

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

JARDIANCE 10 mg film coated tablets

JARDIANCE 25 mg film coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### JARDIANCE 10 mg film coated tablets

Each film coated tablet contains 10 mg empagliflozin.

Excipient with known effect

Each tablet contains lactose monohydrate equivalent to 154.3 mg lactose anhydrous.

### JARDIANCE 25 mg film coated tablets

Each film coated tablet contains 25 mg empagliflozin.

Excipient with known effect

Each tablet contains lactose monohydrate equivalent to 107.4 mg lactose anhydrous.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film coated tablet (tablet).

### JARDIANCE 10 mg film-coated tablets

Pale yellow, round, biconvex and bevel-edged tablets. One side is debossed with the code 'S10', the other side is debossed with the Boehringer Ingelheim company symbol.

### JARDIANCE 25 mg film-coated tablets

Pale yellow, oval, biconvex tablets. One side is debossed with the code 'S25', the other side is debossed with the Boehringer Ingelheim company symbol.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

#### Glycaemic control:

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

#### *Monotherapy*

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

#### *Add-on combination therapy*

In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see Further Information section 5.1).

#### Prevention of cardiovascular events:

JARDIANCE is indicated in 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, JARDIANCE should be used in conjunction with other measures to reduce cardiovascular risk in line with the current standard of care.

## 4.2. Dose and method of administration

### Dose

The recommended starting dose of JARDIANCE 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.

When JARDIANCE 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).

### Special populations

#### *Renal impairment*

JARDIANCE is not recommended for use in patients with eGFR < 30 mL/min/1.73 m<sup>2</sup> (see sections 4.3 and 4.4). No dose adjustment is required for patients with eGFR ≥ 30 mL/min/1.73 m<sup>2</sup>.

#### *Hepatic impairment*

No dose adjustment is recommended for patients with hepatic impairment.

#### *Elderly Patients*

No dosage adjustment is recommended based on age. Therapeutic experience in patients aged 85 years and older is limited. Initiation of empagliflozin therapy in this population is not recommended (see sections 4.3 and 4.4). Patients aged 75 years and older should be prescribed with caution (see sections 4.3 and 4.4).

#### *Paediatric population*

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

### Method of administration

JARDIANCE 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 JARDIANCE (see section 6.1).

Patients with CKD stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR < 30mL/min/1.73 m<sup>2</sup> or CrCl < 30mL/min). The efficacy of JARDIANCE is dependent on renal function (see section 4.4).

## 4.4 Special warnings and precautions for use

### General

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

### Diabetic ketoacidosis

Cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalisation, have been reported in patients 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.

The risk of diabetic 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, JARDIANCE should be discontinued, the patient should be evaluated, and prompt treatment should be instituted.

Patients who may be at higher risk of ketoacidosis while taking JARDIANCE 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, and patients with a history of ketoacidosis. JARDIANCE 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 JARDIANCE consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE in clinical situations known to predispose to ketoacidosis (e.g. prolonged fasting due to acute illness or surgery). In these situations, consider monitoring of ketones, even if JARDIANCE treatment has been interrupted.

#### Necrotising fasciitis of the perineum (Fournier's gangrene)

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

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

#### Use in patients with renal impairment

JARDIANCE is contraindicated for use in patients with eGFR < 30 mL/min/1.73 m<sup>2</sup> (see sections 4.2 and 4.3).

#### Monitoring of renal function

Due to the mechanism of action, the efficacy of empagliflozin is dependent on renal function. Therefore assessment of renal function is recommended:

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

#### Risk for volume depletion

Based on the mode of action of SGLT2 inhibitors, osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in BP. 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 JARDIANCE should be considered until the fluid loss is corrected.

#### Urinary tract infections

In the pooled placebo-controlled double-blind trials of 18 to 24 weeks duration, the overall frequency of urinary tract infection reported as adverse event was higher than placebo in patients treated with empagliflozin 10 mg and similar to placebo in patients treated with empagliflozin 25 mg (see section 4.8). Postmarketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of JARDIANCE should be considered in patients with complicated urinary tract infections.

### Combination with glucagon like peptide (GLP-1) analogues

Empagliflozin has not been studied in combination with glucagon like peptide 1 (GLP-1) analogues.

### Elderly

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

Therapeutic experience in patients aged 85 years and older is limited. Initiation of JARDIANCE therapy in this population is not recommended.

### Urine laboratory assessments

Urine will test positive for glucose while patients are taking JARDIANCE 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 glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

### Pharmacokinetic Interactions

#### *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 JARDIANCE 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.

## **4.6. Fertility, pregnancy and lactation**

### Pregnancy (Category D)

There are limited data from the use of JARDIANCE in pregnant women. It is recommended to avoid the use of JARDIANCE 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. Similar effects have not been excluded for empagliflozin. JARDIANCE should be used in pregnancy only if the expected benefit to the patients justifies the potential risk to the foetus.

### 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 JARDIANCE.

### Effects on fertility

No studies on the effect on human fertility have been conducted for JARDIANCE. 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**

JARDIANCE 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 JARDIANCE is used in combination with a sulfonyleurea and/or insulin.

## **4.8. Undesirable effects**

### a. Summary of the safety profile

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 PPAR $\gamma$  agonist, DPP4 inhibitors, or insulin. This pool includes the EMPA-REG OUTCOME study involving 7,020 patients at high cardiovascular risk (mean age 63.1 years, 9.3% patients at least 75 years old, 28.5% women) treated with JARDIANCE 10 mg/day (n=2345), JARDIANCE 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, JARDIANCE 10 mg and JARDIANCE 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 JARDIANCE 10 mg and 1166 were treated with JARDIANCE 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.

#### 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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 JARDIANCE in placebo-controlled double-blind studies and derived from postmarketing experience.

<b>System Organ class</b>	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<i>Infections and infestations</i>		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections <sup>a</sup>  Urinary tract infection <sup>a</sup> (including pyelonephritis and urosepsis) <sup>b</sup>		Necrotising fasciitis of the perineum (Fournier's gangrene) <sup>b</sup>
<i>Metabolism and nutrition disorders</i>	Hypoglycaemia (when used with sulfonylurea or insulin) <sup>a</sup>		Ketoacidosis <sup>b</sup>	
<i>Skin and subcutaneous tissue disorders</i>		Pruritus Allergic skin reactions (e.g., rash, urticaria) <sup>b</sup>		Angioedema <sup>b</sup>
<i>Vascular disorders</i>			Volume depletion <sup>a</sup>	
<i>Renal and urinary disorders</i>		Increased urination <sup>a</sup>	Dysuria	
<i>General disorders and administration site conditions</i>		Thirst		

System Organ class	Very Common	Common	Uncommon	Not known
<i>Investigations</i>		Serum lipids increased <sup>c</sup>	Glomerular filtration rate decreased <sup>a</sup> Blood creatinine increased <sup>a</sup> Haematocrit increased <sup>c</sup>	

<sup>a</sup> see subsections below for additional information

<sup>b</sup> derived from postmarketing experience

<sup>c</sup> see section 5.1 for additional information

### 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 JARDIANCE 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 JARDIANCE 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 JARDIANCE 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 JARDIANCE 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<sup>1</sup>)

	Placebo	Empagliflozin	
		10 mg	25 mg
<b>Monotherapy (1245.20) (24 weeks)</b>	<b>n=229</b>	<b>n=224</b>	<b>n=223</b>
Overall confirmed (%)	0.4%	0.4%	0.4%
Major (%)	0%	0%	0%
<b>In Combination with Metformin (1245.23 (<i>met</i>)) (24 weeks)</b>	<b>n=206</b>	<b>n=217</b>	<b>n=214</b>
Overall confirmed (%)	0.5%	1.8%	1.4%
Major (%)	0%	0%	0%
<b>In Combination with Metformin + Sulfonylurea (1245.23 (<i>met</i> + <i>SU</i>)) (24 weeks)</b>	<b>n=225</b>	<b>n=224</b>	<b>n=217</b>
Overall confirmed (%)	8.4%	16.1%	11.5%
Major (%)	0%	0%	0%
<b>In Combination with Pioglitazone +/- Metformin (1245.19) (24 weeks)</b>	<b>n=165</b>	<b>n=165</b>	<b>n=168</b>
Overall confirmed (%)	1.8%	1.2%	2.4%
Major (%)	0%	0%	0%
<b>In Combination with Basal Insulin (1245.33) (18 weeks<sup>2</sup> / 78 weeks)</b>	<b>n=170</b>	<b>n=169</b>	<b>n=155</b>
Overall confirmed (%)	20.6%/ 35.3%	19.5%/ 36.1%	28.4%/ 36.1%
Major (%)	0%/ 0%	0%/ 0%	1.3%/ 1.3%

	Placebo	Empagliflozin	
		10 mg	25 mg
<b>In Combination with MDI Insulin +/-Metformin (1245.49) (18 weeks<sup>2</sup> / 52 weeks)</b>	<b>n=188</b>	<b>n=186</b>	<b>n=189</b>
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%
<b>In Combination with Metformin and Linagliptin (1275.9) (24 weeks<sup>3</sup>)</b>	<b>n=110</b>	<b>n=112</b>	<b>n=110</b>
Overall confirmed (%)	0.9%	0.0%	2.7%
Major (%)	0%	0%	0.9%
<b>EMPA-REG OUTCOME (1245.25)</b>	<b>n=2333</b>	<b>n=2345</b>	<b>n=2342</b>
Overall confirmed (%)	27.9%	28%	27.6%
Major (%)	1.5%	1.4%	1.3%

Confirmed: blood glucose  $\leq$ 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 JARDIANCE 25 mg and placebo (7.0% and 7.2%) and higher in patients treated with JARDIANCE 10 mg (8.8%). Similar to placebo, urinary tract infection was reported more frequently for JARDIANCE 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 JARDIANCE 10 mg (4.0%) and JARDIANCE 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.

### *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 JARDIANCE 10 mg (3.5%) and JARDIANCE 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 JARDIANCE (<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 (JARDIANCE 10 mg 0.6%, JARDIANCE 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  $\geq$  75 years of age (pooling of all patients with diabetes, n=13, 402) the frequency of volume depletion events was similar for JARDIANCE 10 mg (2.3%) compared to placebo (2.1%), but it increased with JARDIANCE 25 mg (4.3%).

### *Blood creatinine increased and glomerular filtration rate decreased*

The overall frequency of patients with increased blood creatinine and decreased glomerular filtration rate was similar between 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<sup>2</sup>, empagliflozin 25 mg -1.37 mL/min/1.73m<sup>2</sup>) 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).

#### 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://nzphvc.otago.ac.nz/reporting/>

#### **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, equivalent to 32 times the maximum recommended daily dose, 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<sub>50</sub> of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC<sub>50</sub> 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).

## Clinical efficacy and safety

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 JARDIANCE 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<sub>1c</sub>), 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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> was associated with a greater reduction in HbA<sub>1c</sub>. Clinically meaningful HbA<sub>1c</sub> reduction was seen in patients with eGFR > 30 mL/min/1.73 m<sup>2</sup> (see Dosage and Administration, Patients with Renal impairment). In patients aged 75 years and older, reduced efficacy of JARDIANCE 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<sub>1c</sub> 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 JARDIANCE resulted in statistically significant reductions in HbA<sub>1c</sub>, 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<sub>1c</sub> ≥ 8.5% to ≤ 10% empagliflozin resulted in a reduction in HbA<sub>1c</sub> 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<sub>1c</sub> (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 JARDIANCE daily significantly improved marker of beta cell function HOMA-β.

Table 3 Results of a 24 week (LOCF)<sup>1</sup> placebo-controlled study of JARDIANCE as monotherapy (Full Analysis Set)

JARDIANCE as monotherapy	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg	Sitagliptin 100mg
N	228	224	224	223
<b>HbA<sub>1c</sub> (%)</b>				
Baseline (mean)	7.91	7.87	7.86	7.85
Change from baseline <sup>2</sup>	0.08	-0.66	-0.78	-0.66
Difference from placebo <sup>2</sup>		-0.74*	-0.85*	-0.73
(97.5% CI)		(-0.90, -0.57)	(-1.01, -0.69)	(-0.88, -0.59) <sup>3</sup>

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

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<sub>1c</sub> 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 JARDIANCE resulted in statistically significant improvements in HbA<sub>1c</sub> 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<sub>1c</sub> (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)<sup>3</sup> placebo-controlled study of JARDIANCE as add-on to metformin (Full Analysis Set)

<b>JARDIANCE as add-on to metformin therapy</b>	<b>Placebo</b>	<b>Empagliflozin 10 mg</b>	<b>Empagliflozin 25 mg</b>
N	207	217	213
<b>HbA<sub>1c</sub> (%)</b>			
Baseline (mean)	7.90	7.94	7.86
Change from baseline <sup>1</sup>	-0.13	-0.70	-0.77
Difference from placebo <sup>1</sup> (97.5% CI)		-0.57* (-0.72, -0.42)	-0.64* (-0.79, -0.48)
N	184	199	191
<b>Patients (%) achieving HbA<sub>1c</sub> &lt; 7% with baseline HbA<sub>1c</sub> ≥ 7%<sup>2</sup></b>	12.5	37.7	38.7
N	207	216	213
<b>Fasting plasma glucose (mmol/L)<sup>2</sup></b>			
Baseline (mean)	8.66	8.58	8.29
Change from baseline <sup>1</sup>	0.35	-1.11	-1.24
Difference from placebo <sup>1</sup> (95% CI)		-1.47* (-1.74, -1.20)	-1.59* (-1.86, -1.32)
N	207	217	213
<b>Body weight (kg)</b>			
Baseline (mean)	79.73	81.59	82.21
Change from baseline <sup>1</sup>	-0.45	-2.08	-2.46
Difference from placebo <sup>1</sup> (97.5% CI)		-1.63* (-2.17, -1.08)	-2.01* (-2.56, -1.46)
N	207	217	213
<b>Patients (%) achieving weight loss of &gt;5%<sup>2</sup></b>	4.8	21.2	23.0
N	207	217	213
<b>Systolic blood pressure (mmHg)<sup>2</sup></b>			
Baseline (mean)	128.6	129.6	130.0
Change from baseline <sup>1</sup>	-0.4	-4.5	-5.2
Difference from placebo <sup>1</sup> (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<sub>1c</sub> 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<sub>1c</sub> ≥ 7.0% and treated with empagliflozin in combination with metformin achieved a target HbA<sub>1c</sub> < 7% compared to the individual components (Tables 5 and 6).

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

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

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<sub>1c</sub>; 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<sub>1c</sub>;

\*\* 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)<sup>2</sup> study comparing empagliflozin 25 mg in combination with metformin to the individual monotherapy components

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

	Empagliflozin 25 mg + metformin 1000 mg <sup>a</sup>	Empagliflozin 25 mg + metformin 2000 mg <sup>a</sup>	Empagliflozin 25 mg qd	Metformin 1000 mg <sup>a</sup>	Metformin 2000 mg <sup>a</sup>
N	165	167	162	166	162
<b>Body Weight (kg)</b>					
Baseline (mean)	82.9	83.7	83.4	82.9	83.8
% Change from baseline <sup>1</sup>	-3.6	-4.3	-2.8	-0.4	-1.2
Comparison vs. metformin (95% CI) <sup>1</sup>	-3.1** (-4.1, -2.2) <sup>b</sup>	-3.1** (-4.1, -2.2) <sup>b</sup>			

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<sub>1c</sub>; 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≤0.0056 for HbA<sub>1c</sub>

\*\* 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<sub>1c</sub> 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 JARDIANCE resulted in statistically significant improvements in HbA<sub>1c</sub> 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<sub>1c</sub> (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)<sup>3</sup> placebo-controlled study of JARDIANCE as add-on to metformin and a sulfonylurea (Full Analysis Set)

<b>JARDIANCE as add-on to metformin and a sulfonylurea therapy</b>	<b>Placebo</b>	<b>Empagliflozin 10 mg</b>	<b>Empagliflozin 25 mg</b>
N	225	225	216
<b>HbA<sub>1c</sub> (%)</b>			
Baseline (mean)	8.15	8.07	8.10
Change from baseline <sup>1</sup>	-0.17	-0.82	-0.77
Difference from placebo <sup>1</sup> (97.5% CI)		-0.64* (-0.79, -0.49)	-0.59* (-0.74, -0.44)
N	216	209	202
<b>Patients (%) achieving HbA<sub>1c</sub> &lt; 7% with baseline HbA<sub>1c</sub> ≥ 7%<sup>2</sup></b>	9.3	26.3	32.2
N	224	225	215
<b>Fasting plasma glucose (mmol/L)</b>			
Baseline (mean)	8.42	8.38	8.68
Change from baseline <sup>1</sup>	0.31	-1.29	-1.29
Difference from placebo <sup>1</sup> (95% CI)		-1.60* (-1.90, -1.30)	-1.60* (-1.90, -1.29)
N	225	225	216
<b>Body weight (kg)</b>			
Baseline (mean)	76.23	77.08	77.50
Change from baseline <sup>1</sup>	-0.39	-2.16	-2.39
Difference from placebo <sup>1</sup> (97.5% CI)		-1.76* (-2.25, -1.28)	-1.99* (-2.48, -1.50)
N	225	225	216
<b>Patients (%) achieving weight loss of &gt;5%<sup>2</sup></b>	5.8	27.6	23.6

<b>JARDIANCE as add-on to metformin and a sulfonylurea therapy</b>	<b>Placebo</b>	<b>Empagliflozin 10 mg</b>	<b>Empagliflozin 25 mg</b>
N	225	225	216
<b>Systolic blood pressure (mmHg)<sup>2</sup></b>			
Baseline (mean)	128.8	128.7	129.3
Change from baseline <sup>1</sup>	-1.4	-4.1	-3.5
Difference from placebo <sup>1</sup> (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<sub>1c</sub> 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<sub>1c</sub>, 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<sub>1c</sub> (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)<sup>3</sup> placebo-controlled study of JARDIANCE as add-on to pioglitazone with or without metformin (Full Analysis Set)

<b>Pioglitazone +/- metformin add-on therapy</b>	<b>Placebo</b>	<b>Empagliflozin 10 mg</b>	<b>Empagliflozin 25 mg</b>
N	165	165	168
<b>HbA<sub>1c</sub> (%)</b>			
Baseline (mean)	8.16	8.07	8.06
Change from baseline <sup>1</sup>	-0.11	-0.59	-0.72
Difference from placebo <sup>1</sup> (97.5% CI)		-0.48* (-0.69, -0.27)	-0.61* (-0.82, -0.40)
N	155	151	160
Patients (%) achieving HbA <sub>1c</sub> <7% with baseline HbA <sub>1c</sub> ≥7% <sup>3</sup>	7.7	23.8	30.0
N	165	163	168
<b>Fasting plasma glucose (mmol/L)</b>			
Baseline (mean)	8.43	8.44	8.43
Change from baseline <sup>1</sup>	0.37	-0.94	-1.23
Difference from placebo <sup>1</sup> (97.5% CI)		-1.32* (-1.72, -0.91)	-1.61* (-2.04, -1.12)

<b>Pioglitazone +/- metformin add-on therapy</b>	<b>Placebo</b>	<b>Empagliflozin 10 mg</b>	<b>Empagliflozin 25 mg</b>
N	165	165	168
<b>Body Weight (kg)</b>			
Baseline (mean)	78.1	77.97	78.93
Change from baseline <sup>1</sup>	0.34	-1.62	-1.47
Difference from placebo <sup>1</sup> (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% <sup>3</sup>	5.5	18.8	13.7
N	165	165	168
<b>Systolic blood pressure (mmHg)<sup>2</sup></b>			
Baseline (mean)	125.7	126.5	125.9
Change from baseline <sup>1</sup>	0.7	-3.1	-4.0
Difference from placebo <sup>1</sup> (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 A1C 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 HbA<sub>1c</sub> (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)<sup>1</sup> randomised, double-blind controlled study of empagliflozin and linagliptin as a fixed-dose combination in treatment naïve patients

	<b>Empagliflozin/linagliptin</b>		<b>Empagliflozin</b>		<b>Linagliptin</b>
	<b>25 mg/5 mg</b>	<b>10 mg /5 mg</b>	<b>25 mg</b>	<b>10 mg</b>	<b>5 mg</b>
<b>Primary endpoint: HbA<sub>1c</sub> [%] - 24 weeks</b>					
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 <sup>1,2</sup>	-1.08 (0.07)	-1.24 (0.07)	-0.95 (0.07)	-0.83 (0.07)	-0.67 (0.07)
Comparison vs. empagliflozin <sup>1</sup>	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE) <sup>2</sup>	-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 <sup>1</sup>					
Adjusted mean (SE) <sup>2</sup>	-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	--	--	--
<b>HbA<sub>1c</sub> [%] – 52 weeks<sup>4</sup></b>					
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 <sup>1</sup>	-1.17 (0.08)	-1.22 (0.08)	-1.01 (0.08)	-0.85 (0.08)	-0.51 (0.08)
Comparison vs. empagliflozin <sup>1</sup>	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 <sup>1</sup>					
Adjusted mean (SE)	-0.66 (0.12)	-0.71 (0.12)	--	--	--
95.0% CI	-0.90, -0.43	-0.94, -0.48	--	--	--



	Empagliflozin/linagliptin		Empagliflozin		Linagliptin
	25 mg/5 mg	10 mg /5 mg	25 mg	10 mg	5 mg
<b>Key secondary endpoint: [mmol/L] - 24 weeks</b>					
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 <sup>1,2</sup>	-1.64 (0.15)	-1.57 (0.15)	-1.35 (0.15)	-1.24 (0.15)	-0.33 (0.15)
Comparison vs. empagliflozin <sup>1</sup>	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE) <sup>2</sup>	-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 <sup>1</sup>					
Adjusted mean (SE) <sup>2</sup>	-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	--	--	--
<b>Key secondary endpoint: body weight [kg] - 24 weeks</b>					
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 <sup>1,3</sup>	-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 <sup>1</sup>					
Adjusted mean (SE) <sup>2</sup>	-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	--	--	--
<b>Key secondary endpoint: patients with HbA<sub>1c</sub> &lt;7.0% - 24 weeks</b>					
Number of patients, N (%)	121 (100.0)	122 (100.0)	118 (100.0)	121 (100.0)	127 (100.0)
With HbA <sub>1c</sub> <7.0% at Week 24	67 (55.4)	76 (62.3)	49 (41.5)	47 (38.8)	41 (32.3)
Comparison vs. Empagliflozin <sup>5</sup>	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 <sup>5</sup>					
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<sub>1c</sub>, 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<sub>1c</sub>, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (NCF), patients with HbA<sub>1c</sub> of 7% and above at baseline

In a pre-specified subgroup of patients with baseline HbA<sub>1c</sub> greater or equal than 8.5% the reduction from baseline in HbA<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> ≥7.0% and treated with the empagliflozin/linagliptin FDC achieved a target HbA<sub>1c</sub> 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 HbA<sub>1c</sub> (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)<sup>1</sup> 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		Linagliptin
	25 mg/5 mg	10 mg /5 mg	25 mg	10 mg	5 mg
<b>Primary endpoint: HbA<sub>1c</sub> [%] - 24 weeks</b>					
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 <sup>1,2</sup>	-1.19 (0.06)	-1.08 (0.06)	-0.62 (0.06)	-0.66 (0.06)	-0.70 (0.06)
Comparison vs. empagliflozin <sup>1</sup>	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE) <sup>2</sup>	-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 <sup>1</sup>					
Adjusted mean (SE) <sup>2</sup>	-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	--	--	--
<b>HbA<sub>1c</sub> [%] - 52 weeks<sup>4</sup></b>					
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 52 <sup>1,2</sup>	-1.21 (0.07)	-1.05 (0.07)	-0.64 (0.07)	-0.69 (0.07)	-0.48 (0.07)
Comparison vs. empagliflozin <sup>1</sup>	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE) <sup>2</sup>	-0.57 (0.10)	-0.36 (0.10)	--	--	--
95.0% CI	-0.77, -0.37	-0.56, -0.17	--	--	--
Comparison vs. linagliptin 5 mg <sup>1</sup>					
Adjusted mean (SE) <sup>2</sup>	-0.73 (0.10)	-0.57 (0.10)	--	--	--
95.0% CI	-0.93, -0.53	-0.77, -0.37	--	--	--
<b>Key secondary endpoint: FPG [mmol/L] - 24 weeks</b>					
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 <sup>1,2</sup>	-1.96 (0.14)	-1.79 (0.14)	-1.05 (0.14)	-1.16 (0.14)	-0.72 (0.14)
Comparison vs. empagliflozin <sup>1</sup>	vs. empa 25 mg	vs. empa 10 mg			
Adjusted mean (SE) <sup>2</sup>	-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 <sup>1</sup>					
Adjusted mean (SE) <sup>2</sup>	-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	--	--	--
<b>Key secondary endpoint: body weight [kg] - 24 weeks</b>					
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 <sup>1,2,3</sup>	-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 <sup>1</sup>					
Adjusted mean (SE) <sup>2</sup>	-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	--	--	--

	Empagliflozin/linagliptin		Empagliflozin		Linagliptin
	25 mg/5 mg	10 mg /5 mg	25 mg	10 mg	5 mg
<b>Key secondary endpoint: patients with HbA<sub>1c</sub> &lt; 7.0% - 24 weeks</b>					
Number of patients, N (%)	123 (100.0)	128 (100.0)	132 (100.0)	125 (100.0)	119 (100.0)
With HbA <sub>1c</sub> <7.0% at Week 24	76 (61.8)	74 (57.8)	43 (32.6)	35 (28.0)	43 (36.1)
Comparison vs. empagliflozin <sup>5</sup>	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 <sup>5</sup>					
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<sub>1c</sub>, 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<sub>1c</sub>, baseline eGFR (MDRD), geographical region, and treatment; based on FAS (NCF), patients with HbA<sub>1c</sub> of 7% and above at baseline

In a pre-specified subgroup of patients with baseline HbA<sub>1c</sub> greater or equal than 8.5% the reduction from baseline in HbA<sub>1c</sub> 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 HbA<sub>1c</sub>, FPG and body weight compared to placebo (background linagliptin 5 mg). A statistically significant greater number of patients with a baseline HbA<sub>1c</sub> ≥7.0% and treated with empagliflozin achieved a target HbA<sub>1c</sub> 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 <sup>1</sup>	Empagliflozin 25 mg <sup>1</sup>	Placebo <sup>2</sup>
<b>HbA<sub>1c</sub> (%) - 24 weeks<sup>3</sup></b>			
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) <sup>2</sup>	-0.79 (-1.02, -0.55) p<0.0001	-0.70 (-0.93, -0.46) p<0.0001	
<b>FPG (mmol/L) – 24 weeks<sup>3</sup></b>			
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	
<b>Body Weight-24 weeks<sup>3</sup></b>			
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) <sup>1</sup>	-2.8 ( 3.5, 2.1) p<0.0001	-2.2 ( 2.9, 1.5) p<0.0001	
<b>Patients (%) achieving HbA<sub>1c</sub> &lt;7% with baseline HbA<sub>1c</sub> ≥7% - 24 weeks<sup>4</sup></b>			
N	100	107	100
Patients (%) achieving A1C <7%	37.0	32.7	17.0
Comparison vs. placebo (odds ratio) (95% CI) <sup>5</sup>	4.0 (1.9, 8.7)	2.9 (1.4, 6.1)	

1 Patients randomized 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 randomized to the placebo group were receiving the placebo plus linagliptin 5 mg with background metformin

3 MMRM model on FAS (OC) includes baseline HbA<sub>1c</sub>, 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<sub>1c</sub>, baseline eGFR (MDRD), geographical region, and treatment; based on patients with HbA<sub>1c</sub> of 7% and above at baseline

In a prespecified subgroup of patients with baseline HbA<sub>1c</sub> greater or equal than 8.5% the reduction from baseline in HbA<sub>1c</sub> 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<sub>1c</sub>, 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)<sup>4</sup> in an active controlled study comparing empagliflozin to glimepiride as add on to metformin (Full Analysis Set)

<b>Empagliflozin as add-on to metformin therapy in comparison to glimepiride</b>	<b>Empagliflozin 25 mg</b>	<b>Glimepiride (up to 4 mg)</b>
N	765	780
<b>HbA<sub>1c</sub> (%)</b>		
Baseline (mean)	7.92	7.92
Change from baseline <sup>1</sup>	-0.66	-0.55
Difference from glimepiride <sup>1</sup> (97.5% CI)	-0.11* (-0.20, -0.01)	
N	690	715
<b>Patients (%) achieving HbA<sub>1c</sub> &lt;7% with baseline HbA<sub>1c</sub> ≥7%<sup>2</sup></b>	33.6	30.9
N	764	779
<b>FPG (mmol/L)<sup>2</sup></b>		
Baseline (mean)	8.33	8.32
Change from baseline <sup>1</sup>	-0.85	-0.17
Difference from glimepiride <sup>1</sup> (95% CI)	-0.69 (-0.86,-0.52)	
N	765	780
<b>Body Weight (kg)</b>		
Baseline (mean)	82.52	83.03
Change from baseline <sup>1</sup>	-3.12	1.34
Difference from glimepiride <sup>1</sup> (97.5% CI)	-4.46** (-4.87, -4.05)	
N	765	780
<b>Patients(%) achieving weight loss of &gt;5%<sup>2</sup></b>	27.5	3.8
N	765	780
<b>SBP (mmHg)<sup>3</sup></b>		
Baseline (mean)	133.4	133.5
Change from baseline <sup>1</sup>	-3.1	2.5
Difference from glimepiride <sup>1</sup> (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<sub>1c</sub> compared with placebo (Table 13). A greater proportion of patients with a baseline HbA<sub>1c</sub> ≥ 7.0% (19.5% empagliflozin 10 mg, 31.0% empagliflozin 25 mg) achieved a target HbA<sub>1c</sub> of < 7% compared with placebo (15.1%).

At Week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA<sub>1c</sub> 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)<sup>5</sup> weeks in a placebo-controlled study of empagliflozin as add on to multiple daily doses of insulin with metformin<sup>2</sup>

<b>Empagliflozin as add-on to insulin + metformin therapy</b>	<b>Placebo</b>	<b>Empagliflozin 10 mg</b>	<b>Empagliflozin 25 mg</b>
<b>N</b>	188	186	189
<b>HbA<sub>1c</sub> (%) at week 18</b>			
Baseline (mean)	8.33	8.39	8.29
Change from baseline <sup>1</sup>	-0.50	-0.94	-1.02
Difference from placebo <sup>1</sup> (97.5% CI)		-0.44* (-0.61, -0.27)	-0.52* (-0.69, -0.35)
<b>N</b>	115	119	118
<b>HbA<sub>1c</sub> (%) at week 52<sup>3</sup></b>			
Baseline (mean)	8.25	8.40	8.37
Change from baseline <sup>1</sup>	-0.81	-1.18	-1.27
Difference from placebo <sup>1</sup> (97.5% CI)		-0.38** (-0.62, -0.13)	-0.46* (-0.70, -0.22)
<b>N</b>	113	118	118
<b>Patients (%) achieving HbA<sub>1c</sub> &lt;7% with baseline HbA<sub>1c</sub> ≥7% at week 52<sup>4</sup></b>	26.5	39.8	45.8
<b>N</b>	188	186	189
<b>FPG (mmol/L) at week 52<sup>5</sup></b>			
Baseline (mean)	8.41	8.83	8.34
Change from baseline <sup>1</sup>	-0.02	-1.09	-1.31
Difference from placebo <sup>1</sup> (95% CI)		-1.07 (-1.55, -0.06)	-1.30 (-1.77, -0.83)
<b>N</b>	115	118	117
<b>Insulin dose (IU/day) at week 52<sup>3</sup></b>			
Baseline (mean)	89.94	88.57	90.38
Change from baseline <sup>1</sup>	10.16	1.33	-1.06
Difference from placebo <sup>1</sup> (97.5% CI)		-8.83** (-15.69, -1.97)	-11.22** (-18.09, -4.36)
<b>N</b>	115	119	118
<b>Body Weight (kg) at week 52<sup>3</sup></b>			
Baseline (mean)	96.34	96.47	95.37
Change from baseline <sup>1</sup>	0.44	-1.95	-2.04
Difference from placebo <sup>1</sup> (97.5% CI)		-2.39* (-3.54, -1.24)	-2.48* (-3.63, -1.33)
<b>N</b>	188	186	189
<b>SBP (mmHg)<sup>6</sup></b>			
Baseline (mean)	132.6	134.2	132.9
Change from baseline <sup>1</sup>	-2.6	-3.9	-4.0
Difference from placebo <sup>1,4</sup> (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<sub>1c</sub> 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<sub>1c</sub> 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<sub>1c</sub> compared to placebo. A greater proportion of patients with a baseline HbA<sub>1c</sub> ≥ 7.0% achieved a target HbA<sub>1c</sub> of <7% compared to placebo. At 78 weeks, empagliflozin resulted in

a statistically significant decrease in HbA<sub>1c</sub> 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 JARDIANCE as add on to basal insulin with or without metformin or sulfonylurea (Full Analysis Set - Completers)

<b>Basal insulin +/- metformin or sulfonylurea add-on therapy</b>	<b>Placebo</b>	<b>Empagliflozin 10 mg</b>	<b>Empagliflozin 25 mg</b>
<b>N</b>	125	132	117
<b>HbA<sub>1c</sub> (%) at week 18</b>			
Baseline (mean)	8.10	8.26	8.34
Change from baseline <sup>1</sup>	-0.01	-0.57	-0.71
Difference from placebo <sup>1</sup> (97.5% CI)		-0.56*	-0.70*
		(-0.78,-0.33)	(-0.93, -0.47)
<b>N</b>	112	127	110
<b>HbA<sub>1c</sub> (%) at week 78</b>			
Baseline (mean)	8.09	8.27	8.29
Change from baseline <sup>1</sup>	-0.02	-0.48	-0.64
Difference from placebo <sup>1</sup> (97.5% CI)		-0.46*	-0.62*
		(-0.73, -0.19)	(-0.90, -0.34)
<b>N</b>	112	127	110
<b>Basal insulin dose (IU/day) at week 78</b>			
Baseline (mean)	47.84	45.13	48.43
Change from baseline <sup>1</sup>	5.45	-1.21	-0.47
Difference from placebo <sup>1</sup> (97.5% CI)		-6.66**	-5.92**
		(-11.56, -1.77)	(-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 Hb1Ac 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 JARDIANCE led to statistically significant reduction of HbA<sub>1c</sub> and clinically meaningful improvement in FPG, body weight and BP compared to placebo at Week 24 (Table 15). The improvement in HbA<sub>1c</sub>, FPG, body weight, and BP was sustained up to 52 weeks.

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

	eGFR ≥ 60 to <90mL/min/1.73m <sup>2</sup>			eGFR ≥30 to <60mL/min/1.73m <sup>2</sup>	
	Placebo	Empagliflozin		Placebo	Empagliflozin
		10 mg	25 mg		25 mg
<b>N</b>	95	98	97	187	187
<b>HbA<sub>1c</sub> (%)</b>					
Baseline (mean)	8.09	8.02	7.96	8.04	8.03
Change from baseline <sup>1</sup>	0.06	-0.46	-0.63	0.05	-0.37
Difference from placebo <sup>1</sup> (95% CI)		-0.52* (-0.72, -0.32)	-0.68* (-0.88, -0.49)		-0.42* (-0.56, -0.28)
<b>N</b>	89	94	91	178	175
<b>Patients (%) achieving HbA<sub>1c</sub> &lt;7% with baseline HbA<sub>1c</sub> ≥7%<sup>2</sup></b>	6.7	17.0	24.2	7.9	12.0
<b>N</b>	95	98	97	187	187
<b>Fasting plasma glucose (mmol/L)<sup>2</sup></b>					
Baseline (mean)	8.04	8.10	8.24	7.98	7.92
Change from baseline <sup>1</sup>	0.31	-0.77	-1.00	0.56	-0.51
Difference from placebo <sup>1</sup> (95% CI)		-1.09 (-1.62, -0.55)	-1.32 (-1.86, -0.78)		-11.08* (-1.51, -0.64)
<b>N</b>	95	98	97	187	187
<b>Body Weight (kg)<sup>2</sup></b>					
Baseline (mean)	86.00	92.05	88.06	82.49	83.22
Change from baseline <sup>1</sup>	-0.33	-1.76	-2.33	-0.08	-0.98
Difference from placebo <sup>1</sup> (95% CI)		-1.43 (-2.09, -0.77)	-2.00 (-2.66, -1.34)		-0.91 (-1.41, -0.41)
<b>N</b>	95	98	97	187	187
<b>Systolic blood pressure (mmHg)<sup>2</sup></b>					
Baseline (mean)	134.69	137.37	133.68	136.38	136.64
Change from baseline <sup>1</sup>	0.65	-2.92	-4.47	0.40	-3.88
Difference from placebo <sup>1</sup> (95% CI)		-3.57 (-6.86, -0.29)	-5.12 (-8.41, -1.82)		-4.28 (-6.88, -1.68)

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 HbA<sub>1c</sub> >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<sub>1c</sub> 11.15%) resulted in a clinically meaningful reduction in HbA<sub>1c</sub> 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<sub>1c</sub> 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)<sup>3</sup> in a placebo-controlled study of JARDIANCE in patients with type 2 diabetes and uncontrolled blood pressure (Full Analysis Set)

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
N	271	276	276
<b>HbA<sub>1c</sub> (%)</b>			
Baseline (mean)	7.90	7.87	7.92
Change from baseline <sup>1</sup>	0.03	-0.59	-0.62
Difference from placebo <sup>1</sup> (95% CI)		-0.62* (-0.72, -0.52)	-0.65* (-0.75, -0.55)
<b>24 hour systolic blood pressure (mmHg)</b>			
Baseline (mean)	131.72	131.34	131.18
Change from baseline <sup>1</sup>	0.48	-2.95	-3.68
Difference from placebo <sup>1</sup> (95% CI)		-3.44* (-4.78, -2.09)	-4.16* (-5.50, -2.83)
<b>24 hour diastolic blood pressure (mmHg)</b>			
Baseline (mean)	75.16	75.13	74.64
Change from baseline <sup>1</sup>	0.32	-1.04	-1.40
Difference from placebo <sup>1</sup> (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 JARDIANCE 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 JARDIANCE (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<sup>2</sup>, 17.8% of 45-60 mL/min/1.73 m<sup>2</sup> and 7.7% of 30-45 mL/min/1.73 m<sup>2</sup>. 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*

JARDIANCE 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).

JARDIANCE also improved overall survival (Table 17 and Figure 2), which was driven by a reduction in cardiovascular death with JARDIANCE. 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
<b>Time to first occurrence of CV death, nonfatal MI, or non-fatal stroke N (%)</b>	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
<b>CV Death N (%)</b>	137 (5.9)	172 (3.7)
Hazard ratio vs. placebo (95% CI)		0.62 (0.49, 0.77)
p-value		<0.0001
<b>Non-fatal MI N (%)</b>	121 (5.2)	213 (4.5)
Hazard ratio vs. placebo (95% CI)		0.87 (0.70, 1.09)
p-value		0.2189
<b>Non-fatal stroke N (%)</b>	60 (2.6)	150 (3.2)
Hazard ratio vs. placebo (95% CI)		1.24 (0.92, 1.67)
p-value		0.1638
<b>All-cause mortality N (%)</b>	194 (8.3)	269 (5.7)
Hazard ratio vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		<0.0001
<b>Non-CV mortality N (%)</b>	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

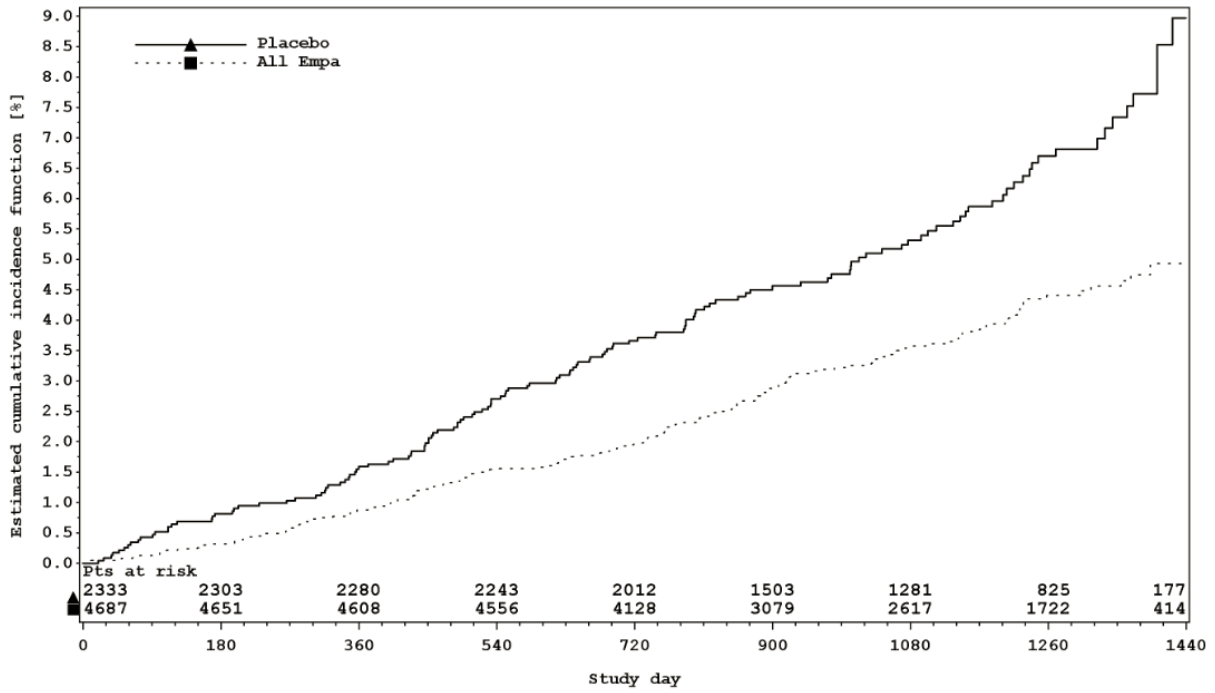
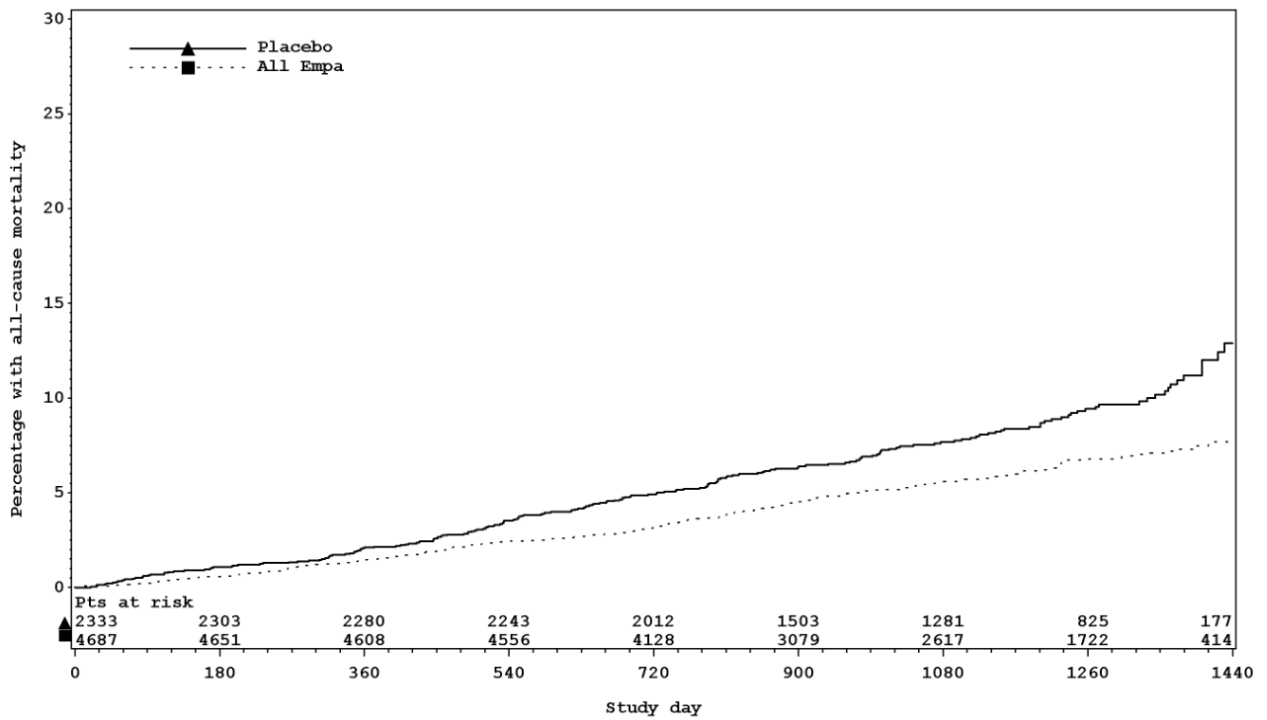


Figure 2 Time to occurrence of all-cause mortality\*



\*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*

JARDIANCE 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\*)

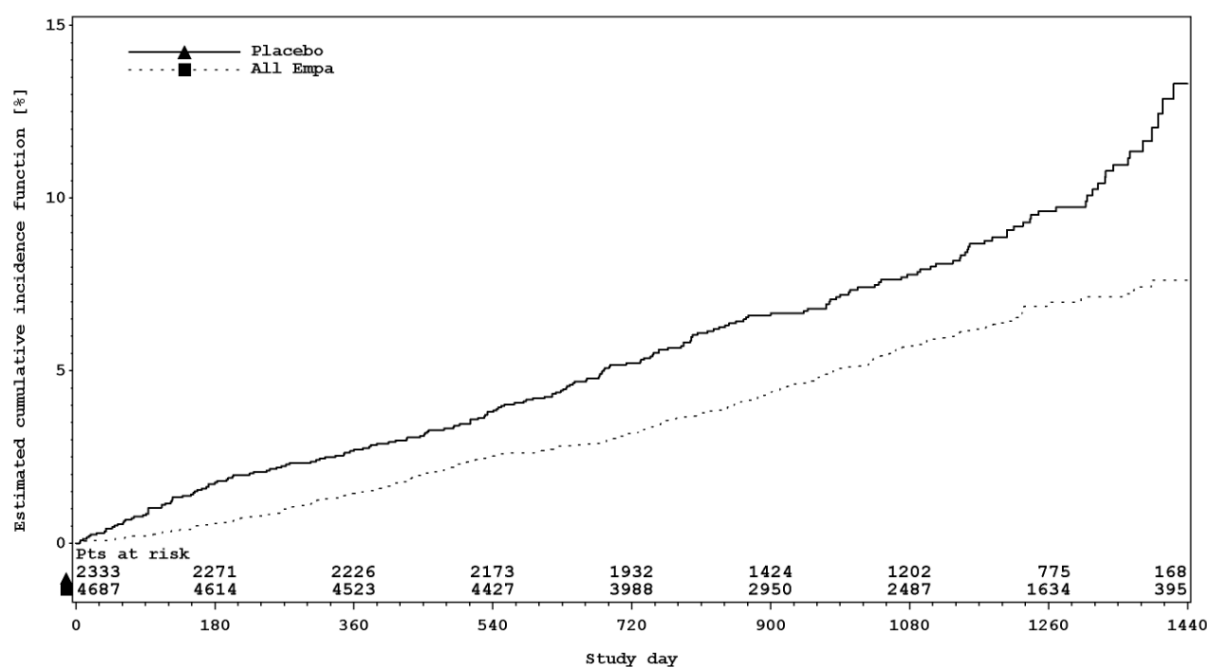
	Placebo	Empagliflozin ** (10 and 25 mg, pooled)
N	2333	4687
<b>Heart failure requiring hospitalisation or CV death (excluding fatal stroke) N (%)***</b>	198 (8.5)	265 (5.7)
HR (95% CI)		0.66 (0.55, 0.79)
p-value		<0.0001
<b>Heart failure requiring hospitalisation N (%)</b>	95 (4.1)	126 (2.7)
HR (95%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

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

\*\*empagliflozin 10 mg and 25 mg showed consistent results

\*\*\* time to first event

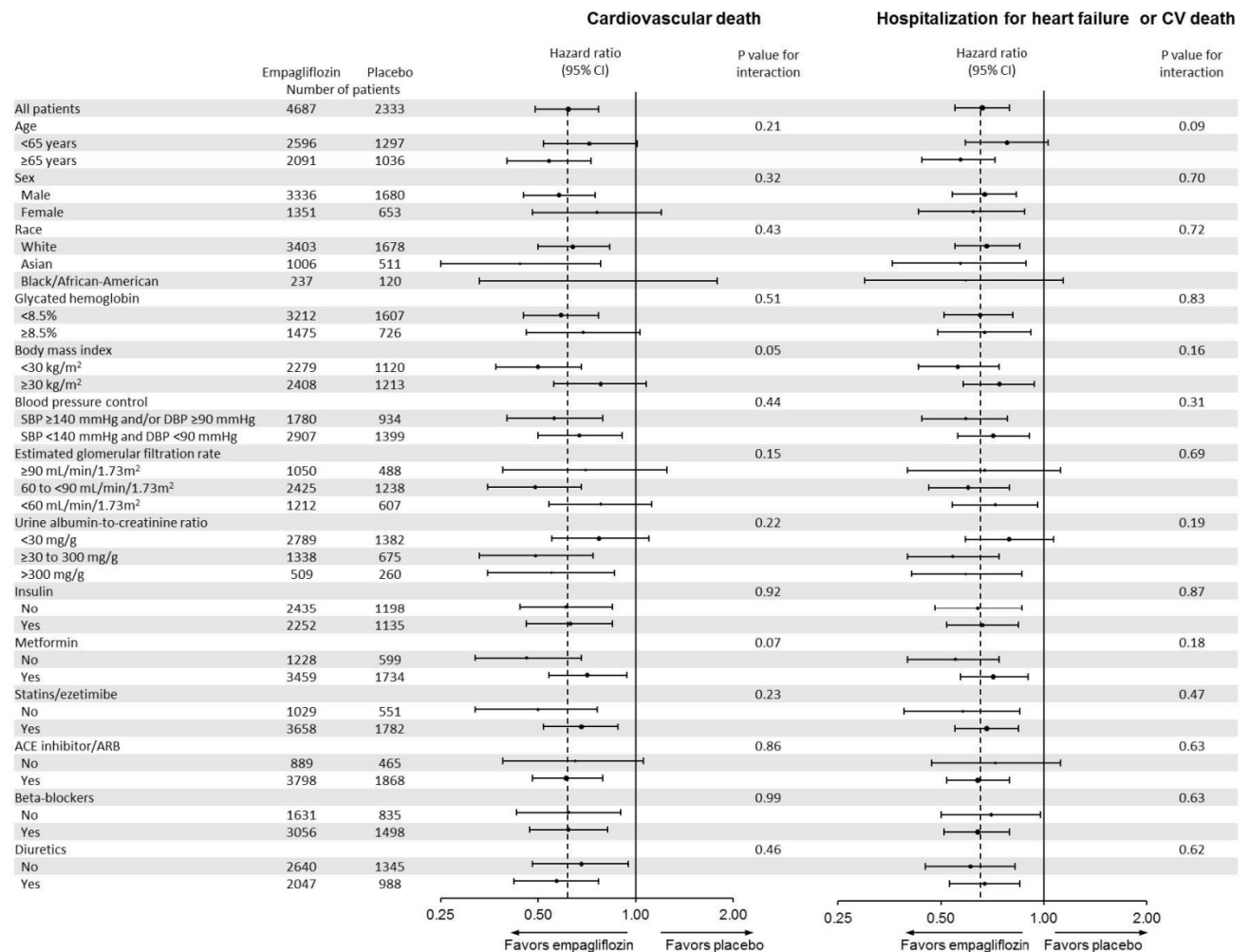
Figure 3 Time to first occurrence of first heart failure hospitalisation or CV death\*



\*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 JARDIANCE 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).

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

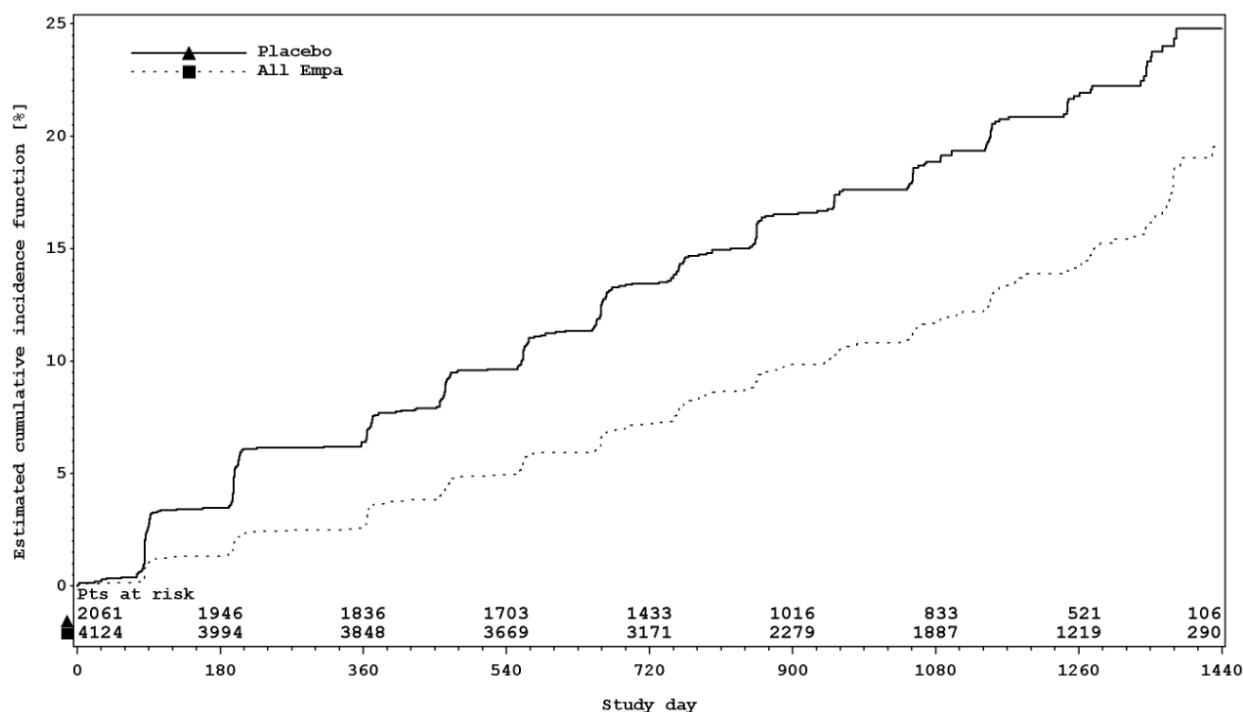
\*i.e. patients who had received at least one dose of study drug

\*\*Accompanied by an eGFR  $\leq 45$  mL/min/1.73m<sup>2</sup>

\*\*\* Urine Albumin Creatinine Ratio >33.9 mg/mmol

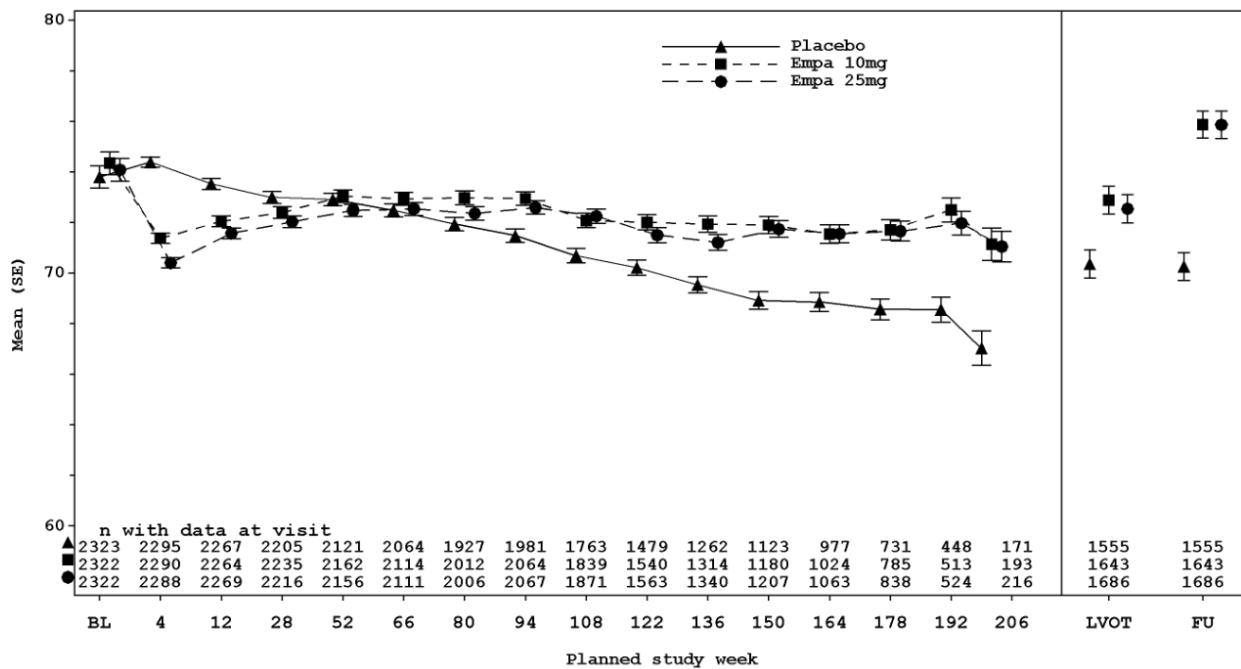
\*\*\*\* Due to low event rate, HR not calculated

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<sup>2</sup>) 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.

## 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 [<sup>14</sup>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 [<sup>14</sup>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<sup>2</sup>), moderate (eGFR: 30 - < 60 mL/min/1.73 m<sup>2</sup>), severe (eGFR: <30 mL/min/1.73 m<sup>2</sup>) 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<sub>max</sub> 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<sup>2</sup> compared to non-Asian patients with a BMI of 25 kg/m<sup>2</sup>.

### *Elderly*

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

### *Paediatric population*

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

## **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 rats 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 doses 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 weeks drug-free recovery period.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

#### Tablet core

Colloidal silicon dioxide

Croscarmellose sodium

Hyprolose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose.

#### Film coating

Hypromellose

Titanium dioxide (E171)

Talc

Macrogol 400

Iron oxide yellow (E172)

### **6.2. Incompatibilities**

Not applicable

### **6.3. Shelf life**

36 months.

### **6.4. Special precautions for storage**

Store at or below 30°C. Protect from light.

### **6.5. Nature and contents of container**

PVC/ aluminium perforated unit dose blisters.

Pack size of 10 (sample) or 30 film coated tablets.

*Note: not all pack sizes may be available.*

### **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 Medicine

## **8. SPONSOR**

Boehringer Ingelheim (N.Z.) Limited

P.O. Box 76-216

Manukau City

Auckland

NEW ZEALAND

Telephone 0800 802 461

## 9. DATE OF FIRST APPROVAL

23 April 2015

## 10. DATE OF REVISION OF THE TEXT

04 December 2019

## SUMMARY TABLE OF CHANGES

<b>Section changed</b>	<b>Summary of new information</b>
4.4	Update to subsection Diabetic ketoacidosis
5.1	Minor editorial changes