NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Pharmacor Empagliflozin 10 mg film coated tablets

Pharmacor Empagliflozin 25 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pharmacor Empagliflozin (Empagliflozin 10 mg Film-coated Tablets)

Each film coated tablet contains 10 mg empagliflozin.

Pharmacor Empagliflozin (Empagliflozin 25 mg Film-coated Tablets)

Each film coated tablet contains 25 mg empagliflozin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet (tablet).

Pharmacor Empagliflozin (Empagliflozin 10 mg Film-coated Tablets)

Pale yellow, round shaped, biconvex film-coated tablets, debossed with "E10" on one side and plain on other side.

Pharmacor Empagliflozin (Empagliflozin 25 mg Film-coated Tablets)

Pale yellow, oval shaped, biconvex film-coated tablets, debossed with “E25” on one side and plain on other side

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Type 2 diabetes mellitus

Glycaemic control:

Pharmacor Empagliflozin is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults and children aged 10 years and above 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 Further Information section 5.1).

Prevention of cardiovascular events:

Pharmacor Empagliflozin is indicated in adult patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death (see section 5.1).

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

Heart failure

Pharmacor Empagliflozin 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

Pharmacor Empagliflozin is indicated in adults for the treatment of chronic kidney disease.

4.2. Dose and method of administration

Dose

Type 2 diabetes mellitus

The recommended starting dose of Pharmacor Empagliflozin is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily. Pharmacor Empagliflozin can be taken with or without food.

Combination therapy

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

Heart failure

The recommended dose of Pharmacor Empagliflozin is 10 mg once daily (see section 5.1).

Chronic kidney disease

The recommended dose of Pharmacor Empagliflozin is 10 mg once daily (see section 5.1).

Special populations

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 Pharmacor Empagliflozin 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 m2 the recommended dose of empagliflozin is limited to 10 mg and additional glucose lowering treatment should be considered if needed (see Section 4.4 Special warnings and precautions for use).

Hepatic impairment

Empagliflozin exposure is increased in patients with severe hepatic impairment (see Section 5.2). No dose adjustment is recommended for patients with hepatic impairment.

Elderly Patients

No dosage adjustment is recommended based on age.

Paediatric population

Type 2 diabetes mellitus

The recommended starting dose of Pharmacor Empagliflozin is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg once daily (See general information above in Dosage and Administration). No data are available for children with eGFR <60 mL/min/1.73 m² and children below 10 years of age.

Heart failure

Safety and effectiveness of Pharmacor Empagliflozin for the treatment of heart failure in children under 18 years of age have not been established.

Chronic kidney disease

Safety and effectiveness of Pharmacor Empagliflozin for the treatment of CKD in children under 18 years of age have not been established.

Method of administration

Pharmacor Empagliflozin can be taken with or without food.

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 in empagliflozin (see section 6.1).

4.4 Special warnings and precautions for use

General

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

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. 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 should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis generally requires insulin, fluid, potassium and carbohydrate replacement. Ketoacidosis and glucosuria may be prolonged after discontinuation of empagliflozin in some patients, i.e. it may last longer than expected from 5 plasma half-lives of empagliflozin (see Section 5.2 Pharmacokinetic properties).

Restarting SGLT2 inhibitor treatment in patients with previous ketoacidosis while on SGLT2 inhibitor

treatment is not recommended, unless another clear precipitating factor is identified and resolved. Before initiating empagliflozin, consider factors in the patient history that may predispose to ketoacidosis.

Patients who may be at higher risk of ketoacidosis while taking empagliflozin include patients on 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, surgery, malnourished/reduced caloric intake , increased insulin requirements due to infections, and patients with a history of ketoacidosis. empagliflozin 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 consider monitoring for ketoacidosis and temporarily discontinuing empagliflozin in clinical situations known to predispose to ketoacidosis (e.g. prolonged fasting due to acute illness or surgery). In these situations, consider monitoring of ketones, even if empagliflozin treatment has been interrupted. Measurement of blood ketone levels is preferred to urine. An increase in other glucose lowering agents may be required during this time. Patients scheduled for non-urgent surgery who have not ceased empagliflozin should be assessed and consideration should be given to postponing the procedure. Treatment with empagliflozin may be restarted once the patient's condition has stabilised and oral intake is normal.

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 treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalisation, multiple surgeries, and death.

Patients treated with empagliflozin who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotising fasciitis. Be aware that uro-genital infection may precede necrotising fasciitis. If necrotising fasciitis suspected, empagliflozin 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 on dialysis.

Glycaemic efficacy of empagliflozin 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 empagliflozin initiation and periodically during treatment, i.e. at least yearly;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter.

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 BP.

Volume depletion is a known risk factor for renal impairment. Patients with hypovolaemia may be more susceptible to these changes. There have been postmarketing reports of acute kidney injury, some requiring hospitalisation and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including empagliflozin.

Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in BP 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, BP 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.

Complicated urinary tract infections

Cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin (see section 4.8). Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections.

Elderly

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

Urine laboratory assessments

Urine will test positive for glucose while patients are taking empagliflozin due to the nature of the mechanism of action of the SGLT2 inhibitors (see section 5.1).

Lactose

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.

4.5. Interaction with other medicines 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.

Insulin and Insulin Secretagogues

Insulin and insulin secretagogues, such as sulfonylureas, 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.

In vitro assessment of drug interactions

Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin

does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. At therapeutic doses, the potential for empagliflozin to reversibly inhibit or inactivate the major CYP450 and UGT isoforms is remote. Drug-drug interactions involving the major CYP450 and UGT isoforms with empagliflozin and

concomitantly administered substrates of these enzymes are therefore considered unlikely.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein, but it does not inhibit these efflux transporters at therapeutic doses. Based on *in vitro* studies, empagliflozin is considered unlikely to cause interactions with drugs that are P-gp substrates. Empagliflozin is a substrate of the human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin does not inhibit any of these human uptake transporters at clinically relevant plasma concentrations and, as such, drug-drug interactions with substrates of these uptake transporters are considered unlikely.

In vivo assessment of drug interactions

No clinically meaningful pharmacokinetic interactions were observed when empagliflozin was co-administered with other commonly used medicinal products. Based on results of pharmacokinetic studies no dose adjustment of empagliflozin is recommended when co- administered with commonly prescribed 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, and oral contraceptives when co-administered in healthy volunteers.

Paediatric population

Interaction studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

Pregnancy (Category D)

There are limited data from the use of emagliflozin in pregnant women. It is recommended to avoid the use of empagliflozin during pregnancy unless clearly needed.

Empagliflozin administered to female rats from gestation day 6 to lactation day 20 resulted in reduced weight gain in offspring at >30 mg/kg/day (maternal exposures approximately 4- and 11-times those seen with a clinical dose of 25 mg and 10 mg, respectively). No adverse effects on postnatal development were noted at 10 mg/kg/day (maternal exposures approximately equivalent to those seen with a clinical dose of 25 mg).

Specialised studies in rats with other members of the pharmacological class have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 5.3). Similar effects have been seen for empagliflozin at approximately 11 times the clinical AUC exposure associated with the 25 mg dose. These findings were absent after a 13-week drug-free recovery period.

Breast-feeding

No data in humans are available on excretion of empagliflozin into milk. Available nonclinical data in animals have shown excretion of empagliflozin in milk. Reduced body weight was observed in rats exposed to empagliflozin *in utero* and through the consumption of maternal milk (see section 4.6). Adverse effects on renal development have been observed in juvenile rats treated with other members of this pharmacological class. A risk to human newborns/infants cannot be excluded. It is recommended to discontinue breast feeding during treatment with empagliflozin.

Effects on fertility

No studies on the effect on human fertility have been conducted for empagliflozin. Studies in rats at doses up to 700 mg/kg/day, do not indicate direct or indirect harmful effects with respect to fertility. In

female rats this dose was 90- and 155-fold the systemic AUC exposure anticipated with a human dose of 10 and 25 mg.

4.7. Effects on ability to drive and use machines

Empagliflozin has a 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 is used in combination with a sulfonylurea and/or insulin.

4.8. Undesirable effects

a. Summary of the safety profile

Type 2 diabetes mellitus

A total of 15,582 patients with T2DM 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 sulfonylurea, 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 empagliflozin 10 mg/day (n=2345), empagliflozin 25 mg/day (n=2342), or placebo (n=2333) up to 4.5 years. The overall safety profile of empagliflozin in this study was comparable to the previously known safety profile. In these trials, the frequency of adverse effects leading to discontinuation was similar by treatment groups for placebo, empagliflozin 10 mg and empagliflozin 25 mg.

Placebo controlled double-blind trials of 18 to 24 weeks of exposure included 3534 patients, of which 1183 were treated with placebo, 1185 were treated with empagliflozin 10 mg and 1166 were treated with empagliflozin 25 mg. The overall incidence of adverse events in patients treated with empagliflozin was similar to placebo. The most frequent adverse drug reaction was hypoglycaemia, which depended on the type of background therapy used in the respective studies.

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.

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

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

b. 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 and derived from postmarketing experience are presented in Table 1 below. Frequency categories 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), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1 Adverse reactions reported in patients who received empagliflozin in placebo- controlled double-blind studies of 18 to 24 weeks, classified by MedDRA System Organ Class and MedDRA Preferred terms.

		Adult		Paediatric	Adult
System Organ Class	**Adverse Reaction**	**Type 2 diabetes mellitus empagliflozin 10 mg**	**Type 2 diabetes mellitus empagliflozin 25 mg**	**Type 2 diabetes mellitus empagliflozin pooled: 10 mg and 25 mg**	**Heart failure[d] empagliflozin 10 mg**
Infections and infestations	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection[a]	Common	Common	Common	Common
	Urinary tract infectiona (including pyelonephritis and urosepsis)[b]	Common	Common	Common	Common
	Necrotising fasciitis of the perineum (Fournier´s gangrene)[b]	Not known	Not known	Not known	Rare
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulfonylurea or insulin)[a]	Very common	Very common	Very common	Common
	Ketoacidosis[b]	Uncommon	Not known	Not known	Uncommon
Gastrointestinal disorders	Constipation	Common	Uncommon	Not known	Common
Skin and subcutaneous tissue disorders	Pruritus	Common	Common	Not known	Common
	Allergic skin reaction (e.g., rash, urticaria)[b]	Common	Common	Common	Common
	Angioedema[b]	Not known	Not known	Not known	Uncommon
Vascular disorders	Volume depletion[a]	Uncommon	Uncommon	Not known	Very common
Renal and urinary disorders	Increased urination[a]	Common	Common	Common	Uncommon
	Dysuria	Uncommon	Uncommon	Not known	Uncommon
General disorders and administration site conditions	Thirst	Common	Common	Common	Uncommon
Investigations	Glomerular filtration rate decreased[a]	Uncommon	Not known	Not known	Uncommon
	Blood creatinine increased[a]	Uncommon	Uncommon	Not known	Uncommon
	Haematocrit increased[c]	Rare	Uncommon	Not known	Uncommon
	Serum lipids increased[c]	Common	Common	Common	Common

[a] see subsections below for additional information in patients with diabetes mellitus
[b] derived from postmarketing experience
[c] see section 5.1 for additional information
[d] in patients with and without type 2 diabetes mellitus

c. Description of selected adverse reactions

The frequencies below are calculated for adverse reactions regardless of causality.

Hypoglycaemia

The frequency of hypoglycaemia depended on the background therapy in the respective studies and was similar for empagliflozin and placebo as monotherapy, as add-on to metformin, as add-on to pioglitazone +/- metformin, and as add-on to linagliptin + metformin. The frequency of patients with hypoglycaemia was increased in patients treated with empagliflozin compared to placebo when given as add-on to metformin plus sulfonylurea, and as add-on to insulin +/- metformin and +/-

sulfonylurea (see section 4.2; Table 2).

Major hypoglycaemia (events requiring assistance)

The frequency of patients with major hypoglycaemic events was low (<1%) and similar for empagliflozin and placebo as monotherapy, as add-on to metformin +/- sulfonylurea, as add- on to pioglitazone +/- metformin, and as add-on to linagliptin + metformin.

The frequency of patients with major hypoglycaemic events was increased in patients treated with empagliflozin compared to placebo when given as add-on to insulin +/- metformin and +/- sulfonylurea.

Table 2 Frequency of patients with confirmed hypoglycaemic events per trial (1245.19, 1245.20, 1245.23*(met)*, 1245.23*(met+SU)*, 1245.33, 1245.49 and 1275.9*(lina+met)* and 1245.25 –Treated Set[1])

	Placebo	**Empagliflozin**	
		10 mg	**25 mg**
Monotherapy (1245.20) (24 weeks)	**n=229**	**n=224**	**n=223**
Overall confirmed (%)	0.4%	0.4%	0.4%
Major (%)	0%	0%	0%
In Combination with Metformin (1245.23 *(met)*) (24 weeks)	**n=206**	**n=217**	**n=214**
Overall confirmed (%)	0.5%	1.8%	1.4%
Major (%)	0%	0%	0%
In Combination with Metformin + Sulfonylurea (1245.23 *(met + SU)*) (24 weeks)	**n=225**	**n=224**	**n=217**
Overall confirmed (%)	8.4%	16.1%	11.5%
Major (%)	0%	0%	0%
In Combination with Pioglitazone +/- Metformin (1245.19) (24 weeks)	**n=165**	**n=165**	**n=168**
Overall confirmed (%)	1.8%	1.2%	2.4%
Major (%)	0%	0%	0%
In Combination with Basal Insulin (1245.33) (18 weeks[2] / 78 weeks)	**n=170**	**n=169**	**n=155**
Overall confirmed (%)	20.6%/ 35.3%	19.5%/ 36.1%	28.4%/ 36.1%
Major (%)	0%/ 0%	0%/ 0%	1.3%/ 1.3%
In Combination with MDI Insulin +/-Metformin (1245.49) (18 weeks[2] / 52 weeks)	**n=188**	**n=186**	**n=189**
Overall confirmed (%)	37.2%/ 58.0%	39.8%/ 51.1%	41.3%/ 57.7%
Major (%)	0.5%/ 1.6%	0.5%/ 1.6%	0.5%/ 0.5%
In Combination with Metformin and Linagliptin (1275.9) (24 weeks[3])	**n=110**	**n=112**	**n=110**
Overall confirmed (%)	0.9%	0.0%	2.7%
Major (%)	0%	0%	0.9%
EMPA-REG OUTCOME (1245.25)	**n=2333**	**n=2345**	**n=2342**
Overall confirmed (%)	27.9%	28%	27.6%
Major (%)	1.5%	1.4%	1.3%

Confirmed: blood glucose ≤3.9 mmol/L or required assistance
Major: required assistance
1. i.e. patients who had received at least one dose of study drug
2 The dose of insulin as background medication was to be stable for the first 18 weeks
3 This was a fixed-dose combination of empagliflozin with linagliptin 5 mg with a background treatment with metformin (see section 5.1).
MDI = multiple daily injections

Urinary tract infection

The overall frequency of urinary tract infection was similar in patients treated with empagliflozin 25 mg and placebo (7.0% and 7.2%) and higher in patients treated with empagliflozin10 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 of urinary tract infections was similar to placebo for mild, moderate, and severe intensity reports. Urinary tract infection events were reported more frequently for empagliflozin compared to placebo in female patients, but not in male patients.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for empagliflozin 10 mg (4.0%) and empagliflozin 25 mg (3.9%) compared to placebo (1.0%) and were reported more frequently for empagliflozin compared to placebo in female patients, and the difference in frequency was less pronounced in male patients. The genital tract infections were mild and moderate in intensity, none was severe in intensity.

Cases of phimosis/ acquired phimosis have been reported concurrent with genital infections.

Increased urination

As expected via its mechanism of action, increased urination (as assessed by preferred term search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with empagliflozin 10 mg (3.5%) and 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 comparable between placebo and empagliflozin (<1%).

Volume depletion

The overall frequency of volume depletion (including the predefined terms BP (ambulatory) decreased, SBP decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension and syncope) was similar to placebo (empagliflozin 10 mg 0.6%, empagliflozin 25 mg 0.4% and placebo 0.3%). 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. In patients ≥ 75 years of age (pooling of all patients with diabetes, n=13, 402) the frequency of volume depletion events was similar for empagliflozin 10 mg (2.3%) compared to placebo (2.1%), but it increased with empagliflozin 25 mg (4.3%).

Blood creatinine increased and glomerular filtration rate decreased

Use of empagliflozin was associated with initial transient increases in serum creatinine and initial transient decreases in eGFR. These changes were observed to reverse after treatment discontinuation, suggesting acute haemodynamic changes play a role in the renal function abnormalities observed with empagliflozin. Renal-related adverse reactions (e.g. acute kidney injury, renal impairment, acute prerenal failure) may occur in patients treated with empagliflozin.

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 0.0011 mmol/L, empagliflozin 25 mg 0.0006 mmol/L) 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 5.1, Figure 6 for the eGFR course in the EMPA-REG OUTCOME study).

Paediatric population

In the DINAMO trial 157 children aged 10 years and above with type 2 diabetes were treated, in which 52 patients received empagliflozin, 52 linagliptin and 53 placebo (see Section 5.1 Pharmacodynamic Properties - Clinical trials). During the placebo-controlled phase, the most frequent adverse drug reaction was hypoglycaemia (empagliflozin 10 mg and 25 mg, pooled: 23.1%, placebo: 9.4%). None of these events was severe or required assistance. Overall, the safety profile in children was similar to the safety profile in adults with T2DM.

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 professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

During controlled clinical trials in healthy subjects, single doses of up to 800 mg empagliflozin, , were well tolerated.

Treatment

In the event of an overdose, supportive 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. Pharmacodynamic properties

Pharmacotherapeutic group: SGLT2 Inhibitor, ATC code: A10BK03.

Mechanism of action

Empagliflozin is a reversible competitive inhibitor of SGLT2 with an IC_{50} of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC_{50} of 6278 nM), 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 re-absorption 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 re-absorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and glomerular filtration rate (GFR). Through inhibition of SGLT2 in patients with T2DM and hyperglycaemia, excess glucose is excreted in the urine.

In patients with T2DM, 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 4-week treatment period, averaging approximately 78 g/day with empagliflozin 25 mg once daily. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with T2DM.

Empagliflozin (10 mg and 25 mg) 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) and proinsulin to insulin ratio were 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 (BP).

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 remodeling, 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 efficacy and safety

Type 2 diabetes mellitus

A total of 17331 patients with T2DM were evaluated 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, sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitors, and insulin lead to clinically relevant improvements in glycated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG), body weight, systolic BP (SBP) and diastolic BP (DBP). Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving an HbA_{1c} 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 HbA_{1c} in all subgroups of gender, race, geographic region, time since diagnosis of T2DM, BMI, insulin resistance based on HOMA-IR, and beta cell function based on HOMA-β. Higher baseline HbA_{1c} was associated with a greater reduction in HbA_{1c}. Clinically meaningful HbA_{1c} reduction was seen in patients with eGFR > 30 mL/min/1.73 m² (see Dosage and Administration, Patients with Renal impairment). In patients aged 75 years and older, reduced efficacy of empagliflozin was observed.

Empagliflozin as monotherapy

The efficacy and safety of empagliflozin (10 mg and 25 mg) as monotherapy was evaluated in a double-blind, placebo- and active-controlled study of 24 weeks duration in treatment-naïve patients. The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and blood pressure (SBP and DBP) after 24 weeks of treatment.

Treatment with empagliflozin resulted in statistically significant reductions in HbA_{1c}, body weight and SBP compared to placebo (Table 3) and a clinically meaningful decrease in FPG. A numerical decrease in DBP was seen but did not reach statistical significance versus placebo (-1.0 mmHg for empagliflozin 10 mg, -1.9 mmHg for empagliflozin 25 mg, -0.5 mmHg for placebo, and +0.7 mmHg for sitagliptin).

In a prespecified analysis of patients (n=201) with a baseline HbA_{1c} ≥ 8.5% to ≤ 10% empagliflozin resulted in a reduction in HbA_{1c} from baseline of -1.44% for empagliflozin 10 mg, -1.43% for empagliflozin 25 mg, +0.01% for placebo, and -1.04% for sitagliptin.

In the double-blind placebo-controlled extension of this study, reductions of HbA_{1c} (change from baseline of -0.65% for empagliflozin 10 mg, -0.76% for empagliflozin 25 mg, +0.13% for placebo, and -0.53% for sitagliptin), body weight (change from baseline of -2.24 kg for empagliflozin 10 mg, -2.45 kg for empagliflozin 25 mg, -0.43 kg for placebo, and +0.10 kg for sitagliptin) and BP (SBP: change from baseline of -4.1 mmHg for empagliflozin 10 mg, -4.2 mmHg for empagliflozin 25 mg, -0.7 mmHg for placebo, and -0.3 mmHg for sitagliptin, DBP: change from baseline of -1.6 mmHg for empagliflozin 10 mg, -1.6 mmHg for empagliflozin 25 mg, +0.6 mmHg for placebo, and -0.1 mmHg for sitagliptin) were sustained up to 76 weeks of treatment.

Treatment with empagliflozin daily significantly improved marker of beta cell function HOMA-β.

Table 3 Results of a 24week (LOCF)[1] placebo-controlled study of empagliflozin as monotherapy (Full Analysis Set)

Empagliflozin as monotherapy	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Sitagliptin 100mg
N	228	224	224	223
HbA_{1c} (%)				
Baseline (mean)	7.91	7.87	7.86	7.85
Change from baseline[2]	0.08	-0.66	-0.78	-0.66
Difference from placebo[2]		-0.74*	-0.85*	-0.73
(97.5% CI)		(-0.90, -0.57)	(-1.01, -0.69)	(-0.88, -0.59)[3]
N	208	204	202	200
Patients (%) achieving HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7%[4]	12.0	35.3	43.6	37.5
N	226	223	233	223
Fasting plasma glucose (mmol/L)[4]				
Baseline (mean)	8.59	8.48	8.47	8.17
Change from baseline[2]	0.65	-1.08	-1.36	-0.38
Difference from placebo[2]		-1.73*	-2.01*	-1.04*
(95% CI)		(-2.03, -1.43)	(-2.31, -1.71)	(-1.34, -0.73)
N	228	224	224	223
Body weight (kg)				
Baseline (mean)	78.23	78.35	77.80	79.31
Change from baseline[2]	-0.33	-2.26	-2.48	0.18
Difference from placebo[2]		-1.93*	-2.15*	0.52
(97.5% CI)		(-2.48, -1.38)	(-2.70,-1.60)	(-0.04, 1.00)[4]
N	228	224	224	223
Patients(%) achieving weight loss of >5%[5]	4.4	22.8	29.0	6.3
N	228	224	224	223
Systolic blood pressure (mmHg)[2]				
Baseline (mean)	130.4	133.0	129.9	132.5
Change from baseline[2]	-0.3	-2.9	-3.7	0.5
Difference from placebo[2]		-2.6*	-3.4*	0.8
(97.5% CI)		(-5.2, 0.0)	(-6.0, -0.9)	(-1.4, 3.1)[4]

1. Last observation (prior to glycaemic rescue) carried forward (LOCF)
2. Mean adjusted for baseline value and stratification
3. Last observation (prior to glycaemic rescue or antihypertensive rescue) carried forward (LOCF)
4. 95% CI
5. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints

* p value <0.0001

Empagliflozin as add on to metformin therapy

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients with T2DM not controlled on metformin. The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean daily plasma glucose (MDG) after 24 weeks of treatment.

Treatment with empagliflozin resulted in statistically significant improvements in HbA_{1c} and body weight, and clinically meaningful reductions in FPG and BP compared to placebo (Table 4).

In the double-blind placebo-controlled extension of this study, reductions of HbA_{1c} (change from baseline of -0.62% for empagliflozin 10 mg, -0.74% for empagliflozin 25 mg and -0.01% for placebo), body weight (change from baseline of -2.39 kg for empagliflozin 10 mg, -2.65 kg for empagliflozin 25 mg and -0.46 kg for placebo) and BP (SBP: change from baseline of -5.2 mmHg for

empagliflozin 10 mg, -4.5 mmHg for empagliflozin 25 mg and -0.8 mmHg for placebo, DBP: change from baseline of -2.5 mmHg for empagliflozin 10 mg, -1.9 mmHg for empagliflozin 25 mg and -0.5 mmHg for placebo) were sustained up to 76 weeks of treatment.

Table 4 Results of a 24 week (LOCF)[3] placebo-controlled study of empagliflozin as add-on to metformin (Full Analysis Set)

Empagliflozin as add-on to metformin therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	207	217	213
HbA_{1c} (%)			
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 HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7%[2]	12.5	37.7	38.7
N	207	216	213
Fasting plasma glucose (mmol/L)[2]			
Baseline (mean)	8.66	8.58	8.29
Change from baseline[1]	0.35	-1.11	-1.24
Difference from placebo[1] (95% CI)		-1.47* (-1.74, -1.20)	-1.59* (-1.86, -1.32)
N	207	217	213
Body weight (kg)			
Baseline (mean)	79.73	81.59	82.21
Change from baseline[1]	-0.45	-2.08	-2.46
Difference from placebo[1] (97.5% CI)		-1.63* (-2.17, -1.08)	-2.01* (-2.56, -1.46)
N	207	217	213
Patients (%) achieving weight loss of >5%[2]	4.8	21.2	23.0
N	207	217	213
Systolic blood pressure (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)

1. Mean adjusted for baseline value and stratification
2. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
3. Last observation (prior to glycaemic rescue) carried forward (LOCF)
* p-value <0.0001

Empagliflozin and metformin combination therapy 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 (5 mg and 500 mg; 5 mg and 1000 mg; 12.5 mg and 500 mg, and 12.5 mg and 1000 mg given twice daily) provided statistically significant improvements in HbA_{1c} and led to significantly greater reductions in FPG and body weight compared to the individual components. A greater proportion of patients with a baseline HbA_{1c} ≥ 7.0% and treated with empagliflozin in combination with metformin achieved a target HbA_{1c} < 7% compared to the individual components (Tables 5 and 6).

Table 5 Results of a 24 week (OC)[2] study comparing empagliflozin 10 mg in combination with metformin to the individual components

	Empagliflozin 10 mg + metformin 1000 mg[a]	**Empagliflozin 10 mg + metformin 2000 mg[a]**	**Empagliflozin 10 mg (qd)**	**Metformin 1000 mg[a]**	**Metformin 2000 mg[a]**
N	161	167	169	167	162
HbA_{1c} (%)					
Baseline (mean)	8.7	8.7	8.6	8.7	8.6
Change from baseline[1]	-2.0	-2.1	-1.4	-1.2	-1.8
Comparison vs. empagliflozin (95% CI)[1]	-0.6* (-0.9, -0.4)[b]	-0.7* (-1.0, -0.5)[b]			
Comparison vs. metformin (95% CI)[1]	-0.8* (-1.0, -0.6)[b]	-0.3* (-0.6, -0.1)[b]			
N	153	161	159	166	159
Patients (%) achieving HbA_{1c} <7% with baseline HbA_{1c} ≥7%	96 (63%)	112 (70%)	69 (43%)	63 (38%)	92 (58%)
N	161	166	168	165	164
FPG (mmol/L)					
Baseline (mean)	9.2	9.1	9.4	9.6	9.4
Change from baseline[1]	-2.5	-2.7	-1.8	-1.0	-1.8
Comparison vs. empagliflozin (95% CI)[1]	-0.7** (-1.1, -0.3)[b]	-0.8** (-1.2, -0.5)[b]			
Comparison vs. metformin (95% CI)[1]	-1.6** (-1.9, -1.2)[b]	-0.9** (-1.2, -0.5)[b]			
N	161	165	168	166	162
Body Weight (kg)					
Baseline (mean)	82.3	83.0	83.9	82.9	83.8
% Change from baseline[1]	-3.1	-4.1	-2.7	-0.4	-1.2
Comparison vs. metformin (95% CI)[1]	-2.7** (-3.6, -1.8)[b]	-2.8** (-3.8, -1.9)[b]			

a Given in two equally divided doses per day

b. Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA_{1c}; FPG included baseline FPG in addition; weight included baseline weight in addition.

1. Mean adjusted for baseline value

2. Analyses were performed on the full analysis set (FAS) using an observed cases (OC) approach

* p≤0.0062 for HbA_{1c};

** Analysis in an exploratory manner: p≤0.0002 for FPG and p<0.0001 for body weight

Table 6 Results of a 24 week (OC)[2] study comparing empagliflozin 25 mg in combination with metformin to the individual monotherapy components

	Empagliflozin 25 mg + metformin 1000 mg[a]	**Empagliflozin 25 mg + metformin 2000 mg[a]**	**Empagliflozin 25 mg qd**	**Metformin 1000 mg[a]**	**Metformin 2000 mg[a]**
N	165	169	163	167	162
HbA_{1c} (%)					
Baseline (mean)	8.8	8.7	8.9	8.7	8.6
Change from baseline[1]	-1.9	-2.1	-1.4	-1.2	-1.8
Comparison vs. empagliflozin (95% CI)[1]	-0.6* (-0.8, -0.3)[b]	-0.7* (-1.0, -0.5)[b]			
Comparison vs. metformin (95% CI)[1]	-0.8* (-1.0, -0.5)[b]	-0.3* (-0.6, -0.1)[b]			
N	159	163	158	166	159
Patients (%) achieving HbA_{1c} <7% with baseline HbA_{1c} ≥7%	91 (57%)	111 (68%)	51 (32%)	63 (38%)	92 (58%)
N	163	167	163	165	164
FPG (mmol/L)					
Baseline (mean)	9.5	9.3	9.8	9.6	9.4
Change from baseline[1]	-2.4	-2.8	-1.6	-1.0	-1.8
Comparison vs. empagliflozin (95% CI)[1]	-0.9** (-1.3, -0.5)[b]	-1.3** (-1.6, -0.9)[b]			
Comparison vs. metformin (95% CI)[1]	-1.5** (-1.9, -1.1)[b]	-1.0** (-1.4, -0.7)[b]			
N	165	167	162	166	162
Body Weight (kg)					
Baseline (mean)	82.9	83.7	83.4	82.9	83.8

% Change from baseline[1]	-3.6	-4.3	-2.8	-0.4	-1.2
Comparison vs. metformin (95% CI)[1]	-3.1** (-4.1, -2.2)[b]	-3.1** (-4.1, -2.2)[b]			

a. Given in two equally divided doses per day
b. Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA_{1c}; FPG included baseline FPG in addition; weight included baseline weight in addition.
1. Mean adjusted for baseline value
2. Analyses were performed on the full analysis set (FAS) using an observed cases (OC) approach
* $p \leq 0.0056$ for HbA_{1c}
** Analysis in an exploratory manner: $p<0.0001$ for FPG and $p<0.0001$ for body weight

Empagliflozin as add on to a combination of metformin and sulfonylurea therapy

A double-blind, placebo-controlled study of 24 weeks duration was conducted to evaluate the efficacy and safety of empagliflozin in patients not sufficiently treated with a combination of metformin and a sulfonylurea. The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean daily plasma glucose (MDG) after 24 weeks of treatment.

Treatment with empagliflozin resulted in statistically significant improvements in HbA_{1c} and body weight and clinically meaningful reductions in FPG and BP compared to placebo (Table 7).

In the double-blind placebo-controlled extension of this study, reductions of HbA_{1c} (change from baseline of -0.74% for empagliflozin 10 mg, -0.72% for empagliflozin 25 mg and -0.03% for placebo), body weight (change from baseline of -2.44 kg for empagliflozin 10 mg, -2.28 kg for empagliflozin and -0.63 kg for placebo) and BP (SBP: change from baseline of -3.8 mmHg for empagliflozin 10 mg, -3.7 mmHg for empagliflozin 25 mg and -1.6 mmHg for placebo, DBP: change from baseline of -2.6 mmHg for empagliflozin 10 mg, -2.3 mmHg for empagliflozin 25 mg and -1.4 mmHg for placebo) were sustained up to 76 weeks of treatment.

Table 7 Results of a 24 week (LOCF)[3] placebo-controlled study of empagliflozin as add-on to metformin and a sulfonylurea (Full Analysis Set)

empagliflozin as add-on to metformin and a sulfonylurea therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	225	225	216
HbA_{1c} (%)			
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 HbA_{1c} < 7% with baseline HbA_{1c} ≥ 7%[2]	9.3	26.3	32.2
N	224	225	215
Fasting plasma glucose (mmol/L)			
Baseline (mean)	8.42	8.38	8.68
Change from baseline[1]	0.31	-1.29	-1.29
Difference from placebo[1] (95% CI)		-1.60* (-1.90, -1.30)	-1.60* (-1.90, -1.29)
N	225	225	216
Body weight (kg)			
Baseline (mean)	76.23	77.08	77.50
Change from baseline[1]	-0.39	-2.16	-2.39
Difference from placebo[1] (97.5% CI)		-1.76* (-2.25, -1.28)	-1.99* (-2.48, -1.50)
N	225	225	216
Patients (%) achieving weight loss of >5%[2]	5.8	27.6	23.6
N	225	225	216
Systolic blood pressure (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)

1. Mean adjusted for baseline value and stratification
2. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
3. Last observation (prior to glycaemic rescue) carried forward (LOCF)
* p-value <0.0001

2 hour post-prandial glucose

Treatment with empagliflozin (10 mg or 25 mg) as add-on to metformin or metformin plus sulfonylurea resulted in clinically meaningful improvement of 2-hour post-prandial glucose (meal tolerance test) at 24 weeks (add-on to metformin: -2.55 mmol/L for empagliflozin 10 mg (n=52), -2.47 mmol/L for empagliflozin 25 mg (n=58) and +0.33 mmol/L for placebo (n=57); add-on to metformin plus sulfonylurea: -1.98 mmol/L for empagliflozin 10 mg (n=44), -2.03 mmol/L for empagliflozin 25 mg (n=46) and -0.13 mmol/L for placebo (n=35)).

Empagliflozin as add on to a combination of pioglitazone therapy (+/- metformin)

The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo-controlled study of 24 weeks duration in patients with T2DM not controlled on a combination of metformin and pioglitazone or pioglitazone alone. The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. The key secondary endpoints were the change from baseline in FPG and body weight after 24 weeks of treatment.

Empagliflozin in combination with pioglitazone (dose ≥ 30 mg) with or without metformin resulted in statistically significant reductions in HbA_{1c}, FPG, and body weight and clinically meaningful reductions in BP compared to placebo (Table 8).

In the double-blind placebo-controlled extension of this study, reductions of HbA_{1c} (change from baseline of -0.61% for empagliflozin 10 mg, -0.70% for empagliflozin 25 mg and -0.01% for placebo), body weight (change from baseline of -1.47 kg for empagliflozin 10 mg, -1.21 kg for empagliflozin 25 mg and +0.50 kg for placebo) and BP (SBP: change from baseline of -1.71 mmHg for empagliflozin 10 mg, -3.4 mmHg for empagliflozin 25 mg and +0.3 mmHg for placebo, DBP: change from baseline of -1.3 mmHg for empagliflozin 10 mg, -2.0 mmHg for empagliflozin 25 mg and +0.2 mmHg for placebo) were sustained up to 76 weeks of treatment.

Table 8 Results of a 24 week (LOCF)[3] placebo-controlled study of empagliflozin as add-on to pioglitazone with or without metformin (Full Analysis Set)

Pioglitazone +/- metformin add-on therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	165	165	168
HbA_{1c} (%)			
Baseline (mean)	8.16	8.07	8.06
Change from baseline[1]	-0.11	-0.59	-0.72
Difference from placebo1 (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 HbA_{1c} ≥7%[3]	7.7	23.8	30.0
N	165	163	168
Fasting plasma glucose (mmol/L)			
Baseline (mean)	8.43	8.44	8.43
Change from baseline[1]	0.37	-0.94	-1.23
Difference from placebo1 (97.5% CI)		-1.32* (-1.72, -0.91)	-1.61* (-2.04, -1.12)
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 placebo1 (97.5% CI)		-1.95* (-2.64, -1.27)	-1.81* (-2.49, -1.13)
N	165	165	168
Patients(%) achieving weight loss of >5%[3]	5.5	18.8	13.7
N	165	165	168

Systolic blood pressure (mmHg)[2]			
Baseline (mean)	125.7	126.5	125.9
Change from baseline[1]	0.7	-3.1	-4.0
Difference from placebo[1] (95% CI)		-3.9 (-6.2, -1.5)	-4.7 (-7.1, -2.4)

1. Mean adjusted for baseline value and stratification
2. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
3. Last observation (prior to glycaemic rescue) carried forward (LOCF)
   * p-value <0.0001

Empagliflozin and linagliptin in treatment naïve patients

After 24-weeks treatment, empagliflozin 25 mg/linagliptin 5 mg in treatment naïve patients provided statistically significant improvement in HbA1c compared to linagliptin 5 mg but there was no statistically significant difference between the FDC empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 25 mg (Table 9). Compared to linagliptin 5 mg both doses of the empagliflozin/linagliptin FDC provided statistically relevant improvements in body weight. After 24 weeks' treatment with empagliflozin/linagliptin, both SBP and DBPs were reduced, -2.9/-1.1 mmHg (n.s. versus linagliptin 5 mg for SBP and DBP) for empagliflozin 25 mg/linagliptin 5 mg and -3.6/-0.7 mmHg (p<0.05 versus linagliptin 5 mg for SBP, n.s. for DBP) for empagliflozin 10 mg/linagliptin 5 mg. Rescue therapy was used in 2 (1.5%) patients treated with empagliflozin 25 mg/linagliptin 5 mg and in 1 (0.7%) patient treated with empagliflozin 10 mg /linagliptin 5 mg compared to 11 (8.3%) patients treated with linagliptin 5 mg, 1 (0.8%) patients treated with empagliflozin 25 mg and 4 (3.0%) patients treated with empagliflozin 10 mg. Clinically meaningful reductions in HbA1c (Table 9) and SBPs were observed at week 52, -2.0 mmHg (n.s. versus linagliptin 5 mg) for empagliflozin 25 mg/linagliptin 5 mg and -1.7 mmHg (n.s. versus linagliptin 5 mg) for empagliflozin 10 mg/linagliptin 5 mg.

Table 9 Results of a 24 and 52-week (LOCF)1 randomised, double-blind controlled study of empagliflozin and linagliptin as a fixed-dose combination in treatment naïve patients

	Empagliflozin/linagliptin		**Empagliflozin**		**Linagliptin**
	25mg / 5mg	**10mg / 5mg**	**25mg**	**10mg**	**5mg**
Primary endpoint: HbA1c [%] - 24 weeks					
Number of patients analysed	134	135	133	132	133
Baseline mean (SE)	7.99 (0.08)	8.04 (0.08)	7.99 (0.08)	8.05 (0.09)	8.05 (0.08)
Adjusted mean (SE) change from baseline at Week 24[1,2]	−1.08 (0.07)	−1.24 (0.07)	−0.95 (0.07)	−0.83 (0.07)	−0.67 (0.07)
Comparison vs. empagliflozin[1]	vs. empa 25 mg	vs. empa 10 mg	-	-	-
Adjusted mean (SE)[2]	−0.14 (0.10)	−0.41 (0.10)	-	-	-
95.0% CI	−0.33, 0.06	−0.61, −0.21	-	-	-
p-value	0.1785	not assessed	-	-	-
Comparison vs. linagliptin 5 mg[1]					
Adjusted mean (SE) [2]	−0.41 (0.10)	−0.57 (0.10)	-	-	-
95.0% CI	−0.61, −0.22	−0.76, −0.37	-	-	-
p-value	<0.0001	not assessed	-	-	-
HbA1c [%] – 52 weeks[4]					
Baseline mean (SE)	7.99 (0.08)	8.04 (0.08)	7.99 (0.08)	8.05 (0.09)	8.05 (0.08)
Adjusted mean (SE) change from baseline at Week 52[1]	-1.17 (0.08)	-1.22 (0.08)	-1.01 (0.08)	-0.85 (0.08)	-0.51 (0.08)
Comparison vs. empagliflozin[1]	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE)	−0.16 (0.12)	−0.37 (0.12)			
95.0% CI	−0.39, 0.07	−0.60, −0.14			
Comparison vs. linagliptin 5 mg[1]					
Adjusted mean (SE)	−0.66 (0.12)	−0.71 (0.12)			
95.0% CI	−0.90, −0.43	−0.94, −0.48			
Key secondary endpoint:					

[mmol/L] - 24 weeks					
Number of patients analysed	134	135	133	132	133
Baseline mean (SE)	8.66 (0.17)	8.27 (0.17)	8.48 (0.19)	8.89 (0.20)	8.66 (0.18)
Adjusted mean (SE) change from baseline at Week 24[1,2]	−1.64 (0.15)	−1.57 (0.15)	−1.35 (0.15)	−1.24 (0.15)	−0.33 (0.15)
Comparison vs. empagliflozin[1]	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE) [2]	−0.29 (0.21)	−0.32 (0.21)			
95.0% CI	−0.71, 0.12	−0.74, 0.09			
p-value	not assessed	not assessed			
Comparison vs. linagliptin 5 mg[1]					
Adjusted mean (SE) [2]	−1.31 (0.21)	−1.24 (0.21)			
95.0% CI	−1.72, −0.90	−1.65, −0.83			
p-value	not assessed	not assessed			
Key secondary endpoint: body weight [kg] - 24 weeks					
Number of patients analysed	134	135	133	132	133
Baseline mean (SE)	87.92 (1.57)	87.30 (1.59)	86.73 (1.71)	87.82 (2.08)	89.51 (1.74)
Adjusted mean (SE) change from baseline at Week 24[1,2]	−2.00 (0.36)	−2.74 (0.36)	−2.13 (0.36)	−2.27 (0.37)	−0.78 (0.36)
Comparison vs. linagliptin 5 mg[1]					
Adjusted mean (SE) [2]	−1.22 (0.51)	−1.96 (0.51)	-	-	-
95.0% CI	−2.23, −0.21	−2.97, −0.95	-	-	-
p-value	not assessed	not assessed	-	-	-
Key secondary endpoint: patients with HbA_{1c} <7.0% - 24 weeks					
Number of patients, N (%)	121 (100.0)	122 (100.0)	118 (100.0)	121 (100.0)	127 (100.0)
With HbA_{1c} <7.0% at Week 24	67 (55.4)	76 (62.3)	49 (41.5)	47 (38.8)	41 (32.3)
Comparison vs. Empagliflozin[5]	vs. empa 25 mg	vs. empa 10 mg			
Odds ratio	1.893	2.961	-	-	-
95.0% CI	1.095, 3.274	1.697, 5.169	-	-	-
p-value	not assessed	not assessed	-	-	-
Comparison vs. lina 5 mg[5]					
Odds ratio	3.065	4.303	-	-	-
95.0% CI	1.768, 5.314	2.462, 7.522	-	-	-
p-value	not assessed	not assessed	-	-	-

1. Last observation (prior to glycaemic rescue) carried forward (LOCF)
2. Mean adjusted for baseline value and stratification
3. ANCOVA model includes baseline body weight, baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (LOCF). The comparisons vs. empa were exploratory and not part of the testing hierarchy (empa 25 mg/lina 5 mg vs. empa 25 mg: adjusted mean 0.19 (95% CI −0.65, 1.03) kg; empa 10 mg/lina 5 mg vs. empa 10 mg: −0.07 (0.91, 0.77) kg)
4. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints. Specification 'not assessed' means that the previous hierarchical test in the confirmatory sequence failed so no subsequent testing was performed.
5. Logistic regression includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (NCF), patients with HbA_{1c} of 7% and above at baseline

In a pre-specified subgroup of patients with baseline HbA_{1c} greater or equal than 8.5% the reduction from baseline in HbA_{1c} with empagliflozin 25 mg/linagliptin 5 mg was -1.9% at 24 weeks (p<0.0001 versus linagliptin 5 mg, n.s. versus empagliflozin 25 mg) and -2.0% at 52 weeks (p<0.0001 versus linagliptin 5 mg, p<0.05 versus empagliflozin 25 mg) and with empagliflozin 10 mg/linagliptin 5 mg -1.9% at 24 weeks (p<0.0001 versus linagliptin 5 mg, p<0.05 versus empagliflozin 10 mg) and -2.0% at 52 weeks (p<0.0001 versus linagliptin 5 mg, p<0.05 versus empagliflozin 10 mg).

Empagliflozin and linagliptin as add on therapy to metformin

In patients inadequately controlled on metformin 24-weeks treatment with both doses of the empagliflozin/linagliptin FDC provided statistically significant improvements in HbA_{1c} and FPG compared to linagliptin 5 mg and also compared to empagliflozin 10 or 25 mg. Compared to

linagliptin 5 mg both doses of the empagliflozin/linagliptin FDC provided statistically significant improvements in body weight. A greater proportion of patients with a baseline HbA_{1c} ≥7.0% and treated with the empagliflozin/linagliptin FDC achieved a target HbA_{1c} of <7% compared to the individual components (Table 10). After 24 weeks treatment with empagliflozin/linagliptin, both SBPs and DBPs were reduced, -5.6/-3.6 mmHg (p<0.001 versus linagliptin 5 mg for SBP and DBP) for empagliflozin 25 mg/linagliptin 5 mg and -4.1/-2.6 mmHg (p<0.05 versus linagliptin 5 mg for SBP, n.s. for DBP) for empagliflozin 10 mg/linagliptin 5 mg. Clinically meaningful reductions in HbA1C (Table 10) and both SBPs and DBPs were observed at week 52, -3.8/-1.6 mmHg (p<0.05 versus linagliptin 5 mg for SBP and DBP) for empagliflozin 25 mg/linagliptin 5 mg and -3.1/-1.6 mmHg (p<0.05 versus linagliptin 5 mg for SBP, n.s. for DBP) for empagliflozin 10 mg/linagliptin 5 mg.

After 24 weeks, rescue therapy was used in 1 (0.7%) patient treated with empagliflozin 25 mg/linagliptin 5 mg and in 3 (2.2%) patients treated with empagliflozin 10 mg /linagliptin 5 mg,

compared to 4 (3.1%) patients treated with linagliptin 5 mg and 6 (4.3%) patients treated with empagliflozin 25 mg and 1 (0.7%) patient treated with empagliflozin 10 mg.

Table 10 Results of a 24- and 52- week (LOCF)1 randomised, double-blind controlled study of empagliflozin and linagliptin as a fixed dose combination as add-on Therapy in Patients Inadequately Controlled on Metformin

	Empagliflozin/linagliptin		**Empagliflozin**		**Linaglipton 5 mg**
	25 mg/ 5 mg	**10 mg / 5 mg**	**25 mg**	**10 mg**	
Primary endpoint: HbA_{1c} [%] - 24 weeks					
Number of patients analysed	134	135	140	137	128
Baseline mean (SE)	7.90 (0.07)	7.95 (0.07)	8.02 (0.07)	8.00 (0.08)	8.02 (0.08)
Adjusted mean (SE) change from baseline at Week 24[1, 2]	−1.19 (0.06)	−1.08 (0.06)	−0.62 (0.06)	−0.66 (0.06)	−0.70 (0.06)
Comparison vs. empagliflozin[1]	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE)[2]	−0.58 (0.09)	−0.42 (0.09)	-	-	-
95.0% CI	−0.75, −0.41	−0.59, −0.25	-	-	-
p-value	<0.0001	<0.0001	-	-	-
Comparison vs. linagliptin 5 mg[1]					
Adjusted mean (SE) [2]	−0.50 (0.09)	−0.39 (0.09)	-	-	-
95.0% CI	−0.67, −0.32	−0.56, −0.21	-	-	-
p-value	<0.0001	<0.0001	-	-	-
HbA_{1c} [%] - 52 weeks[4]					
Baseline mean (SE)	7.90 (0.07)	7.95 (0.07)	8.02 (0.07)	8.00 (0.08)	8.02 (0.08)
Adjusted mean (SE) change from baseline at Week 24[1, 2]	−1.21 (0.07)	−1.05 (0.07)	−0.64 (0.07)	−0.69 (0.07)	−0.48 (0.07)
Comparison vs. empagliflozin[1]	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE)[2]	−0.57 (0.10)	−0.36 (0.10)	-	-	-
95.0% CI	−0.77, −0.37	−0.56, −0.17	-	-	-
Comparison vs. linagliptin 5 mg[1]					
Adjusted mean (SE) [2]	−0.73 (0.10)	−0.57 (0.10)	-	-	-
95.0% CI	−0.93, −0.53	−0.77, −0.37	-	-	-
Key secondary endpoint: FPG [mmol/L] - 24 weeks					
Number of patients analysed	133	134	139	136	127
Baseline mean (SE)	8.58 (0.16)	8.70 (0.17)	8.87 (0.18)	8.97 (0.17)	8.68 (0.15)
Adjusted mean (SE) change from baseline at Week 24[1, 2]	−1.96 (0.14)	−1.79 (0.14)	−1.05 (0.14)	−1.16 (.014)	−0.72 (0.14)
Comparison vs. empagliflozin[1]	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE)[2]	−0.91 (0.20)	−0.63 (0.20)	-	-	-
95.0% CI	−1.30, −0.53	−1.02, −0.24	-	-	-
p-value	<0.0001	0.0015	-	-	-
Comparison vs. linagliptin 5 mg[1]					
Adjusted mean (SE) [2]	−1.23 (0.20)	−1.06 (0.20)	-	-	-
95.0% CI	−1.63, −0.84	−1.45, −0.67	-	-	-
p-value	<0.0001	<0.0001	-	-	-
Key secondary endpoint: body weight [kg] – 24 weeks					
Number of patients analysed	134	135	140	137	128
Baseline mean (SE)	85.47 (1.76)	86.57 (1.64)	87.68(1.49)	86.14(1.55)	85.01(1.62)
Adjusted mean (SE) change from baseline at Week 24[1, 2,3]	−2.99 (0.31)	−2.60 (0.30)	−3.18(0.30)	−2.53(0.30)	−0.69(0.31)

Comparison vs. linagliptin 5 mg[1]					
Adjusted mean (SE) [2]	−2.30 (0.44)	−1.91 (0.44)	-	-	-
95.0% CI	−3.15, −1.44	−2.77, −1.05	-	-	-
p-value	<0.0001	<0.0001	-	-	-
Key secondary endpoint: patients with HbA_{1c} < 7.0% - 24 weeks					
Number of patients, N (%)	123 (100.0)	128 (100.0)	132 (100.0)	125 (100.0)	119 (100.0)
With HbA_{1c} <7.0% at Week 24	76 (61.8)	74 (57.8)	43 (32.6)	35 (28.0)	43 (36.1)
Comparison vs. empagliflozin[1]	vs. empa 25 mg	vs. empa 10 mg			
Odds ratio	4.191	4.500			
95.0% CI	2.319, 7.573	2.474, 8.184			
p-value	<0.0001	<0.0001			
Comparison vs. linagliptin 5 mg[1]					
Odds ratio	3.495	2.795			
95.0% CI	1.920, 6.363	1.562, 5.001			
p-value	<0.0001	0.0005			

1. Last observation (prior to glycaemic rescue) carried forward (LOCF)
2. Mean adjusted for baseline value and stratification
3. ANCOVA model includes baseline body weight, baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (LOCF). The comparisons vs. empagliflozin were exploratory and not part of the testing hierarchy (empa 25/lina 5 vs. empa 25: adjusted mean 0.19 (95% CI −0.65, 1.03) kg; empa 10/lina 5 vs. empa 10: −0.07 (−0.91, 0.77) kg)
4. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
5. Logistic regression includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (NCF), patients with HbA_{1c} of 7% and above at baseline

In a pre-specified subgroup of patients with baseline HbA1c greater or equal than 8.5% the reduction from baseline in HbA1c with empagliflozin 25 mg/linagliptin 5 mg was -1.8% at 24 weeks (p<0.0001 versus linagliptin 5 mg, p<0.001 versus empagliflozin 25 mg) and -1.8% at 52 weeks (p<0.0001 versus linagliptin 5 mg, p<0.05 versus empagliflozin 25 mg) and with empagliflozin 10 mg/5 mg linagliptin -1.6% at 24 weeks (p<0.01 versus linagliptin 5 mg, n.s. versus empagliflozin 10 mg) and -1.5% at 52 weeks (p<0.01 versus linagliptin 5 mg, n.s. versus empagliflozin 10 mg).

Empagliflozin vs. placebo in patients inadequately controlled on metformin and linagliptin

In patients inadequately controlled on metformin and linagliptin, 24-weeks treatment with both doses (10 mg and 25 mg) of empagliflozin provided statistically significant improvements in HbA1c, FPG and body weight compared to placebo (background linagliptin 5 mg). A statistically significant greater number of patients with a baseline HbA1c ≥7.0% and treated with empagliflozin achieved a target HbA1c of <7% compared to placebo (background linagliptin 5 mg) (Table 11). After 24 weeks' treatment with empagliflozin, both SBPs and DBPs were reduced, -2.6/-1.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 25 mg/linagliptin 5 mg and -1.3/-0.1 mmHg (n.s. versus placebo for SBP and DBP) for empagliflozin 10 mg/linagliptin 5 mg.

After 24 weeks, rescue therapy was used in 4 (3.6%) patients treated with empagliflozin 25 mg/linagliptin 5 mg and in 2 (1.8%) patients treated with empagliflozin 10 mg/linagliptin 5 mg, compared to 13 (12.0%) patients treated with placebo (background linagliptin 5 mg).

Table 11 Efficacy Parameters Comparing Empagliflozin to placebo as Add-on Therapy in Patients Inadequately Controlled on Metformin and Linagliptin 5 mg

	Metformin + Linagliptin 5 mg		
	Empagliflozin 10 mg[1]	**Empagliflozin 25 mg[1]**	**Placebo[2]**
HbA1c (%) - 24 weeks3			
N	109	110	106
Baseline (mean)	7.97	7.97	7.96
Change from baseline (adjusted mean)	-0.65	-0.56	0.14
Comparison vs. placebo (adjusted mean) (95% CI)[2]	-0.79 (-1.02, -0.55) p<0.0001	-0.70 (-0.93, -0.46) p<0.0001	
FPG (mmol/L) – 24 weeks[3]			
N	109	109	106
Baseline (mean)	9.3	9.5	9.1
Change from baseline (adjusted mean)	-1.5	-1.8	0.3
Comparison vs. placebo (adjusted mean) (95% CI)	-1.8 (-2.3, -1.3) p<0.0001	-2.1 (-2.6, -1.6) p<0.0001	
Body Weight-24 weeks[3]			
N	109	110	106
Baseline (mean) in kg	88.4	84.4	82.3
Change from baseline (adjusted mean)	-3.1	-2.5	-0.3

Comparison vs. placebo (adjusted mean) (95% CI)[1]	-2.8 (3.5, 2.1) p<0.0001	-2.2 (2.9, 1.5) p<0.0001	
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7% - 24 weeks[4]			
N	100	107	100
Patients (%) achieving A1C <7%	37.0	32.7	17.0
Comparison vs. placebo (odds ratio) (95% CI)[5]	4.0 (1.9, 8.7)	2.9 (1.4, 6.1)	

1 Patients randomised to the empagliflozin 10 mg group were receiving empagliflozin 10 mg/linagliptin 5 mg or empagliflozin 25 mg/linagliptin 5 mg with background metformin

2 Patients randomised to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin

3 MMRM model on FAS (OC) includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, visit, treatment,and visit by treatment interaction. For FPG, baseline FPG is also included. For weight, baseline weight is also included.

4 not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints

5 Logistic regression on FAS (NCF) includes baseline HbA_{1c}, baseline eGFR (MDRD), geographical region, and treatment; based on patients with HbA_{1c} of 7% and above at baseline

In a prespecified subgroup of patients with baseline HbA_{1c} greater or equal than 8.5% the reduction from baseline in HbA_{1c} with empagliflozin 25 mg/ linagliptin 5 mg was -1.3% at 24 weeks (p<0.0001 versus placebo [background linagliptin 5 mg]) and with empagliflozin 10 mg/linagliptin 5 mg -1.3% at 24 weeks (p<0.0001 versus placebo [background linagliptin 5 mg]).

Empagliflozin 2-year data, as add on to metformin in comparison to glimepiride

In a study comparing the efficacy and safety of empagliflozin 25 mg versus glimepiride (1-4 mg) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin 25 mg daily resulted in superior reduction in HbA_{1c}, and a clinically meaningful reduction in FPG, compared to glimepiride (Table 12). Empagliflozin 25 mg daily resulted in a statistically significant reduction in body weight, systolic and diastolic blood pressure (change from baseline in DBP of -1.8 mmHg for empagliflozin and +0.9 mmHg for glimepiride, p<0.0001).

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

Table 12 Results at 104 weeks (LOCF)[4] in an active controlled study comparing empagliflozin to glimepiride as add on to metformin (Full Analysis Set)

Empagliflozin as add-on to metformin therapy in comparison to glimepiride	**Empagliflozin 25 mg**	**Glimepiride (up to 4 mg)**
N	765	780
HbA_{1c} (%)		
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 HbA_{1c} <7% with baseline HbA_{1c} ≥7%[2]	33.6	30.9
N	764	779
FPG (mmol/L)[2]		
Baseline (mean)	8.33	8.32
Change from baseline[1]	-0.85	-0.17
Difference from glimepiride[1] (95% CI)	-0.69 (-0.86,-0.52)	
N	765	780
Body Weight (kg)		
Baseline (mean)	82.52	83.03
Change from baseline[1]	-3.12	1.34
Difference from glimepiride[1] (97.5% CI)	-4.46** (-4.87, -4.05)	
N	765	780
Patients(%) achieving weight loss of >5%[2]	27.5	3.8
N	765	780
SBP (mmHg)[3]		
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)	

1. Mean adjusted for baseline value and stratification

2. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints

3. Last observation (prior glycaemic rescue or to antihypertensive rescue) carried forward (LOCF)

4. Last observation (prior to glycaemic rescue) carried forward (LOCF)
* p-value <0.0001 for non-inferiority, and p-value = 0.0153 for superiority
** p-value <0.0001

Empagliflozin as add on to multiple daily insulin therapy and metformin

The efficacy and safety of empagliflozin as add-on to multiple daily insulin with or without concomitant metformin therapy (71.0% of all patients were on metformin background) 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 to be kept stable, but was adjusted to achieve pre-prandial glucose levels < 5.5 mmol/L, and post-prandial glucose levels < 7.8 mmol/L between Weeks 19 and 40.

At Week 18, empagliflozin provided statistically significant improvement in HbA_{1c} compared with placebo (Table 13). A greater proportion of patients with a baseline HbA_{1c} ≥ 7.0% (19.5% empagliflozin 10 mg, 31.0% empagliflozin 25 mg) achieved a target HbA_{1c} of < 7% compared with placebo (15.1%).

At Week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA_{1c} and insulin sparing compared with placebo and a reduction in FPG (change from baseline of −0.02 mmol/L for placebo, −1.09 mmol/L for empagliflozin 10 mg, and −1.31 mmol/L for empagliflozin 25 mg), body weight, and blood pressure (SBP: change from baseline of −2.6 mmHg for placebo, −3.9 mmHg for empagliflozin 10 mg and -4.0 mmHg for empagliflozin 25 mg, DBP: change from baseline of −1.0 mmHg for placebo, -1.4 mmHg for empagliflozin 10 mg and -2.6 mmHg for empagliflozin 25 mg).

Table 13 Results at 18 and 52 (LOCF)[5] weeks in a placebo-controlled study of empagliflozin as add on to multiple daily doses of insulin with metformin[2]

Empagliflozin as add-on to insulin + metformin therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	188	186	189
HbA_{1c} (%) 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
HbA_{1c} (%) at week 52[3]			
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 HbA_{1c} <7% with baseline HbA_{1c} ≥7% at week 52[4]	26.5	39.8	45.8
N	188	186	189
FPG (mmol/L) at week 52[5]			
Baseline (mean)	8.41	8.83	8.34
Change from baseline[1]	-0.02	-1.09	-1.31
Difference from placebo[1] (95% CI)		-1.07 (-1.55, -0.06)	-1.30 (-1.77, -0.83)
N	115	118	117
Insulin dose (IU/day) at week 52[3]			
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[3]			
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)

N	188	186	189
SBP (mmHg)[6]			
Baseline (mean)	132.6	134.2	132.9
Change from baseline[1]	-2.6	-3.9	-4.0
Difference from placebo[1,4] (95% CI)		-1.4 (-3.6, 0.9)	-1.4 (-3.7, 0.8)

1. Mean adjusted for baseline value and stratification
2. Week 18: FAS; week 52: PPS-Completers-52
3. Week 19-40: treat-to-target regimen for insulin dose adjustment to achieve pre-defined glucose target levels (pre-prandial <5.5 mmol/L, post-prandial <7.8 mmol/L
4. Not evaluated for statistical significance; not part of sequential testing procedure for the secondary endpoints
5. Last observation (prior to glycaemic rescue) carried forward (LOCF)
6. Week 52: FAS

* p-value <0.0001
** p-value <0.005

Empagliflozin as add on to basal insulin therapy

The efficacy and safety of empagliflozin (10 mg or 25 mg) as add on to basal insulin with or without concomitant metformin and/or sulfonylurea therapy was evaluated in a double-blind, placebo-controlled trial of 78 weeks duration. The primary endpoint was the change from baseline in HbA_{1c} after 18 weeks of treatment. The key secondary endpoints were the change from baseline in dose of basal insulin dose after 78 weeks of treatment and change from baseline in HbA_{1c} after 78 weeks of treatment.

During the initial 18 weeks the insulin dose was to be kept stable, but was adjusted to achieve a FPG < 6.10 mmol/L in the following 60 weeks.

At week 18, empagliflozin (10 mg or 25 mg) provided statistically significant improvement in HbA_{1c} compared to placebo. A greater proportion of patients with a baseline HbA_{1c} ≥ 7.0% achieved a target HbA_{1c} of <7% compared to placebo. At 78 weeks, empagliflozin resulted in a statistically significant decrease in HbA_{1c} and insulin sparing compared to placebo (Table 14).

At week 78, empagliflozin resulted in a reduction in FPG (-0.58 mmol/L for empagliflozin 10 mg, -0.97 mmol/L for empagliflozin 25 mg and -0.30 mmol/L for placebo), body weight (-2.47 kg for empagliflozin 10 mg, -1.96 kg for empagliflozin 25 mg and +1.16 kg for placebo, p< 0.0001), BP (SBP: -4.1 mmHg for empagliflozin 10 mg, -2.4 mmHg for empagliflozin 25 mg and +0.1 mmHg for placebo, DBP: -2.9 mmHg for empagliflozin 10 mg, -1.5 mmHg for empagliflozin 25 mg and -0.3 mmHg for placebo).

Table 14 Results at 18 and 78 weeks (LOCF) in a placebo-controlled study of empagliflozin as add on to basal insulin with or without metformin or sulfonylurea (Full Analysis Set - Completers)

Basal insulin +/- metformin or sulfonylurea add-on therapy	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	125	132	117
HbA_{1c} (%) 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
HbA_{1c} (%) 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)

1. Mean adjusted for baseline value and stratification
* p-value ≤0.0001; ** p-value <0.025

Empagliflozin as add on to DPP-4 inhibitor therapy

The efficacy and safety of empagliflozin as add on to DPP-4 inhibitors plus metformin, with or without one additional oral anti-diabetic drug was evaluated in 160 patients with T2DM and high cardiovascular risk. Treatment with empagliflozin for 28 weeks reduced HbA_{1c} compared to placebo (change from baseline -0.54% for empagliflozin 10 mg, -0.52% for empagliflozin 25 mg and -0.02% for placebo).

Patients with renal impairment, 52 weeks placebo controlled data

The efficacy and safety of empagliflozin as add on to anti-diabetic therapy was evaluated in patients with mild and moderate renal impairment in a double-blind, placebo-controlled study for 52 weeks.

Treatment with empagliflozin led to statistically significant reduction of HbA_{1c} and clinically meaningful improvement in FPG, body weight and BP compared to placebo at Week 24 (Table 15). The improvement in HbA_{1c}, FPG, body weight, and BP was sustained up to 52 weeks.

Table 15 Results at 24 weeks (LOCF) in a placebo-controlled study of empagliflozin in renally impaired type 2 diabetes patients (Full Analysis Set)

	eGFR ≥60 to <90 mL/min/1.73m²			**eGFR ≥45 to <60 mL/min/1.73m²**	
	Placebo	**Empagliflozin**		**Placebo**	**Empagliflozin**
		10 mg	**25 mg**		**25 mg**
N	95	98	97	89	91
HbA1c (%)					
Baseline (mean)	8.09	8.02	7.96	8.08	8.12
Change from baseline1	0.06	-0.46	-0.63	-0.08	-0.54
Difference from placebo1 (95% CI)		-0.52* (-0.72, -0.32)	-0.68* (-0.88, -0.49)		-0.46* (-0.66, -0.27)
N	89	94	91	84	86
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%2	6.7	17.0	24.2	10.7	15.1
N	95	98	97	89	90
Fasting Plasma Glucose (mmol/L)					
Baseline (mean)	8.04	8.10	8.24	8.55	8.02
Change from baseline1	0.31	-0.77	-1.00	0.37	-0.82
Difference from placebo1 (95% CI)		-1.09 (-1.62, -0.55)	-1.32 (-1.86, -0.78)		-1.19 (-1.77, -0.60)
N	95	98	97	89	91
Body Weight (kg)2					
Baseline (mean)	86.00	92.05	88.06	83.20	84.90
Change from baseline1	-0.33	-1.76	-2.33	-0.25	-0.98
Difference from placebo1 (95% CI)		-1.43 (-2.09, -0.77)	-2.00 (-2.66, -1.34)		-0.74 (-1.50, -0.03)
N	95	98	97	89	91
Systolic blood pressure (mmHg)2					
Baseline (mean)	134.69	137.37	133.68	137.29	135.04
Change from baseline1	0.65	-2.92	-4.47	0.37	-5.69
Difference from placebo1 (95% CI)		-3.57 (-6.86, -0.29)	-5.12 (-8.41, -1.82)		-6.07 (-9.79, -2.34)

[1] mean adjusted for baseline value and stratification

[2] not evaluated for statistical significance; not part of sequential testing procedure for the secondary

endpoints
* p<0.0001

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 HbA_{1c} 11.15%) resulted in a clinically meaningful reduction in HbA_{1c} from baseline (-3.27%) at week 24.

Body weight

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

Waist circumference

At 24 weeks, treatment with empagliflozin as monotherapy or as add-on to metformin, pioglitazone, or metformin plus sulfonylurea resulted in sustained reduction of waist circumference over the duration of studies in a range of -1.7 cm to -0.9 cm for empagliflozin and -0.5 cm to +0.2 cm for placebo.

Blood pressure

The efficacy and safety of empagliflozin (10 mg or 25 mg) was evaluated in a double-blind, placebo-controlled study of 12 weeks duration in patients with T2DM and high BP on different oral anti-diabetic drugs and up to 2 antihypertensive agents (Table 16). Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA_{1c} and reduction in 24 hour mean SBP and DBP as determined by ambulatory BP monitoring. Treatment with empagliflozin also provided reductions in seated SBP (change from baseline of -0.67 mmHg for placebo, -4.60 mmHg for empagliflozin 10 mg and -5.47 mmHg for empagliflozin 25 mg) and seated DBP (change from baseline of -1.13 mmHg for placebo, -3.06 mmHg for empagliflozin 10 mg and -3.02 mmHg for empagliflozin 25 mg).

Table 16 Results at 12 weeks (LOCF)[3] in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressure (Full Analysis Set)

	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	271	276	276
HbA_{1c} (%)			
Baseline (mean)	7.90	7.87	7.92
Change from baseline[1]	0.03	-0.59	-0.62
Difference from placebo[1] (95% CI)		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
24 hour systolic blood pressure (mmHg)			
Baseline (mean)	131.72	131.34	131.18
Change from baseline[1]	0.48	-2.95	-3.68
Difference from placebo[1] (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
24 hour diastolic blood pressure (mmHg)			
Baseline (mean)	75.16	75.13	74.64
Change from baseline[1]	0.32	-1.04	-1.40
Difference from placebo[1] (95% CI)		-1.36** (-2.15, -0.56)	-1.72* (-2.51, -0.93)

1. Mean adjusted for baseline value and stratification
2. Last observation (prior to antihypertensive rescue) carried forward (LOCF)
3. Last observation (prior to glycaemic rescue) carried forward (LOCF)
* p-value <0.0001
** p-value = 0.0008

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

Laboratory parameters

Haematocrit increased

In a pooled safety analysis (pooling of all patients with diabetes, n=13,402), 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.

Serum lipids increased

In a pooled safety analysis (pooling of all patients with diabetes, n=13,402), 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%.

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 (CV) events in patients with type 2 diabetes and one or more CV 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 7020 patients were treated with empagliflozin (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) 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 sulfonylurea.

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, Low Density Lipoprotein 2.2 mmol/L, High Density Lipoprotein 1.1 mmol/L and urinary albumin to creatinine ratio (UACR) 19.8 mg/mmol at baseline.

Reductions in risk of CV death and all-cause mortality

Empagliflozin 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 17 and Figure 1).

Empagliflozin also improved overall survival (Table 17 and Figure 2), which was driven by a reduction in cardiovascular death with empagliflozin. There was no statistically significant difference between empagliflozin and placebo in non-cardiovascular mortality.

Table 17 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, nonfatal 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

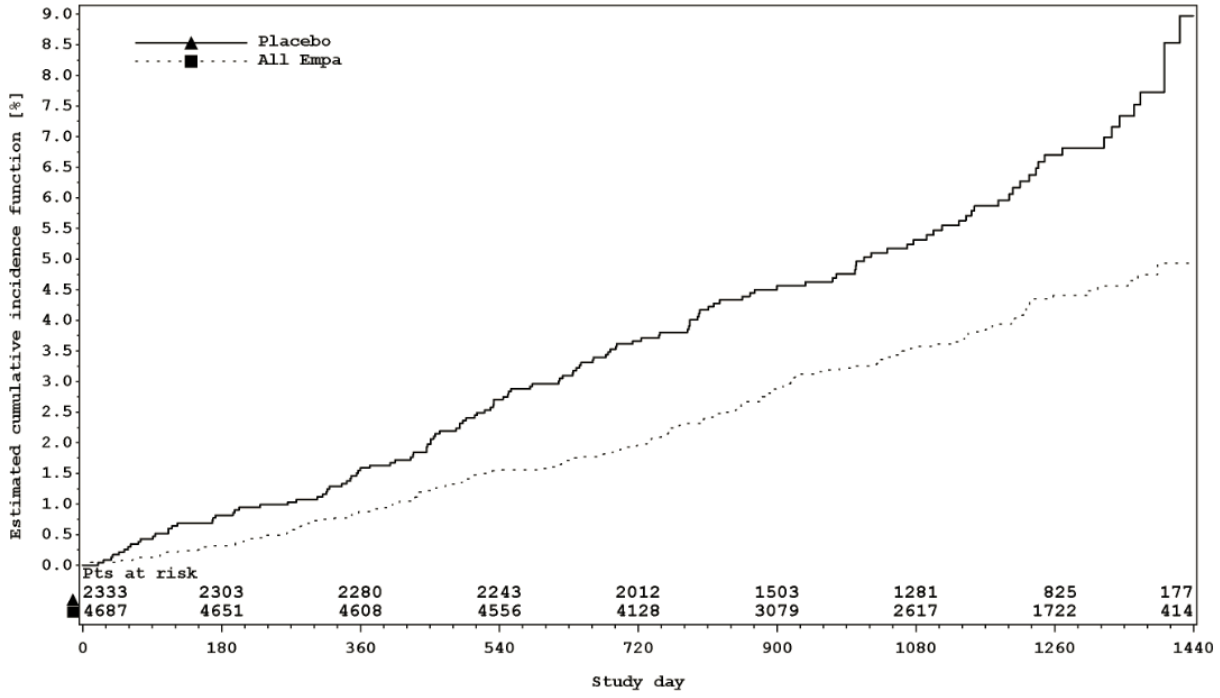
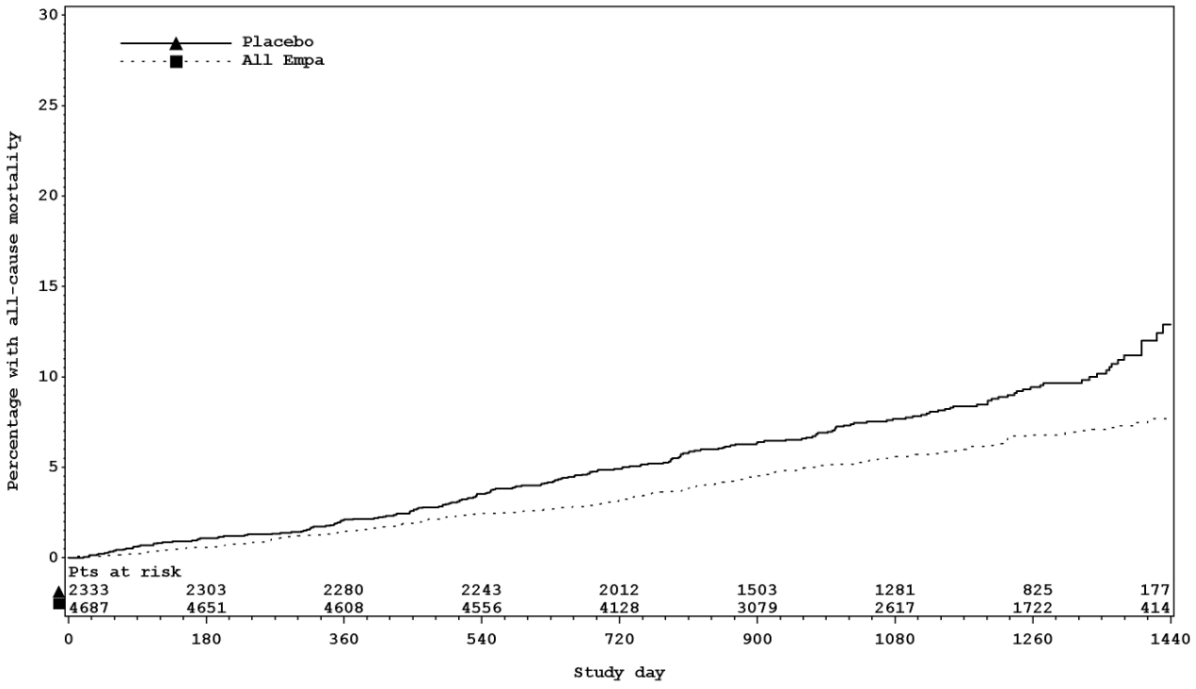


Figure 2 Time to occurrence of all-cause mortality*



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

Reductions in risk of heart failure requiring hospitalisation or CV death

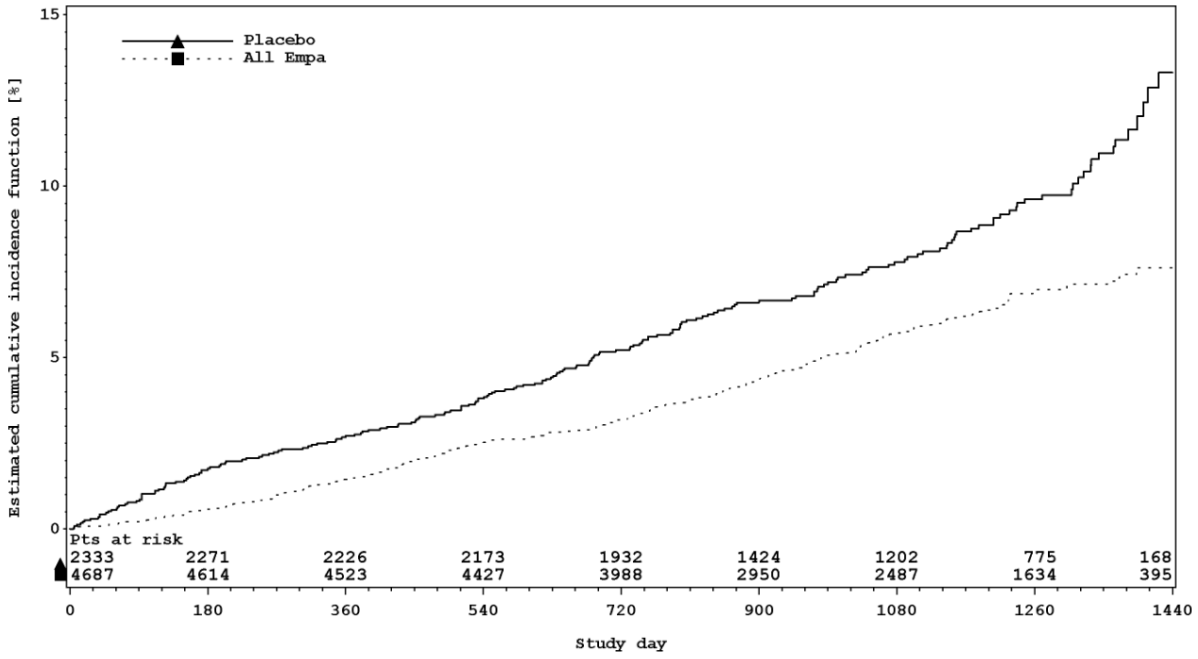
Empagliflozin significantly reduced the risk of hospitalisation for heart failure and cardiovascular death or hospitalisation for heart failure compared with placebo (Table 18 and Figure 3).

Table 18 Treatment effect for hospitalisation 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 hospitalisation 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 (048, 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

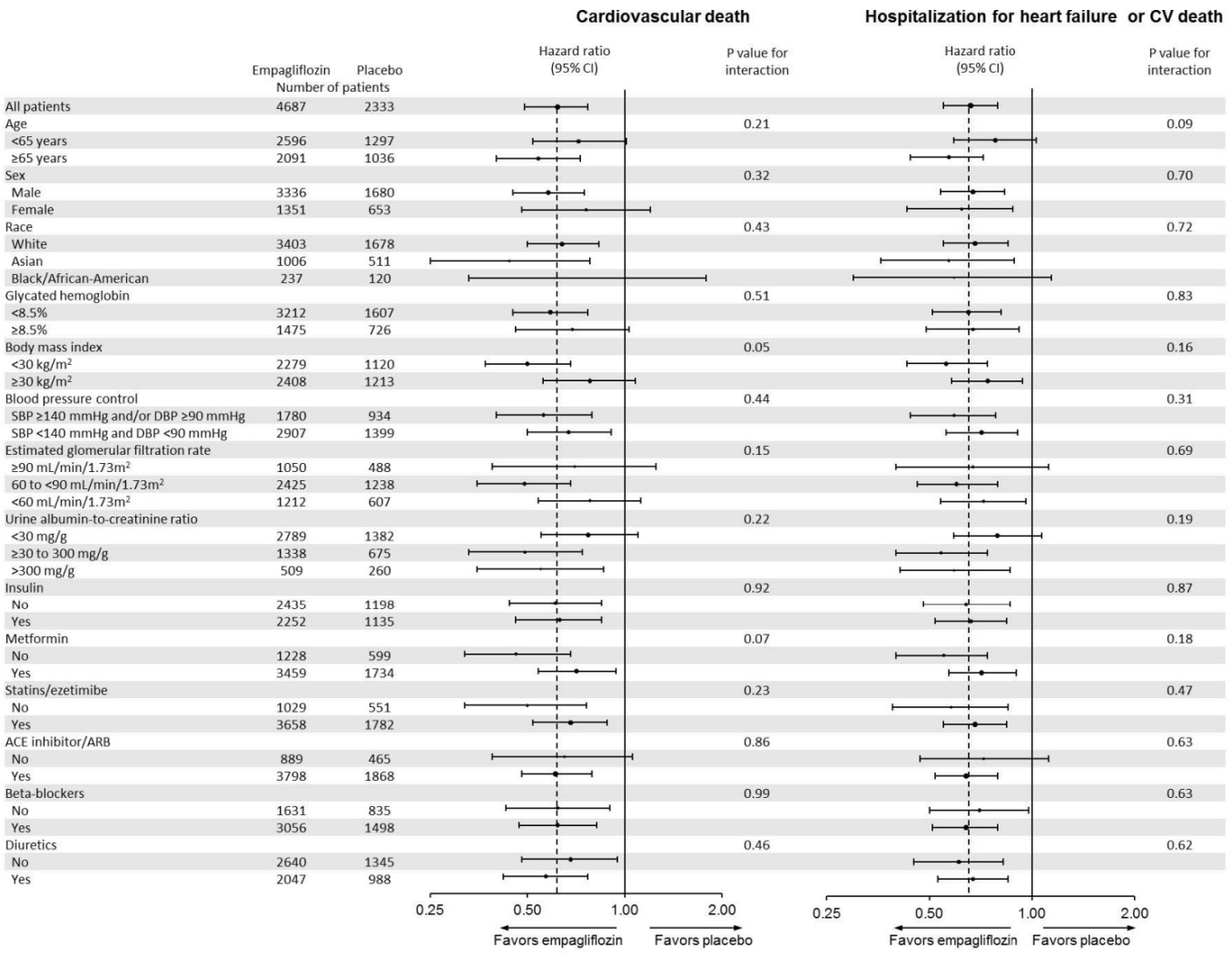
Figure 3 Time to first occurrence of first heart failure hospitalisation or CV death*



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

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

Figure 4 Subgroup analyses for CV death and hospitalisation for heart failure or CV death*,**



* Hospitalisation 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. haemodialysis)) was significantly reduced in empagliflozin group compared to placebo (Table 19 and Figure 5).

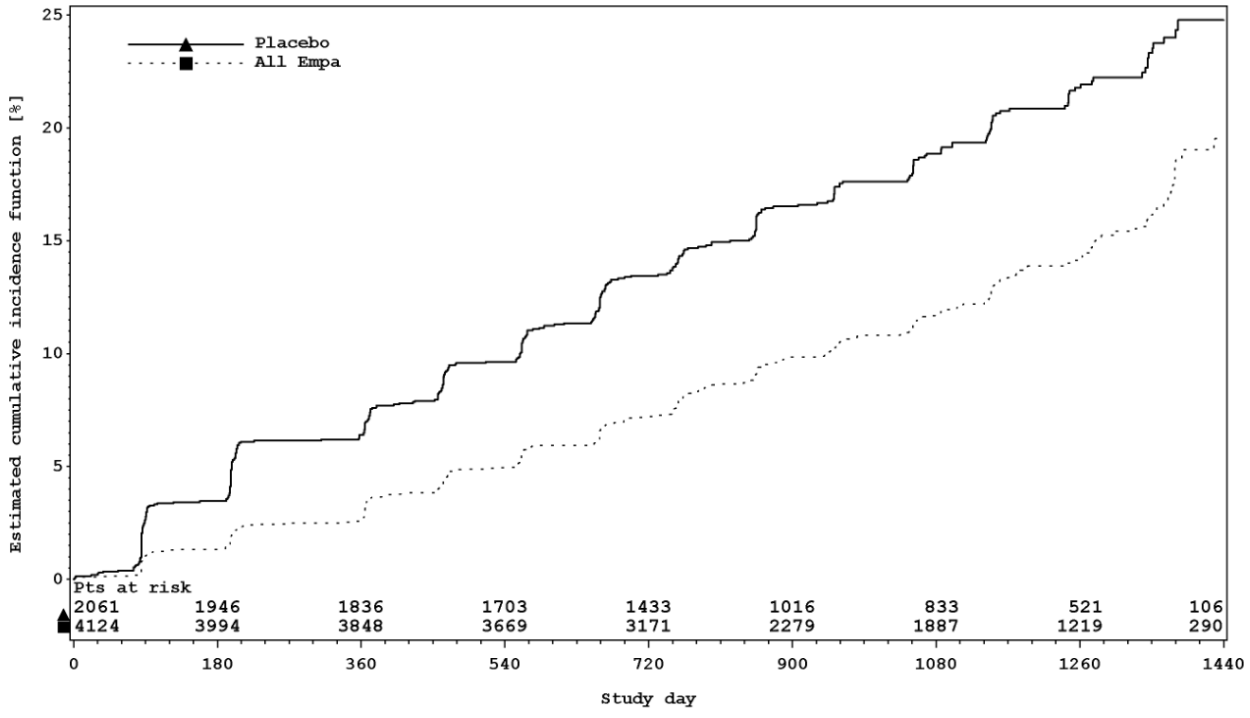
Empagliflozin compared with placebo showed a significantly higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria (HR 1.82, 95% CI 1.40, 2.37).

Table 19 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 levelN (%)**	60 (2.6)	70 (1.5)
HR (95% CI)		0.56 (0.39, 0.79)
p−value		0.0009
	Placebo	**Empagliflozin (10 and 25 mg, pooled)**
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)

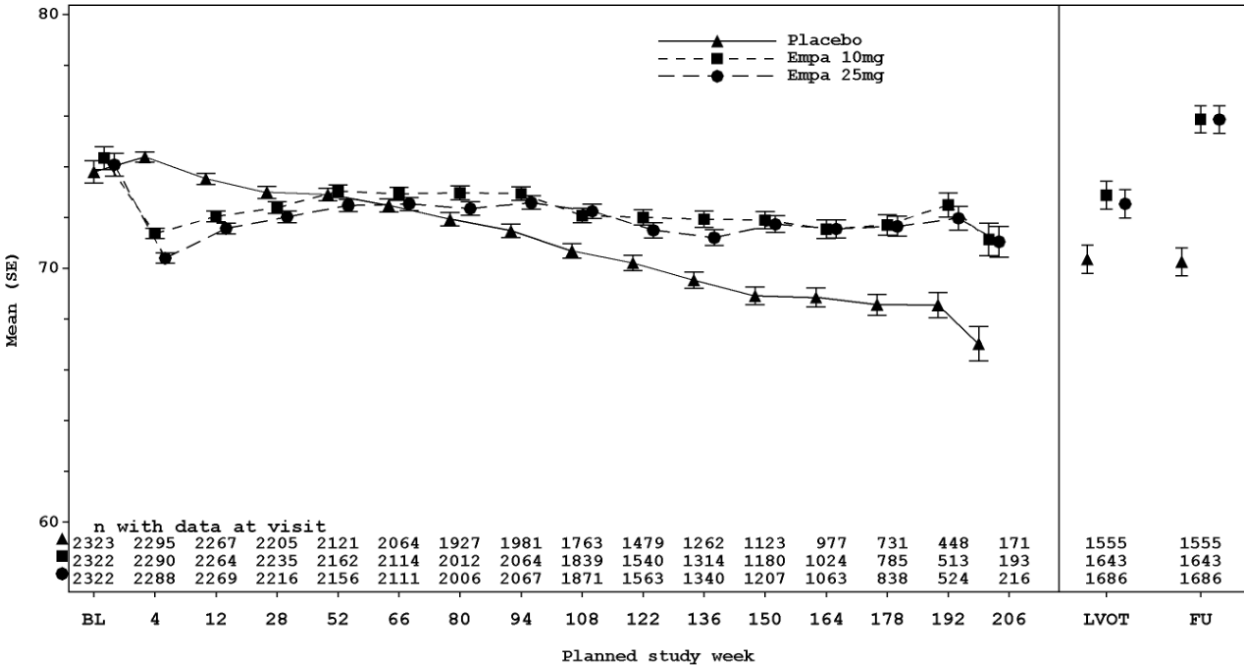
*i.e. patients who had received at least one dose of study drug
**Accompanied by an eGFR ≤45 mL/min/1.73m^2
*** Urine Albumin Creatinine Ratio >33.9 mg/mmol
**** Due to low event rate, HR not calculated

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 patients with heart failure and reduced ejection fraction

A randomised, double-blind, placebo-controlled study (EMPEROR-Reduced) was conducted in 3730 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 1863 patients were randomised to empagliflozin 10 mg (placebo: 1867) 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 20).

Table 20 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 of 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		< 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 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 CV death or HHF

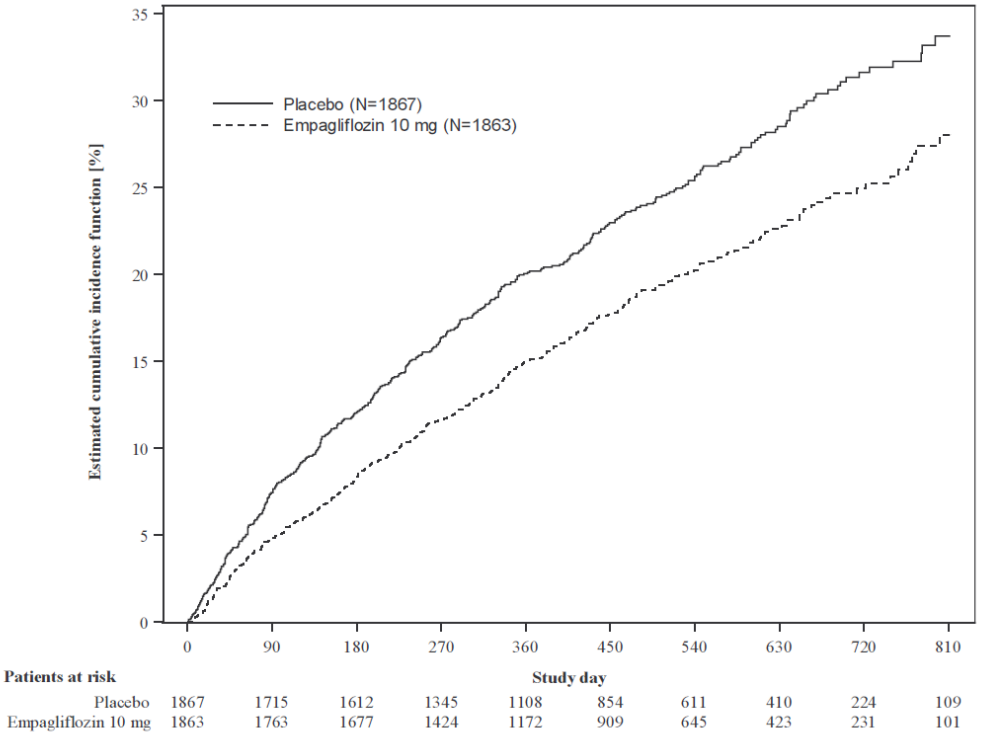
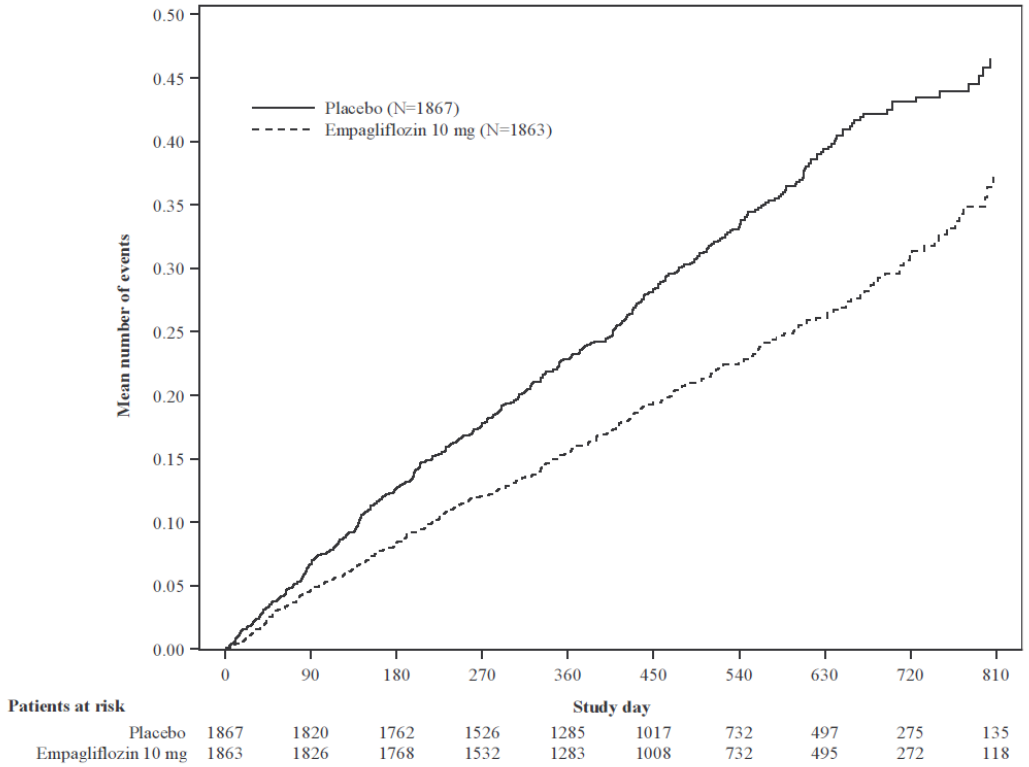
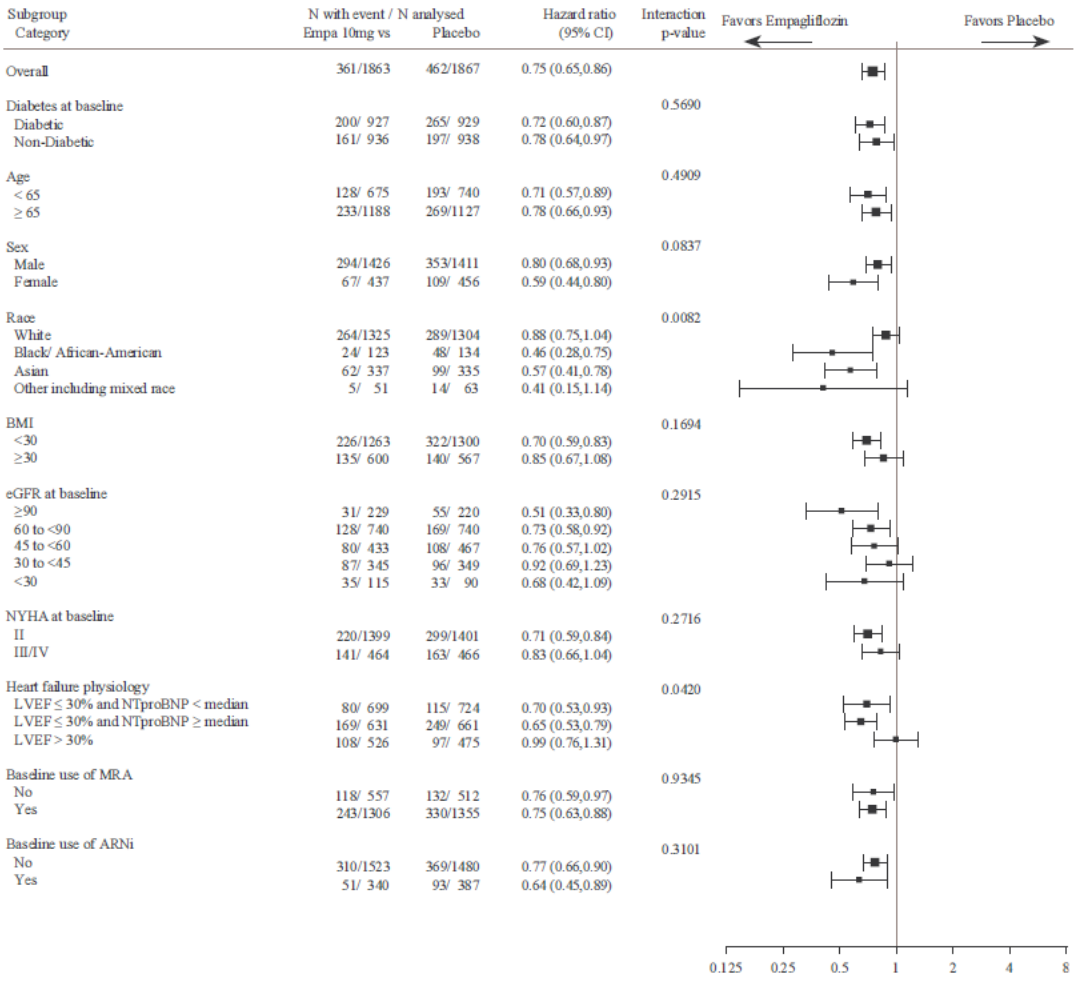


Figure 8 Time to event of adjudicated HHF



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 9).

Figure 9 Subgroup analyses for the time to the first event of adjudicated of CV death or HHF

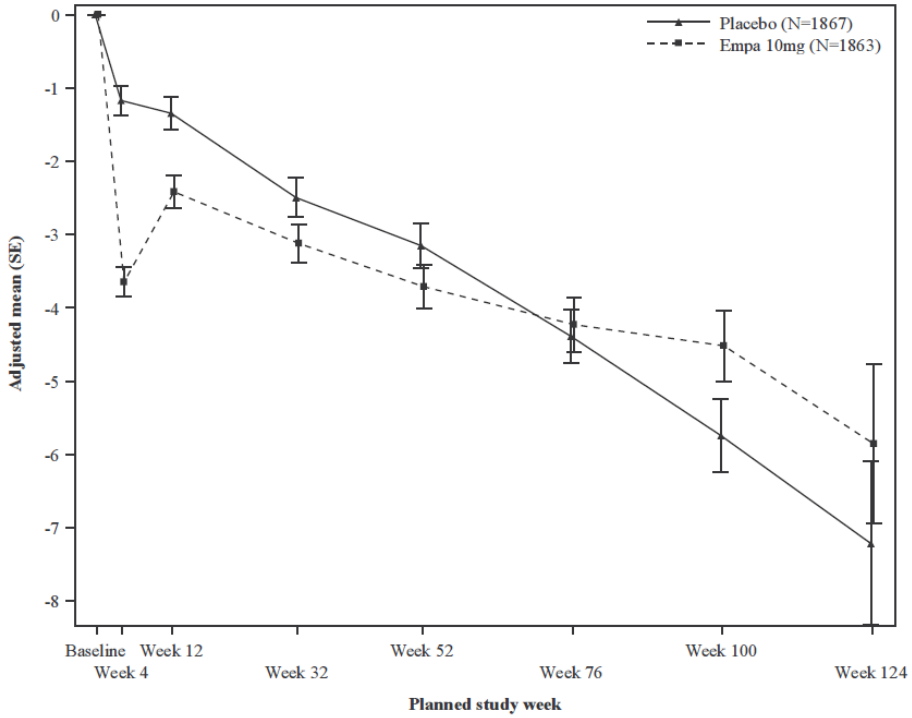


LVEF > 30%: Includes both above and below the median NTproBNP. To be eligible for inclusion, patients with an LVEF > 30% were required to meet a higher NTproBNP threshold than those with LVEF ≤ 30%, unless they additionally had a history of HHF within the past 12 months.

Renal Outcome

During treatment, eGFR decline over time was slower in the empagliflozin group compared to the placebo group (see Figure 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 20). 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 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).

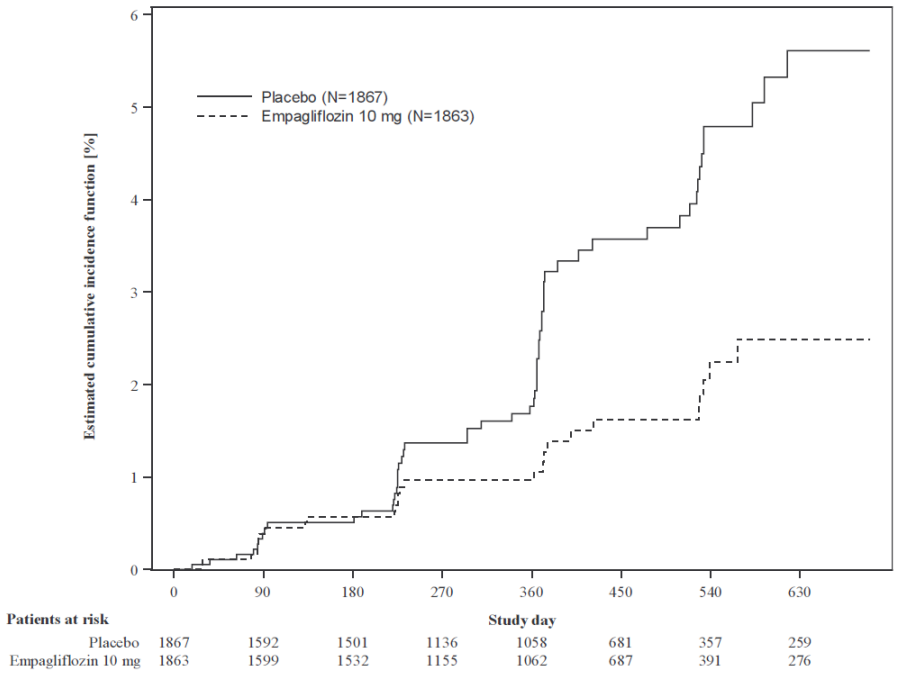
Empagliflozin reduced the risk of the renal composite endpoint defined as time to first event of chronic dialysis or renal transplant or sustained reduction in eGFR compared with placebo (Table 21 and Figure 11).

Table 21 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 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 22).

Table 22 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 = 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 12 Time to first event of adjudicated CV death or HHF

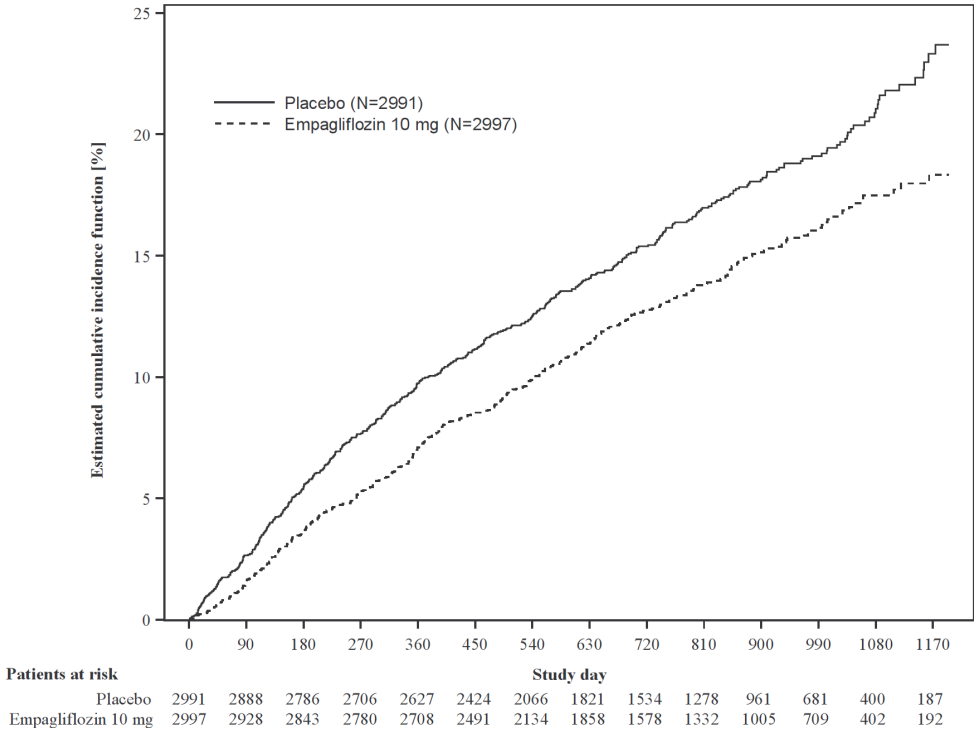
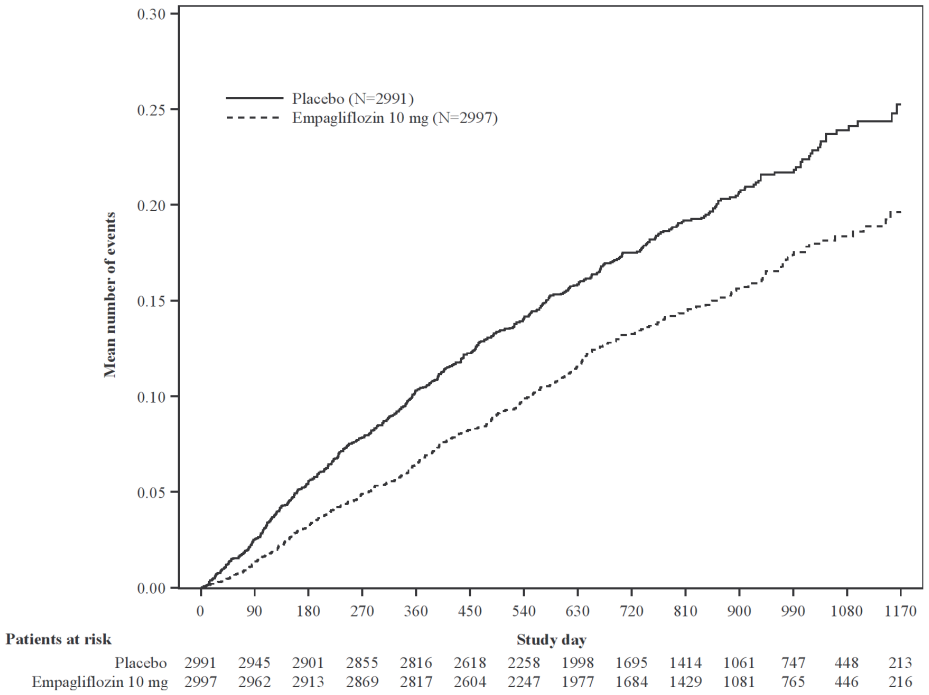
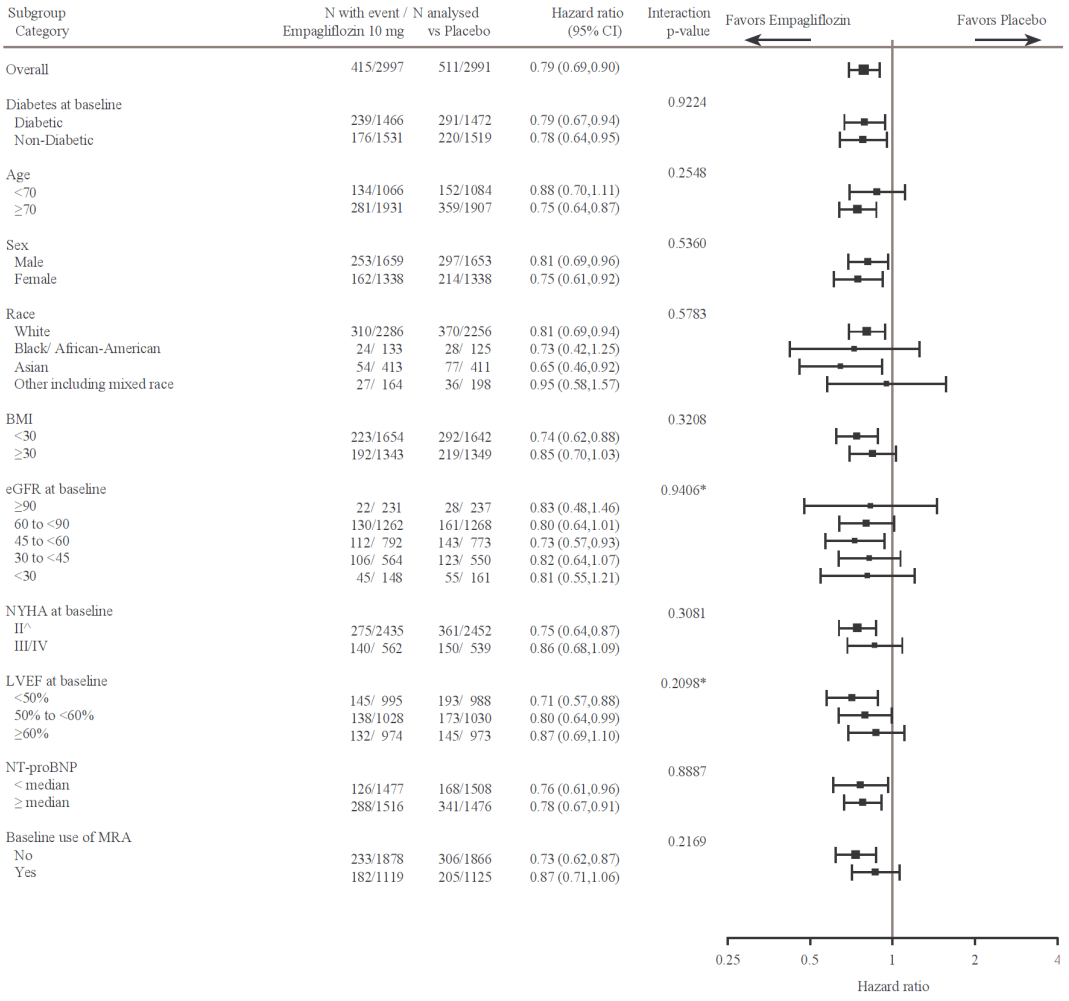


Figure 13 Time to event of adjudicated HHF



The results of the primary composite endpoint were consistent across each of the pre-specified subgroups categorised 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

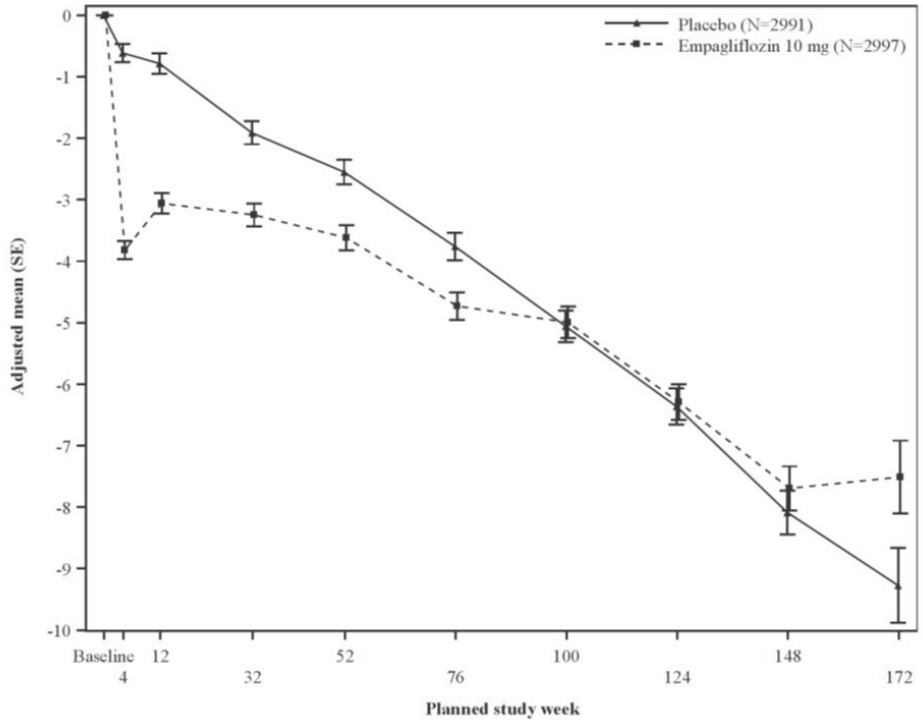


^4 patients with NYHA class I are counted in subgroup NYHA class II
*trend test

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 22). 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 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.

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 Summary 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 ≤40%, and 31.9% with LVEF >40%. At baseline, 36.6% of patients had an eGFR of ≥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 ≥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 empagliflozin 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 23).

Table 23 Win ratio of clinical benefit

	Placebo	**Empagliflozin (10 mg)**
Number of comparisons1 [100%]	39162	
Wins based on time to death [%]	4.01	7.15
Wins based on frequency of HFE2 [%]	7.65	10.59
Wins based on time to HFE [%]	0.57	0.24
Wins based on ≥5 points difference in change from baseline in KCCQ-TSS3 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 Summary 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 6609 patients with chronic kidney disease (eGFR ≥20 - <45 mL/min/1.73 m^2; or eGFR ≥45 - <90 mL/min/1.73 m^2 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 m^2, 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 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 m^2, 21.2% patients had an eGFR of ≥45 mL/min/1.73 m^2, 44.3% of 30 to <45 mL/min/1.73 m^2 and 34.5% <30 mL/min/1.73 m^2 including 254 patients with an eGFR <20 mL/min/1.73 m^2. The median UACR was 329 mg/g, 20.1% patients had an UACR <30 mg/g, 28.2% had an UACR 30 to ≤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 28% compared with placebo (HR 0.72, 95% CI 0.59 to 0.89, nominal p = 0.0017). Additionally, empagliflozin significantly reduced the risk of all-cause hospitalisation (first and recurrent). (see Table 20)

Table 20 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	3305	3304
Time to first occurrence of kidney disease progression (sustained ≥40% eGFR decline from randomisation, sustained eGFR <10 mL/min/1.73 m^2, 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 m^2, N (%)	222 (6.7)	157 (4.8)
Hazard ratio vs. placebo (95% CI)		0.68 (0.55, 0.84)
p-value		0.0002
Renal death, N (%)**	4 (0.1)	4 (0.1)
Hazard ratio vs. placebo (95% CI)		
p-value		
CV Death, N (%)	70 (2.1)	59 (1.8)
Hazard ratio vs. placebo (95% CI)		0.83 (0.59, 1.17)
p-value		02932
Occurrence of all-cause hospitalisation (first and recurrent), N of events	1895	1612
Hazard ratio vs. placebo (99.03% CI)		0.86 (0.76, 0.98)
p-value		0.0022
Time to first occurrence of HHF or CV death, N (%)	153 (4.6)	131 (4.0)
Hazard ratio vs. placebo (98.55% CI)		0.84 (0.63, 1.12)
p-value		0.1363
HHF (first occurrence), N (%)	107 (3.2)	88 (2.7)
Hazard ratio vs. placebo (95% CI)		0.80 (0.60, 1.06)
p-value		0.1262
Time to all-cause mortality N (%)	168 (5.1)	149 (4.5)
Hazard ratio vs. placebo (97.1% CI)		0.87 (0.68, 1.11)
p-value		0.2122

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

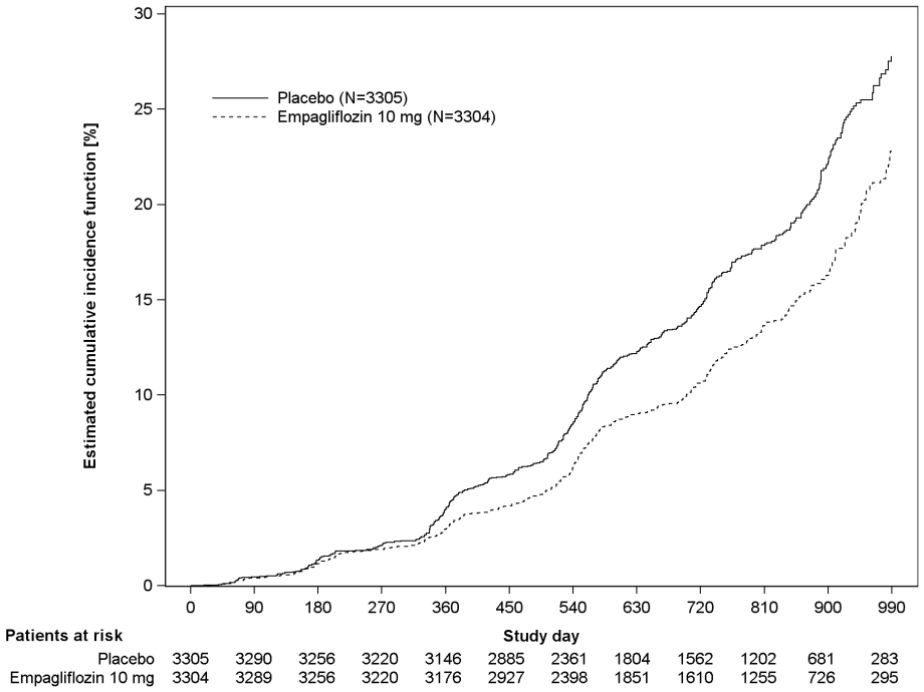
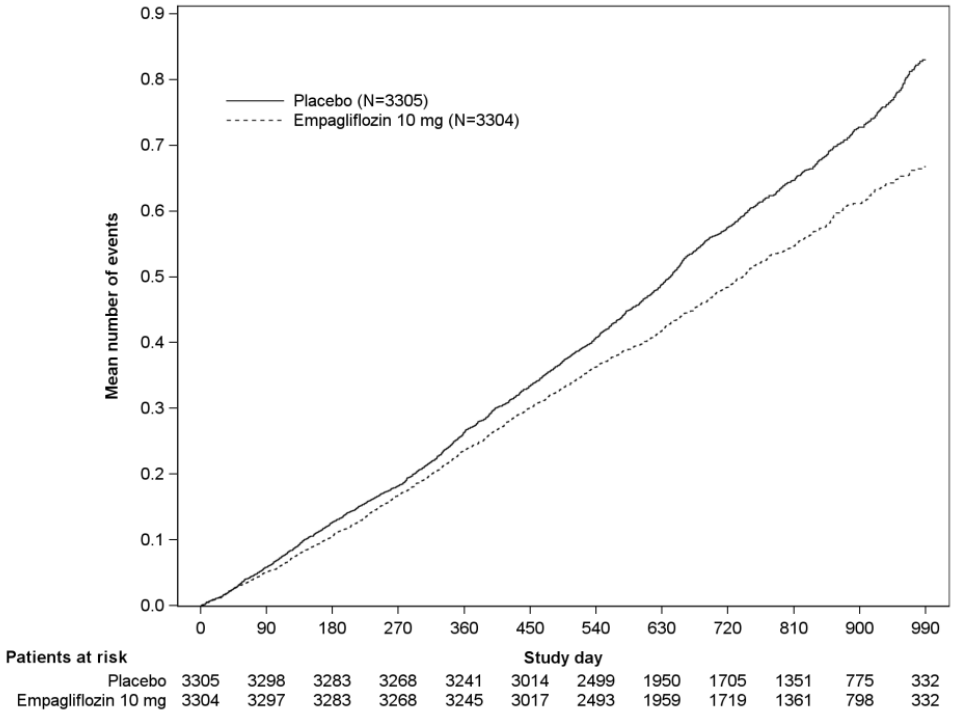


Figure 17 Occurrence of all-cause hospitalisation (first and recurrent), mean cumulative function



The results of the primary composite endpoint were generally consistent across the prespecified 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 1.38 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 empagliflozin is also likely to be effective in patients with less pronounced albuminuria.

Paediatric population

The clinical efficacy and safety of empagliflozin 10 mg with a possible dose-increase to 25 mg or linagliptin 5 mg once daily has been studied in children and adolescents from 10 to 17 years of age with T2DM in a double-blind, randomised, placebo-controlled, parallel group study (DINAMO) over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks.

A total of 157 patients were treated with either empagliflozin (10 mg or 25 mg; N=52), linagliptin (N=52), or placebo (N=53). Background therapies as adjunct to diet and exercise included metformin (51%), a combination of metformin and insulin (40.1%), insulin (3.2%), or none (5.7%). The mean HbA1c was 8.03% at baseline. The study population consisted of 38.2% male and 61.8% female patients with a mean age of 14.5 years (range: 10 to 17 years); 51.6% were 15 years of age or older. 49.7% of the study population were White, 5.7% Asian and 31.2% Black/African American. The mean BMI was 36.04 kg/m^2, the mean body weight was 99.92 kg. Only patients with an eGFR of ≥60 mL/min/1.73 m^2 were included in the DINAMO study.

Empagliflozin was superior to placebo in reducing the primary endpoint change in HbA1c from baseline to the end of 26 weeks regardless of rescue therapy or treatment discontinuation. In addition, treatment with empagliflozin resulted in clinically meaningful decrease in FPG (Table 21).

Table 21 Results of a 26-week in placebo-controlled study of empagliflozin in paediatric patients with type 2 diabetes (modified Intention To Treat Set)

	Placebo	**Empagliflozin**
N	53	52
HbA_{1c} (%)[1]		
Baseline (mean)	8.05	8.00
Change from baseline[2]	0.68	-0.17
Difference from placebo[2] (95% CI)		-0.84 (-1.50, -0.19)
p-value for superiority		0.0116
N	52	48
FPG (mg/dL) [mmol/L] [3,4]		
Baseline (mean)	158.6 [8.80]	154.4 [8.57]
Change from baseline[2]	15.7 [0.87]	-19.5 [-1.08]
Difference from placebo[2] (95% CI)		-35.2 (-58.6, -11.7) [-1.95 (-3.25, -0.65)]
nominal p-value		0.0035

1 Multiple imputation with 500 iterations for missing data
2 mean adjusted for baseline value and stratification
3 Last observation carried forward (LOCF), including baseline values
4 not evaluated for statistical significance; not part of sequential testing procedure

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 rapidly absorbed with peak plasma concentrations (C_{max}) with a median time to reach C_{max} (t_{max}) of 1.5 h 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 area under the curve (AUC) was 4740 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.

Special populations

Renal impairment

In patients with mild (eGFR: 60 - < 90 mL/min/1.73m^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/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. In line with the Phase I study, 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.

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. Based on pharmacokinetics, no dosage adjustment is recommended in patients with 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. Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

Race

No dosage adjustment is necessary based on race. Based on the population pharmacokinetic analysis, AUC was estimated to be 13.5% higher in Asian patients with a BMI of 25 kg/m^2 compared to non-Asian patients with a BMI of 25 kg/m^2.

Elderly

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

Paediatric population

Pharmacokinetics and pharmacodynamics of a single dose of empagliflozin 5 mg, 10 mg and 25 mg were investigated in children and adolescents 10 to 17 years of age with T2DM. The observed pharmacokinetics and the pharmacokinetics-pharmacodynamics (urinary glucose excretion) relationship of adult and paediatric patients was comparable after accounting for significant covariates.

Pharmacokinetics and pharmacodynamics (HbA_{1c} change from baseline) of empagliflozin 10 mg with a possible dose-increase to 25 mg were investigated in children and adolescents 10 to 17 years of age with T2DM. The observed exposure-response relationship was overall comparable in adults and children and adolescents. Oral administration of empagliflozin resulted in an exposure within the range observed in adult patients. The observed geometric mean trough concentrations and geometric mean concentrations at 1.5 hours post-administration at steady state were 26.6 nmol/L and 308 nmol/L with empagliflozin 10 mg once daily and 67.0 nmol/L and 525 nmol/L with empagliflozin 25 mg once daily.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, fertility and early embryonic development.

Carcinogenicity

Two-year oral carcinogenicity studies were conducted in mice and rats. There was an increase in renal adenomas and carcinomas in male mice given empagliflozin at 1000 mg/kg/day. No renal tumours were seen at 300 mg/kg/day (11- and 28-times the exposure at the clinical dose of 25mg and 10 mg, respectively). These tumours are likely associated with a metabolic pathway not present in humans, and are considered to be irrelevant to patients given 10 or 25 mg empagliflozin. No drug-related tumours were seen in female mice or female rates at doses up to 1000 and 700 mg/kg/day, respectively, resulting in exposures at least 60 times that expected at the clinical dose of 10 or 25 mg empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node, were observed at 700 mg/kg/day, but not at 300 mg/kg/day (approximately 26- and 65-times the exposure at the clinical does of 25 mg and 10 mg, respectively). These tumours are common in rats and are unlikely to be relevant to humans.

Genotoxicity

Empagliflozin was not mutagenic or clastogenic in a battery of genotoxicity studies, including the Ames bacterial mutagenicity assay (bacterial reverse mutation), *in vitro* mouse lymphoma tk assays and *in vivo* rat bone marrow micronucleus assays.

Reproduction toxicity

Nonclinical 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. Empagliflozin administered during the period of organogenesis was not teratogenic at

doses up to 300 mg/kg in the rat or rabbit, which corresponds to approximately 48- and 122- times or 128- and 325- times the clinical dose of empagliflozin based on AUC exposure associated with the 25 mg and 10 mg doses, respectively. Doses of empagliflozin causing maternal toxicity in the rat also caused the malformation of bent limb bones at exposures approximately 155- and 393- times the clinical dose associated with the 25 mg and 10 mg doses, respectively. Maternally toxic doses in the rabbit also caused increased embryo-foetal loss at doses approximately 139- and 353- times the clinical dose associated with the 25 mg and 10 mg doses, respectively.

In pre- and postnatal toxicity studies in rats, reduced weight gain in offspring was observed at maternal exposures approximately 4- and 11-times the clinical dose associated with the 25 mg and 10 mg doses, respectively.

In a juvenile toxicity study in the rat, when empagliflozin was administered from postnatal day 21 until postnatal day 90, non-adverse, minimal to mild renal tubular and pelvic dilation in juvenile rats was seen only at 100 mg/kg/day, which approximates 11-times the maximum clinical dose of 25 mg. These findings were absent after a 13-week drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Each Pharmacor Empagliflozin Tablet Contains:

Tablet core:
Microcrystalline Cellulose
Maize Starch
Croscarmellose Sodium
Hypromellose
Colloidal Silicon Dioxide
Magnesium Stearate

Tablet coating (Opadry 02B38190 Yellow):
Hypromellose E464
Titanium Dioxide E171
Purified Talc E553b
Macrogol E1521
Iron oxide yellow E172

6.2. Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. Shelf life

Shelf life- 30 months.

In-use shelf life (After first opening)- 90 days

6.4. Special precautions for storage

Store below 25°C. Protect from light.

6.5. Nature and Contents of container

Tablets are supplied in

- Al - Al Desiccant Blister Pack containing 10 tablets (sample) and 30 tablets
- HDPE Bottle Pack containing 30 tablets, 90# tablets and 1000# tablets

 # For Dispensing Only. Not for Individual Patient Supply.

6.6. Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription only Medicine

8. SPONSOR

Pharmacor Limited
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9. DATE OF FIRST APPROVAL

10 September 2026

10. DATE OF REVISION OF THE TEXT

DD/MM/YY

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information