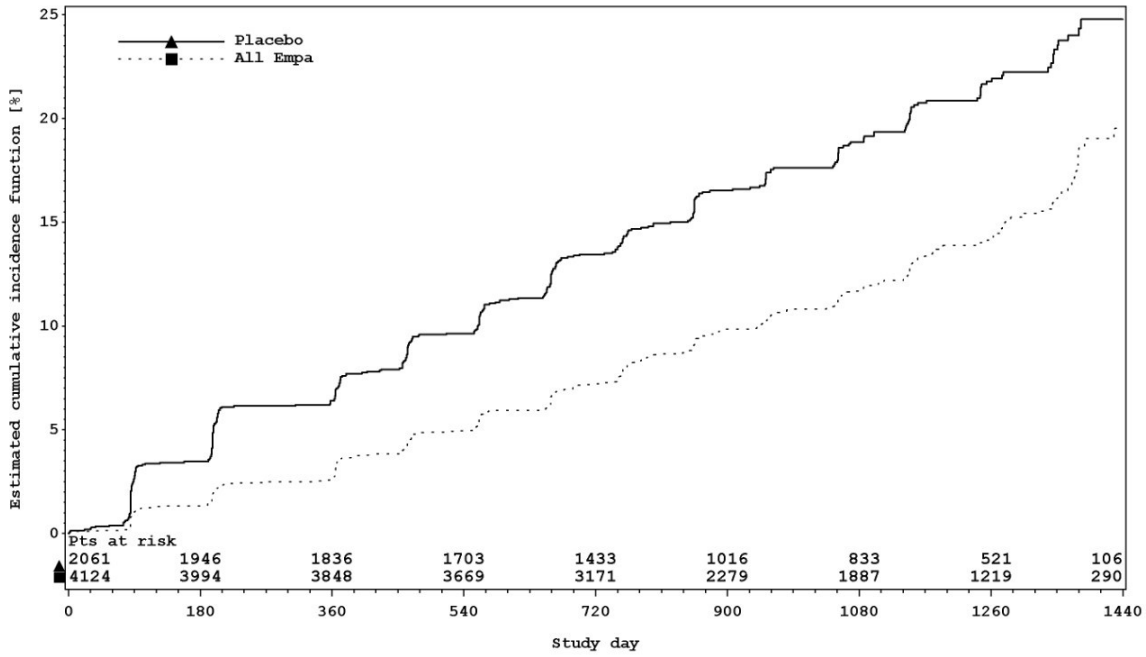
*i.e. patients who had received at least one dose of study drug

**Accompanied by an eGFR ≤45 mL/min/1.73m^2

*** Urine Albumin Creatinine Ratio >300 mg/g

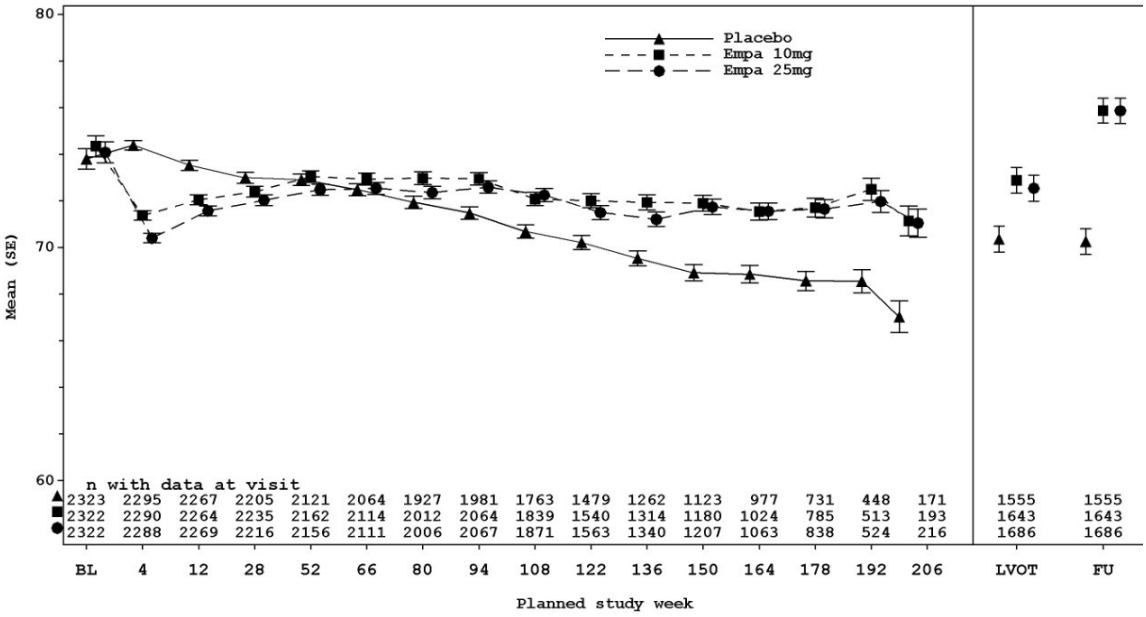
**** Due to low event rate, HR not calculated

Figure 5: Time to first new or worsening of nephropathy



Treatment with empagliflozin preserved eGFR and eGFR increased during the post treatment 4-week follow up. However, the placebo group showed a gradual decline in GFR during the course of the study with no further change during 4-week follow up (see Figure 6).

Figure 6: eGFR over time*



*eGFR (MDRD) (mL/min/1.73m^2) MMRM results over time, unadjusted last value on treatment and follow-up value - treated set – right side based on patients with available last value on treatment (LVOT) and follow-up (FU).

Thorough QTc study

In a randomised, placebo-controlled, active-comparator, crossover study of 30 healthy subjects, no increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

Heart failure

Empagliflozin in patient with heart failure with 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 ≤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 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%. 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 hospitalization 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 13)

Table 13: 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	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
eGFR (CKD EPI)cr slope, Rate of decline (ml/min/1.73m^2/year)	-2.28	-0.55
Treatment difference vs. placebo (99.9% CI)***		1.73 (0.67, 2.80)
p-value		p< 0.0001

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 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 7: Time to first event of adjudicated cardiovascular death or hospitalization for heart failure

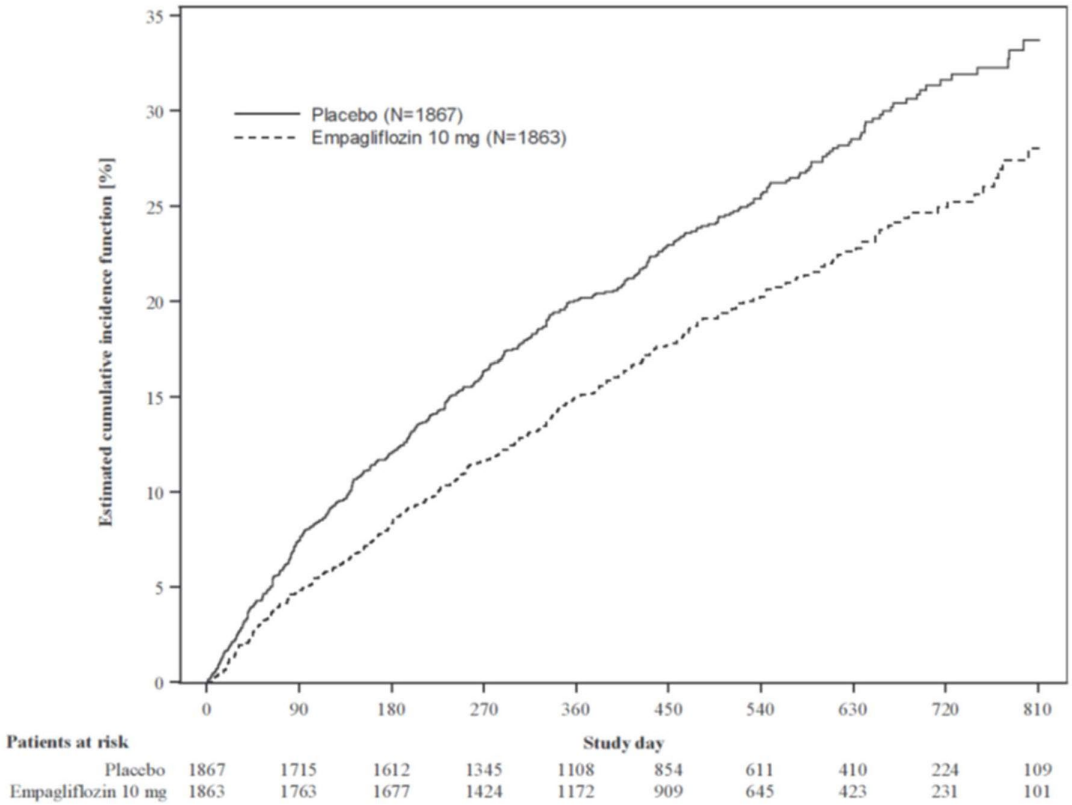
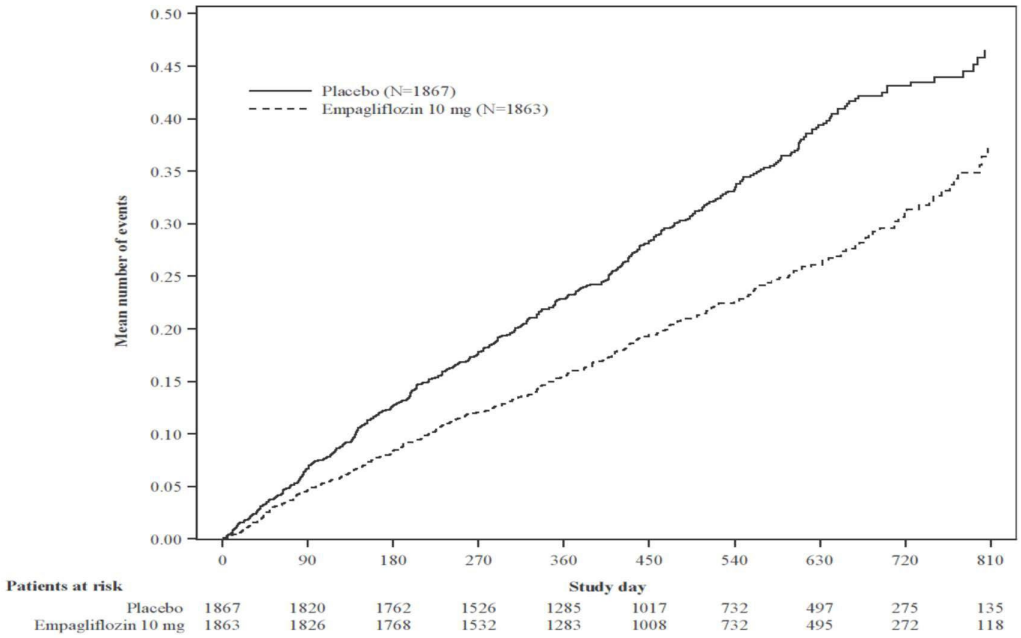
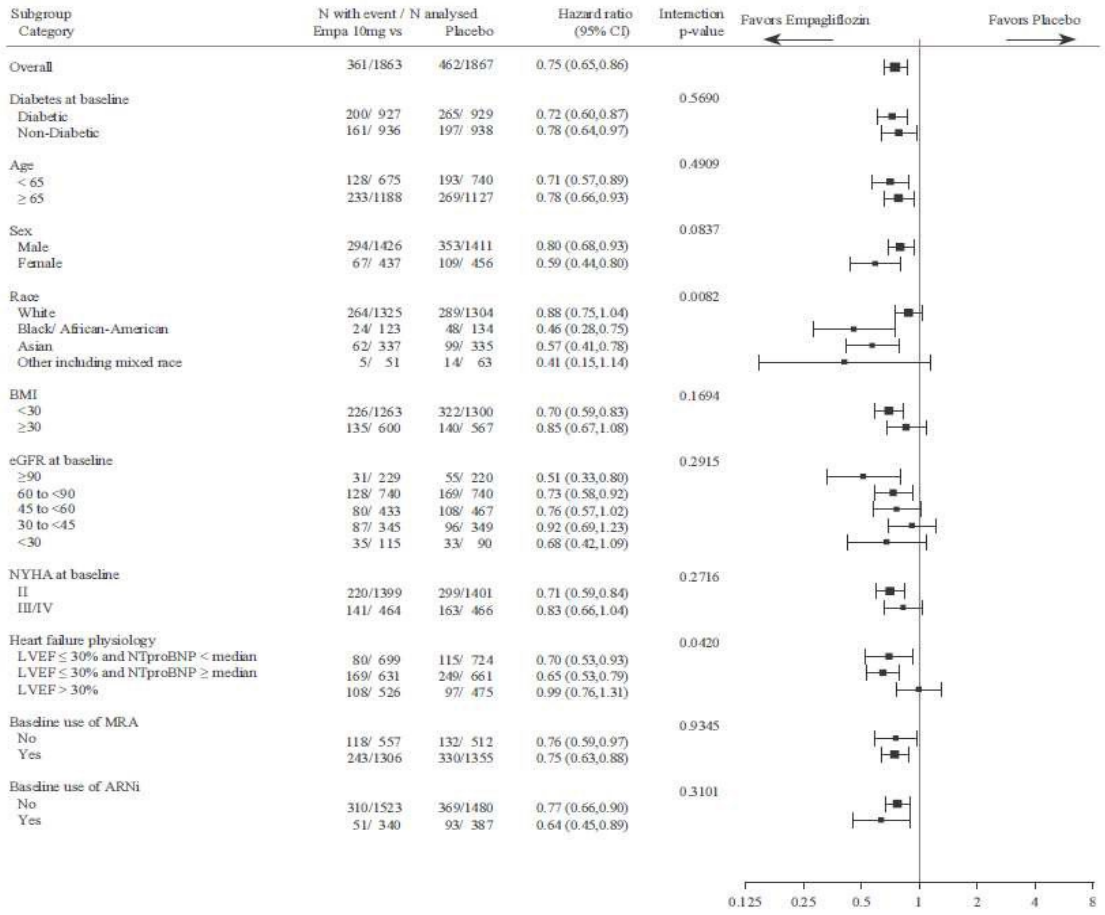


Figure 8: Time to event of adjudicated hospitalization for heart failure



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 9).

Figure 9: Subgroup analyses for the time to the first event of adjudicated of cardiovascular death or hospitalization for heart failure

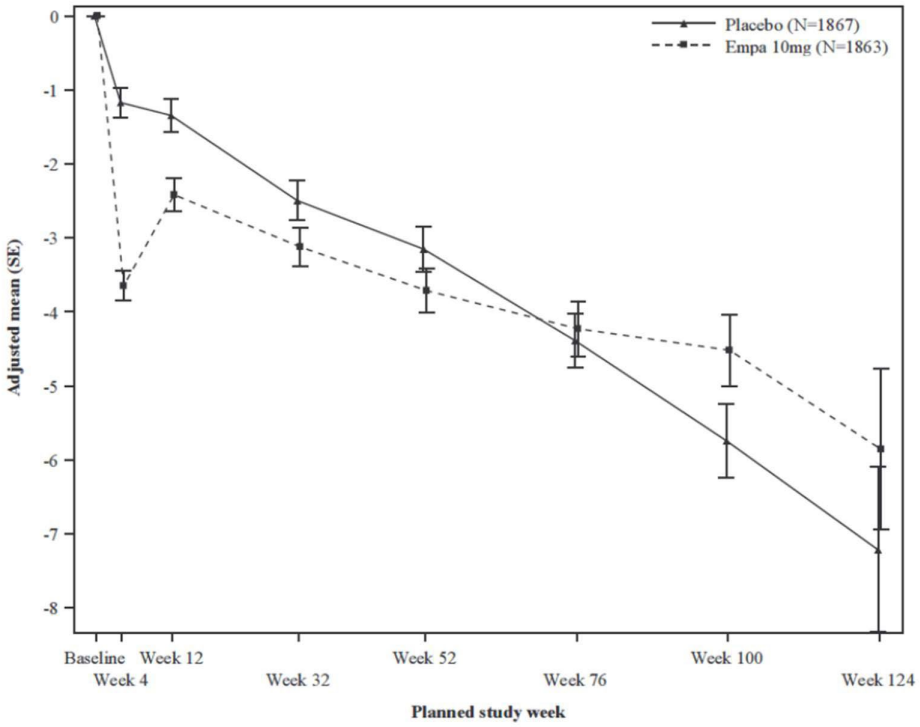


LVEF > 30%: Includes both above and below the median NTproBNP. To be eligible for inclusion, patients with an LVEF > 30% were required to meet a higher NTproBNP threshold than those with LVEF ≤3 0%, unless they additionally had a history of HHF within the past 12 months.

Renal Outcome

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (see Figure 10). Treatment with empagliflozin 10 mg significantly reduced the rate of eGFR decline and the effect was consistent across all pre-specified subgroups (see Table 14). 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 oneGFR.

Figure 10: Change in eGFR over time*



*eGFR (CKD-EPI) (mL/min/1.73m^2) MMRM results over time - randomised 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).

Empagliflozin Tablets 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 14 and Figure 11).

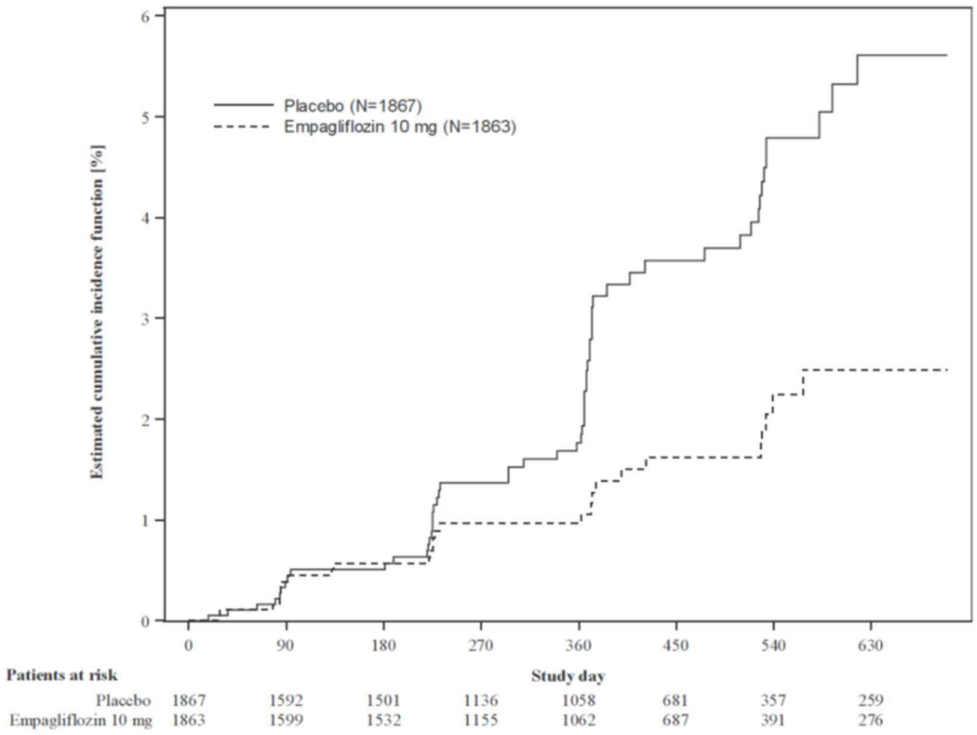
Table 14: Time to first event of composite renal endpoint and its components

	Placebo	Empagliflozin (10 mg)
N	1867	1863
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 < 30mL/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 11: 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 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 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 2997 patients were randomised 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 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 hospitalization 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 15)

Table 15: 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	2991	2997
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/1.73m^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 = 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 95.03% 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 12: Time to first event of adjudicated CV death or HHF

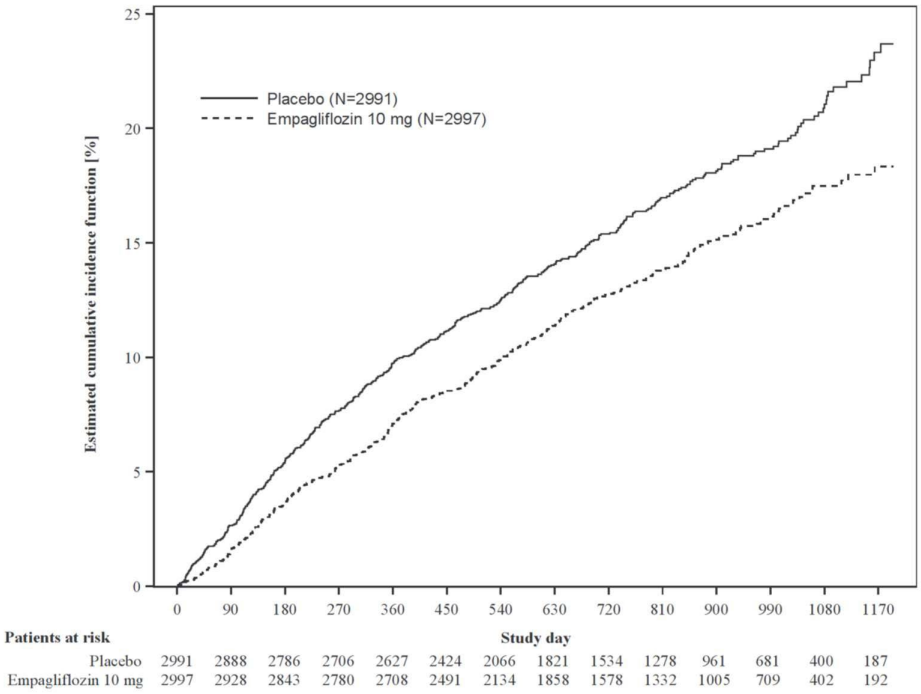
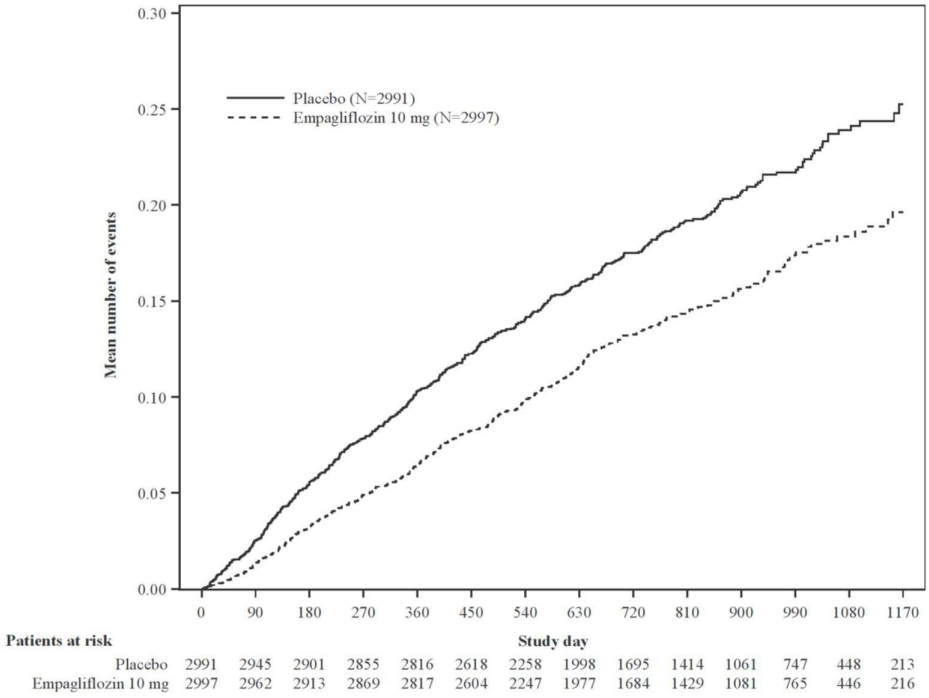
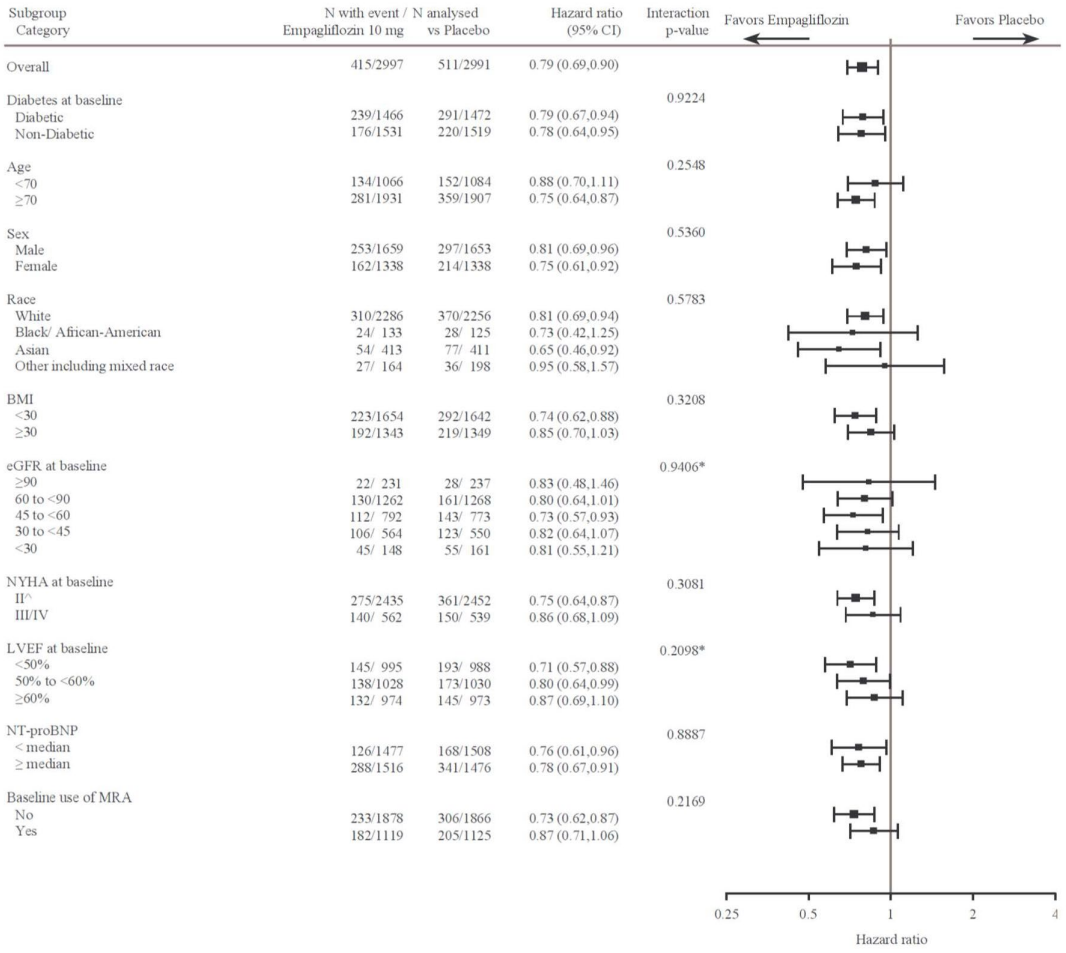


Figure 13: Time to event of adjudicated HHF



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 14).

Figure 14: Subgroup analyses for the time to the first event of adjudicated CV death or HHF

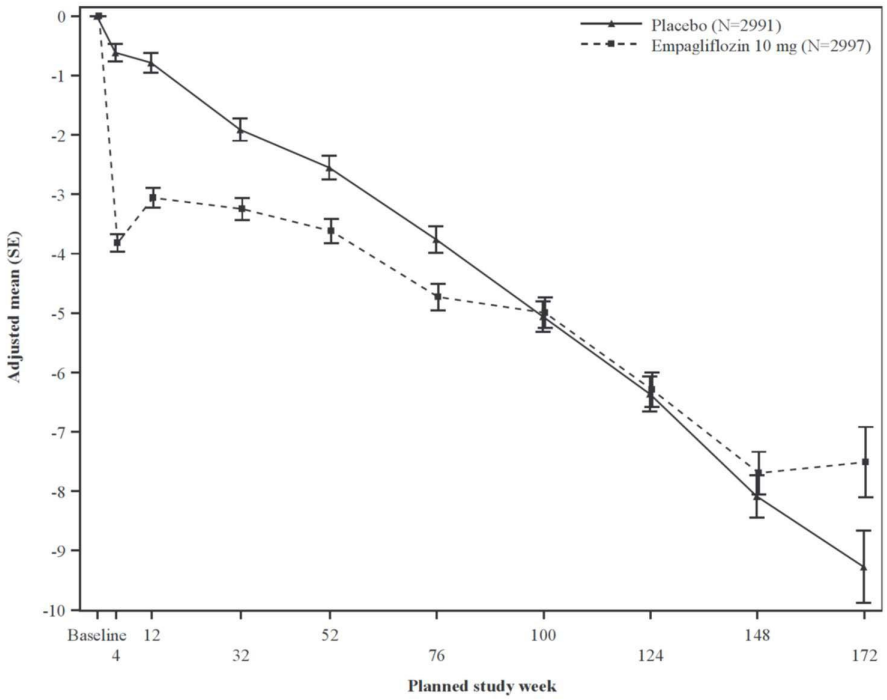


^4 patients with NYHA class I are counted in subgroup NYHA class II
*trend test

Renal Outcome

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (see Figure 15). Treatment with empagliflozin 10 mg significantly reduced the rate of eGFR decline and the effect was consistent across all pre-specified subgroups (see Table 16). 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 oneGFR.

Figure 15: Change in eGFR over time*



*eGFR (CKD-EPI) (mL/min/1.73m^2) MMRM results over time - randomised 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) 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.

Chronic kidney disease

A randomised, double-blind, placebo-controlled study of empagliflozin 10 mg once daily (EMPA-KIDNEY) was conducted in 6609 patients with chronic kidney disease (eGFR ≥20 - <45 ml/min/1.73 m2; or eGFR ≥45 - <90 ml/min/1.73 m2 with urinary albumin to creatinine ratio (UACR) ≥200 mg/g) to assess cardio-renal outcomes as adjunct to standard of care therapy. Once enrolled, patients were not required to discontinue therapy for worsening of eGFR to less than 20 mL/min/1.73 m2 or initiation of 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. First occurrence of hospitalisation for

heart failure or CV death, all-cause hospitalisation (first and recurrent), 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 3304 patients were randomised to empagliflozin 10 mg (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.
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 CKD 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 (see Table 16). Additionally, empagliflozin significantly reduced the risk of all-cause hospitalisation (first and recurrent).

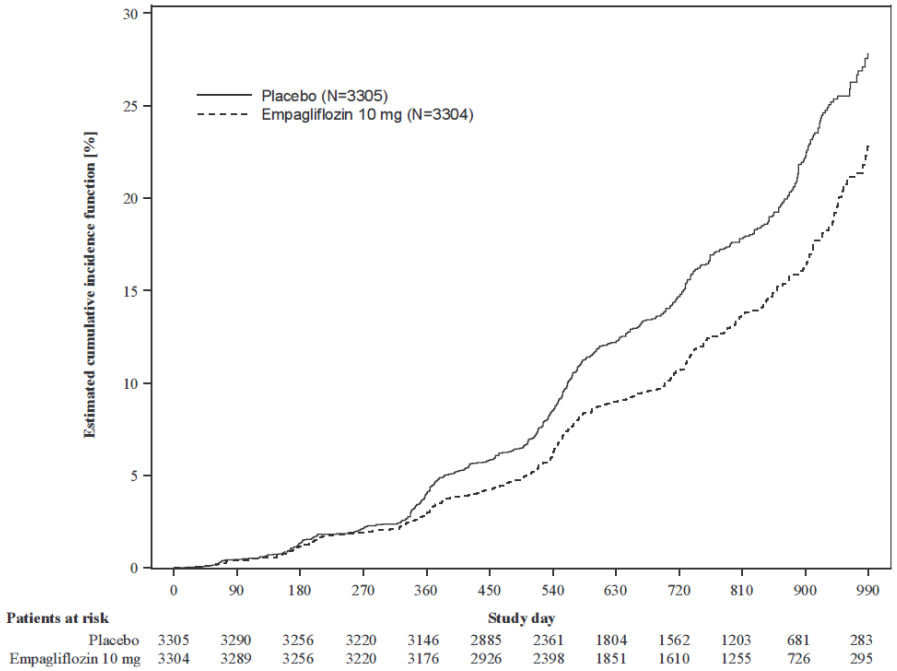
Table 16: Treatment effect for the primary composite and key secondary endpoints included in the prespecified confirmatory testing and its components

	Placebo	**Empagliflozin 10 mg**
N	3305	3304
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* (ESKD), or renal death) or CV death, N (%)	558 (16.9)	432 (13.1)
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
ESKD or CV Death, N (%)#	217 (6.6)	163 (4.9)
Hazard ratio vs. placebo (95% CI)		0.73 (0.59, 0.89)
p-value		0.0023
Occurrence of all-cause hospitalisation (first and recurrent), N of events	1895	1611
Hazard ratio vs. placebo (99.03% CI)		0.86 (0.75, 0.98)
p-value		0.0025

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.
# Predefined as one of the two stopping criteria in the pre-planned interim analysis.

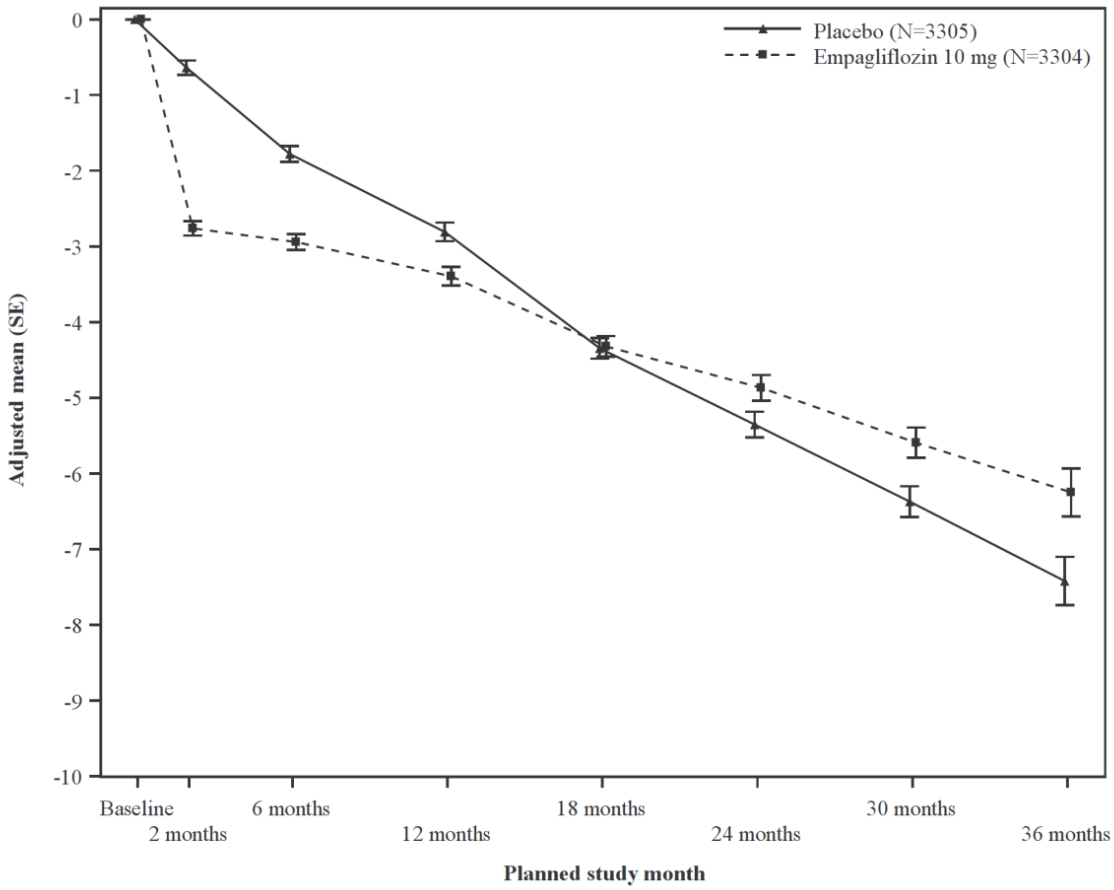
Figure 16: Time to first event of kidney disease progression or adjudicated CV death, estimated cumulative incidence function



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.

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (Figure 17). Empagliflozin slowed the annual rate of eGFR decline compared to placebo by 1.37 ml/min/1.73 m2/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. Patients treated with empagliflozin experienced an initial drop in eGFR which returned towards baseline after treatment discontinuation as demonstrated in several of the empagliflozin studies, supporting that haemodynamic changes play a role in the acute effects of empagliflozin on eGFR.

Figure 17: Change in eGFR over time*



*eGFR (CKD-EPI) (ml/min/1.73 m2) MMRM results over time - randomised set.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with type 2 diabetes. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median tmax of 1.5 hours post-dose. Thereafter, plasma

concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily. Systemic exposure of empagliflozin increased in a dose-proportional manner. The single-dose and steady-state pharmacokinetic 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 type 2 diabetes.
Administration of empagliflozin 25 mg after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} 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 the population pharmacokinetic analysis. Following administration of an oral [^{14}C]-empagliflozin solution to healthy volunteers, the red blood cell partitioning was approximately 37% and plasma protein binding was 86%.

Metabolism
No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-, 3-, 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
Based on the population pharmacokinetic analysis, the apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 hours and apparent oral clearance was 10.6 l/hour. 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 the 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 volunteers, approximately 96% of the drug-related radioactivity was eliminated in faeces (41%) or urine (54%). 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.

Special populations

Renal impairment
In patients with mild (eGFR: 60 - < 90 ml/min/1.73m^2), moderate (eGFR: 30 - < 60 ml/min/1.73m^2) or severe renal impairment (eGFR <30 ml/min/1.73 m^2) and patients with kidney failure/end stage renal disease (ESRD), 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. The population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR leading to an increase in drug exposure. Based on pharmacokinetics, no dosage adjustment is recommended in patients with renal insufficiency (see section 4.2).

Hepatic impairment
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.

Body Mass Index
Body mass index had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the

population pharmacokinetic analysis. In this analysis, AUC was estimated to be 5.82%, 10.4%, and 17.3% lower in subjects with BMI of 30, 35, and 45 kg/m^2, respectively, compared to subjects with a body mass index of 25 kg/m^2.

Gender
Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race
In the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asians with a body mass index of 25 kg/m^2 compared to non-Asians with a body mass index of 25 kg/m^2.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core: Lactose Monohydrate (Pharmatose 200M), Microcrystalline cellulose (Avicel PH 101), Croscarmellose Sodium, Hvdroxypropyl cellulose (Klucel EF), Colloidal Silicon dioxide (Aerosil 200Pharma), Magnesium Stearate

Film coating (Opadry Yellow - 02B620014-CN): Hypromellose 2910, Titanium dioxide, Iron Oxide Black, Macrogol 400, Iron oxide yellow

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store below 30°C

6.5 Nature and contents of container
PVC/Aluminium blisters in cartons containing 10 film-coated tablets. 3 such blisters in a carton with a pack insert.

7. MANUFACTURER
Dr. Reddy's Laboratories Ltd.,
Formulation Tech Ops – II,
Survey No 42p,43,44p,45p,46p,53,54&83,
Bachupally Village, Bachupally Mandal,
Medchal – Malkajgiri District, Pincode 500090, Telangana State, India

8. PRODUCT REGISTRATION HOLDER
Dr. Reddy’s Laboratories Malaysia Sdn. Bhd.
UNIT NO. SO-29-07 AND SO-29-08, MENARA 1, STRATA OFFICE,
NO. 3, JALAN BANGSAR, KL ECO CITY, 59200 KUALA LUMPUR, MALAYSIA

9. DATE OF REVISION OF THE TEXT

Sep 2025