For the use only of Registered Medical Practitioner (for indications i, iii and iv) / Nephrologist and Cardiologist (for indication ii) or a Hospital or a Laboratory

COSPIAQ®

Empagliflozin tablets 10 mg/25 mg

1. INDICATIONS AND USAGE

COSPIAQ is indicated:

i. to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.

ii. to reduce the risk of sustained decline in eGFR (only for patients with eGFR 30-90 ml/min/1.73m^2), end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression

iii. to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

iv. as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

COSPIAQ is not recommended for use in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions (5.1)]*.

COSPIAQ is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. COSPIAQ is likely to be ineffective in this setting based upon its mechanism of action.

COSPIAQ should be prescribed only to the Heart Failure patients with eGFR more than 30mL/min/1.73 m^2.

COSPIAQ is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of intravenous immunosuppressive therapy or greater than 45 mg of prednisone or equivalent for kidney disease *[see Clinical Studies (14.4)]*. COSPIAQ is not expected to be effective in these populations.

2. DOSAGE AND ADMINISTRATION

2.1. Testing Prior to Initiation of COSPIAQ

- Assess renal function before initiating COSPIAQ and as clinically indicated *[see Warnings and Precautions (5.2)]*.
- Assess volume status. In patients with volume depletion, correct this condition before initiating COSPIAQ *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.5, 8.6)]*.

2.2. Recommended Dosage

Table 1 presents the recommended dosage of COSPIAQ.

Table 1 Recommended Dosage of COSPIAQ

Indication	Recommended Dosage
Reduce the risk of cardiovascular death and hospitalization in patients with heart failure	• 10 mg orally once daily in the morning, taken with or without food.
Reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression	
Reduce the risk of cardiovascular death in patients with type 2 diabetes mellitus with established cardiovascular disease	
Glycemic control in type 2 diabetes mellitus	• 10 mg orally once daily in the morning, taken with or without food. • For additional glycemic control, may increase to 25 mg orally once daily in patients tolerating 10 mg once daily.

3. DOSAGE FORMS AND STRENGTHS

COSPIAQ tablets available as:

- 10 mg pale yellow, round, biconvex and bevel-edged, film-coated tablets debossed with "S 10" on one side and the Boehringer Ingelheim company symbol on the other side.
- 25 mg pale yellow, oval, biconvex, film-coated tablets debossed with "S 25" on one side and the Boehringer Ingelheim company symbol on the other side.

4. CONTRAINDICATIONS

- COSPIAQ is contraindicated in patients:
    - with a hypersensitivity to empagliflozin or any of the excipients in COSPIAQ, reactions such as angioedema have occurred *[see Warnings and Precautions (5.8)]*.

5. WARNINGS AND PRECAUTIONS

5.1. Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including COSPIAQ. Although ketoacidosis is less likely to occur in patients without diabetes mellitus, cases have also been reported in these patients. Fatal cases of ketoacidosis have been reported in patients taking COSPIAQ. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. COSPIAQ is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with COSPIAQ who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with COSPIAQ may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, COSPIAQ should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile

illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating COSPIAQ, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing COSPIAQ for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

Consider monitoring for ketoacidosis and temporarily discontinuing COSPIAQ in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting COSPIAQ.

Educate all patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue COSPIAQ and seek medical attention immediately if signs and symptoms occur.

5.2. Volume Depletion

COSPIAQ can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions (6.1)]*. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including COSPIAQ. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating COSPIAQ in patients with one or more of these characteristics, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating COSPIAQ. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy

5.3. Urosepsis and Pyelonephritis

There have been reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including COSPIAQ. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6)]*.

5.4. Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The risk of hypoglycemia is increased when COSPIAQ is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with COSPIAQ.

5.5. Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in patients with diabetes mellitus receiving SGLT2 inhibitors, including COSPIAQ. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with COSPIAQ presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue COSPIAQ, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.6. Genital Mycotic Infections

COSPIAQ increases the risk for genital mycotic infections *[see Adverse Reactions (6.1)]*. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop genital mycotic infections. Monitor and treat as appropriate.

5.7. Lower Limb Amputation

In some clinical studies with SGLT2 inhibitors an imbalance in the incidence of lower limb amputation has been observed. Across four COSPIAQ outcome trials, lower limb amputation event rates were 4.3 and 5.0 events per 1,000 patient-years in the placebo group and the COSPIAQ 10 mg or 25 mg dose group, respectively, with a HR of 1.05 (95 % CI) (0.81, 1.36).

In a long-term cardio-renal outcome trial *[see Clinical Studies 14.4]*, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1000 patient- years in the placebo, and COSPIAQ 10 mg treatment arms, respectively. Amputation of the toe and mid-foot were most frequent (21 out of 28 COSPIAQ 10 mg treated patients with lower limb amputations), and some involving above and below the knee. Some patients had multiple amputations.

Peripheral artery disease, and diabetic foot infection (including osteomyelitis), were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of diabetic foot, peripheral artery disease (including previous amputation) or diabetes.

Counsel patients about the importance of routine preventative foot care. Monitor patients receiving COSPIAQ for signs and symptoms of diabetic foot infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and institute appropriate treatment.

5.8. Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions, (e.g., angioedema) in patients treated with COSPIAQ. If a hypersensitivity reaction occurs, discontinue COSPIAQ; treat promptly per standard of care, and monitor until signs and symptoms resolve. COSPIAQ is contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in COSPIAQ *[see Contraindications (4)]*.

6. ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Ketoacidosis *[see Warnings and Precautions (5.1)]*
- Volume Depletion *[see Warnings and Precautions (5.2)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.3)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.5)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

COSPIAQ has been evaluated in clinical trials in patients with type 2 diabetes mellitus, in patients with heart failure, and in patients with chronic kidney disease. The overall safety profile of COSPIAQ was generally consistent across the studied indications.

Clinical Trials in Patients with Type 2 Diabetes Mellitus

The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin in patients with type 2 diabetes mellitus. COSPIAQ was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (14)]*.

These data reflect exposure of 1,976 patients to COSPIAQ with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), COSPIAQ 10 mg (N=999), or COSPIAQ 25 mg (N=977) once daily. The mean age of the population was 56 years and 3% were older than 75 years of age. More than half (55%) of the population was male; 46% were White, 50% were Asian, and 3% were Black or African American. At baseline, 57% of the population had diabetes mellitus more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes mellitus at baseline included diabetic nephropathy (7%), retinopathy (8%), or neuropathy (16%). Baseline renal function was normal or mildly impaired in 91% of patients and moderately impaired in 9% of patients (mean eGFR 86.8 mL/min/1.73 m^2).

Table 2 shows common adverse reactions (excluding hypoglycemia) that were not present at baseline, occurred more commonly in COSPIAQ-treated patients than on placebo and occurred in greater than or equal to 2% COSPIAQ-treated patients.

Table 2 Adverse Reactions Reported in ≥2% of Patients with Type 2 Diabetes Mellitus Treated with COSPIAQ and Greater than Placebo in Pooled Placebo-Controlled Clinical Trials of COSPIAQ Monotherapy or Combination Therapy

Adverse Reactions	Placebo (%) N=995	COSPIAQ 10 mg (%) N=999	COSPIAQ 25 mg (%) N=977
Urinary tract infection[a]	7.6	9.3	7.6
Female genital mycotic infections[b]	1.5	5.4	6.4
Upper respiratory tract infection	3.8	3.1	4.0
Increased urination[c]	1.0	3.4	3.2
Dyslipidemia	3.4	3.9	2.9
Arthralgia	2.2	2.4	2.3
Male genital mycotic infections[d]	0.4	3.1	1.6
Nausea	1.4	2.3	1.1

[a]Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis
[b]Female genital mycotic infections include the following adverse reactions: vulvovaginal mycotic infection, vaginal infection, vulvitis, vulvovaginal candidiasis, genital infection, genital candidiasis, genital infection fungal, genitourinary tract infection, vulvovaginitis, cervicitis, urogenital infection fungal, vaginitis bacterial. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=481), COSPIAQ 10 mg (N=443), COSPIAQ 25 mg (N=420).
[c]Predefined adverse event grouping, including, but not limited to, polyuria, pollakiuria, and nocturia
[d]Male genital mycotic infections include the following adverse reactions: balanoposthitis, balanitis, genital infections fungal, genitourinary tract infection, balanitis candida, scrotal abscess, penile infection. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=514), COSPIAQ 10 mg (N=556), COSPIAQ 25 mg (N=557).

Thirst (including polydipsia) was reported in 0%, 1.7%, and 1.5% for placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg, respectively.

Volume Depletion

COSPIAQ causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. In the pool of five placebo-controlled clinical trials, adverse reactions related to volume depletion (e.g., blood pressure (ambulatory) decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, and syncope) were reported by 0.3%, 0.5%, and 0.3% of patients treated with placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg respectively. COSPIAQ may increase the risk of hypotension in patients at risk for volume contraction *[see Use in Specific Populations (8.5, 8.6)]*.

Increased Urination

In the pool of five placebo-controlled clinical trials, adverse reactions of increased urination (e.g., polyuria, pollakiuria, and nocturia) occurred more frequently on COSPIAQ than on placebo (see Table 1).

Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg, respectively.

Hypoglycemia in Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus

The incidence of hypoglycemia by trial is shown in Table 3. The incidence of hypoglycemia increased when COSPIAQ was administered with insulin or sulfonylurea.

Table 3 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Trials for Glycemic Control in Patients with Type 2 Diabetes Mellitus[c]

Monotherapy (24 weeks)	**Placebo (n=229)**	**COSPIAQ 10 mg (n=224)**	**COSPIAQ 25 mg (n=223)**
Overall (%)	0.4	0.4	0.4
Severe (%)	0	0	0
In Combination with Metformin (24 weeks)	**Placebo+ Metformin (n=206)**	**COSPIAQ 10 mg + Metformin (n=217)**	**COSPIAQ 25 mg + Metformin (n=214)**
Overall (%)	0.5	1.8	1.4
Severe (%)	0	0	0
In Combination with Metformin + Sulfonylurea (24 weeks)	**Placebo (n=225)**	**COSPIAQ 10 mg + Metformin + Sulfonylurea (n=224)**	**COSPIAQ 25 mg+ Metformin + Sulfonylurea (n=217)**
Overall (%)	8.4	16.1	11.5
Severe (%)	0	0	0
In Combination with Pioglitazone +/- Metformin (24 weeks)	**Placebo (n=165)**	**COSPIAQ 10 mg + Pioglitazone +/- Metformin (n=165)**	**COSPIAQ 25 mg + Pioglitazone +/- Metformin (n=168)**
Overall (%)	1.8	1.2	2.4
Severe (%)	0	0	0
In Combination with Basal Insulin +/- Metformin (18 weeks[d])	**Placebo (n-170)**	**COSPIAQ 10 mg (n=169)**	**COSPIAQ 25 mg (n=155)**
Overall (%)	20.6	19.5	28.4
Severe (%)	0	0	1.3
In Combination with MDI Insulin +/-Metformin (18 weeks[d])	**Placebo (n=188)**	**COSPIAQ 10 mg (n=186)**	**COSPIAQ 25 mg (n=189)**
Overall (%)	37.2	39.8	41.3
Severe (%)	0.5	0.5	0.5

[a]Overall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL
[b]Severe hypoglycemic events: requiring assistance regardless of blood glucose
[c]Treated set (patients who had received at least one dosage of trial drug)

[d]Insulin dosage could not be adjusted during the initial 18-week treatment period

Other Adverse Reactions in Clinical Trials for Glycemic Control in Adults with Type 2 Diabetes Mellitus

Genital Mycotic Infections

In the pool of five placebo-controlled clinical trials, the incidence of genital mycotic infections (e.g., vaginal mycotic infection, vaginal infection, genital infection fungal, vulvovaginal candidiasis, and vulvitis) was increased in patients treated with COSPIAQ compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg, respectively. Discontinuation from trial due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either COSPIAQ 10 mg or 25 mg.

Genital mycotic infections occurred more frequently in female than male patients (see Table 2).

Phimosis occurred more frequently in male patients treated with COSPIAQ 10 mg (less than 0.1%) and COSPIAQ 25 mg (0.1%) than placebo (0%).

Urinary Tract Infections

In the pool of five placebo-controlled clinical trials, the incidence of urinary tract infections (e.g., urinary tract infection, asymptomatic bacteriuria, and cystitis) was increased in patients treated with COSPIAQ compared to placebo (see Table 2). Patients with a history of chronic or recurrent urinary tract infections were more likely to experience a urinary tract infection. The rate of treatment discontinuation due to urinary tract infections was 0.1%, 0.2%, and 0.1% for placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg was 3.2%, 3.6%, and 4.1%, respectively *[see Use in Specific Populations (8.5)]*.

Clinical Trials in Patients with Heart Failure

No new adverse reactions were identified in EMPEROR-Reduced or EMPEROR-Preserved heart failure trials.

Clinical Trial in Patients with Chronic Kidney Disease

The safety profile in patients with chronic kidney disease was generally consistent with that observed across the studied indications. In a long-term cardio-renal outcome trial *[see Clinical Studies 14.4]*, in patients with chronic kidney disease, the occurrence of lower limb amputations was reported with event rates of 2.9, and 4.3 events per 1,000 patient-years in the placebo, and COSPIAQ 10 mg treatment arms, respectively *[see Warnings and Precautions (5.7)]*.

Laboratory Test Abnormalities in Clinical Trials

Increases in Serum Creatinine and Decreases in eGFR

Initiation of COSPIAQ causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a trial of patients with moderate renal impairment, larger mean changes were observed. In a long-term cardiovascular outcomes trial, the increase in serum creatinine and decrease in eGFR generally did not exceed 0.1 mg/dL and -9.0 mL/min/1.73 m^2, respectively, at Week 4, and reversed after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with COSPIAQ.

Increase in Low-Density Lipoprotein Cholesterol (LDL-C)

Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with COSPIAQ. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg, respectively. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups.

Increase in Hematocrit

In a pool of four placebo-controlled studies, median hematocrit decreased by 1.3% in placebo and increased by 2.8% in COSPIAQ 10 mg and 2.8% in COSPIAQ 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg, respectively.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of COSPIAQ. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Constipation

Infections: Necrotizing fasciitis of the perineum (Fournier's gangrene), urosepsis and pyelonephritis

Metabolism and Nutrition Disorders: Ketoacidosis

Renal and Urinary Disorders: Acute kidney injury

Skin and Subcutaneous Tissue Disorders: Angioedema, skin reactions (e.g., rash, urticaria)

7. DRUG INTERACTIONS

See Table 4 for clinically relevant interactions with COSPIAQ.

Table 4 Clinically Relevant Interactions with COSPIAQ

Diuretics	
Clinical Impact	Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
Intervention	Before initiating COSPIAQ, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating COSPIAQ. Monitor for signs and symptoms of volume depletion, and renal function after initiating therapy.
Insulin or Insulin Secretagogues	
Clinical Impact	The risk of hypoglycemia is increased when COSPIAQ is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of COSPIAQ with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower dosages of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
Lithium	
Clinical Impact	Concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations.
Intervention	Monitor serum lithium concentration more frequently during COSPIAQ initiation and dosage changes.
Positive Urine Glucose Test	
Clinical Impact	SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests.
Intervention	Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
Interference with 1,5-anhydroglucitol (1,5-AG) Assay	
Clinical Impact	Measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors.
Intervention	Monitoring glycemic control with 1,5-AG assay is not recommended. Use alternative methods to monitor glycemic control.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, COSPIAQ is not recommended during the second and third trimesters of pregnancy.

The limited available data with COSPIAQ in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal studies, adverse renal changes were observed in rats when empagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy. Doses approximately 13-times the maximum clinical dose caused renal pelvic and tubule dilatations that were reversible. *[see Data]*.

The estimated background risk of major birth defects is 6% to 10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20% to 25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Empagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 10, 30 and 100 mg/kg/day caused increased kidney weights and renal tubular and pelvic dilatation at 100 mg/kg/day, which approximates 13-times the maximum clinical dose of 25 mg, based on AUC. These findings were not observed after a 13-week, drug-free recovery period. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development.

In embryo-fetal development studies in rats and rabbits, empagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. Doses up to 300 mg/kg/day, which approximates 48-times (rats) and 128-times (rabbits) the maximum clinical dose of 25 mg (based on AUC), did not result in adverse developmental effects. In rats, at higher doses of empagliflozin causing maternal toxicity, malformations of limb bones increased in fetuses at 700 mg/kg/day or 154-times the 25 mg maximum clinical dose. Empagliflozin crosses the placenta and reaches fetal tissues in rats. In the rabbit, higher doses of empagliflozin resulted in maternal and fetal toxicity at 700 mg/kg/day, or 139-times the 25 mg maximum clinical dose.

In pre- and postnatal development studies in pregnant rats, empagliflozin was administered from gestation day 6 through to lactation day 20 (weaning) at up to 100 mg/kg/day (approximately 16 times the 25 mg maximum clinical dose) without maternal toxicity. Reduced body weight was observed in the offspring at greater than or equal to 30 mg/kg/day (approximately 4 times the 25 mg maximum clinical dose).

8.2. Lactation

Risk Summary

There is limited information regarding the presence of COSPIAQ in human milk, the effects of COSPIAQ on the breastfed infant or the effects on milk production. Empagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, including the potential for empagliflozin to affect postnatal renal development, advise patients that use of COSPIAQ is not recommended while breastfeeding.

Data

Empagliflozin was present at a low level in rat fetal tissues after a single oral dose to the dams at gestation day 18. In rat milk, the mean milk to plasma ratio ranged from 0.634 to 5, and was greater than one from 2 to 24 hours post-dose. The mean maximal milk to plasma ratio of 5 occurred at 8 hours post-dose, suggesting accumulation of empagliflozin in the milk. Juvenile rats directly exposed to empagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.4. Pediatric Use

The safety and effectiveness of COSPIAQ have not been established in pediatric patients.

8.5. Geriatric Use

In glycemic control trials in patients with type 2 diabetes mellitus, a total of 2,721 (32%) patients treated with COSPIAQ were 65 years of age and older, and 491 (6%) were 75 years of age and older. COSPIAQ is expected to have diminished glycemic efficacy in elderly patients with renal impairment *[see Use in Specific Populations (8.6)]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, COSPIAQ 10 mg, and COSPIAQ 25 mg, respectively *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

In the EMPEROR-Reduced, EMPEROR-Preserved, and EMPA-KIDNEY trials, no overall differences in safety and effectiveness have been observed between patients 65 years of age and older and younger adult patients. EMPEROR-Reduced included 1,188 (64%) patients treated with COSPIAQ 65 years of age and older, and 503 (27%) patients 75 years of age and older. EMPEROR-Preserved included 2,402 (80%) patients treated with COSPIAQ 65 years of age and older, and 1,281 (43%) patients 75 years of age and older. EMPA-KIDNEY included 2,089 (32%) patients treated with COSPIAQ 65 years of age and older, and 1,518 (23%) patients 75 years of age and older.

8.6. Renal Impairment

The efficacy and safety of COSPIAQ for glycemic control were evaluated in a trial of patients with type 2 diabetes mellitus with mild and moderate renal impairment (eGFR 30 to less than 90 mL/min/1.73 m^2) *[see Clinical Studies (14)]*. In this trial, 195 patients exposed to COSPIAQ had an eGFR between 60 and 90 mL/min/1.73 m^2, 91 patients exposed to COSPIAQ had an eGFR between 45 and 60 mL/min/1.73 m^2, and 97 patients exposed to COSPIAQ had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of COSPIAQ 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function *[see Warnings and Precautions (5.2)]*. Use of COSPIAQ for glycemic control in patients without established cardiovascular disease or cardiovascular risk factors is not recommended when eGFR is less than 30 mL/min/1.73 m^2.

COSPIAQ was evaluated in 7,020 adult patients with type 2 diabetes and established cardiovascular disease (eGFR greater than or equal to 30 mL/min/1.73 m^2) in the EMPA-REG OUTCOME trial, in a total of 9,718 patients with heart failure (eGFR greater than or equal to 20 mL/min/1.73 m^2) in the EMPEROR-Reduced and EMPEROR-Preserved trials, and in 6,609 adult patients with chronic kidney disease (eGFR 20 to 90 mL/min/1.73 m^2) in the EMPA-KIDNEY study. The safety profile across eGFR subgroups in these trials was consistent with the known safety profile *[see Adverse Reactions (6.1) and Clinical Studies (14.2, 14.3, 14.4)]*.

Efficacy and safety trials with COSPIAQ did not enroll adult patients with an eGFR less than 20 mL/min/1.73 m^2 or on dialysis. Once enrolled, adult patients in the EMPA-REG OUTCOME, EMPEROR-Reduced, EMPEROR-Preserved, and EMPA-KIDNEY trials were not required to discontinue therapy for worsening of eGFR to less than 20 mL/min/1.73 m^2 or initiation of dialysis *[see Clinical Studies (14.2, 14.3, 14.4)]*.

8.7. Hepatic Impairment

COSPIAQ may be used in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10. OVERDOSAGE

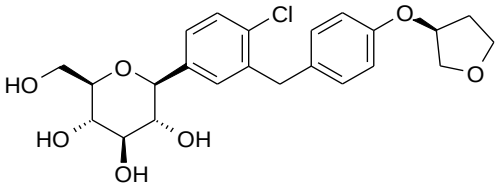
In the event of an overdose with COSPIAQ, contact the Poison Control Center. Removal of empagliflozin by hemodialysis has not been studied.

11. DESCRIPTION

COSPIAQ tablets for oral use contain empagliflozin, an inhibitor of the sodium-glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).

Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91. The structural formula is:



Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile, soluble in 50% acetonitrile/water, and practically insoluble in toluene.

Each film-coated tablet of COSPIAQ contains 10 mg or 25 mg of empagliflozin (free base) and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. In addition, the film coating contains the following inactive ingredients: hypromellose, polyethylene glycol, talc, titanium dioxide, and yellow ferric oxide.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Empagliflozin is an inhibitor of the sodium-glucose co-transporter 2 (SGLT2), the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, increasing tubuloglomerular feedback and reducing intraglomerular pressure, lowering both pre-and afterload of the heart and downregulating sympathetic activity.

12.2. Pharmacodynamics

Urinary Glucose Excretion
In patients with type 2 diabetes mellitus, urinary glucose excretion increased immediately following a dose of empagliflozin and was maintained at the end of a 4-week treatment period averaging at approximately 64 grams per day with 10 mg empagliflozin and 78 grams per day with 25 mg empagliflozin once daily *[see Clinical Studies (14)]*. Data from single oral doses of empagliflozin in healthy subjects indicate that, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg and 25 mg doses.

Urinary Volume
In a 5-day study, mean 24-hour urine volume increase from baseline was 341 mL on Day 1 and 135 mL on Day 5 of empagliflozin 25 mg once daily treatment.

Cardiac Electrophysiology
In a randomized, placebo-controlled, active-comparator, crossover study, 30 healthy subjects were administered a single oral dose of empagliflozin 25 mg, empagliflozin 200 mg (8 times the maximum

dose), moxifloxacin, and placebo. No increase in QTc was observed with either 25 mg or 200 mg empagliflozin.

12.3. Pharmacokinetics

Absorption
The pharmacokinetics of empagliflozin has been characterized in healthy volunteers and patients with type 2 diabetes and no clinically relevant differences were noted between the two populations. After oral administration, peak plasma concentrations of empagliflozin were reached at 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase. The steady state mean plasma AUC and C_{max} were 1870 nmol·h/L and 259 nmol/L, respectively, with 10 mg empagliflozin once daily treatment, and 4740 nmol·h/L and 687 nmol/L, respectively, with 25 mg empagliflozin once daily treatment. Systemic exposure of empagliflozin increased in a dose-proportional manner in the therapeutic dose range. The single-dose and steady-state pharmacokinetic parameters of empagliflozin were similar, suggesting linear pharmacokinetics with respect to time.

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

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

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. Following once-daily dosing, up to 22% accumulation, with respect to plasma AUC, was observed at steady-state, which was consistent with empagliflozin half-life.

Metabolism
No major metabolites of empagliflozin were detected in human plasma and the most abundant metabolites were three glucuronide conjugates (2-O-, 3-O-, and 6-O-glucuronide). Systemic exposure of each metabolite was less than 10% of total drug-related material. *In vitro* studies suggested that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9.

Excretion
Following administration of an oral [^{14}C]-empagliflozin solution to healthy subjects, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%). The majority of drug-related radioactivity recovered in feces was unchanged parent drug and approximately half of drug-related radioactivity excreted in urine was unchanged parent drug.

Specific Populations

Patients with Renal Impairment
In patients with type 2 diabetes mellitus with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and patients on dialysis due to kidney failure, 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 patients with moderate renal impairment and patients on dialysis due to kidney failure compared to subjects with normal renal function. Peak plasma levels of

empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to patients with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

Patients with Hepatic Impairment

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

Effects of Age, Body Mass Index, Gender, and Race

Based on the population PK analysis, age, body mass index (BMI), gender and race (Asians versus primarily Whites) do not have a clinically meaningful effect on pharmacokinetics of empagliflozin *[see Use in Specific Populations (8.5)]*.

Drug Interaction Studies

In vitro Assessment of Drug Interactions

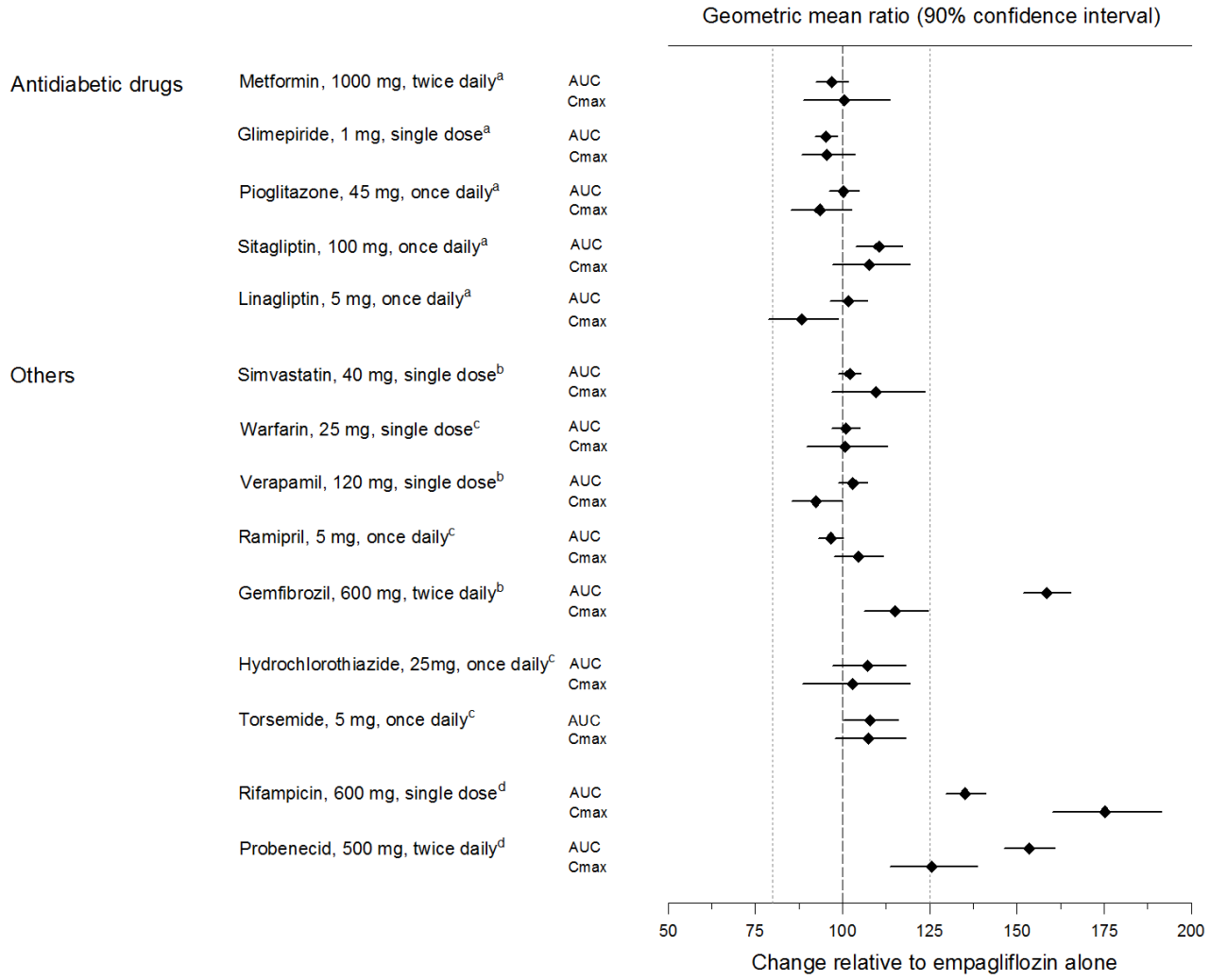
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. Therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of the major CYP450 isoforms or UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. The effect of UGT induction (e.g., induction by rifampicin or any other UGT enzyme inducer) on empagliflozin exposure has not been evaluated.

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, therefore, no effect of empagliflozin is anticipated on concomitantly administered drugs that are substrates of these uptake transporters.

In vivo Assessment of Drug Interactions

Empagliflozin pharmacokinetics were similar with and without coadministration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin in healthy volunteers and with or without coadministration of hydrochlorothiazide and torsemide in patients with type 2 diabetes mellitus (see Figure 1). In subjects with normal renal function, coadministration of empagliflozin with probenecid resulted in a 30% decrease in the fraction of empagliflozin excreted in urine without any effect on 24-hour urinary glucose excretion. The relevance of this observation to patients with renal impairment is unknown.

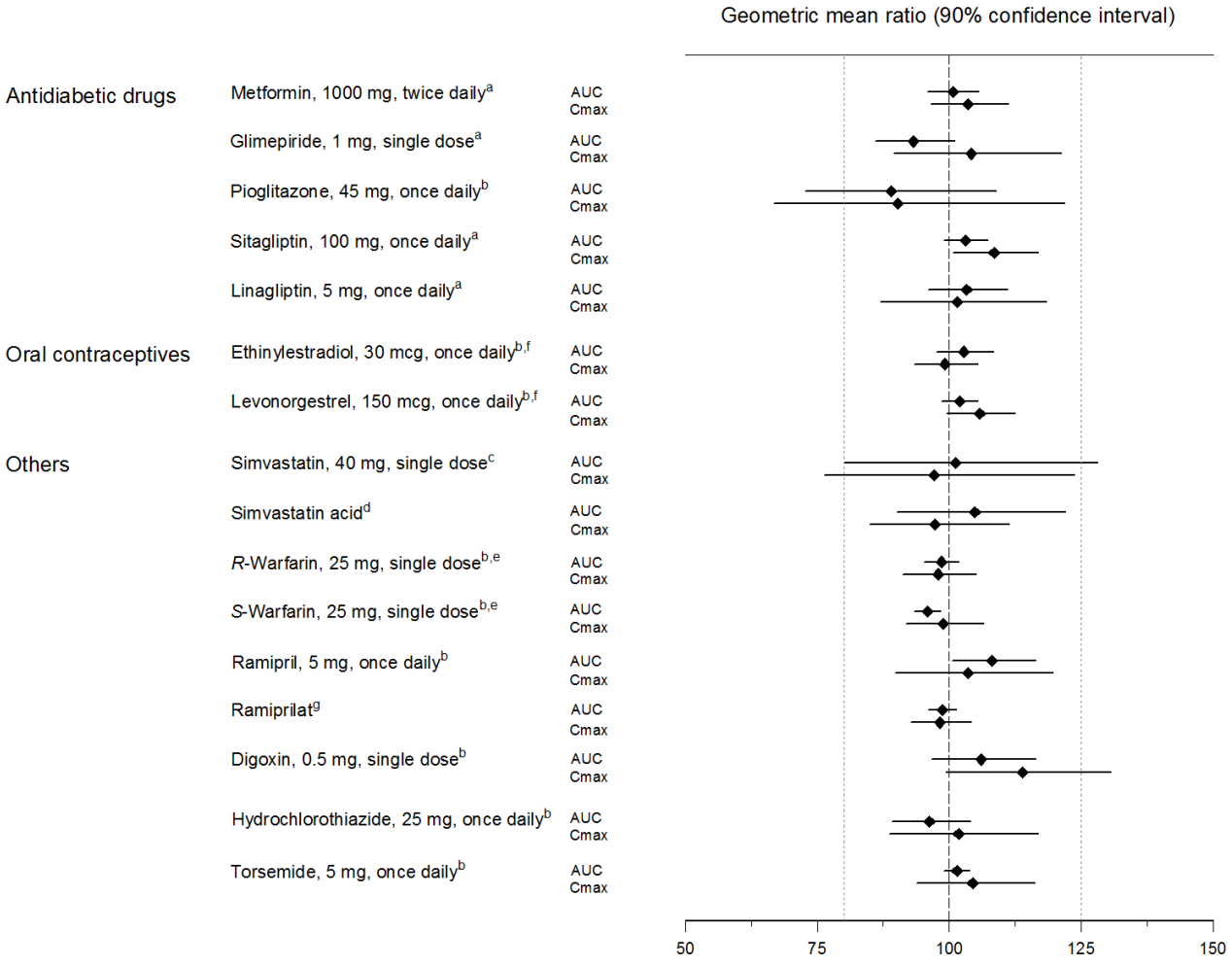
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, single dose; [c]empagliflozin, 25 mg, once daily; [d]empagliflozin, 10 mg, single dose

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torsemide, and oral contraceptives when coadministered in healthy volunteers (see Figure 2).

Figure 2 Effect of Empagliflozin on the Pharmacokinetics of Various Medications as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[a]empagliflozin, 50 mg, once daily; [b]empagliflozin, 25 mg, once daily; [c]empagliflozin, 25 mg, single dose; [d]administered as simvastatin; [e]administered as warfarin racemic mixture; [f]administered as Microgynon®; [g]administered as ramipril

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenesis was evaluated in 2-year studies conducted in CD-1 mice and Wistar rats. Empagliflozin did not increase the incidence of tumors in female rats dosed at 100, 300, or 700 mg/kg/day (up to 72 times the exposure from the maximum clinical dose of 25 mg). In male rats, hemangiomas of the mesenteric lymph node were increased significantly at 700 mg/kg/day or approximately 42 times the exposure from a 25 mg clinical dose. Empagliflozin did not increase the incidence of tumors in female mice dosed at 100, 300, or 1,000 mg/kg/day (up to 62 times the exposure from a 25 mg clinical dose). Renal tubule adenomas and carcinomas were observed in male mice at 1,000 mg/kg/day, which is approximately 45 times the exposure of the maximum clinical dose of 25 mg. These tumors may be associated with a metabolic pathway predominantly present in the male mouse kidney.

Mutagenesis

Empagliflozin was not mutagenic or clastogenic with or without metabolic activation in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* L5178Y $tk^{+/-}$ mouse lymphoma cell assay, and an *in vivo* micronucleus assay in rats.

Impairment of Fertility
Empagliflozin had no effects on mating, fertility or early embryonic development in treated male or female rats up to the high dose of 700 mg/kg/day (approximately 155 times the 25 mg clinical dose in males and females, respectively).

14. CLINICAL STUDIES

14.1. Glycemic Control Trials in Patients with Type 2 Diabetes Mellitus

COSPIAQ has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, linagliptin, and insulin. COSPIAQ has also been studied in patients with type 2 diabetes mellitus with mild or moderate renal impairment.

In patients with type 2 diabetes mellitus, treatment with COSPIAQ reduced hemoglobin A1c (HbA1c), compared to placebo. The reduction in HbA1c for COSPIAQ compared with placebo was observed across subgroups including sex, race, geographic region, baseline BMI and duration of disease.

Monotherapy
A total of 986 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of COSPIAQ monotherapy.

Treatment-naïve patients with inadequately controlled type 2 diabetes mellitus entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, COSPIAQ 10 mg, COSPIAQ 25 mg, or a reference comparator.

At Week 24, treatment with COSPIAQ 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), fasting plasma glucose (FPG), and body weight compared with placebo (see Table 5 and Figure 3).

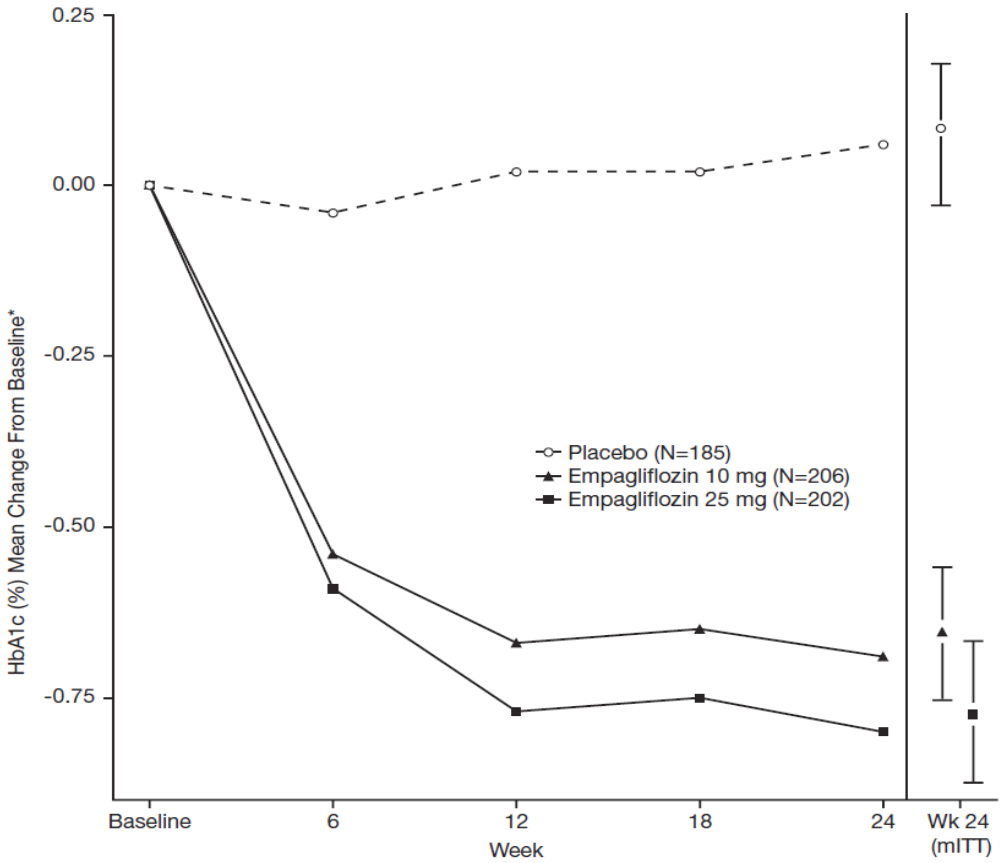
Table 5 Results at Week 24 From a Placebo-Controlled Monotherapy Trial of COSPIAQ

	COSPIAQ 10 mg N=224	**COSPIAQ 25 mg N=224**	**Placebo N=228**
HbA1c (%)[a]			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-0.7b (-0.9, -0.6)	-0.9b (-1.0, -0.7)	--
Patients [n (%) achieving HbA1c <7%	72 (35%)	88 (44%)	25 (12%)
FPG (mg/dL)[c]			
Baseline (mean)	153	153	155
Change from baseline (adjusted mean)	-19	-25	12
Difference from placebo (adjusted mean) (95% CI)	-31 (-37,-26)	-36 (-42,-31)	--
Body Weight			
Baseline (mean) in kg	78	78	78
% change from baseline (adjusted mean)	-2.8	-3.2	-0.4

Difference from placebo (adjusted mean) (95% CI)	-2.5b (-3.1, -1.9)	-2.8b (-3.4, -2.2)	--

[a]Modified intent to treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 9.4%, 9.4%, and 30.7% was imputed for patients randomized to COSPIAQ 10 mg, COSPIAQ 25 mg, and placebo, respectively.
[b]ANCOVA derived p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for COSPIAQ 10 mg, n=223, for COSPIAQ 25 mg, n=223, and for placebo, n=226

Figure 3 Adjusted Mean HbA1c Change at Each Time Point (Completers) and at Week 24 (mITT Population) - LOCF



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, p-value=0.0231) in patients randomized to 10 mg of COSPIAQ and by -3.4 mmHg (placebo-corrected, p-value=0.0028) in patients randomized to 25 mg of COSPIAQ.

Add-On Combination Therapy with Metformin

A total of 637 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of COSPIAQ in combination with metformin.

Patients with type 2 diabetes mellitus inadequately controlled on at least 1,500 mg of metformin per day entered an open-label 2-week placebo run-in. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, COSPIAQ 10 mg, or COSPIAQ 25 mg.

At Week 24, treatment with COSPIAQ 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 6).

Table 6 Results at Week 24 From a Placebo-Controlled Trial for COSPIAQ used in Combination with Metformin

	COSPIAQ 10 mg N=217	COSPIAQ 25 mg N=213	Placebo N=207
HbA1c (%)[a]			
Baseline (mean)	7.9	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.8	-0.1
Difference from placebo + metformin (adjusted mean) (95% CI)	-0.6[b] (-0.7, -0.4)	-0.6[b] (-0.8, -0.5)	--
Patients [n (%)] achieving HbA1c <7%	75 (38%)	74 (39%)	23 (13%)
FPG (mg/dL)[c]			
Baseline (mean)	155	149	156
Change from baseline (adjusted mean)	-20	-22	6
Difference from placebo + metformin (adjusted mean)	-26	-29	--
Body Weight			
Baseline mean in kg	82	82	80
% change from baseline (adjusted mean)	-2.5	-2.9	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.0[b] (-2.6, -1.4)	-2.5[b] (-3.1, -1.9)	--

[a]Modified intent to treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 9.7%, 14.1%, and 24.6% was imputed for patients randomized to COSPIAQ 10 mg, COSPIAQ 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for COSPIAQ 10 mg, n=216, for COSPIAQ 25 mg, n=213, and for placebo, n=207

At Week 24, the systolic blood pressure was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-corrected, p-value <0.0001) for COSPIAQ 10 mg and -4.8 mmHg (placebo-corrected, p-value <0.0001) for COSPIAQ 25 mg.

Initial Combination Therapy with Metformin

A total of 1,364 patients with type 2 diabetes mellitus participated in a double-blind, randomized, active-controlled trial to evaluate the efficacy of COSPIAQ in combination with metformin as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes mellitus entered an open-label placebo run-in for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10.5% were randomized to one of 8 active-treatment arms: COSPIAQ 10 mg or 25 mg; metformin 1,000 mg, or 2,000 mg; COSPIAQ 10 mg in combination with 1,000 mg or 2,000 mg metformin; or COSPIAQ 25 mg in combination with 1,000 mg or 2,000 mg metformin.

At Week 24, initial therapy of COSPIAQ in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 7).

Table 7 Glycemic Parameters at 24 Weeks in a Trial Comparing COSPIAQ and Metformin to the Individual Components as Initial Therapy

	COSPIAQ 10 mg + Metformin 1,000 mg[a] N=161	COSPIAQ 10 mg + Metformin 2,000 mg[a] N=167	COSPIAQ 25 mg + Metformin 1,000 mg[a] N=165	COSPIAQ 25 mg + Metformin 2,000 mg[a] N=169	COSPIAQ 10 mg N=169	COSPIAQ 25 mg N=163	Metformin 1,000 mg[a] N=167	Metformin 2,000 mg[a] N=162
HbA1c (%)								
Baseline (mean)	8.7	8.7	8.8	8.7	8.6	8.9	8.7	8.6
Change from baseline (adjusted mean)	-2.0	-2.1	-1.9	-2.1	-1.4	-1.4	-1.2	-1.8
Comparison vs COSPIAQ (adjusted mean) (95% CI)	-0.6[b] (-0.9, -0.4)	-0.7[b] (-1.0, -0.5)	-0.6[c] (-0.8, -0.3)	-0.7[c] (-1.0, -0.5)	--	--	--	--
Comparison vs metformin (adjusted mean) (95% CI)	-0.8[b] (-1.0, -0.6)	-0.3[b] (-0.6, -0.1)	-0.8[c] (-1.0, -0.5)	-0.3[c] (-0.6, -0.1)	--	--	--	--

[a]Metformin total daily dose, administered in two equally divided doses per day.
[b]p-value ≤0.0062 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).
[c]p-value ≤0.0056 (modified intent to treat population [observed case] MMRM model included treatment, renal function, region, visit, visit by treatment interaction, and baseline HbA1c).

Add-On Combination Therapy with Metformin and Sulfonylurea

A total of 666 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of COSPIAQ in combination with metformin plus a sulfonylurea.

Patients with inadequately controlled type 2 diabetes mellitus on at least 1,500 mg per day of metformin and on a sulfonylurea, entered a 2-week open-label placebo run-in. At the end of the run-in, patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to placebo, COSPIAQ 10 mg, or COSPIAQ 25 mg.

Treatment with COSPIAQ 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 8).

Table 8 Results at Week 24 from a Placebo-Controlled Trial for COSPIAQ in Combination with Metformin and Sulfonylurea

	COSPIAQ 10 mg N=225	COSPIAQ 25 mg N=216	Placebo N=225
HbA1c (%)[a]			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	-0.8	-0.8	-0.2
Difference from placebo (adjusted mean) (95% CI)	-0.6[b] (-0.8, -0.5)	-0.6[b] (-0.7, -0.4)	--
Patients [n (%)] achieving HbA1c <7%	55 (26%)	65 (32%)	20 (9%)
FPG (mg/dL)[c]			
Baseline (mean)	151	156	152
Change from baseline (adjusted mean)	-23	-23	6
Difference from placebo (adjusted mean)	-29	-29	--
Body Weight			
Baseline mean in kg	77	78	76
% change from baseline (adjusted mean)	-2.9	-3.2	-0.5
Difference from placebo (adjusted mean) (95% CI)	-2.4[b] (-3.0, -1.8)	-2.7[b] (-3.3, -2.1)	--

[a]Modified intent to treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 17.8%, 16.7%, and 25.3% was imputed for patients randomized to COSPIAQ 10 mg, COSPIAQ 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for COSPIAQ 10 mg, n=225, for COSPIAQ 25 mg, n=215, for placebo, n=224

In Combination with Linagliptin as Add-On to Metformin Therapy

A total of 686 patients with type 2 diabetes mellitus participated in a double-blind, active-controlled trial to evaluate the efficacy of COSPIAQ 10 mg or 25 mg in combination with linagliptin 5 mg compared to the individual components.

Patients with type 2 diabetes mellitus inadequately controlled on at least 1,500 mg of metformin per day entered a single-blind placebo run-in period for 2 weeks. At the end of the run-in period, patients who remained inadequately controlled and had an HbA1c between 7% and 10.5% were randomized 1:1:1:1:1 to one of 5 active-treatment arms of COSPIAQ 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg COSPIAQ as a fixed dose combination tablet.

At Week 24, COSPIAQ 10 mg or 25 mg used in combination with linagliptin 5 mg provided statistically significant improvement in HbA1c (p-value <0.0001) and FPG (p-value <0.001) compared to the individual components in patients who had been inadequately controlled on metformin. Treatment with COSPIAQ/linagliptin 25 mg/5 mg or COSPIAQ/linagliptin 10 mg/5 mg daily also resulted in a statistically significant reduction in body weight compared to linagliptin 5 mg (p-value <0.0001). There was no statistically significant difference in body weight compared to COSPIAQ alone.

Active-Controlled Trial versus Glimepiride in Combination with Metformin

The efficacy of COSPIAQ was evaluated in a double-blind, glimepiride-controlled, trial in 1,545 patients with type 2 diabetes mellitus with insufficient glycemic control despite metformin therapy.

Patients with inadequate glycemic control and an HbA1c between 7% and 10% after a 2-week run-in period were randomized to glimepiride or COSPIAQ 25 mg.

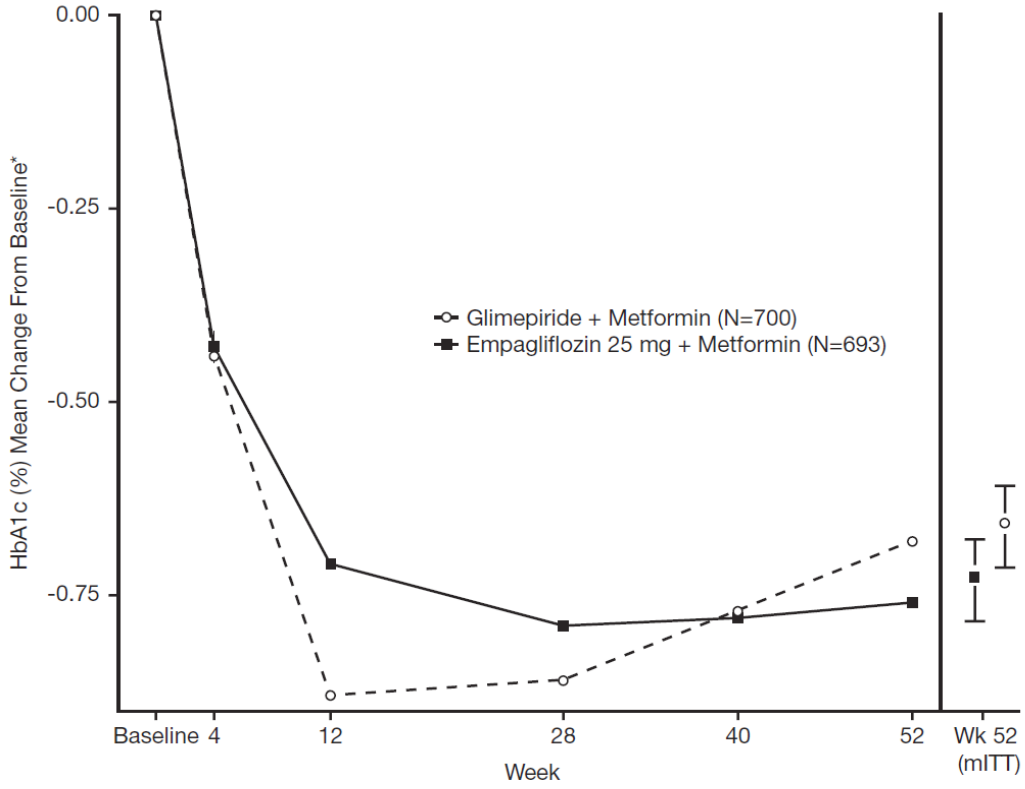
At Week 52, COSPIAQ 25 mg and glimepiride lowered HbA1c and FPG (see Table 9, Figure 4). The difference in observed effect size between COSPIAQ 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dosage of glimepiride was 2.7 mg and the maximal approved dosage in the United States is 8 mg per day.

Table 9 Results at Week 52 from an Active-Controlled Study Comparing COSPIAQ to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

	COSPIAQ 25 mg N=765	**Glimepiride N=780**
HbA1c (%)[a]		
Baseline (mean)	7.9	7.9
Change from baseline (adjusted mean)	-0.7	-0.7
Difference from glimepiride (adjusted mean) (97.5% CI)	-0.07[b] (-0.15, 0.01)	--
FPG (mg/dL)[d]		
Baseline (mean)	150	150
Change from baseline (adjusted mean)	-19	-9
Difference from glimepiride (adjusted mean)	-11	--
Body Weight		
Baseline mean in kg	82.5	83
% change from baseline (adjusted mean)	-3.9	2.0
Difference from glimepiride (adjusted mean) (95% CI)	-5.9[c] (-6.3, -5.5)	--

[a]Modified intent to treat population. Last observation on trial (LOCF) was used to impute data missing at Week 52. At Week 52, data was imputed for 15.3% and 21.9% of patients randomized to COSPIAQ 25 mg and glimepiride, respectively.
[b]Non-inferior, ANCOVA model p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and region)
[c]ANCOVA p-value <0.0001 (Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[d]FPG (mg/dL); for COSPIAQ 25 mg, n=764, for glimepiride, n=779

Figure 4 Adjusted mean HbA1c Change at Each Time Point (Completers) and at Week 52 (mITT Population) - LOCF



*Mean change from baseline adjusted for baseline HbA1c, geographical region, and eGFR at baseline

At Week 52, the adjusted mean change from baseline in systolic blood pressure was -3.6 mmHg, compared to 2.2 mmHg for glimepiride. The differences between treatment groups for systolic blood pressure was statistically significant (p-value <0.0001).

At Week 104, the adjusted mean change from baseline in HbA1c was -0.75% for COSPIAQ 25 mg and -0.66% for glimepiride. The adjusted mean treatment difference was -0.09% with a 97.5% confidence interval of (-0.32%, 0.15%), excluding the pre-specified non-inferiority margin of 0.3%. The mean daily dosage of glimepiride was 2.7 mg and the maximal approved dosage in the United States is 8 mg per day. The Week 104 analysis included data with and without concomitant glycemic rescue medication, as well as off-treatment data. Missing data for patients not providing any information at the visit were imputed based on the observed off-treatment data. In this multiple imputation analysis, 13.9% of the data were imputed for COSPIAQ 25 mg and 12.9% for glimepiride.

At Week 104, COSPIAQ 25 mg daily resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.1 kg for COSPIAQ 25 mg vs. +1.3 kg for glimepiride; ANCOVA-LOCF, p-value <0.0001).

Add-On Combination Therapy with Pioglitazone with or without Metformin

A total of 498 patients with type 2 diabetes mellitus participated in a double-blind, placebo-controlled trial to evaluate the efficacy of COSPIAQ in combination with pioglitazone, with or without metformin.

Patients with inadequately controlled type 2 diabetes mellitus on metformin at a dose of at least 1,500 mg per day and pioglitazone at a dose of at least 30 mg per day were placed into an open-label placebo run-in for 2 weeks. Patients with inadequate glycemic control and an HbA1c between 7% and 10% after the run-in period were randomized to placebo, COSPIAQ 10 mg, or COSPIAQ 25 mg.

Treatment with COSPIAQ 10 mg or 25 mg daily resulted in statistically significant reductions in HbA1c (p-value <0.0001), FPG, and body weight compared with placebo (see Table 10).

Table 10 Results of Placebo-Controlled Trial for COSPIAQ in Combination Therapy with Pioglitazone

	COSPIAQ 10 mg N=165	**COSPIAQ 25 mg N=168**	**Placebo N=165**
HbA1c (%)[a]			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean)	-0.6	-0.7	-0.1
Difference from placebo + pioglitazone (adjusted mean) (95% CI)	-0.5[b] (-0.7, -0.3)	-0.6[b] (-0.8, -0.4)	--
Patients [n (%)] achieving HbA1c <7%	36 (24%)	48 (30%)	12 (8%)
FPG (mg/dL)[c]			
Baseline (mean)	152	152	152
Change from baseline (adjusted mean)	-17	-22	7
Difference from placebo + pioglitazone (adjusted mean) (97.5% CI)	-23[b] (-31.8, -15.2)	-28[b] (-36.7, -20.2)	--
Body Weight			
Baseline mean in kg	78	79	78
% change from baseline (adjusted mean)	-2.0	-1.8	0.6
Difference from placebo (adjusted mean) (95% CI)	-2.6[b] (-3.4, -1.8)	-2.4[b] (-3.2, -1.6)	--

[a]Modified intent to treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 10.9%, 8.3%, and 20.6% was imputed for patients randomized to COSPIAQ 10 mg, COSPIAQ 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication. Body weight and FPG: same model used as for HbA1c but additionally including baseline body weight/baseline FPG, respectively.)
[c]FPG (mg/dL); for COSPIAQ 10 mg, n=163

Add-On Combination with Insulin with or without Metformin and/or Sulfonylureas

A total of 494 patients with type 2 diabetes mellitus inadequately controlled on insulin, or insulin in combination with oral drugs participated in a double-blind, placebo-controlled trial to evaluate the efficacy of COSPIAQ as add-on therapy to insulin over 78 weeks.

Patients entered a 2-week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or sulfonylurea background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of COSPIAQ 10 mg, COSPIAQ 25 mg, or placebo. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 18 weeks of treatment. For the remaining 60 weeks, insulin could be adjusted. The mean total daily insulin dose at baseline for COSPIAQ 10 mg, 25 mg, and placebo was 45 IU, 48 IU, and 48 IU, respectively.

COSPIAQ used in combination with insulin (with or without metformin and/or sulfonylurea) provided statistically significant reductions in HbA1c and FPG compared to placebo after both 18 and 78 weeks of treatment (see Table 11). COSPIAQ 10 mg or 25 mg daily also resulted in statistically significantly greater percent body weight reduction compared to placebo.

Table 11 Results at Week 18 and 78 for a Placebo-Controlled Trial for COSPIAQ in Combination with Insulin

	18 weeks (no insulin adjustment)			78 weeks (adjustable insulin dose after 18 weeks)		
	COSPIAQ 10 mg N=169	**COSPIAQ 25 mg N=155**	**Placebo N=170**	**COSPIAQ 10 mg N=169**	**COSPIAQ 25 mg N=155**	**Placebo N=170**
HbA1c (%)[a]						
Baseline (mean)	8.3	8.3	8.2	8.3	8.3	8.2
Change from baseline (adjusted mean)	-0.6	-0.7	0	-0.4	-0.6	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-0.6[b] (-0.8, -0.4)	-0.7[b] (-0.9, -0.5)	--	-0.5[b] (-0.7, -0.3)	-0.7[b] (-0.9, -0.5)	--
Patients (%) achieving HbA1c <7%	18.0	19.5	5.5	12.0	17.5	6.7
FPG (mg/dL)						
Baseline (mean)	138	146	142	138	146	142
Change from baseline (adjusted mean, SE)	-17.9 (3.2)	-19.1 (3.3)	10.4 (3.1)	-10.1 (3.2)	-15.2 (3.4)	2.8 (3.2)
Difference from placebo (adjusted mean) (95% CI)	-28.2[b] (-37.0, -19.5)	-29.5[b] (-38.4, -20.6)	--	-12.9[c] (-21.9, 3.9)	-17.9[b] (-27.0, -8.8)	--
Body Weight						
Baseline mean in kg	92	95	90	92	95	90
% change from baseline (adjusted mean)	-1.8	-1.4	-0.1	-2.4	-2.4	0.7
Difference from placebo (adjusted mean) (95% CI)	-1.7[d] (-3.0, -0.5)	-1.3[e] (-2.5, -0.0)	--	-3.0[b] (-4.4, -1.7)	-3.0[b] (-4.4, -1.6)	--

[a]Modified intent to treat population. Last observation on trial (LOCF) was used to impute missing data at Week 18 and 78. At Week 18, 21.3%, 30.3%, and 21.8% was imputed for patients randomized to COSPIAQ 10 mg, COSPIAQ 25 mg, and placebo, respectively. At Week 78, 32.5%, 38.1% and 42.4% was imputed for patients randomized to COSPIAQ 10 mg, COSPIAQ 25 mg, and placebo, respectively.
[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, and region; FPG: MMRM model includes baseline FPG, baseline HbA1c, treatment, region, visit and visit by treatment interaction. Body weight: MMRM model includes baseline body weight, baseline HbA1c, treatment, region, visit and visit by treatment interaction.
[c]p-value=0.0049
[d]p-value=0.0052
[e]p-value=0.0463

Add-on Combination with MDI Insulin with or without Metformin

A total of 563 patients with type 2 diabetes mellitus inadequately controlled on multiple daily injections (MDI) of insulin (total daily dose >60 IU), alone or in combination with metformin, participated in a double-blind, placebo-controlled trial to evaluate the efficacy of COSPIAQ as add-on therapy to MDI insulin over 18 weeks.

Patients entered a 2-week placebo run-in period on MDI insulin with or without metformin background therapy. Following the run-in period, patients with inadequate glycemic control were randomized to the addition of COSPIAQ 10 mg, COSPIAQ 25 mg, or placebo. Patients were maintained on a stable dose of insulin prior to enrollment, during the run-in period, and during the first 18 weeks of treatment. The mean total daily insulin dose at baseline for COSPIAQ 10 mg, COSPIAQ 25 mg, and placebo was 88.6 IU, 90.4 IU, and 89.9 IU, respectively.

COSPIAQ 10 mg or 25 mg daily used in combination with MDI insulin (with or without metformin) provided statistically significant reductions in HbA1c compared to placebo after 18 weeks of treatment (see Table 12).

Table 12 Results at Week 18 for a Placebo-Controlled Trial for COSPIAQ in Combination with Insulin and with or without Metformin

	COSPIAQ 10 mg N=186	**COSPIAQ 25 mg N=189**	**Placebo N=188**
HbA1c (%)[a]			
Baseline (mean)	8.4	8.3	8.3
Change from baseline (adjusted mean)	-0.9	-1.0	-0.5
Difference from placebo (adjusted mean) (95% CI)	-0.4[b] (-0.6, -0.3)	-0.5[b] (-0.7, -0.4)	--

[a]Modified intent to treat population. Last observation on trial (LOCF) was used to impute missing data at Week 18. At Week 18, 23.7%, 22.8% and 23.4% was imputed for patients randomized to COSPIAQ 10 mg, COSPIAQ 25 mg, and placebo, respectively.

[b]ANCOVA p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, geographical region, and background medication).

During an extension period with treatment for up to 52 weeks, insulin could be adjusted to achieve defined glucose target levels. The change from baseline in HbA1c was maintained from 18 to 52 weeks with both COSPIAQ 10 mg and 25 mg. After 52 weeks, COSPIAQ 10 mg or 25 mg daily resulted in statistically greater percent body weight reduction compared to placebo (p-value <0.0001). The mean change in body weight from baseline was -1.95 kg for COSPIAQ 10 mg, and -2.04 kg for COSPIAQ 25 mg.

Renal Impairment

A total of 738 patients with type 2 diabetes mellitus and a baseline eGFR less than 90 mL/min/1.73 m^2 participated in a randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of COSPIAQ in patients with type 2 diabetes mellitus and renal impairment. The trial population comprised of 290 patients with mild renal impairment (eGFR 60 to less than 90 mL/min/1.73 m^2), 374 patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and 74 with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2). A total of 194 patients with moderate renal impairment had a baseline eGFR of 30 to less than 45 mL/min/1.73 m^2 and 180 patients had a baseline eGFR of 45 to less than 60 mL/min/1.73 m^2.

At Week 24, COSPIAQ 25 mg provided statistically significant reduction in HbA1c relative to placebo in patients with mild to moderate renal impairment (see Table 13). A statistically significant reduction relative to placebo was also observed with COSPIAQ 25 mg in patients with either mild [-0.7 (95% CI: -0.9, -0.5)] or moderate [-0.4 (95% CI: -0.6, -0.3)] renal impairment and with COSPIAQ 10 mg in patients with mild [-0.5 (95% CI: -0.7, -0.3)] renal impairment.

The glucose lowering efficacy of COSPIAQ 25 mg decreased with decreasing level of renal function in the mild to moderate range. Least square mean HbA1c changes at 24 weeks were -0.6%, -0.5%, and -0.2% for those with a baseline eGFR of 60 to less than 90 mL/min/1.73 m^2, 45 to less than 60 mL/min/1.73 m^2, and 30 to less than 45 mL/min/1.73 m^2, respectively *[see Dosage and Administration (2) and Use in Specific Populations (8.6)]*. For placebo, least square mean HbA1c changes at 24 weeks were 0.1%, -0.1%, and 0.2% for patients with a baseline eGFR of 60 to less than 90 mL/min/1.73 m^2, 45 to less than 60 mL/min/1.73 m^2, and 30 to less than 45 mL/min/1.73 m^2, respectively.

Table 13 Results at Week 24 (LOCF) of Placebo-Controlled Study Trial for COSPIAQ in Patients with Type 2 Diabetes Mellitus and Renal Impairment

	Mild and Moderate Impairment[b]
	COSPIAQ 25 mg
HbA1c	
Number of patients	n=284
Comparison vs placebo (adjusted mean) (95% CI)	-0.5[a] (-0.6, -0.4)

[a]p-value <0.0001 (HbA1c: ANCOVA model includes baseline HbA1c, treatment, renal function, and background medication)
[b]eGFR 30 to less than 90 mL/min/1.73 m^2- Modified intent to treat population. Last observation on trial (LOCF) was used to impute missing data at Week 24. At Week 24, 24.6% and 26.2% was imputed for patients randomized to COSPIAQ 25 mg and placebo, respectively.

For patients with severe renal impairment, the analyses of changes in HbA1c and FPG showed no discernible treatment effect of COSPIAQ 25 mg compared to placebo *[see Indications and Usage (1), Dosage and Administration (2.1, 2.2) and Use in Specific Populations (8.6)]*.

14.2. Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

The effect of COSPIAQ on cardiovascular (CV) risk in adult patients with type 2 diabetes mellitus and established, stable, atherosclerotic CV disease was evaluated in the EMPA-REG OUTCOME trial, a multicenter, multi-national, randomized, double-blind parallel group trial. The trial compared the risk of experiencing a major adverse cardiovascular event (MACE) between COSPIAQ and placebo when these were added to and used concomitantly with standard of care treatments for diabetes mellitus and atherosclerotic CV disease. Concomitant antidiabetic medications were to be kept stable for the first 12 weeks of the trial. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

A total of 7,020 patients were treated (COSPIAQ 10 mg = 2,345; COSPIAQ 25 mg = 2,342; placebo = 2,333) and followed for a median of 3.1 years. Approximately 72% of the trial population was White, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the trial had inadequately controlled type 2 diabetes mellitus at baseline (HbA1c greater than or equal to 7%). The mean HbA1c at baseline was 8.1% and 57% of participants had diabetes mellitus for more than 10 years. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy to investigators respectively and the mean eGFR was 74 mL/min/1.73 m^2. At baseline, patients were treated with one (~30%) or more (~70%) antidiabetic medications including metformin (74%), insulin (48%), and sulfonylurea (43%).

All patients had established atherosclerotic CV disease at baseline including one (82%) or more (18%) of the following: a documented history of coronary artery disease (76%), stroke (23%) or peripheral artery disease (21%). At baseline, the mean systolic blood pressure was 136 mmHg, the mean diastolic blood pressure was 76 mmHg, the mean LDL was 86 mg/dL, the mean HDL was 44 mg/dL, and the mean urinary albumin to creatinine ratio (UACR) was 175 mg/g. At baseline, approximately 81% of patients were treated with renin angiotensin system inhibitors, 65% with beta-blockers, 43% with diuretics, 77% with statins, and 86% with antiplatelet agents (mostly aspirin).

The primary endpoint in EMPA-REG OUTCOME was the time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event was defined as occurrence of either a CV death or a non-fatal myocardial infarction (MI) or a non-fatal stroke. The statistical analysis plan had pre-specified that the 10 and 25 mg doses would be combined. A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and superiority on MACE if non-inferiority was demonstrated. Type-1 error was controlled across multiples tests using a hierarchical testing strategy.

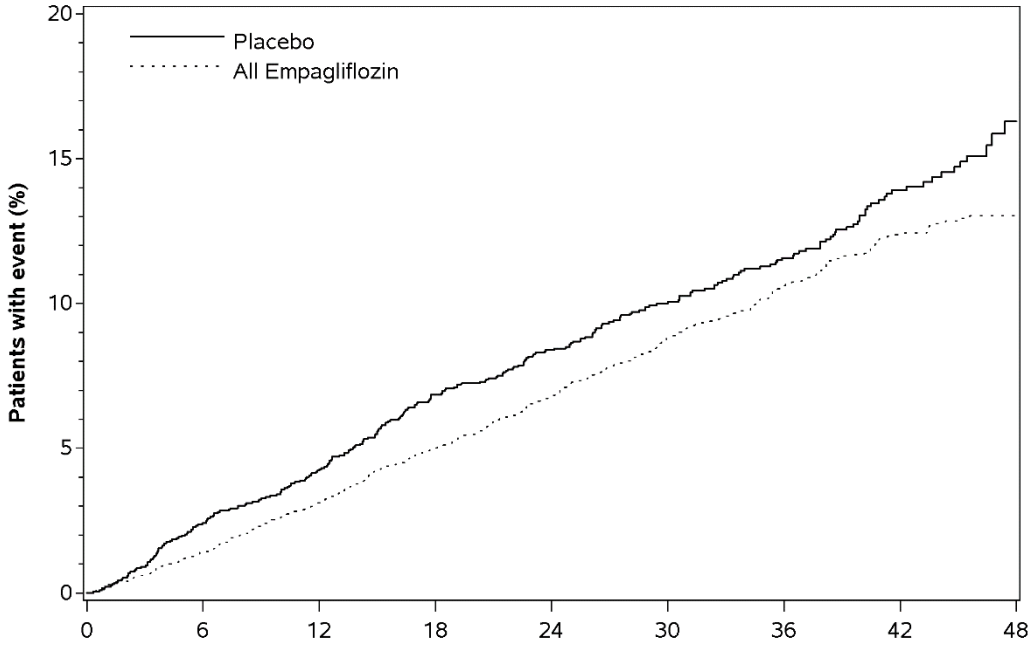
COSPIAQ significantly reduced the risk of first occurrence of primary composite endpoint of CV death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI: 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of CV death in subjects randomized to empagliflozin (HR: 0.62; 95% CI: 0.49, 0.77), with no change in the risk of non-fatal myocardial infarction or non-fatal stroke (see Table 14 and Figures 5 and 6). Results for the 10 mg and 25 mg empagliflozin dosages were consistent with results for the combined dosage groups.

Table 14 Treatment Effect for the Primary Composite Endpoint, and its Components[a]

	Placebo N=2,333	**COSPIAQ N=4,687**	**Hazard ratio vs placebo (95% CI)**
Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (time to first occurrence)[b]	282 (12.1%)	490 (10.5%)	0.86 (0.74, 0.99)
Non-fatal myocardial infarction[c]	121 (5.2%)	213 (4.5%)	0.87 (0.70, 1.09)
Non-fatal stroke[c]	60 (2.6%)	150 (3.2%)	1.24 (0.92, 1.67)
CV death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

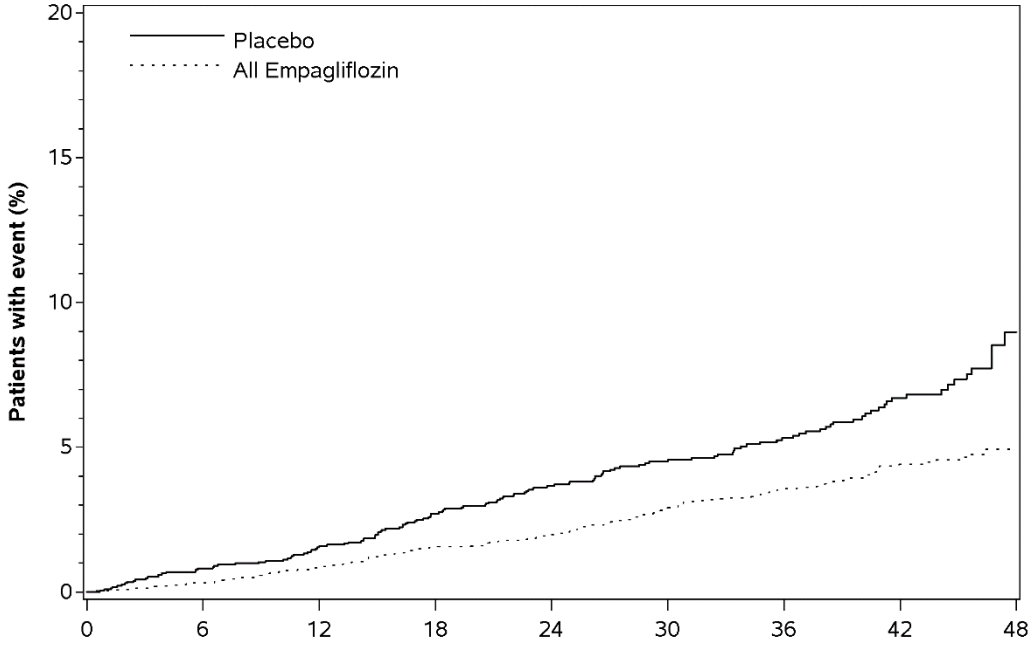
[a]Treated set (patients who had received at least one dose of trial drug)
[b]p-value for superiority (2-sided) 0.04
[c]Total number of events

Figure 5 Estimated Cumulative Incidence of First MACE



Subjects at risk									
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166
All Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370

Figure 6 Estimated Cumulative Incidence of Cardiovascular Death



Subjects at risk									
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177
All Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414

The efficacy of COSPIAQ on CV death was generally consistent across major demographic and disease subgroups.

Vital status was obtained for 99.2% of subjects in the trial. A total of 463 deaths were recorded during the EMPA-REG OUTCOME trial. Most of these deaths were categorized as CV deaths. The non-CV deaths were only a small proportion of deaths and were balanced between the treatment groups (2.1% in patients treated with COSPIAQ, and 2.4% of patients treated with placebo).

14.3. Heart Failure Trials

EMPEROR-Reduced (NCT03057977) was a double-blind trial conducted in patients with chronic heart failure (New York Heart Association [NYHA] functional class II-IV) with left ventricular ejection fraction (LVEF) ≤40%, to evaluate the efficacy of COSPIAQ as adjunct to standard of care heart failure therapy.

Of 3,730 patients, 1,863 were randomized to COSPIAQ 10 mg and 1,867 to placebo and were followed for a median of 16 months. The mean age of the trial population was 67 years (range: 25 to 94 years) and 76% were men, 24% were women, and 27% were 75 years of age or older. Approximately 71% of the trial population were White, 18% Asian and 7% Black or African American. At baseline, 50% of the patients had type 2 diabetes mellitus.

At randomization, 75% of patients were NYHA class II, 24% were class III and 0.5% were class IV. The mean LVEF was 28%. At baseline, the mean eGFR was 62 mL/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g. Approximately half of the patients (52%) had eGFR equal to or above 60 mL/min/1.73 m^2, 24% had eGFR 45 to less than 60 mL/min/1.73 m^2, 19% had eGFR 30 to less than 45 mL/min/1.73 m^2 and 5% had eGFR 20 to less than 30 mL/min/1.73 m^2.

At baseline, 88% of patients were treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI), 95% with beta-blockers, 71% with mineralocorticoid receptor antagonists (MRA), and 95% with diuretics.

The primary endpoint was the time to first event of either cardiovascular (CV) death or hospitalization for heart failure (HHF). First and recurrent HHF was assessed as a key secondary endpoint.

COSPIAQ was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalization for heart failure compared with placebo, mostly through a reduction in hospitalization for heart failure. COSPIAQ reduced the risk of first and recurrent HHF (see Table 15 and Figures 7 and 8).

Table 15 Treatment Effect for the Primary Composite Endpoint, its Components, and Key Secondary Endpoints

	Placebo N=1,867	**COSPIAQ 10 mg N=1,863**	**Hazard ratio vs placebo (95% CI)**	**p-value**
	Number of Patients (%)			
CV death or HHF[a]	462 (24.7%)	361 (19.4%)	0.75 (0.65-0.86)	<0.0001
CV death[a,b]	202 (10.8%)	187 (10.0%)	0.92 (0.75, 1.12)	
HHF[a]	342 (18.3%)	246 (13.2%)	0.69 (0.59, 0.81)	
	Number of Events			
First and recurrent HHF[c]	553	388	0.70 (0.58, 0.85)	0.0003

[a]Time to first event
[b]Includes deaths following hospitalization
[c]Joint frailty model accounting for CV death

Figure 7 **Time to First Occurrence of the Primary Composite Endpoint of CV Death or Hospitalization for Heart Failure**

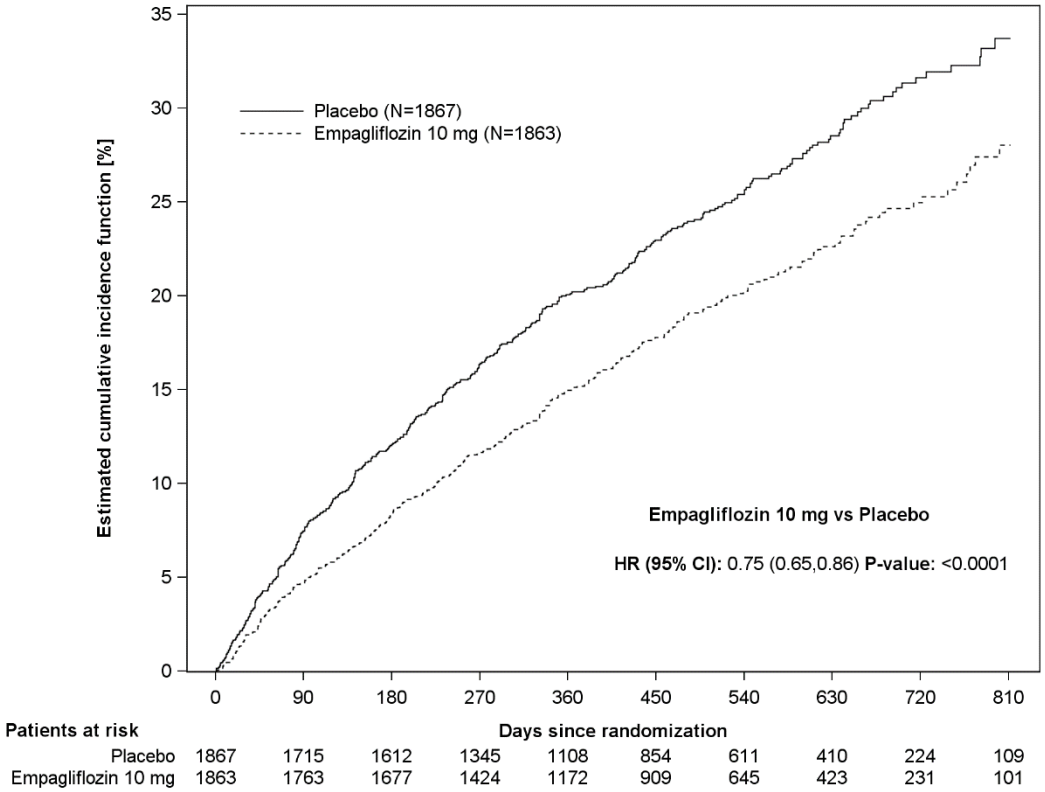
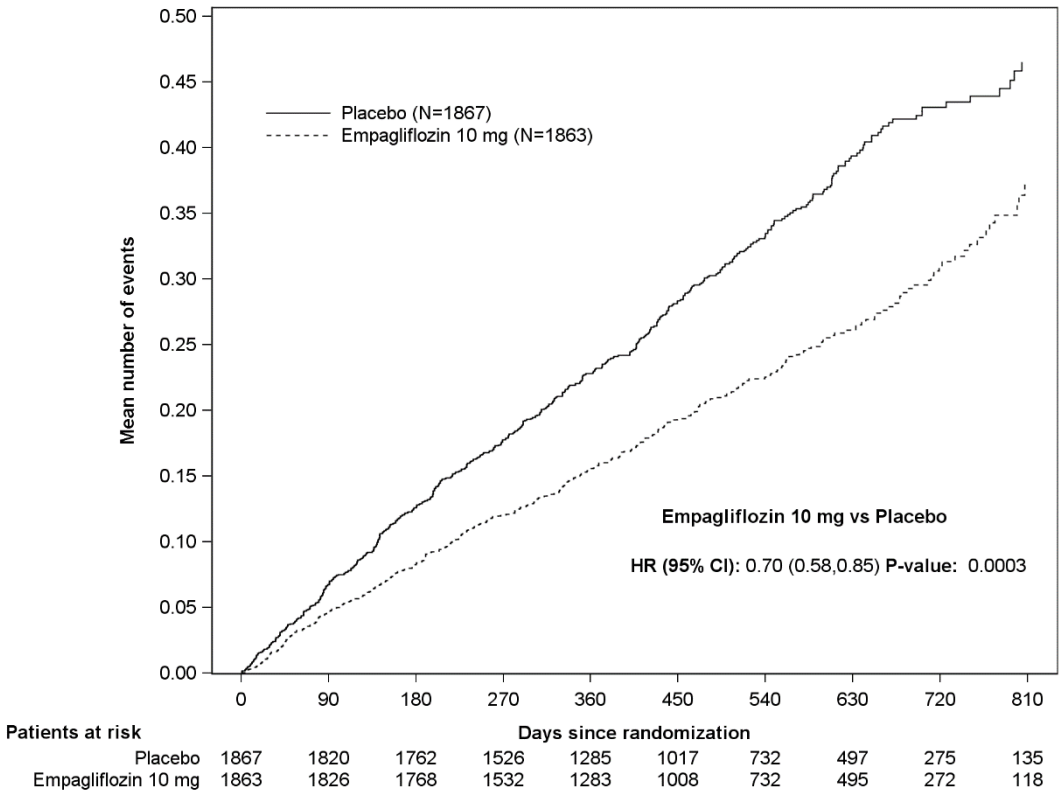
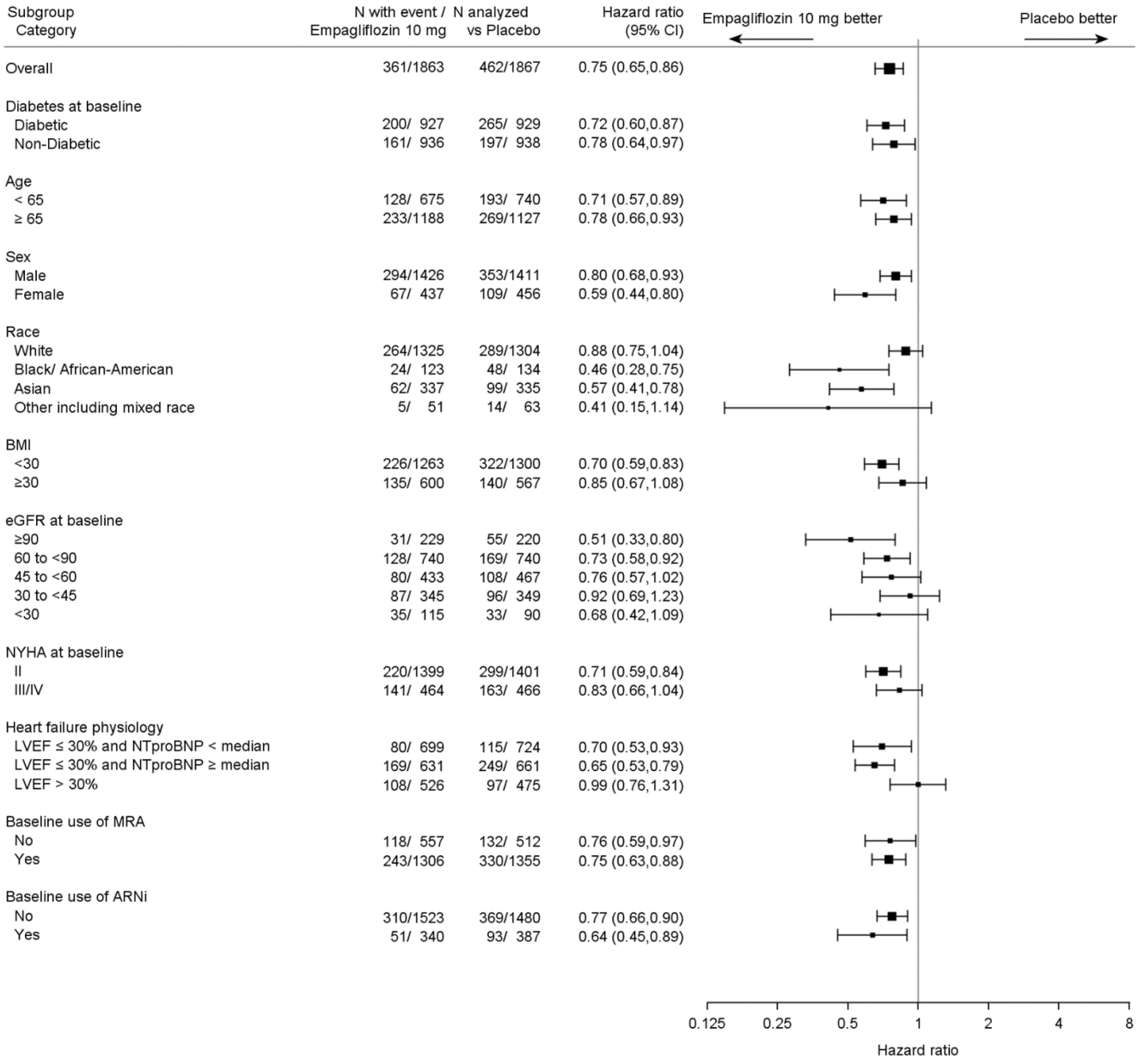


Figure 8 **Time to Event of Hospitalization for Heart Failure (First and Recurrent)**



The results of the primary composite were generally consistent across the pre-specified subgroups (see Figure 9).

Figure 9 Treatment Effects for the Primary Composite Endpoint (CV Death and Hospitalization for Heart Failure) Subgroup Analysis (EMPEROR-Reduced)



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

EMPEROR-Preserved (NCT03057951) was a double-blind trial conducted in patients with chronic heart failure NYHA Class II-IV with LVEF >40% to evaluate the efficacy of COSPIAQ as adjunct to standard of care therapy.

Of 5,988 patients, 2,997 were randomized to COSPIAQ 10 mg and 2,991 to placebo and were followed for a median of 26 months. The mean age of the trial population was 72 years (range: 22 to 100 years) and 55% were men, 45% were women, and 43% were 75 years of age or older. Approximately 76% of the trial population were White, 14% Asian and 4% Black or African American.

At randomization, 82% of patients were NYHA class II, 18% were class III and 0.3% were class IV. The EMPEROR-Preserved trial population included patients with a LVEF <50% (33.1%), with a LVEF 50 to <60% (34.4%) and a LVEF ≥60% (32.5%). At baseline, the mean eGFR was 61 mL/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 21 mg/g. Approximately half of the patients (50%)

had eGFR equal to or above 60 mL/min/1.73 m^2, 26% had eGFR 45 to less than 60 mL/min/1.73 m^2, 19% had eGFR 30 to less than 45 mL/min/1.73 m^2, and 5% had eGFR 20 to less than 30 mL/min/1.73 m^2.

At baseline, 81% of patients were treated with ACE inhibitors, ARBs, or ARNI, 86% with beta-blockers, 38% with MRAs, and 86% with diuretics.

The primary endpoint was the time to first event of either CV death or HHF. First and recurrent HHF was assessed as a key secondary endpoint.

COSPIAQ was superior in reducing the risk of the primary composite endpoint compared with placebo, mostly through a reduction in hospitalization for heart failure. COSPIAQ reduced the risk of first and recurrent HHF (see Table 16 and Figures 10 and 11).

Table 16 Treatment Effect for the Primary Composite Endpoint, its Components, and Key Secondary Endpoints

	Placebo N=2,991	COSPIAQ 10 mg N=2,997	Hazard ratio vs placebo (95% CI)	p-value
	Number of Patients (%)			
CV death or HHF[a]	511 (17.1%)	415 (13.8%)	0.79 (0.69, 0.90)	0.0003
CV death[a,b]	244 (8.2%)	219 (7.3%)	0.91 (0.76, 1.09)	
HHF[a]	352 (11.8%)	259 (8.6%)	0.71 (0.60, 0.83)	
	Number of Events			
First and recurrent HHF[c]	541	407	0.73 (0.61, 0.88)	0.0009

[a]Time to first event
[b]Includes deaths following hospitalization
[c]Joint frailty model accounting for CV death

Figure 10 Time to First Occurrence of the Primary Composite Endpoint of CV Death or Hospitalization for Heart Failure

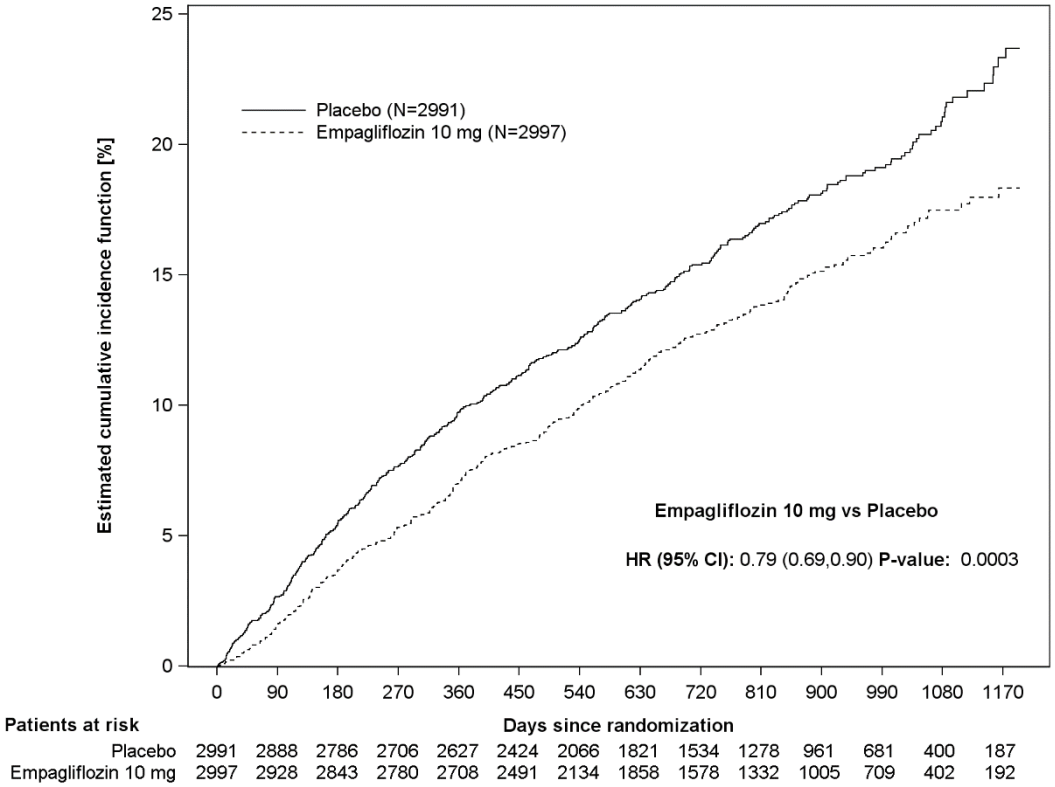
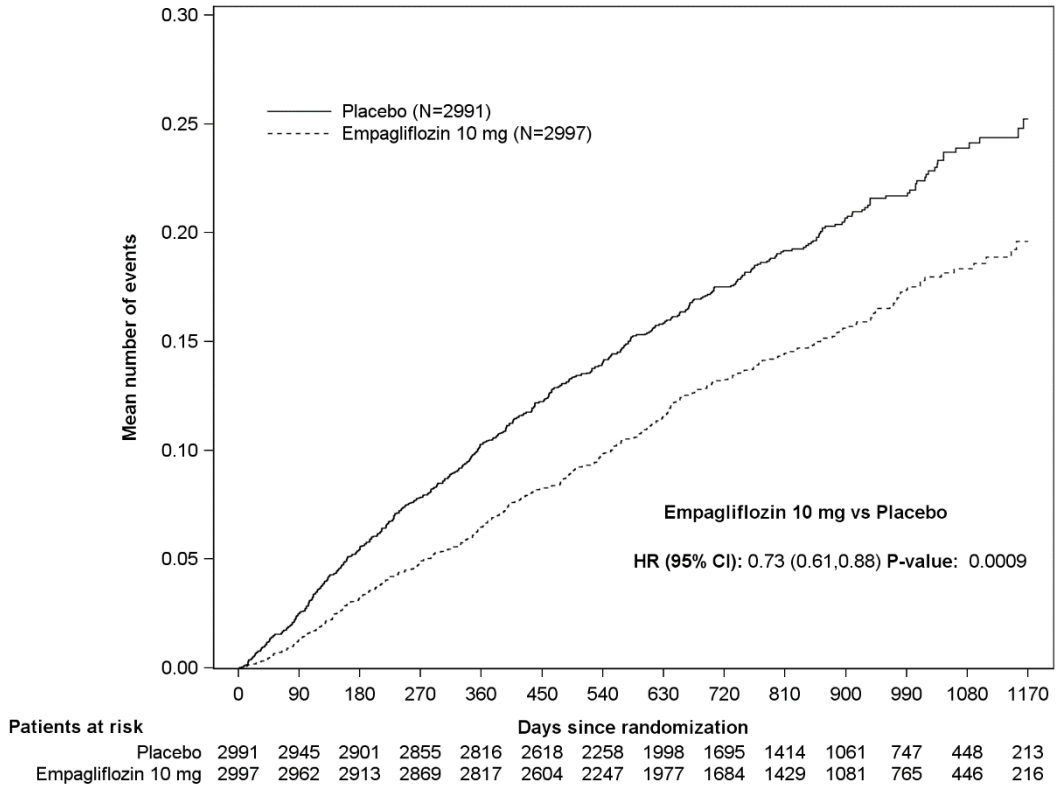
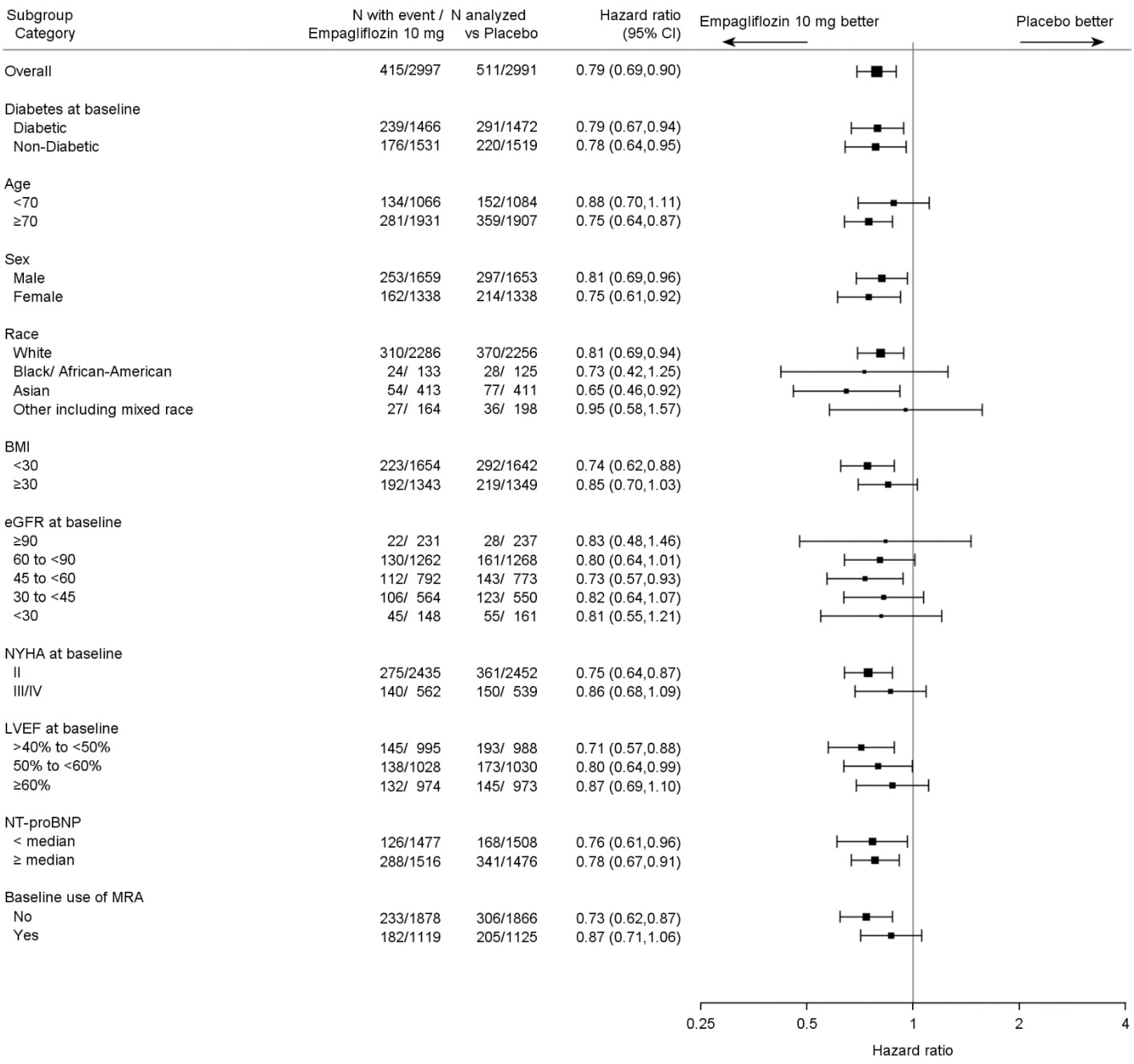


Figure 11 Time to Event of Hospitalization for Heart Failure (First and Recurrent)



The results of the primary composite endpoint were consistent across the pre-specified subgroups (see Figure 12).

Figure 12 Treatment Effects for the Primary Composite Endpoint (CV Death or Hospitalization for Heart Failure) Subgroup Analysis (EMPEROR-Preserved)



14.4. Chronic Kidney Disease Trial

EMPA-KIDNEY (NCT03594110) was a randomized, double-blind, placebo-controlled trial conducted in adults with chronic kidney disease (eGFR ≥20 to <45 mL/min/1.73 m^2; or eGFR ≥45 to <90 mL/min/1.73 m^2 with urine albumin to creatinine ratio [UACR] ≥200 mg/g). The trial excluded patients with polycystic kidney disease or patients requiring intravenous immunosuppressive therapy in the preceding three months or >45 mg of prednisone (or equivalent) at the time of screening. The primary objective of the trial was to assess the effects of empagliflozin as an adjunct to standard of care therapy, including RAS-inhibitor therapy when appropriate, on time to kidney disease progression or cardiovascular death.

A total of 6,609 patients, were equally randomized to COSPIAQ 10 mg or placebo and were followed for a median of 24 months.

The mean age of the study population was 63 years (range: 18 to 94 years) and 67% were male. Approximately 58% of the study population were White, 36% Asian, and 4% Black or African American. Approximately 44% of the patients had type 2 diabetes mellitus.

At baseline, the mean eGFR was 37 mL/min/1.73 m^2, 21% of patients had an eGFR equal to or above 45 mL/min/1.73 m^2, 44% had an eGFR 30 to less than 45 mL/min/1.73 m^2, and 35% had an eGFR less than

30 mL/min/1.73 m^2. The median UACR was 329 mg/g, 20% of patients had a UACR <30 mg/g, 28% had a UACR 30 to ≤300mg/g, and 52% had a UACR >300 mg/g. Approximately 1% of patients had type 1 diabetes at baseline. The most common etiologies of CKD were diabetic nephropathy/diabetic kidney disease (31%), glomerular disease (25%), hypertensive/renovascular disease (22%) and other/unknown (22%).

At baseline, 85% of patients were treated with ACE inhibitor or ARB, 64% with statins, and 34% with antiplatelet agents.

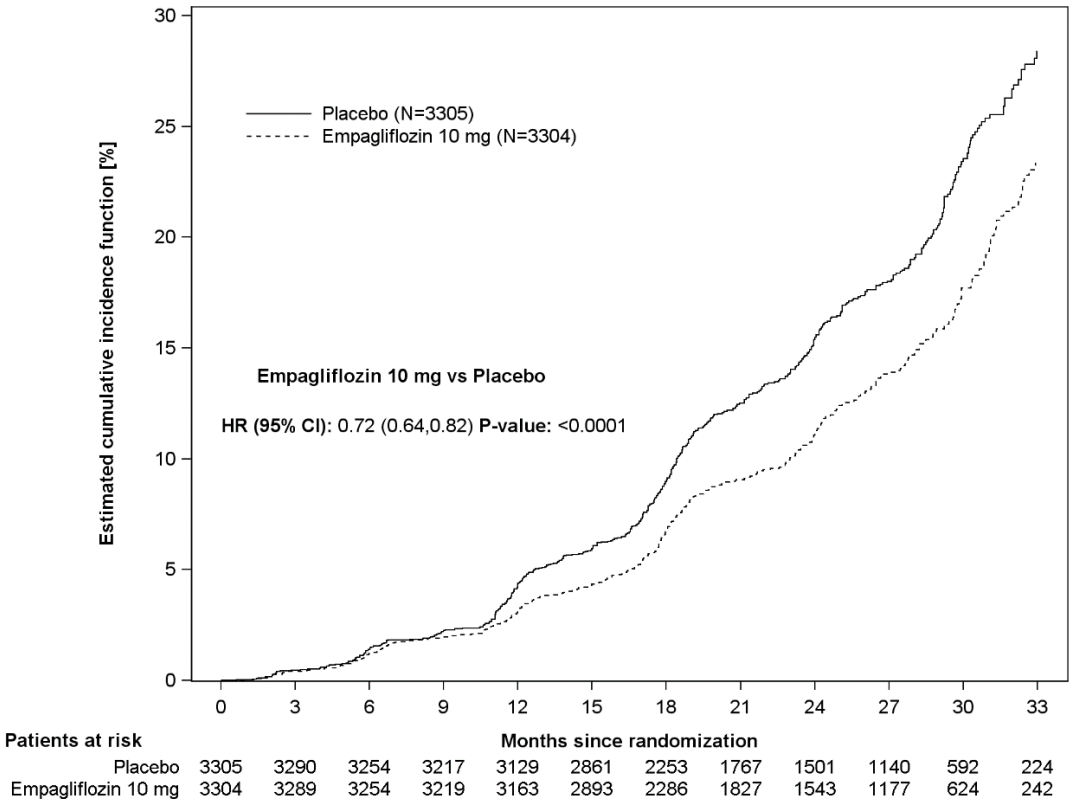
COSPIAQ was superior to placebo in reducing the risk of the primary composite endpoint of sustained ≥40% eGFR decline, sustained eGFR <10 mL/min/1.73 m^2, progression to end-stage kidney disease, or CV or renal death. The treatment effect reflected a reduction in a sustained ≥40% eGFR decline, sustained eGFR <10 mL/min/1.73 m^2, progression to end-stage kidney disease, and CV death. There were few renal deaths during the trial. COSPIAQ also reduced the risk of first and recurrent hospitalization (see Table 17 and Figure 13); information collected on the reason for hospitalization was insufficient to further characterize the benefit.

Table 17 Treatment Effect for the Primary Composite Endpoint, its Components and Key Secondary Endpoints

	Placebo N=3,305	COSPIAQ 10 mg N=3,304	Hazard ratio vs placebo (95% CI)	p-value
	Number of Patients (%)			
Composite of sustained ≥40% eGFR decline, sustained eGFR <10 mL/min/1.73 m^2, ESKD[a], or CV or renal death (time to first occurrence)	558 (16.9)	432 (13.1)	0.72 (0.64, 0.82)	<0.0001
Sustained ≥40% eGFR decline	474 (14.3)	359 (10.9)	0.70 (0.61, 0.81)	
ESKD[a] or sustained eGFR <10 mL/min/1.73 m^2	221 (6.7)	157 (4.8)	0.69 (0.56, 0.84)	
Renal death[b]	4 (0.1)	4 (0.1)		
CV death	69 (2.1)	59 (1.8)	0.84 (0.60, 1.19)	
	Number of Events			
First and recurrent hospitalization [c]	1,895	1,611	0.86 (0.78, 0.95)	0.0025

CV=Cardiovascular, eGFR=Estimated glomerular filtration rate, ESKD=End-stage kidney disease
[a]ESKD is defined as the initiation of maintenance dialysis or receipt of a kidney transplant.
[b]There were too few events of renal death to compute a reliable hazard ratio.
[c]Information collected on the reason for hospitalization was insufficient to further characterize the benefit.

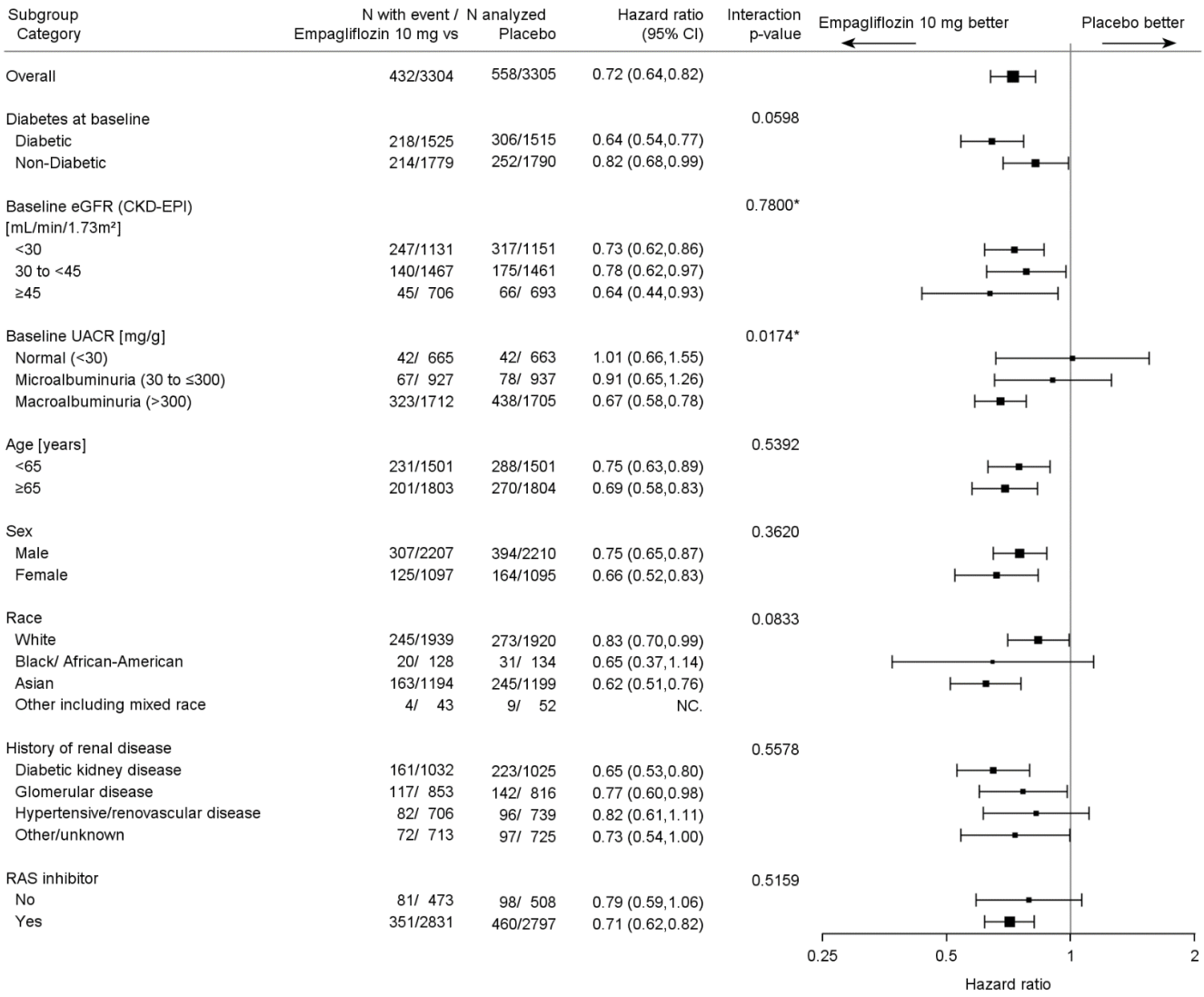
Figure 13 Time to First Occurrence of the Primary Composite Endpoint, Sustained ≥40% eGFR Decline, Sustained eGFR <10 mL/min/1.73 m^2, ESKD or Renal Death, or CV Death



The results of the primary composite endpoint were generally consistent across the pre-specified subgroups examined, including eGFR categories, underlying cause of kidney disease, diabetes status, or background use of RAS inhibitors (see Figure 14). The treatment benefit with COSPIAQ on the primary

composite endpoint was not evident in patients with very low levels of albuminuria, however there were few events in these patients.

Figure 14 Treatment Effects for the Primary Composite Endpoint (Sustained ≥40% eGFR Decline, Sustained eGFR <10 mL/min/1.73 m^2, ESKD or Renal Death, or CV Death) Subgroup Analysis (EMPA-KIDNEY)



*=Trend test

16. HOW SUPPLIED/STORAGE AND HANDLING

This product is supplied as a pack of 90 (9X10) Film Coated tablets.

Each blister contains 10 tablets.

Storage:

Keep out of reach of children.

Do not store above 30°C.

Shelf Life:

36 Months

17. PATIENT COUNSELLING INFORMATION

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of COSPIAQ, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue COSPIAQ and seek medical attention immediately *[see Warnings and Precautions (5.1)]*.

Volume Depletion

Inform patients that symptomatic hypotension may occur with COSPIAQ and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.2)]*. Inform patients that dehydration may increase the risk for hypotension, and to maintain adequate fluid intake.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions (5.3)]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Inform patients that the incidence of hypoglycemia is increased when COSPIAQ is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin and that a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.4)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with COSPIAQ. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.5)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis)

Inform male patients that yeast infection of the penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with chronic and recurrent infections. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.6)]*.

Lower Limb Amputation

Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Warnings and Precautions (5.7)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions, such as urticaria and angioedema, have been reported with COSPIAQ. Advise patients to report immediately any skin reaction or angioedema, and to discontinue drug until they have consulted prescribing healthcare provider *[see Warnings and Precautions (5.8)]*.

Laboratory Tests

Inform patients that elevated glucose in urinalysis is expected when taking COSPIAQ *[see Drug Interactions (7)]*.

Pregnancy

Advise pregnant patients, and patients of reproductive potential, of the potential risk to a fetus with treatment with COSPIAQ *[see Use in Specific Populations (8.1)]*. Instruct patients to report pregnancies to their healthcare provider as soon as possible.

Lactation

Advise patients that breastfeeding is not recommended during treatment with COSPIAQ *[see Use in Specific Populations (8.2)]*.

Missed Dose

Instruct patients to take COSPIAQ only as prescribed. If a dose is missed, it should be taken as soon as the patient remembers. Advise patients not to double their next dose.

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59320 Ennigerloh,

Germany

OR

Boehringer Ingelheim Pharma GmbH & Co. KG

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Germany

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Shree Arihant Compound, Ground floor,
Reti Bunder Road, Kalher, Bhiwandi
Thane, Maharashtra (India) - 421302

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Torrent Pharmaceuticals Limited,

Indrad – 382 721, Dist. Mehsana, India.

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