Boehringer Ingelheim

Jardiance Duo®

COMPOSITION

1 film-coated tablet contains:
D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3- furanyl]oxy]phenyl]methyl]phenyl]-, (1S) (= empagliflozin) 5 or 12.5 mg and
N,N-dimethylimidodicarbonimidic diamide hydrochloride (= metformin hydrochloride)
500 mg, 850 mg, or 1000 mg

JARDIANCE DUO film-coated tablets 5 mg/500 mg
Orange yellow, oval, biconvex film-coated tablets debossed with "S5" and the Boehringer Ingelheim logo on one side and "500" on the other side.

JARDIANCE DUO film-coated tablets 12.5 mg/500 mg
Pale brownish purple, oval, biconvex film-coated tablets debossed with "S12" and the Boehringer Ingelheim logo on one side and "500" on the other side.

JARDIANCE DUO film-coated tablets 12.5 mg/850 mg
Pinkish white, oval, biconvex film coated tablets debossed with "S12" and the Boehringer Ingelheim logo on one side and "850" on the other side.

JARDIANCE DUO film-coated tablets 12.5 mg/1000 mg
Dark brownish purple, oval, biconvex film coated tablets debossed with "S12" and the Boehringer Ingelheim logo on one side and "1000" on the other side.

CLINICAL PARTICULARS

Therapeutic indications

Glycaemic control:

JARDIANCE DUO is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus

- inadequately controlled with metformin
- inadequately controlled with metformin in combination with other glucose lowering products including insulin (see section Clinical Trials)
- already treated with empagliflozin and metformin co-administered as separate tablets

JARDIANCE DUO is indicated in adult patients with type 2 diabetes mellitus and established cardiovascular disease when treatment with empagliflozin and metformin is appropriate and empagliflozin is needed to reduce the incidence of cardiovascular death (see section 5.1).

Posology and method of administration

Adults with normal renal function (GFR ≥ 90ml/min)

The recommended dose is one tablet twice daily. The dosage should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability. The maximum recommended daily dose of JARDIANCE DUO is 25 mg of empagliflozin and 2000 mg of metformin (see table 1 for additional dosing information).

- In patients not adequately controlled on metformin twice daily alone or in combination with other products, including insulin, the recommended starting dose of JARDIANCE DUO should provide empagliflozin 5 mg twice daily (10 mg total daily dose) and the dose of metformin similar to the dose already being taken. In patients tolerating a total daily dose of empagliflozin 10 mg and who need a tighter glycemic control, the dose can be increased to a total daily dose of empagliflozin 25 mg.
- Patients switching from separate tablets of empagliflozin (10 mg or 25 mg total daily dose) and metformin (dose taken twice-daily) to JARDIANCE DUO should receive the same daily dose of empagliflozin and metformin.

When JARDIANCE DUO is used in combination with a sulphonylurea and/or insulin, a lower dose of sulphonylurea and/or insulin may be required to reduce the risk of hypoglycaemia (see sections Interactions and Undesirable Effects.)

For the different doses of metformin, JARDIANCE DUO is available in strengths of 5 mg empagliflozin plus 500 mg, 850 mg or 1000 mg metformin hydrochloride or 12.5 mg empagliflozin plus 500 mg, 850 mg or 1000 mg metformin hydrochloride. Not all strength presentation may be available locally.

JARDIANCE DUO should be given with meals to reduce the gastrointestinal undesirable effects associated with metformin.

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken at the same time. In that case, the missed dose should be skipped.

Special Populations

*Patients with renal impairmen*t

No dose adjustment is recommended for patients with mild renal impairment.

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Table 1 Posology for renally impaired patients*

eGFR ml/min	Metformin	Empagliflozin
60 - 89	Maximum daily dose is 3000 mg.*	Maximum daily dose is 25 mg. No dose adjustment is required.

	Dose reduction may be considered in relation to declining renal function.	
45 - 59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	No dose adjustment is required.
30 - 44	Maximum daily dose is 1000 mg.* The starting dose is at most half of the maximum dose.	Empagliflozin Should not be initiated Empagliflozin should be discontinued if eGFR is persistently less than 45 ml/min/1.73m2 or CrCl below 45 ml/min
<30	Metformin is contraindicated.	Empagliflozin is not recommended

* If no adequate strength of JARDIANCE DUO is available, individual monocomponents should be used instead of the fixed dose combination.

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

Elderly patients
In patients 75 years and older, an increased risk for volume depletion should be taken into account. In patients aged 85 years and older, initiation of empagliflozin therapy is not recommended due to the limited therapeutic experience.

Contraindications

- Hypersensitivity to active ingredients empagliflozin and/or metformin or to any of the excipients (see section Composition)
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma
- Severe renal failure (CrCl <30 ml/min) or eGFR <30 ml/min/1.73m^2, due to its metformin component.
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock, intravascular administration of iodinated contrast agents (see section Special warnings and precautions)
- Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (see section Interactions)

Special warnings and precautions for use

General

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

Diabetic ketoacidosis

Cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, 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 (250 mg/dl).

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 DUO should be discontinued, patient should be evaluated, and prompt treatment should be instituted.

Patients who may be at higher risk of ketoacidosis while taking JARDIANCE DUO 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 DUO should be used with caution in these patients. When reducing the insulin dose (see Dosage and Administration) caution should be taken. In patients treated with JARDIANCE DUO consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE DUO 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 DUO treatment has been interrupted

Lactic acidosis

Lactic acidosis, a very rare, but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.
In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see section Contraindications and Interactions).

Patients and/or care-givers should be informed of the risk of lactic acidosis.

Lactic acidosis is characterised by acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention.

Diagnostic laboratory findings are decreased blood pH (<7.35), increased plasma lactate levels (>5 mmol/l), and an increased anion gap and lactate/pyruvate ratio.

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis.

In patient with eGFR > 60 ml/min/1.73m2, Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections Posology and Interactions.

In patients with moderate renal impairment, Metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Necrotizing fasciitis of the perineum (Fournier's gangrene)

Postmarketing cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection, have been reported in female and male patients with diabetes mellitus treated with SGLT2 inhibitors, including empagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death.
Patients treated with JARDIANCE DUO who present with pain or tenderness, erythema, swelling in the genital or perineal area, fever, malaise should be evaluated for necrotizing fasciitis. If suspected, JARDIANCE DUO should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Renal function

Due to the mechanism of action, the efficacy of empagliflozin is dependent on renal function.

GFR should be assessed before treatment initiation and regularly thereafter, see section Posology. JARDIANCE DUO is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal function, see section Contraindications.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal impairment. In patients with stable chronic heart failure, JARDIANCE DUO may be used with a regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, JARDIANCE DUO is contraindicated due to the metformin component (see section Contraindications).

Elderly patients

The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status. Patients age 75 years and older may be at an increased risk of volume depletion, therefore, JARDIANCE DUO should be prescribed with caution in these patients (see section Undesirable effects). Therapeutic experience in patients aged 85 years and older is limited. Initiation of treatment in this population is not recommended.

Use in patients at risk for volume depletion

Based on the mode of action of SGLT-2 inhibitors, **osmotic diuresis accompanying therapeutic glucosuria may lead to a modest decrease in blood pressure. Therefore, caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk**, such as patients with known cardiovascular disease, patients on anti- hypertensive therapy with a history of hypotension or patients aged 75 years and older.

In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), **careful monitoring of volume status** (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) **and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with JARDIANCE DUO 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 in patients treated with empagliflozin 10 mg plus metformin as compared to patients treated with placebo plus metformin or empagliflozin 25 mg plus metformin (see section Undesirable effects). Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with empagliflozin. Temporary interruption of treatment should be considered in patients with complicated urinary tract infections.

Surgery

JARDIANCE DUO must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Vitamin B12

The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

Hepatic injury

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

Interaction with other medicinal products and other forms of interaction

Empagliflozin

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 sulphonylureas, may increase the risk of hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin (see sections Posology and method of administration and Undesirable effects).

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

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

In vitro assessment of drug interactions
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The potential for empagliflozin to reversibly inhibit or inactivate the major CYP450 isoforms or UGT1A1 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. The effect of UGT induction on empagliflozin has not been studied. Co-medication with known inducers of UGT enzymes should be avoided due to a potential risk of decreased efficacy.

Empagliflozin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but it does not inhibit these efflux transporters at therapeutic doses. Based on in vitro studies, 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 coadministered with other commonly used medicinal products. Based on results of pharmacokinetic studies no dose adjustment of empagliflozin is recommended when co-administered with commonly prescribed medicinal products.

Empagliflozin pharmacokinetics were similar with and without co-administration of glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide and hydrochlorothiazide 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 glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide and oral contraceptives when co-administered in healthy volunteers.

Metformin

Concomitant use not recommended

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis particularly in cases of fasting, malnutrition or hepatic insufficiency.

Iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis.

In patient with eGFR > 60 ml/min/1.73m^2, Metformin must be discontinued prior to or at the time of the imaging procedure and not be restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see section Posology and Special warnings and precautions for use).

In patients with moderate renal impairment, Metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Combination requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with:

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of JARDIANCE DUO or its individual components in pregnant women.
Animal studies show that empagliflozin crosses the placenta during late gestation to a very limited extend but do not indicate direct or indirect harmful effects with respect to early embryonic development. However, animal studies have shown adverse effects on postnatal development.
Animal studies with the combination of empagliflozin and metformin or with metformin alone have shown reproductive toxicity at higher doses of metformin only (See section Toxicology).
As a precautionary measure, JARDIANCE DUO is not recommended during pregnancy. When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with JARDIANCE DUO but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus associated with abnormal blood glucose levels.

Lactation

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants; however only limited data are available. It is unknown whether empagliflozin is excreted in human milk.
Available nonclinical data in animals have shown excretion of empagliflozin in milk. A risk to human newborns/infants cannot be excluded.
This medicinal product should not be used during breast feeding.

Fertility

No studies on the effect on human fertility have been conducted with JARDIANCE DUO or its individual components.
Non-clinical studies in animals with the individual components do not indicate direct or indirect harmful effects with respect to fertility.

Effect on ability to drive and use machines

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

Undesirable effects

A total of 12245 patients with type 2 diabetes were treated in clinical studies to evaluate the safety of empagliflozin plus metformin, of which 8199 patients were treated with empagliflozin plus metformin, either alone, or in addition to a sulfonylurea, pioglitazone, DPP4 inhibitors, or insulin. In these trials 2910 patients received treatment with empagliflozin 10 mg plus metformin and 3699 patients treatment with empagliflozin 25 mg plus metformin for at least 24 weeks and 2151 or 2807 patients for at least 76 weeks.

The overall safety profile of empagliflozin plus metformin for patients enrolled in the EMPA-REG OUTCOME® study was comparable to the previously known safety profile.

Placebo controlled, double-blind trials of 18 to 24 weeks of exposure included 3456 patients, of which 1271 were treated with empagliflozin 10 mg plus metformin and 1259 with empagliflozin 25 mg plus metformin.

The most frequently reported adverse event in clinical trials were hypoglycaemia, in combination with insulin and/or sulphonylurea, urinary tract infections, genital tract infections and increased urination (See Description of selected side effects).
No additional side effects were identified in clinical trials with empagliflozin plus metformin compared to the side effects of the single components.

Table 2 Side effects reported in patients who received empagliflozin monotherapy or combination therapy of empagliflozin and metformin in placebo controlled double-blind studies of up to 24 weeks (regardless of investigator reported causality assessment), and side effects derived from postmarketing experience with empagliflozin monotherapy or combination therapy of empagliflozin and metformin, classified by MedDRA System organ class and MedDRA Preferred terms

System Organ class	**Empagliflozin and metformin Side effect**
Infections and infestations	Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections[1, 2] Urinary tract infection[1, 2] (including pyelonephritis and urosepsis)[~~6~~5] **Necrotizing fasciitis of the perineum (Fournier´s gangrene)**[2,~~6~~5]
Gastrointestinal disorders[5]	Nausea[3] Vomiting[3] Diarrhoea[3] Abdominal pain[3] Loss of appetite[3] Constipation
Metabolism and nutrition disorders	Hypoglycaemia (when used with sulphonylurea or insulin)[1] Lactic acidosis[3] Vitamin B12 ~~absorption~~ decrease/deficiency[3,~~4~~] Ketoacidosis[~~6~~5]
Hepatobiliary disorders	Liver function tests abnormalities[3], Hepatitis[3]
Nervous system disorders	Taste disturbance[3]
Skin and subcutaneous tissue disorders	Pruritus[2, 3] Allergic skin reactions (e.g. Rash[~~6~~5], Urticaria[3,~~6~~5], Erythema[3]) Angioedema[2,~~6~~5]
Vascular disorders	Volume depletion[1,2]
Renal and urinary disorders	Increased urination[1,2] Dysuria[2]
General disorders and administration site conditions	Thirst[2]
Investigations	Glomerular filtration rate decreased[1] Blood creatinine increased[1] Haematocrit increased[2,~~7~~6] Serum lipids increased[2,~~7~~6]

[1] See subsections below for additional information
[2] Identified side effects of empagliflozin monotherapy
[3] Identified side effects, based on metformin PI
[4] ~~Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may result in clinically significant vitamin B12 deficiency (e.g. megaloblastic anaemia)~~
[54] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.
[65] Identified side effects from postmarketing experience
[76] See section clinical trials for additional information

Description of selected side effects

The frequencies below are calculated for side effects regardless of causality.

Hypoglycaemia
The frequency of hypoglycaemia depended on the background therapy in the respective studies.

Confirmed hypoglycaemia
The frequency of patients with confirmed hypoglycaemia was similar for empagliflozin plus metformin, placebo plus metformin and as add-on with linagliptin plus metformin. An increased frequency was noted when given as add-on to a sulfonylurea (empagliflozin 10mg: 16.1%, empagliflozin 25mg: 11.5% and placebo: 8.4%), and add-on to insulin with or without a sulphonylurea (empagliflozin 10mg: 31.3%, empagliflozin 25mg: 36.2% and placebo: 34.7%).

Major hypoglycaemia (events requiring assistance)
The overall frequency of patients with major hypoglycaemic events was low (<1%) and similar for empagliflozin and placebo on a background of metformin. The frequency of major hypoglycaemia depended on the background therapy in the respective studies. (see section Dosage and Administration; see Table 3 below)

Table 3 Frequency of patients with confirmed hypoglycaemic events per trial and indication (1245.19, 1245.23(met), 1245.23(met+SU), 1245.33, 1245.49, 1276.1 and 1276.10, 1275.9, and 1245.25 – TS[1])

Treatment group	**Placebo**	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
In combination with metformin (1245.23 *(met)*) (24 weeks)			
N	**206**	**217**	**214**
Overall confirmed (%)	0.5%	1.8%	1.4%
Major (%)	0%	0%	0%
In Combination with Metformin + Sulfonylurea (1245.23 *(met + SU)*) (24 weeks)			
N	**225**	**224**	**217**
Overall confirmed (%)	8.4%	16.1%	11.5%
Major (%)	0%	0%	0%
In Combination with Pioglitazone +/- Metformin (1245.19) (24 weeks)			
N	**165**	**165**	**168**
Overall confirmed (%)	1.8%	1.2%	2.4%

Major (%)	0%	0%	0%
In Combination with Basal Insulin +/- Metformin +/- Sulfonylurea (1245.33) (18 weeks[2] / 78 weeks)			
N	**170**	**169**	**155**
Overall confirmed (%)	20.6% / 35.3%	19.5 % / 36.1%	28.4% / 36.1%
Major (%)	0% / 0%	0% / 0%	1.3% / 1.3%
In Combination with MDI Insulin +/-Metformin (1245.49) (18 weeks[2] / 52 weeks)			
N	**188**	**186**	**189**
Overall confirmed (%)	37.2% / 58.0%	39.8% / 51.1%	41.3% / 57.7%
Major (%)	0.5 % / 1.6%	0.5 % / 1.6%	0.5% / 0.5%
Empagliflozin BID versus QD as add on to metformin (1276.10) (16 weeks)			
	Placebo	**Empa 10 mg**	**Empa 25 mg**
N	**107**	**439**	**437**
Overall confirmed (%)	0.9%	0.5%	0.2%
Major (%)	0%	0%	0%
In Combination with metformin in drug-naïve patients (1276.1[3]) (24 weeks)			
	Met 500/1000 mg BID	**Empa 10/25 mg QD**	**Empa (5/12.5 mg) + Met (500/1000 mg) BID**
N	**341**	**339**	**680**
Overall confirmed (%)	0.6%	0.6%	1.0%
Major (%)	0%	0%	0%
In Combination with metformin and linagliptin (1275.9) (24 weeks)[3]			
N	n=110	n=112	n=110
Overall confirmed (%)	0.9%	0.0%	2.7%
Major (%)	0%	0%	0.9%
Empa Reg Outcome Study (1245.25)			
	Placebo	**Empagliflozin 10 mg**	**Empagliflozin 25 mg**
N	2333	2345	2342
Overall confirmed (%)	27.9%	28%	27.6%
Major (%)	1.5%	1.4%	1.3%

Confirmed: blood glucose ≤70 ml/dL 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] Eight treatment arms: 4 combination treatments of empagliflozin (5 mg or 12.5 mg BID) and metformin (500 or 1000 mg BID) and treatment with the individual components of empagliflozin (10 mg or 25 mg QD) or metformin (500 mg or 1000 mg BID).

[3]This was a fixed-dose combination of empagliflozin with linagliptin 5 mg with a background treatment with metformin. (see also Clinical Trials section).

Urinary tract infection

The overall frequency of urinary tract infection adverse events was higher in patients treated with empagliflozin 10 mg plus metformin (8.8%) as compared to empagliflozin 25 mg plus metformin (6.6%) or placebo plus metformin (7.8%). Similar to placebo, urinary tract infection was reported more frequently for empagliflozin plus metformin in patients with a history of chronic or recurrent urinary tract infections. The intensity of urinary tract infections was similar to placebo. Urinary tract infection events were reported more frequently for empagliflozin 10 mg plus metformin compared with placebo in female patients, but not for empagliflozin 25 mg plus metformin. The frequencies of urinary tract infections were low for male patients and were balanced across treatment groups.

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection

Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for empagliflozin 10 mg plus metformin (4.0%) and empagliflozin 25 mg plus metformin (3.9%) compared to placebo plus metformin (1.3%), and were reported more frequently for empagliflozin plus metformin compared to placebo in female patients. The difference in frequency was less pronounced in male patients. 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 PT search including pollakiuria, polyuria, nocturia) was observed at higher frequencies in patients treated with empagliflozin 10 mg plus metformin (3.0%) and empagliflozin 25 mg plus metformin (2.9%) compared to placebo plus metformin (1.4%). Increased urination was mostly mild or moderate in intensity. The frequency of reported nocturia was comparable between placebo and empagliflozin, both on a background of metformin (<1%).

Volume depletion

The overall frequency of volume depletion (including the predefined terms blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolaemia, orthostatic hypotension, and syncope) was low and comparable to placebo (empagliflozin 10 mg plus metformin (0.6%), empagliflozin 25 mg plus metformin (0.3%) and placebo plus metformin (0.1%). The effect of empagliflozin on urinary glucose excretion is associated with osmotic diuresis, which could affect the hydration status of patients age 75 years and older. In patients ≥75 years of age volume depletion events have been reported in a single patient treated with empagliflozin 25 mg plus metformin.

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 as add-on to metformin (blood creatinine increased: empagliflozin 10 mg 0.5%, empagliflozin 25 mg 0.1%, placebo 0.4%; glomerular filtration rate decreased: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0%, placebo 0.2%).

In these placebo-controlled, double-blind studies up to 24 weeks, initial transient increases in creatinine (mean change from baseline after 12 weeks: empagliflozin 10 mg 0.02 mg/dL, empagliflozin 25 mg 0.02 mg/dL) and initial transient decreases in estimated glomerular filtration rates (mean change from baseline after 12 weeks: empagliflozin 10 mg -1.46 mL/min/1.73m2, empagliflozin 25 mg -2.05 mL/min/1.73m2) have been observed. In the long term studies, these changes were generally reversible during continuous treatment or after drug discontinuation (see section Clinical Trials figure 6 for the eGFR course in the EMPA-REG outcome® study)**.**

Overdose

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.

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin hydrochloride or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

Therapy

In the event of an overdose, supportive treatment should be initiated as appropriate to the patient's clinical status. The most effective method to remove lactate and metformin hydrochloride is haemodialysis whereas removal of empagliflozin by haemodialysis has not been studied.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics properties

Pharmacotherapeutic group: Combinations of oral blood glucose lowering drugs, ATC code: A10BD20

Mode of Action

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an IC_{50} of 1.3 nM. It has a 5000-fold selectivity over human SGLT1 (IC_{50} of 6278 nM), responsible for glucose absorption in the gut. Furthermore high selectivity could be shown toward other glucose transporters (GLUTs) responsible for glucose homeostasis in the different tissues.

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

Empagliflozin improves glycaemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent upon the blood glucose concentration and GFR. Through inhibition of SGLT-2 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 25 mg empagliflozin once daily. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with T2DM.

Empagliflozin improves both fasting and post-prandial plasma glucose levels.

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

Improvement of surrogate markers of beta cell function including Homeostasis Model Assessment-B (HOMA-β) was noted. In addition urinary glucose excretion triggers calorie loss, associated with body fat loss and body weight reduction.

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

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin hydrochloride may act via 3 mechanisms:

(1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
(2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
(3) and delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin hydrochloride increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.
In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium- term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical Trials

A total of 10224 patients with type 2 diabetes were treated in 9 double- blind, placebo or active-controlled clinical studies of at least 24 weeks duration, of which 2947 patients received empagliflozin 10 mg and 3703 received empagliflozin 25 mg as add-on to metformin therapy.
Treatment with empagliflozin in combination with metformin with or without other background (pioglitazone, sulfonylurea, DPP-4 inhibitors, and insulin) led to clinically relevant improvements in HbA1c, fasting plasma glucose, body weight, systolic and diastolic blood pressure. Administration of empagliflozin 25 mg resulted in a higher proportion of patients achieving HbA1c goal of less than 7% and fewer patients needing glycaemic rescue compared to empagliflozin 10 mg and placebo. In patients age 75 years and older, numerically lower reductions in HbA1c were observed with empagliflozin treatment. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Empagliflozin in combination with metformin in drug-naïve patients led to clinically meaningful reductions in HbA1c, FPG, body weight and BP.

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 not sufficiently treated with metformin. Treatment with empagliflozin resulted in statistically significant improvements in HbA1c and body weight, and clinically meaningful reductions in FPG and blood pressure compared to placebo (Table 4).

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

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

Empagliflozin as add-on to metformin therapy	**Placebo**	**Empagliflozin 10mg**	**Empagliflozin 25mg**
N	207	217	213
HbA1c (%)			
Baseline (mean)	7.90	7.94	7.86
Change from baseline[1]	-0.13	-0.70	-0.77
Difference from placebo[1] (97.5% CI)		-0.57* (-0.72, -0.42)	-0.64* (-0.79, -0.48)
N	184	199	191
Patients (%) achieving HbA1c < 7% with baseline HbA1c ≥7%[2]	12.5	37.7	38.7
N	207	216	213
FPG (mg/-dL) [mmol/l][2]			
Baseline (mean)	156.0 [8.66]	154.6 [8.58]	149.4 [8.29]
Change from baseline[1]	6.4 [0.35]	-20.0 [-1.11]	-22.3 [-1.24]
Difference form placebo[1] (95% CI)		-26.4* (-31.3, -21.6) [-1.47* (-1.74, -1.20)]	-28.7* (-33.6, -23.8) [-1.59* (-1.86, -1.32)]

N	207	217	213
Body weight (kg)			
Baseline (mean)	79.73	81.59	82.21
Change from baseline[1]	-0.45	-2.08	-2.46
Difference from placebo[1] (97.5% CI)		-1.63* (-2.17, -1.08)	-2.01 (-2.56, -1.46)
N	207	217	213
Patients (%) achieving weight loss of > 5%[2]	4.8	21.2	23.0
N	207	217	213
SBP (mmHg)[2]			
Baseline (mean)	128.6	129.6	130.0
Change from baseline[1]	-0.4	-4.5	-5.2
Difference from placebo[1] (95% CI)		-4.1* (-6.2, -2.1)	-4.8* (-6.9, -2.7)

[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 glycemic 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 HbA1c and led to significantly greater reductions in FPG and body weight compared to the individual components. A greater proportion of patients with a baseline HbA1c ≥7.0% and treated with empagliflozin in combination with metformin achieved a target HbA1c <7% compared to the individual components (Tables 5 and 6).

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

	Empagliflozin10mg +metformin1000mg[a]	**Empagliflozin10mg +metformin 2000mg[a]**	**Empagliflozin 10mg (qd)**	**Metformin1 000mg[a]**	**Metformin2 000mg[a]**
N	161	167	169	167	162
HbA1c (%)					
Baseline (mean)	8.7	8.7	8.6	8.7	8.6
Change from baseline[1]	-2.0	-2.1	-1.4	-1.2	-1.8
Comparison vs.empagliflozin (95% CI)[1]	-0.6* (-0.9, -0.4)[b]	-0.7* (-1.0, -0.5)[b]			
Comparison vs.metformin (95%CI)[1]	-0.8* (-1.0, -0.6)[b]	-0.3* (-0.6, -0.1)[b]			
N	153	161	159	166	159
Patients (%) achieving HbA1c <7% with baseline HbA1c ≥7%	96 (63%)	112 (70%)	69 (43%)	63 (38%)	92 (58%)
N	161	166	168	165	164
FPG (mg/dL) [mmol/L]					

Baseline (mean)	165.9 [9.2]	163.7 [9.1]	170.0 [9.4]	172.6 [9.6]	169.0[9.4]
Change from baseline[1]	-45.5 [-2.5]	-47.8 [-2.7]	-32.9 [-1.8]	-17.2 [-1.0]	-32.1 [-1.8]
Comparison vs.empagliflozin (95% CI)[1]	-12.6** (-19.1, -6.0)[b][-0.7 (-1.1, -0.3)]	-14.8** (-21.4,-8.2)[b] [-0.8 (-1.2, -0.5)]			
Comparison vs.metformin (95%CI)[1]	-28.2** (-35.0, -21.5)[b] [-1.6 (-1.9, -1.2)]	-15.6** (-22.3,-8.9)[b] [-0.9 (-1.2, -0.5)]			
N	161	165	168	166	162
Body Weight (kg)					
Baseline (mean)	82.3	83.0	83.9	82.9	83.8
% Change from baseline[1]	-3.1	-4.1	-2.7	-0.4	-1.2
Comparison vs.metformin (95%CI)[1]	-2.7** (-3.6, -1.8)[b]	-2.8** (-3.8, -1.9)[b]			

[a] Given in two equally divided doses per day

[b] Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c; 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 HbA1c;

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

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

	Empagliflozin25mg +metformin1000mg[a]	**Empagliflozin 25mg +metformin 2000mg[a]**	**Empagliflozin 25mg qd**	**Metformin1 000mg[a]**	**Metformin2 000mg[a]**
N	165	169	163	167	162
HbA1c (%)					
Baseline(mean)	8.8	8.7	8.9	8.7	8.6
Change frombaseline [1]	-1.9	-2.1	-1.4	-1.2	-1.8
Comparison vs.empagliflozin (95% CI)[1]	-0.6* (-0.8, -0.3)[b]	-0.7* (-1.0, -0.5)[b]			
Comparison vs.metformin (95%CI)[1]	-0.8* (-1.0, -0.5)[b]	-0.3* (-0.6, -0.1)[b]			
N	159	163	158	166	159
Patients (%) achieving HbA1c <7% with baseline HbA1c≥7%	91 (57%)	111 (68%)	51 (32%)	63 (38%)	92 (58%)
N	163	167	163	165	164
FPG (mg/dL) [mmol/L]					
Baseline(mean)	171.2 [9.5]	167.9 [9.3]	176.9[9.8]	172.6[9.6]	169.0[9.4]
Change frombaseline[1]	-44.0 [-2.4]	-51.0 [-2.8]	-28.0 [-1.6]	-17.2[-1.0]	-32.1 [-1.8]
Comparison vs.empagliflozin (95% CI)[1]	-16.0** (-22.8,-9.2)[b] [-0.9 (-1.3, -0.5)]	-23.0** (-29.7,-16.3)[b] [-1.3 (-1.6, -0.9)]			

Comparison vs.metformin (95%CI)[1]	-26.7** (-33.5,-20.0)[b] [-1.5 (-1.9, -1.1)]	-18.8** (-25.5,-12.2)[b] -1.0 (-1.4, -0.7)]			
N	165	167	162	166	162
Body Weight (kg)					
Baseline (mean)	82.9	83.7	83.4	82.9	83.8
% Change frombaseline[1]	-3.6	-4.3	-2.8	-0.4	-1.2
Comparison vs.metformin (95%CI)[1]	-3.1** (-4.1, -2.2)[b]	-3.1** (-4.1, -2.2)[b]			

[a] Given in two equally divided doses per day

[b] Full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c; 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 HbA1c

** 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 sulphonylurea 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 sulphonylurea. Treatment with empagliflozin resulted in statistically significant improvements in HbA1c and body weight and clinically meaningful reductions in FPG and blood pressure compared to placebo (Table 7).

In the double-blind placebo-controlled extension of this study, reductions of HbA1c (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 25 mg and -0.63 kg for placebo) and blood pressure (SBP: change from baseline of -, -3.8 mmHg for empagliflozin 10mg, -3.7 mmHg for empagliflozin 25 mg and -1.6 mmHg for placebo, DBP: change from baseline of -2.6 mmHg for empagliflozin10 mg, -2.3mmHg for empagliflozin 25 mg and -1.4mmHg for placebo) were sustained up to Week 76.

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

Empagliflozin as add-on to metformin and a sulphonylurea therapy	**Placebo**	**Empagliflozin 10mg**	**Empagliflozin 25mg**
N	225	225	216
HbA1c (%)			
Baseline (mean)	8.15	8.07	8.10
Change from baseline[1]	-0.17	-0.82	-0.77
Difference from placebo[1] (97.5% CI)		-0.64* (-0.79, -0.49)	-0.59* (-0.74, -0.44)
N	216	209	202
Patients (%) achieving HbA1c < 7% with baseline HbA1c ≥7%[2]	9.3	26.3	32.2
N	224	225	215
FPG (mg/dl) [mmol/l][2]			
Baseline (mean)	151.7 [8.42]	151.0 [8.38]	156.5 [8.68]
Change from baseline[1]	5.5 [0.31]	-23.3 [-1.29]	-23.3 [-1.29]
Difference form placebo[1] (95% CI)		-28.8* (-34.2, -23.4) [-1.60* (-1.90, -1.30)]	-28.8* (-34.3, -23.3) [-1.60* (-1.90, -1.29)]
N	225	225	216
Body weight (kg)			
Baseline (mean)	76.23	77.08	77.50
Change from baseline[1]	-0.39	-2.16	-2.39

Difference from placebo[1] (97.5% CI)		-1.76* (-2.25, -1.28)	-1.99* (-2.48, -1.50)
N	225	225	216
Patients (%) achieving weight loss of > 5%[2]	5.8	27.6	23.6
N	225	225	216
SBP (mmHg)[2]			
Baseline (mean)	128.8	128.7	129.3
Change from baseline[1]	-1.4	-4.1	-3.5
Difference from placebo[1] (95% CI)		-2.7 (-4.6, -0.8)	-2.1 (-4.0, -0.2)

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

Empagliflozin as add on to a combination of pioglitazone therapy (+/- metformin)
The efficacy and safety of empagliflozin in combination with pioglitazone, with or without metformin (75.5% of all patients were on metformin background) was evaluated in a double- blind, placebo-controlled study of 24 weeks duration. Empagliflozin in combination with pioglitazone (mean dose ≥30 mg) with or without metformin resulted in statistically significant reductions in HbA1c, fasting plasma glucose, and body weight and clinically meaningful reductions in blood pressure compared to placebo (Table 8).

In the double-blind placebo-controlled extension of this study, reductions of HbA1c (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 blood pressure (SBP: change from baseline of -1.7mmHg for empagliflozin 10 mg, -3.4mmHg for empagliflozin 25 mg and +0.3 mmHg for placebo, DBP: change from baseline of -1.43 mmHg for empagliflozin 10 mg, -2.0 mmHg for empagliflozin 25 mg and +0.2 mmHg for placebo) were sustained up to Week 76.

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

Pioglitazone +/- metformin add-on therapy	**Placebo**	**Empagliflozin 10mg**	**Empagliflozin 25mg**
N	165	165	168
HbA1c (%)			
Baseline (mean)	8.16	8.07	8.06
Change from baseline[1]	-0.11	-0.59	-0.72
Difference from placebo[1] (97.5% CI)		-0.48* (-0.69, -0.27)	-0.61* (-0.82, -0.40)
N	155	151	160
Patients (%) achieving HbA1c < 7% with baseline HbA1c ≥7%[3]	7.7	23.8	30.0
N	165	163	168
FPG (mg/dl) [mmol/l]			
Baseline (mean)	151.93 [8.43]	152.0 [8.44]	151.86 [8.43]
Change from baseline[1]	6.47 [0.37]	-17.0 [-0.94]	-21.99 [-1.23]
Difference form placebo[1] (95% CI)		-23.5* (-31.8, -15.2) [-1.32 (-1.72, -0.91)]	-28.5* (-36.7, -20.2) [-1.61 (-2.01, -1.21)]
N	165	165	168
Body weight (kg)			
Baseline (mean)	78.1	77.97	78.93

Change from baseline[1]	0.34	-1.62	-1.47
Difference from placebo[1] (97.5% CI)		-1.95* (-2.64, -1.27)	-1.81* (-2.49, -1.13)
N	165	165	168
Patients (%) achieving weight loss of > 5%[3]	5.5	18.8	13.7
N	165	165	168
SBP (mmHg)[2,3]			
Baseline (mean)	125.7	126.5	125.9
Change from baseline[1]	0.7	-3.1	-4.0
Difference from placebo[1] (95% CI)		-3.9 (-6.2, -1.5)	-4.7 (-7.1, -2.4 7)

[1] mean adjusted for baseline value and stratification

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

[3]Last observed (prior to glycemic rescue) carried forward (LOCF)

* p-value <0.0001

Empagliflozin and linagliptin as add on therapy to metformin

In a factorial design study, patients inadequately controlled on metformin, 24-weeks treatment with both doses of empagliflozin 10 mg and 25 mg administered together with linagliptin 5 mg provided statistically significant improvements in HbA1c and FPG compared to linagliptin 5 mg and also compared to empagliflozin 10 or 25 mg. Compared to linagliptin 5mg, both doses of empagliflozin plus linagliptin 5 mg provided statistically significant reductions in body weight and blood pressure. A greater proportion of patients with a baseline HbA1c ≥7.0% and treated with empagliflozin plus linagliptin achieved a target HbA1c of <7% compared to linagliptin 5 mg (Table 9).

After 24 weeks' treatment with empagliflozin+linagliptin, both systolic and diastolic blood pressures 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 blood pressure were maintained for 52 weeks, -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 9 Results of a 24 week (OC) placebo-controlled study of empagliflozin and linagliptin as fixed dose combination as add-on therapy to metformin (Full Analysis Set)

	Empagliflozin/ linagliptin (25mg/5mg)	**Empagliflozin/ linagliptin (10mg/5mg)**	**Empagliflozin 25mg**	**Empagliflozin 10mg**	**Linagliptin 5mg**
N	134	135	140	137	128
HbA1c (%) – 24 weeks					
Baseline (mean)	7.9	8.0	8.0	8.0	8.0
Change from baseline (adjusted mean)	-1.2	-1.1	-0.6	-0.7	-0.7
Comparison vs. linagliptin 5mg (adjusted mean) (95% CI)[2]	-0.5 (-0.7, -0.3)*	-0.4 (-0.6, -0.2)*			
N	134	135	140	137	128
HbA1c (%) – 52 weeks[1]					
Baseline (mean)	7.9	8.0	8.0	8.0	8.0
Change from baseline (adjusted mean)	-1.2	-1.0	-0.7	-0.7	-0.5
Comparison vs. linagliptin 5mg (adjusted mean) (95% CI)[2]	-0.8 (-1.0, -0.6)*	-0.6 (-0.8, -0.4)*			
N	134	135	140	137	128
Body weight – 24 weeks					
Baseline (mean) in kg	85	87	88	86	85
Change from baseline (adjusted mean)	-3.0	-2.6	-3.2	-2.5	-0.7
Comparison vs. linagliptin 5mg (adjusted mean) (95% CI)[4]	-2.3 (-3.2, -1,4)*	-1.9 (-2.8, -1.1)*			
N	123	128	132	125	119
Patient achieving HbA1c <7% with baseline HbA1c ≥7% - 24 weeks	62	58	33	28	36
Comparison vs. linagliptin 5mg (odd ratio) (95% CI)[3]	3.5 (1.9, 6.4)*	2.8 (1.6, 5.0)**			

[1]not evaluated for statistical significance as a result of the sequential confirmatory procedure

[2]full analysis population (observed case) using MMRM. MMRM model included treatment, renal function, region, visit, visit by treatment interaction and baseline HbA1c.

[3]full analysis population with non-completers considered failure. Logistic regression included treatment, baseline renal function, geographical region and baseline HbA1c.

[4]full analysis population using last observation carried forward, ANCOVA model included treatment, renal function, region, baseline weight and baseline HbA1c.

*P<0.0001

**P<0.001

Empagliflozin in patients inadequately controlled on metformin and linagliptin

In patients inequately controlled on metformin and linagliptin 5 mg, 24-weeks treatment with both GLYXAMBI 10 mg/5mg and GLYXAMBI 25 mg/5 mg provided statistically significant improvements in HbA1c, FPG and body weight compared to placebo+linagliptin 5 mg. A statistically significantly greater number of patients with a baseline HbA1c ≥7.0% and treated with both doses of empagliflozin achieved a target HbA1c of <7% compared to placebo+linagliptin 5 mg (Table 9). After 24 weeks' treatment with empagliflozin, both systolic and diastolic blood pressures 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+linagliptin 5 mg.

Table 10 Efficacy Parameters Comparing Empagliflozin to Placebo as Add-on Therapy in Patients Inadequately Controlled on Metformin and Linagliptin 5 mg

	Metformin + Linagliptin 5 mg		
	Empagliflozin 10 mg[1]	**Empagliflozin 25 mg[1]**	**Placebo[2]**
HbA1c (%) – 24 weeks[3]			
N	109	110	106
Baseline (mean)	7.97	7.97	7.96
Change from baseline (adjusted mean)	-0.65	-0.56	-0.14
Comparison vs. placebo (adjusted mean) (95% CI)[2]	-0.79 (-1.02, -0.55) P<0.0001	-0.70 (-0.93, -0.46) P<0.0001	
FPG (mg/dL) – 24 weeks[3]			
N	109	109	106
Baseline (mean)	167.9	170.1	162.9
Change from baseline (adjusted mean)	-26.3	-31.6	6.1
Comparison vs. placebo (adjusted mean) (95% CI)	-32.4 (-41.7, -23.0) p<0.0001	-37.7 (-47.0, -28.3) p<0.0001	
Body weight – 24 weeks[3]			
N	109	110	106
Baseline (mean) in kg	88.4	84.4	82.3
Change from baseline (adjusted mean)	-3.1	-2.5	-0.3
Comparison vs. placebo (adjusted mean) (95% CI)[1]	-2.8 (-3.5, -2.1) P<0.0001	-2.2 (-2.9, -1.5) P<0.0001	
Patient (%) achieving HbA1c <7% with baseline HbA1c ≥7% - 24 weeks[4]			
N	100	107	100
Patients (%) achieving A1C <7%	37.0	32.7	17.0
Comparison vs. placebo (odds ratio) (95% CI)[5]	4.0 (1.9, 8.7) P=0.0004	2.9 (1.4, 6.1) p=0.0061	

[1]Patients randomized to the empagliflozin 10 mg or 25 mg groups were receiving GLYXAMBI® 10 mg/5 mg or 25 mg/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_{1c}, baseline eGFR (MDRD), geographical region, visit treatment,and treatment by visit 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 HbA1c, baseline eGFR (MDRD), geographical region, and treatment; based on patients with HbA1c of 7% and above at baseline

In a prespecified subgroup of patients with baseline HbA1c greater or equal than 8.5% the reduction from baseline in HbA1c with empagliflozin 25 mg+linagliptin 5 mg was -1.3% at 24 weeks (p<0.0001 versus placebo+linagliptin 5 mg) and with empagliflozin 10 mg+linagliptin 5 mg -1.3% at 24 weeks (p<0.0001 versus placebo+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 (4 mg) in patients with inadequate glycaemic control on metformin alone, treatment with empagliflozin daily resulted in superior reduction in HbA1c, and a clinically meaningful reduction in FPG, compared to glimepiride (Table 11). Empagliflozin 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 resulted in statistically significantly lower proportion of patients with hypoglycaemic events compared to glimepiride (2.5% for empagliflozin, 24.2% for glimepiride, p<0.0001).

Table 11 Results at 104 week (LOCF)[4] in an active controlled study comparing empagliflozin to glimepiride as add on to metformin (Full Analysis Set)

Empagliflozin as add-on to metformin therapy in comparison to glimepride	**Empagliflozin 25mg**	**Glimepride (up to 4mg)**
N	765	780
HbA1c (%)		
Baseline (mean)	7.92	7.92
Change from baseline[1]	-0.66	-0.55
Difference from glimepride[1] (97.5% CI)	-0.11*(-0.20,-0.01)	
N	690	715
Patient (%) achieving HbA1c <7% with baseline HbA1c ≥7% [2]	33.6	30.9
N		
FPG (mg/dL) [mmol/L]		
Baseline (mean)	150.00	149.82
Change from baseline[1]	-15.36	-2.98
Difference from glimepride[1] (95% CI)	-12.37**(-15.47,-9.27)	
N	765	780
Body weight (kg)		
Baseline (mean)	82.52	83.03
Change from baseline[1]	-3.12	1.34
Difference from glimepride[1] (97.5% CI)	-4.46**(-4.87,-4.05)	
N	765	780
Patient (%) achieving weight loss of >5%	27.5	3.8
N	765	780
SBP (mmHg)		

Baseline (mean)	133.4	133.5
Change from baseline[1]	-3.1	2.5
Difference from glimepride[1] (97.5% CI)	-5.6**(-7.0,-4.2)	

[1]mean adjusted for baseline value and stratification

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

[3]LOCF, values after antihypertensive rescue censored

[4] Last observation (prior to glycemic rescue) carried forward (LOCF)

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

**P<0.001

Empagliflozin as add on to basal insulin therapy

The efficacy and safety of empagliflozin as add on to basal insulin with or without concomitant metformin and/or sulfonylurea therapy (79.8% of all patients were on metformin background) was evaluated in a double-blind, placebo-controlled trial of 78 weeks duration. During the initial 18 weeks the insulin dose was to be kept stable, but was adjusted to achieve a FPG <110 mg/dL in the following 60 weeks.

At week 18, empagliflozin provided statistically significant improvement in HbA1c compared to placebo. A greater proportion of patients with a baseline HbA1c ≥7.0% achieved a target HbA1c of <7% compared to placebo. At 78 weeks, empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared to placebo (Table 12).

At week 78, empagliflozin resulted in a reduction in FPG -10.51 mg/dl [-0.58 mmol/l] for empagliflozin 10 mg, -17.43 mg/dL [0.3 mmol/L] for empagliflozin 25 mg and -5.48 mg/dL [-0.97 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), blood pressure (SBP: -4.1 mmHg for empagliflozin 10 mg, -2.4 mmHg for empagliflozin 25 mg and +0.1 mmHg for placebo, DPB: -2.9 mmHg for empagliflozin 10 mg, -1.5 mmHg for empagliflozin 25 mg and -0.3 mmHg for placebo).

Table 12 Results at 18, 78 week (LOCF)[2] in a placebo-controlled study of empagliflozin as add on to basal insulin with or without metformin and/or sulphonylurea (Full Analysis Set - Completers)

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

Difference from placebo[1] (97.5% CI)	-6.66***(-11.56,-1.77)	-5.92***(-11.00,-0.85)

[1]mean adjusted for baseline value and stratification

[2] Last observation (prior to glycemic rescue) carried forward (LOCF)

*p-value <0.0001

***p-value < 0.01

Empagliflozin as add on to MDI 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 kept stable, but was adjusted to achieve pre-prandial glucose levels <100 mg/dl [5.5 mmol/l], and post-prandial glucose levels <140 mg/dl [7.8 mmol/l] between Weeks 19 and 40.
At Week 18, empagliflozin provided statistically significant improvement in HbA1c compared with placebo (Table 13). A greater proportion of patients with a baseline HbA1c ≥7.0% (19.5% empagliflozin 10 mg, 31.0% empagliflozin 25 mg) achieved a target HbA1c of <7% compared with placebo (15.1%).

At Week 52, treatment with empagliflozin resulted in a statistically significant decrease in HbA1c and insulin sparing compared with placebo and a reduction in FPG (change from baseline of −0.3 mg/dl [−0.02 mmol/l] for placebo, −19.7 mg/dl [−1.09 mmol/l] for empagliflozin 10 mg, and −23.7 mg/dl [−1.31 mmol/l] for empagliflozin 25 mg), body weight, and blood pressure (SBP: change from baseline of −2.6 mmHg for placebo, −3.9 mmHg for empagliflozin 10 mg and 4.0 mmHg for empagliflozin 25 mg, DBP: change from baseline of −1.0 mmHg for placebo, −1.4 mmHg for empagliflozin 10 mg and -2.6 mmHg for empagliflozin 25 mg).

Table 13 Results at 18 and 52 (LOCF)[5] weeks in a placebo-controlled study of empagliflozin as add on to multiple daily doses of insulin with metformin2

Empagliflozin as add-on to insulin + metformin therapy	**Placebo**	**Empagliflozin 10mg**	**Empagliflozin 25mg**
N	188	186	189
HbA1c (%) at week 18			
Baseline (mean)	8.33	8.39	8.29
Change from baseline[1]	-0.50	-0.94	-1.02
Difference from placebo[1] (97.5% CI)		-0.44* (-0.61, -0.27)	-0.52* (-0.69, -0.35)
N	115	119	118
HbA1c (%) at week 52[3]			
Baseline (mean)	8.25	8.40	8.37
Change from baseline[1]	-0.81	-1.18	-1.27
Difference from placebo[1] (97.5% CI)		-0.38** (-0.62, -0.13)	-0.46* (-0.70, -0.22)
N	113	118	118
Patient (%) achieving HbA1c <7% with baseline HbA1c ≥ 7% at week 52[4]	26.5	39.8	45.8
N	188	186	189
FPG (mg/dL) [mmol/L] at week 52[5]			
Baseline (mean)	151.6 [8.41]	159.1 [8.83]	150.3 [8.34]
Change from baseline[1]	-0.3 [-0.02]	-19.7 [-1.09]	-23.7 [-1.31]
Difference from placebo[1] (95% CI)		-19.3 (-27.9, -10.8) [-1.07(-1.55, -0.6)]	-23.4 (-31.8, -14.9) [-1.30(-1.77, -0.83)]
N	115	118	117
Insulin dose (IU/day) at week 52[3]			
Baseline (mean)	89.94	88.57	90.38
Change from baseline[1]	10.16	1.33	-1.06
Difference from placebo[1] (97.5% CI)		-8.83** (-15.69, -1.97)	-11.22**(-18.09, -4.36)
N	115	119	118
Boday weight (kg) at week 52[3]			
Baseline (mean)	96.34	96.47	95.37
Change from baseline[1]	0.44	-1.95	-2.04
Difference from placebo[1] (97.5% CI)		-2.39* (-3.54, -1.24)	-2.48* (-3.63, -1.33)
N	188	186	189
SBP (mmHg)[5]			
Baseline (mean)	132.6	134.2	132.9
Change from baseline[1]	-2.6	-3.9	-4.0
Difference from placebo[1,4] (95% CI)		-1.4 (-3.6, 0.9)	-1.4 (-3.7, 0.8)

[1]mean adjusted for baseline value and stratification

[2]week 18: FAS; week 52: PPS-Completers-52

[3]week 19-40: treat-to-target regimen for insulin dose adjustment to achieve pre-defined glucose target levels (pre-prandial < 100 mg/dl (5/5mmol/l), post-prandial < 140 mg.dl (7.8mmol/l)

[4]not evaluated for statistical significance ; not partof the sequential testing procedure for the secondary endpoints

[5] Last observation (prior to glycemic rescue) carried forward (LOCF)

[6] Week 52: FAS

*p-value <0.0001

**p-value < 0.01

Empagliflozin twice daily versus once daily as add on to metformin therapy
The efficacy and safety of empagliflozin twice daily versus once daily (daily dose of 10 mg and 25 mg) as add-on therapy in patients with insufficient glycaemic control on metformin monotherapy was evaluated in a double blind placebo-controlled study of 16 weeks duration.
All treatments with empagliflozin resulted in significant reductions in HbA1c from baseline (total mean 7.8%) after 16 weeks of treatment compared with placebo. Empagliflozin twice daily dose regimens led to comparable reductions in HbA1c versus once daily dose regimens with a treatment difference in HbA1c reductions from baseline to week 16 of -0.02% (95% CI -0.16, 0.13) for empagliflozin 5 mg twice daily vs. 10 mg once daily, and -0.11% (95% CI - 0.26, 0.03) for empagliflozin 12.5 mg twice daily vs. 25 mg once daily.

2 hour postprandial glucose
Treatment with empagliflozin 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, placebo (n=57): +5.9 mg/dL, empagliflozin 10 mg (n=52): -46.0 mg/dl, empagliflozin 25 mg (n=58): -44.6 mg/dL; add-on to metformin plus sulphonylurea, placebo (n=35): -2.3 mg/dL, empagliflozin 10 mg (n=44): -35.7 mg/dl, empagliflozin 25 mg (n=46): -36.6 mg/dL).

Patients with baseline HbA1c ≥9%
In a pre-specified analysis of subjects with baseline HbA1c ≥9.0%, treatment with empagliflozin 10 mg or 25 mg as add-on to metformin resulted in statistically significant reductions in HbA1c at Week 24 (adjusted mean change from baseline of -1.49% for empagliflozin 25 mg, -1.40% for empagliflozin 10 mg, and -0.44% for placebo).

Body weight
In a pre-specified pooled analysis of 4 placebo controlled studies, treatment with empagliflozin (68% of all patients were on metformin background) 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).

Blood pressure
The efficacy and safety of empagliflozin was evaluated in a double-blind, placebo controlled study of 12 weeks duration in patients with type 2 diabetes and high blood pressure on different antidiabetic (67.8% treated with metformin with or without other antidiabetic drugs including insulin) and up to 2 antihypertensive therapies (Table 14). Treatment with empagliflozin once daily resulted in statistically significant improvement in HbA1c, 24 hour mean systolic and diastolic blood pressure as determined by ambulatory blood pressure monitoring. Treatment with empagliflozin 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 14 Results at 12 week (LOCF)[3] in a placebo-controlled study of empagliflozin in patients with type 2 diabetes and uncontrolled blood pressure (Full Analysis Set)

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

[1] Mean adjusted for value and stratification

[2] Last observation (prior to antihypertensive rescue) carried forward (LOCF)LOCF, values after antihypertensive rescue censored value

3 Last observation (prior to glycemic 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 (68% of all patients were on metformin background) resulted in a reduction in systolic blood pressure (empagliflozin 10 mg -3.9 mmHg, empagliflozin 25 mg -4.3 mmHg) compared with placebo (-0.5 mmHg), and in diastolic blood pressure (empagliflozin 10 mg - 1.8 mmHg, empagliflozin 25 mg -2.0 mmHg) compared with placebo (-0.5 mmHg), at week 24, that were maintained up to week 76.

Laboratory parameters

Haematocrit increased

In a pooled safety analysis of all trials with metformin background treatment, mean changes from baseline in haematocrit were 3.6% and 4.0% for empagliflozin 10 mg and 25 mg, respectively, compared to 0% 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 of all trials with metformin background treatment, mean percent increases from baseline for empagliflozin 10 mg and 25 mg versus placebo, respectively, were total cholesterol 5.0% and 5.2% versus 3.7%; HDL-cholesterol 4.6% and 2.7% versus -0.5%; LDL-cholesterol 9.1% and 8.7% versus 7.8%; triglycerides 5.4% and 10.8% versus 12.1%.

<u>Cardiovascular outcome</u>

The double-blind, placebo-controlled EMPA-REG OUTCOME study compared pooled doses of empagliflozin 10 mg and 25 mg with placebo as adjunct to standard care therapy in patients with

type 2 diabetes and established cardiovascular disease. A total of 7020 patients were treated (empagliflozin 10 mg: 2345, empagliflozin 25 mg: 2342, placebo: 2333) and followed for a median of 3.1 years. The mean age was 63 years, the mean HbA1c was 8.1%, and 71.5% were male. At baseline, 74% of patients were being treated with metformin, 48% with insulin, and 43% with a sulfonylurea. About half of the patients (52.2%) had an eGFR of 60-90 ml/min/1.73 m^2, 17.8% of 45-60 ml/min/1.73 m^2 and 7.7% of 30-45 ml/min/1.73 m^2.

At week 12, an adjusted mean (SE) improvement in HbA1c when compared to baseline of 0.11% (0.02) in the placebo group, 0.65% (0.02) and 0.71% (0.02) in the empagliflozin 10 and 25 mg groups was observed. After the first 12 weeks glycaemic control was optimized independent of investigative treatment. Therefore the effect was attenuated at week 94, with an adjusted mean (SE) improvement in HbA1c of 0.08% (0.02) in the placebo group, 0.50% (0.02) and 0.55% (0.02) in the empagliflozin 10 and 25 mg groups.

Empagliflozin was superior in reducing the primary combined endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, as compared with placebo. The treatment effect was driven by a significant reduction in cardiovascular death with no significant change in non-fatal myocardial infarction, or non-fatal stroke. The reduction of cardiovascular death was comparable for empagliflozin 10 mg and 25 mg (Figure 1) and confirmed by an improved overall survival (Table 10).

The efficacy for preventing cardiovascular mortality has not been conclusively established in users of DPP-4 inhibitors or in Black patients because the representation of these groups in the EMPA-REG OUTCOME study was limited.

Table 15 Treatment effect for the primary composite endpoint, its components and mortality[a]

	Placebo	**Empagliflozin[b]**
N	2333	4687
Time to first occurrence of CV death, non-fatal MI, or non-fatal stroke N (%)	282 (12.1)	490 (10.5)
Hazard ratio vs. placebo (95.02% CI)*		0.86 (0.74, 0.99)
p−value for superiority		0.0382
CV Death N (%)	137 (5.9)	172 (3.7)
Hazard ratio vs. placebo (95% CI)		0.62 (0.49, 0.77)
p-value		<0.0001
Non-fatal MI N (%)	121 (5.2)	213 (4.5)
Hazard ratio vs. placebo (95% CI)		0.87 (0.70, 1.09)
p−value		0.2189
Non-fatal stroke N (%)	60 (2.6)	150 (3.2)
Hazard ratio vs. placebo (95% CI)		1.24 (0.92, 1.67)
p−value		0.1638
All-cause mortality N (%)	194 (8.3)	269 (5.7)
Hazard ratio vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		<0.0001
Non-CV mortality N (%)	57 (2.4)	97 (2.1)
Hazard ratio vs. placebo (95% CI)		0.84 (0.60, 1.16)

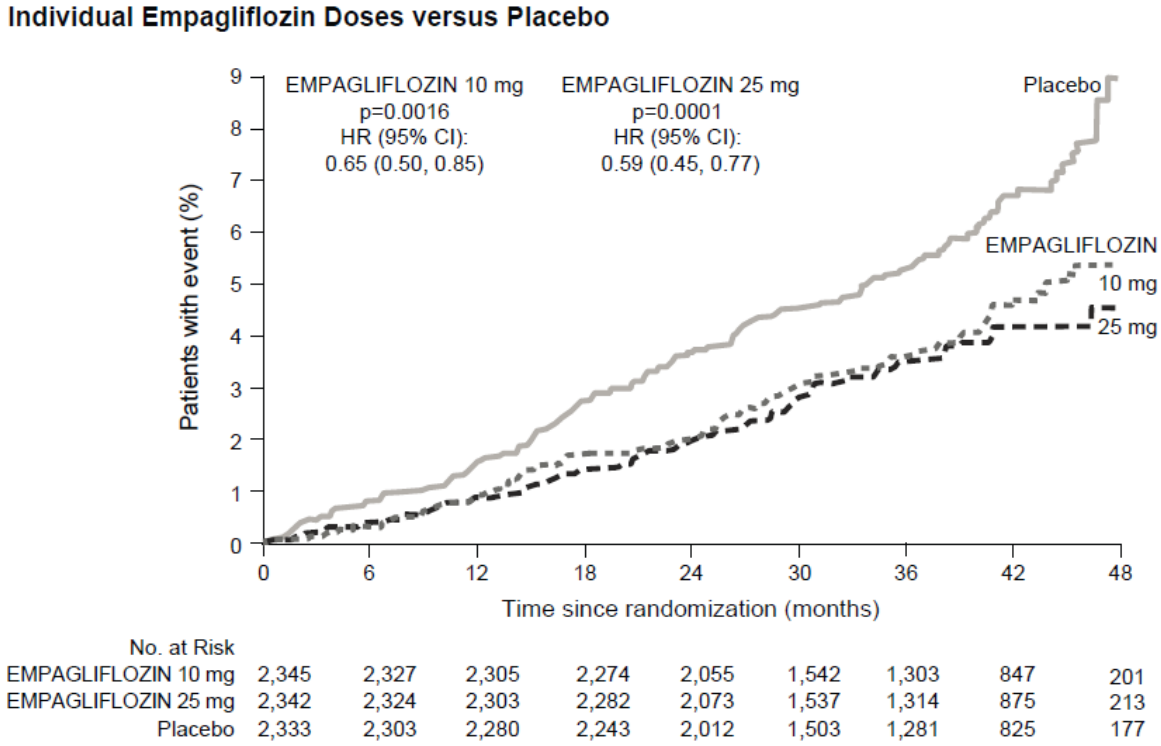
CV = cardiovascular, MI = myocardial infarction

[a]Treated set (TS), i.e. patients who had received at least one dose of study drug

[b] Pooled doses of empagliflozin 10 mg and 25 mg

*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 first occurrence of cardiovascular death in the EMP-REG OUTCOME study



Pharmacokinetic properties

JARDIANCE DUO

The results of bioequivalence studies in healthy subjects demonstrated that JARDIANCE DUO (empagliflozin/metformin hydrochloride) 5 mg/500 mg, 12.5 mg/500 mg, 12.5 mg/850 mg, and 12.5 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of empagliflozin and metformin as individual tablets.

Administration of 12.5 mg empagliflozin/1000 mg metformin under fed conditions resulted in a 9% decrease in AUC and a 28% decrease in Cmax for empagliflozin, when compared to fasted conditions. For metformin, AUC decreased by 12% and Cmax decreased by 26% compared to fasting conditions. The observed effect of food on empagliflozin and metformin is not considered to be clinically relevant. However, as metformin is recommended to be given with meals, is also proposed to be given with food.

The following data are findings in studies performed with empagliflozin or metformin individually.

Empagliflozin

Absorption

The pharmacokinetics of empagliflozin have been extensively characterized in healthy volunteers and patients with T2DM. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} 1.5 h post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1870 nmol.h and 259 nmol/l with empagliflozin 10 mg and 4740 nmol.h/L and 687 nmol/L with empagliflozin 25 mg once daily, respectively. 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 type 2 diabetes mellitus.
The pharmacokinetics of 5 mg empagliflozin twice daily and 10 mg empagliflozin once daily were compared in healthy subjects. Overall exposure (AUC_{ss}) of empagliflozin over a 24- hour period with 5 mg administered twice daily was similar to 10 mg administered once daily. As expected, empagliflozin 5 mg administered twice daily compared with 10 mg empagliflozin once daily resulted in lower C_{max} and higher trough plasma empagliflozin concentrations (C_{min}).
Administration of 25 mg empagliflozin after intake of a high-fat and high calorie meal resulted in slightly lower exposure; AUC decreased by approximately 16% and C_{max} decreased by approximately 37%, compared to fasted condition. The observed effect of food on empagliflozin pharmacokinetics was not considered clinically relevant and empagliflozin may be administered with or without food.

Distribution
The apparent steady-state volume of distribution was estimated to be 73.8 L, based on a population pharmacokinetic analysis. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, the red blood cell partitioning was approximately 36.8% and plasma protein binding was 86.2%.

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, UGT1A3, UGT1A8, UGT1A9, and UGT2B7.

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 the half-life, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state. Following administration of an oral [14C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug related radioactivity was eliminated in faeces (41.2%) or urine (54.4%). The majority of drug related radioactivity recovered in faeces was unchanged parent drug and approximately half of drug related radioactivity excreted in urine was unchanged parent drug.

<u>Specific Populations</u>

Renal Impairment
In patients with mild (eGFR: 60 - <90 mL/min/1.73 m^2), moderate (eGFR: 30 - <60 mL/min/1.73 m^2), severe (eGFR: <30 mL/min/1.73 m^2) renal impairment and patients with kidney failure/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.

Hepatic Impairment
In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, AUC of empagliflozin increased approximately by 23%, 47%, and 75% and C_{max} by approximately 4%, 23%, and 48%, respectively, compared to subjects with normal hepatic function.

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

Gender
No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of empagliflozin based on the population pharmacokinetic analysis.

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

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

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

Metformin

Absorption
After an oral dose of metformin, T_{max} is reached in 2.5 hours. Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption are non-linear.

At the recommended metformin hydrochloride doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/mL. In controlled clinical trials, maximum metformin hydrochloride plasma levels (C_{max}) did not exceed 5 µg/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin hydrochloride. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution
Plasma protein binding is negligible. Metformin hydrochloride partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 L.

Biotransformation
Metformin hydrochloride is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination
Renal clearance of metformin hydrochloride is >400 mL/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in plasma.

Special populations

Renal impairment
The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations (see section Dosage and administration).

Paediatric
Single dose study: After single doses of metformin 500 mg, paediatric patients, have shown a similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were approximately 33% and 40% lower, respectively, compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

TOXICOLOGY

Empagliflozin and metformin

General toxicity studies in rats up to 13 weeks were performed with the combination of empagliflozin and metformin. In a 13 week combination study with empagliflozin and metformin in rats the No-observed-adverse-effect-level (NOAEL) was based on hypochloremia seen at exposures of approximately 24- and 9-times the clinical AUC exposure of empagliflozin associated with the 10 and 25 mg doses, respectively.

An embryofetal development study in pregnant rats did not indicate a teratogenic effect attributed to the co-administration of empagliflozin and metformin at exposures of approximately 35- and 14-times the clinical AUC exposure of empagliflozin associated with the 10 and 25 mg doses, respectively, and 4-times the clinical AUC exposure of metformin associated with the 2000 mg dose. At dose levels of 600 mg/kg/day, associated with 8-times the maximum recommended human dose (MRHD) of metformin in humans, teratogenicity of metformin was observed.

The following data are findings in studies performed with empagliflozin or metformin individually.

Empagliflozin

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

In long term toxicity studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the clinical dose of empagliflozin. Most toxicity was consistent with secondary pharmacology related to urinary glucose loss and electrolyte imbalances including decreased body weight and body fat, increased food consumption, diarrhea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the clinical AUC exposure of empagliflozin associated with the 25 mg dose.

Empagliflozin is not genotoxic.

In a 2 year carcinogenicity study, empagliflozin did not increase the incidence of tumors in female rats up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72-times the maximal clinical AUC exposure to empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26-times the maximal clinical exposure to empagliflozin. Interstitial cell tumors in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to approximately 18-times the maximal clinical exposure to empagliflozin. Both tumors are common in rats and are unlikely to be relevant to humans.

Empagliflozin did not increase the incidence of tumors in female mice at doses up to 1000 mg/kg/day, which corresponds to approximately 62-times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumors in male mice at 1000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11-times the maximal clinical exposure to empagliflozin. The mode of action for these tumors is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumors are considered not relevant to humans.

At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit.

In pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear.

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

Metformin

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity reproduction.

PHARMACEUTICAL PARTICULARS

List of excipients

Tablet cores : Maize starch, copovidone, colloidal silica anhydrous, magnesium stearate.
Film-coating : Hypromellose 2910, titanium dioxide (E171), polyethylene glycol 400, iron oxide [5 mg strengths: iron oxide yellow (E172); 12.5 mg strengths: iron oxide red and black (E172)], talc.

Storage condition

Store at or below 30°C.

Nature and contents of container

Blister card of aluminium lidding foil, polyvinyl chloride (PVC) and polychlorotrifluoro ethylene (PCTFE) based forming film.
Blister of 10 film-coated tablets. Box of 1 or 6 blisters.

Manufactured by

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Straße 173
55216 Ingelheim am Rhein
Germany

Or

Boehringer Ingelheim Hellas Single Member S.A.
5th km Paiania-Markopoulo
Koropi Attiki
19441
Greece

For

Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

Date of revision: 25 October 2022