CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204629Orig1s033

Trade Name:	JARDIANCE
Generic or Proper Name:	(empagliflozin)
Sponsor:	Boehringer Ingelheim Pharmaceuticals Inc.
Approval Date:	February 24, 2022
Indication:	JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated: • to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure. • to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. • as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use JARDIANCE is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients JARDIANCE 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 m2

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 204629/S-033

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Mark J. DeBellis
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Mr. DeBellis:

Please refer to your supplemental new drug application (sNDA) dated September 13, 2021, received September 13, 2021, and your amendments, submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jardiance (empagliflozin) tablets.

This Prior Approval supplemental new drug application provides for addition of new clinical study (EMPEROR-Preserved) results, and broadening of the patient population.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. The precise mechanism(s) through which empagliflozin's beneficial effect in heart failure is exerted is not defined. While there are a number of proposed theoretical mechanisms of action, there are only a limited number of measurable biomarkers that can be considered as surrogate endpoints and none apply at this time. Given the lack of a bridging biomarker, studies in pediatric patients with heart failure are not feasible at this time.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

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[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Alexis Childers, Regulatory Project Manager at (301) 796-0442.

Sincerely,
{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, & Nephrology
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
02/24/2022 11:17:56 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JARDIANCE safely and effectively. See full prescribing information for JARDIANCE.

JARDIANCE® (empagliflozin tablets), for oral use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	2/2022
Dosage and Administration (2.1)	6/2021
Dosage and Administration (2.2)	8/2021
Dosage and Administration (2.3) – Removed	8/2021
Contraindications (4)	6/2021
Warnings and Precautions (5.1, 5.2)	6/2021
Warnings and Precautions (5.3, 5.5)	8/2021
Warnings and Precautions (5.9) – Removed	6/2021

----------INDICATIONS AND USAGE----------

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure. (1)
- to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. (1)
- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)

Limitations of Use:

- Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients (1)
- 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 (1)

----------DOSAGE AND ADMINISTRATION----------

- Assess volume status and correct volume depletion before initiating (2.1)
- The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food (2.2)
- For additional glycemic control, dose may be increased to 25 mg in patients tolerating JARDIANCE (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 10 mg, 25 mg (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to empagliflozin or any of the excipients in JARDIANCE (4)
- Patients on dialysis (4)

----------WARNINGS AND PRECAUTIONS----------

- *Ketoacidosis:* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level. If suspected, discontinue JARDIANCE, evaluate and treat promptly. Before initiating JARDIANCE, consider risk factors for ketoacidosis. Patients on JARDIANCE may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.1)
- *Volume Depletion:* Before initiating JARDIANCE, assess volume status and renal function in patients with impaired renal function, elderly patients, or patients on loop diuretics. Monitor for signs and symptoms during therapy. (5.2, 6.1)
- *Urosepsis and Pyelonephritis:* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.3)
- *Hypoglycemia:* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating JARDIANCE (5.4)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):* Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.5)
- *Genital Mycotic Infections:* Monitor and treat as appropriate (5.6)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., angioedema) have occurred with JARDIANCE. If hypersensitivity reactions occur, discontinue JARDIANCE, treat promptly, and monitor until signs and symptoms resolve. (5.7)

----------ADVERSE REACTIONS----------

- The most common adverse reactions associated with JARDIANCE (5% or greater incidence) were urinary tract infections and female genital mycotic infections (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* Advise females of the potential risk to a fetus especially during the second and third trimesters (8.1)
- *Lactation:* JARDIANCE is not recommended when breastfeeding (8.2)
- *Geriatric Patients:* Higher incidence of adverse reactions related to volume depletion and reduced renal function (5.2, 8.5, 8.6)
- *Renal Impairment:* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

JARDIANCE is indicated:

- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.
- to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.
- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use

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

JARDIANCE 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. JARDIANCE is likely to be ineffective in this setting based upon its mechanism of action.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of JARDIANCE

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

2.2 Recommended Dosage

- The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food.
- For additional glycemic control, the dose may be increased to 25 mg in patients tolerating JARDIANCE.
- Use for glycemic control is not recommended in patients with an eGFR less than 30 mL/min/1.73 m^2.
- Data are insufficient to provide a dosing recommendation in patients;
  - who have type 2 diabetes and established cardiovascular disease with an eGFR less than 30 mL/min/1.73 m^2, or
  - who have heart failure with an eGFR less than 20 mL/min/1.73 m^2 *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.
- JARDIANCE is contraindicated in patients on dialysis *[see Contraindications (4)]*.

3 DOSAGE FORMS AND STRENGTHS

JARDIANCE 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

- Hypersensitivity to empagliflozin or any of the excipients in JARDIANCE, reactions such as angioedema have occurred *[see Warnings and Precautions (5.7)]*.
- Patients on dialysis *[see Use in Specific Populations (8.6)]*.

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 JARDIANCE. Fatal cases of ketoacidosis have been reported in patients taking JARDIANCE. 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. JARDIANCE is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with JARDIANCE 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 JARDIANCE may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, JARDIANCE 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 JARDIANCE, 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 JARDIANCE for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

Consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE 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 JARDIANCE.

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

5.2 Volume Depletion

JARDIANCE 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 JARDIANCE. 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 JARDIANCE 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 JARDIANCE. 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 JARDIANCE. 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 JARDIANCE 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 JARDIANCE.

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 JARDIANCE. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with JARDIANCE 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 JARDIANCE, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.6 Genital Mycotic Infections

JARDIANCE 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 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., angioedema) in patients treated with JARDIANCE. If a hypersensitivity reaction occurs, discontinue JARDIANCE; treat promptly per standard of care, and monitor until signs and symptoms resolve. JARDIANCE is contraindicated in patients with hypersensitivity to empagliflozin or any of the excipients in JARDIANCE *[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 (5.7)]*

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.

JARDIANCE has been evaluated in clinical trials in patients with type 2 diabetes mellitus and in patients with heart failure. The overall safety profile of JARDIANCE 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. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (14)]*.

These data reflect exposure of 1976 patients to JARDIANCE with a mean exposure duration of approximately 23 weeks. Patients received placebo (N=995), JARDIANCE 10 mg (N=999), or JARDIANCE 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 more than 5 years and had a mean hemoglobin A1c (HbA1c) of 8%. Established microvascular complications of diabetes 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 1 shows common adverse reactions (excluding hypoglycemia) associated with the use of JARDIANCE. The adverse reactions were not present at baseline, occurred more commonly on JARDIANCE than on placebo and occurred in greater than or equal to 2% of patients treated with JARDIANCE 10 mg or JARDIANCE 25 mg.

Table 1 Adverse Reactions Reported in ≥2% of Patients Treated with JARDIANCE and Greater than Placebo in Pooled Placebo-Controlled Clinical Studies of JARDIANCE Monotherapy or Combination Therapy

Adverse Reactions	Placebo (%) N=995	JARDIANCE 10 mg (%) N=999	JARDIANCE 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), JARDIANCE 10 mg (N=443), JARDIANCE 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), JARDIANCE 10 mg (N=556), JARDIANCE 25 mg (N=557).

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

Volume Depletion
JARDIANCE 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, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. JARDIANCE 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 JARDIANCE than on placebo (see Table 1). Specifically, nocturia was reported by 0.4%, 0.3%, and 0.8% of patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

Hypoglycemia
The incidence of hypoglycemia by study is shown in Table 2. The incidence of hypoglycemia increased when JARDIANCE was administered with insulin or sulfonylurea.

Table 2 Incidence of Overall[a] and Severe[b] Hypoglycemic Events in Placebo-Controlled Clinical Studies[c]

Monotherapy (24 weeks)	**Placebo (n=229)**	**JARDIANCE 10 mg (n=224)**	**JARDIANCE 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)**	**JARDIANCE 10 mg + Metformin (n=217)**	**JARDIANCE 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)**	**JARDIANCE 10 mg + Metformin + Sulfonylurea (n=224)**	**JARDIANCE 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)**	**JARDIANCE 10 mg + Pioglitazone +/- Metformin (n=165)**	**JARDIANCE 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)**	**JARDIANCE 10 mg (n=169)**	**JARDIANCE 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)**	**JARDIANCE 10 mg (n=186)**	**JARDIANCE 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 dose of study drug)
[d]Insulin dose could not be adjusted during the initial 18 week treatment period

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 JARDIANCE compared to placebo, occurring in 0.9%, 4.1%, and 3.7% of patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with either JARDIANCE 10 or 25 mg.

Genital mycotic infections occurred more frequently in female than male patients (see Table 1).

Phimosis occurred more frequently in male patients treated with JARDIANCE 10 mg (less than 0.1%) and JARDIANCE 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 JARDIANCE compared to placebo (see Table 1). 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, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

Urinary tract infections occurred more frequently in female patients. The incidence of urinary tract infections in female patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg was 16.6%, 18.4%, and 17.0%, respectively. The incidence of urinary tract infections in male patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 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
The EMPEROR-Reduced study included 3730 patients with heart failure and left ventricular ejection fraction (LVEF) ≤40% followed for a median of 16 months, and EMPEROR-Preserved included 5988 patients with heart failure and LVEF >40% followed for a median of 26 months. In both studies, patients were randomized to JARDIANCE 10 mg or placebo. The safety profile in patients with heart failure was generally consistent with that observed in patients with type 2 diabetes mellitus.

Laboratory Tests
Increases in Serum Creatinine and Decreases in eGFR
Initiation of JARDIANCE causes an increase in serum creatinine and decrease in eGFR within weeks of starting therapy and then these changes stabilize. In a study 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 JARDIANCE.

Increase in Low-Density Lipoprotein Cholesterol (LDL-C)
Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with JARDIANCE. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, JARDIANCE 10 mg, and JARDIANCE 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 JARDIANCE 10 mg and 2.8% in JARDIANCE 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, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively.

6.2 Postmarketing Experience
Additional adverse reactions have been identified during postapproval use of JARDIANCE. 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.

- Ketoacidosis
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene)
- Angioedema
- Acute Kidney Injury

- Skin Reactions (e.g., rash, urticaria)

7 DRUG INTERACTIONS

Table 3 Clinically Relevant Interactions with JARDIANCE

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 JARDIANCE, assess volume status and renal function. In patients with volume depletion, correct this condition before initiating JARDIANCE. 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 JARDIANCE is used in combination with insulin secretagogues (e.g., sulfonylurea) or insulin.
Intervention	Coadministration of JARDIANCE with an insulin secretagogue (e.g., sulfonylurea) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
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, JARDIANCE is not recommended during the second and third trimesters of pregnancy.

The limited available data with JARDIANCE 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 JARDIANCE in human milk, the effects of JARDIANCE 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 JARDIANCE 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 JARDIANCE have not been established in pediatric patients.

8.5 Geriatric Use

In glycemic control studies in patients with type 2 diabetes mellitus, a total of 2721 (32%) patients treated with JARDIANCE were 65 years of age and older, and 491 (6%) were 75 years of age and older. JARDIANCE 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, JARDIANCE 10 mg, and JARDIANCE 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, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

In heart failure studies, EMPEROR-Reduced included 1188 (64%) patients treated with JARDIANCE 65 years of age and older, and 503 (27%) patients 75 years of age and older. EMPEROR-Preserved included 2402 (80%) patients treated with JARDIANCE 65 years of age and older, and 1281 (43%) patients 75 years of age and older. Safety and efficacy were similar for patients 65 years and younger and those older than 65 years.

8.6 Renal Impairment

The efficacy and safety of JARDIANCE for glycemic control were evaluated in a study 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 study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 m^2, 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 m^2, and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of JARDIANCE 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 JARDIANCE 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.

In a large cardiovascular outcomes study of patients with type 2 diabetes and established cardiovascular disease, there were 1819 patients with eGFR below 60 mL/min/1.73 m^2. The cardiovascular death findings in this subgroup were consistent with the overall findings *[see Clinical Studies (14)]*.

Studies of patients with heart failure *[see Clinical Studies (14)]* enrolled patients with eGFR equal to or above 20 mL/min/1.73 m^2. No dose adjustment is recommended for these patients. There are insufficient data to support a dosing recommendation in patients with eGFR below 20 mL/min/1.73 m^2.

Efficacy and safety studies with JARDIANCE did not enroll patients with an eGFR less than 20 mL/min/1.73 m^2. JARDIANCE is contraindicated in patients on dialysis *[see Contraindications (4)]*.

8.7 Hepatic Impairment

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

10 OVERDOSAGE

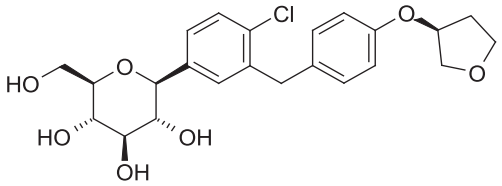
In the event of an overdose with JARDIANCE, contact the Poison Control Center. Removal of empagliflozin by hemodialysis has not been studied.

11 DESCRIPTION

JARDIANCE 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 JARDIANCE contains 10 mg or 25 mg of empagliflozin (free base) and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, 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 such as lowering both pre-and afterload of the heart and downregulating sympathetic activity.

12.2 Pharmacodynamics

Urinary Glucose Excretion

In patients with type 2 diabetes, 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
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 subjects 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.

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 Interactions

In vitro Assessment of Drug Interactions

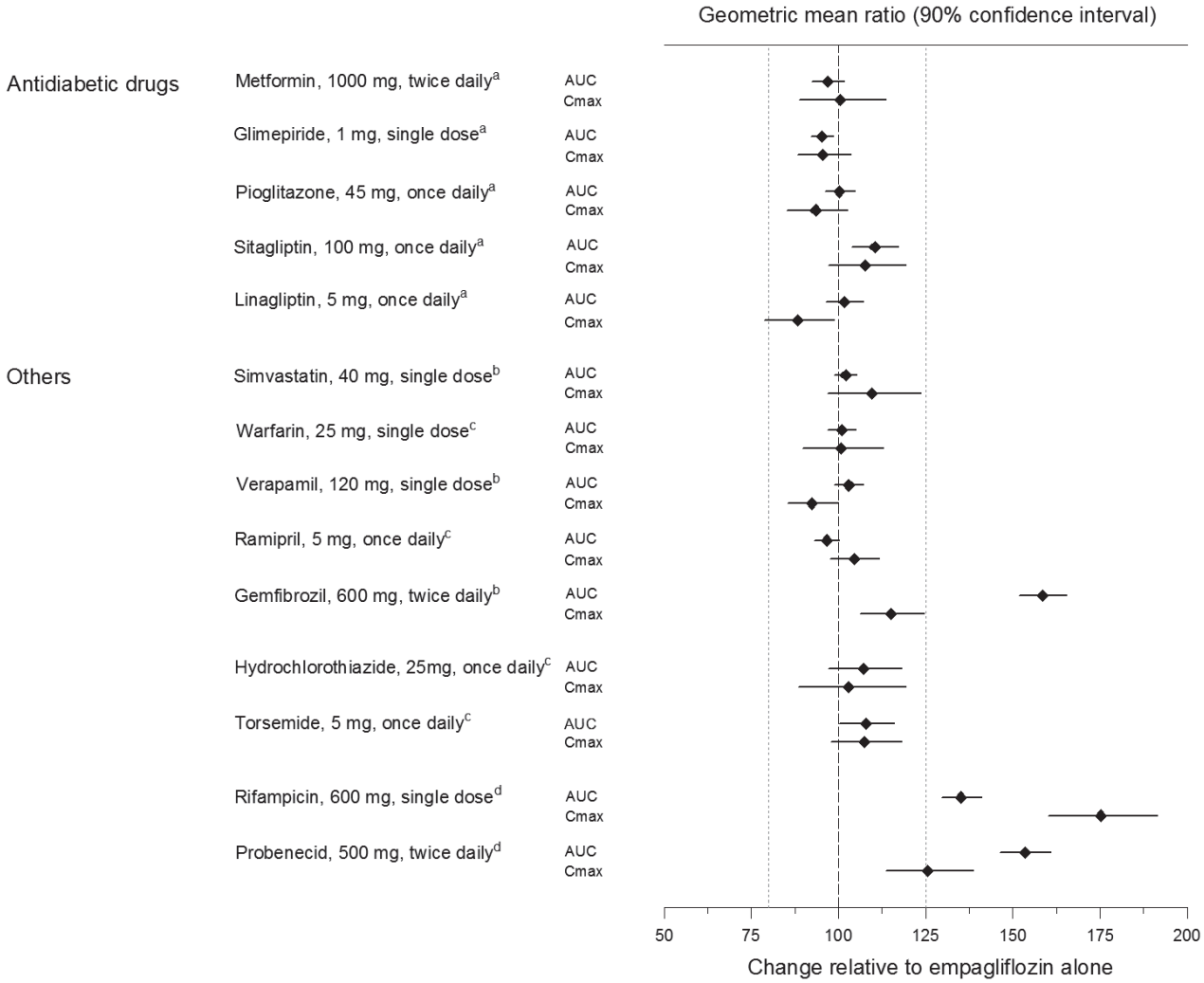
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1, 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 (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.

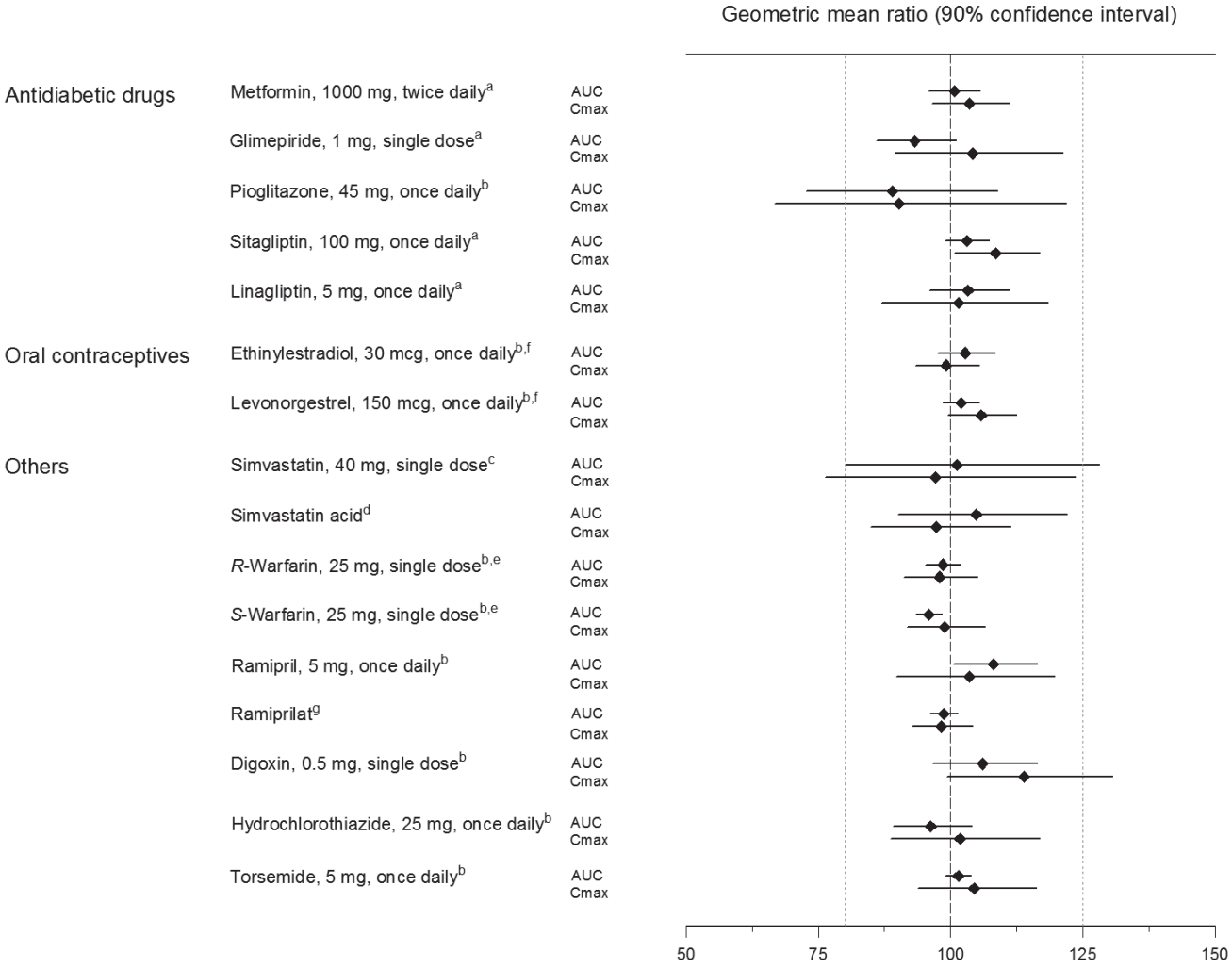
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[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 1000 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 1000 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

Glycemic Control in Patients with Type 2 Diabetes Mellitus
JARDIANCE has been studied as monotherapy and in combination with metformin, sulfonylurea, pioglitazone, linagliptin, and insulin. JARDIANCE has also been studied in patients with type 2 diabetes with mild or moderate renal impairment.

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

Monotherapy
A total of 986 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE monotherapy.

Treatment-naïve patients with inadequately controlled type 2 diabetes 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, JARDIANCE 10 mg, JARDIANCE 25 mg, or a reference comparator.

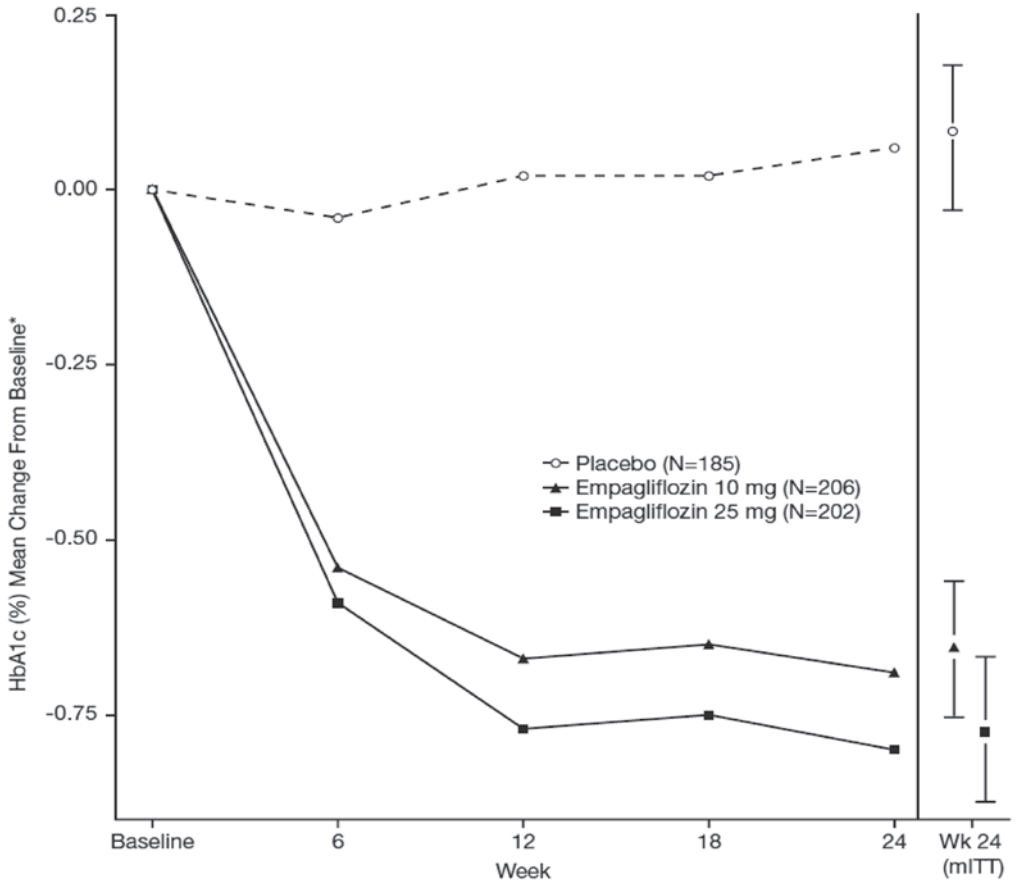
At Week 24, treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), fasting plasma glucose (FPG), and body weight compared with placebo (see Table 4 and Figure 3).

Table 4 Results at Week 24 From a Placebo-Controlled Monotherapy Study of JARDIANCE

	JARDIANCE 10 mg N=224	JARDIANCE 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)	-0.7[b] (-0.9, -0.6)	-0.9[b] (-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)	-2.5[b] (-3.1, -1.9)	-2.8[b] (-3.4, -2.2)	--

[a]Modified intent to treat population. Last observation on study (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 JARDIANCE 10 mg, JARDIANCE 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 JARDIANCE 10 mg, n=223, for JARDIANCE 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 JARDIANCE and by -3.4 mmHg (placebo-corrected, p-value=0.0028) in patients randomized to 25 mg of JARDIANCE.

Add-On Combination Therapy with Metformin
A total of 637 patients with type 2 diabetes participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin.

Patients with type 2 diabetes inadequately controlled on at least 1500 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, JARDIANCE 10 mg, or JARDIANCE 25 mg.

At Week 24, treatment with JARDIANCE 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 5).

Table 5 Results at Week 24 From a Placebo-Controlled Study for JARDIANCE used in Combination with Metformin

	JARDIANCE 10 mg + Metformin N=217	JARDIANCE 25 mg + Metformin N=213	Placebo + Metformin 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 study (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 JARDIANCE 10 mg, JARDIANCE 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 JARDIANCE 10 mg, n=216, for JARDIANCE 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 JARDIANCE 10 mg and -4.8 mmHg (placebo-corrected, p-value <0.0001) for JARDIANCE 25 mg.

Initial Combination Therapy with Metformin
A total of 1364 patients with type 2 diabetes participated in a double-blind, randomized, active-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin as initial therapy compared to the corresponding individual components.

Treatment-naïve patients with inadequately controlled type 2 diabetes 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: JARDIANCE 10 mg or 25 mg; metformin 1000 mg, or 2000 mg; JARDIANCE 10 mg in combination with 1000 mg or 2000 mg metformin; or JARDIANCE 25 mg in combination with 1000 mg or 2000 mg metformin.

At Week 24, initial therapy of JARDIANCE in combination with metformin provided statistically significant reductions in HbA1c (p-value <0.01) compared to the individual components (see Table 6).

Table 6 Glycemic Parameters at 24 Weeks in a Study Comparing JARDIANCE and Metformin to the Individual Components as Initial Therapy

	JARDIANCE 10 mg + Metformin 1000 mg[a] N=161	JARDIANCE 10 mg + Metformin 2000 mg[a] N=167	JARDIANCE 25 mg + Metformin 1000 mg[a] N=165	JARDIANCE 25 mg + Metformin 2000 mg[a] N=169	JARDIANCE 10 mg N=169	JARDIANCE 25 mg N=163	Metformin 1000 mg[a] N=167	Metformin 2000 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 JARDIANCE (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 participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with metformin plus a sulfonylurea.

Patients with inadequately controlled type 2 diabetes on at least 1500 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, JARDIANCE 10 mg, or JARDIANCE 25 mg.

Treatment with JARDIANCE 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 7).

Table 7 Results at Week 24 from a Placebo-Controlled Study for JARDIANCE in Combination with Metformin and Sulfonylurea

	JARDIANCE 10 mg + Metformin + SU N=225	JARDIANCE 25 mg + Metformin + SU N=216	Placebo + Metformin + SU 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 study (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 JARDIANCE 10 mg, JARDIANCE 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 JARDIANCE 10 mg, n=225, for JARDIANCE 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 participated in a double-blind, active-controlled study to evaluate the efficacy and safety of JARDIANCE 10 mg or 25 mg in combination with linagliptin 5 mg compared to the individual components.

Patients with type 2 diabetes inadequately controlled on at least 1500 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 JARDIANCE 10 mg or 25 mg, linagliptin 5 mg, or linagliptin 5 mg in combination with 10 mg or 25 mg JARDIANCE as a fixed dose combination tablet.

At Week 24, JARDIANCE 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 JARDIANCE/linagliptin 25 mg/5 mg or JARDIANCE/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 JARDIANCE alone.

Active-Controlled Study versus Glimepiride in Combination with Metformin
The efficacy of JARDIANCE was evaluated in a double-blind, glimepiride-controlled, study in 1545 patients with type 2 diabetes 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 JARDIANCE 25 mg.

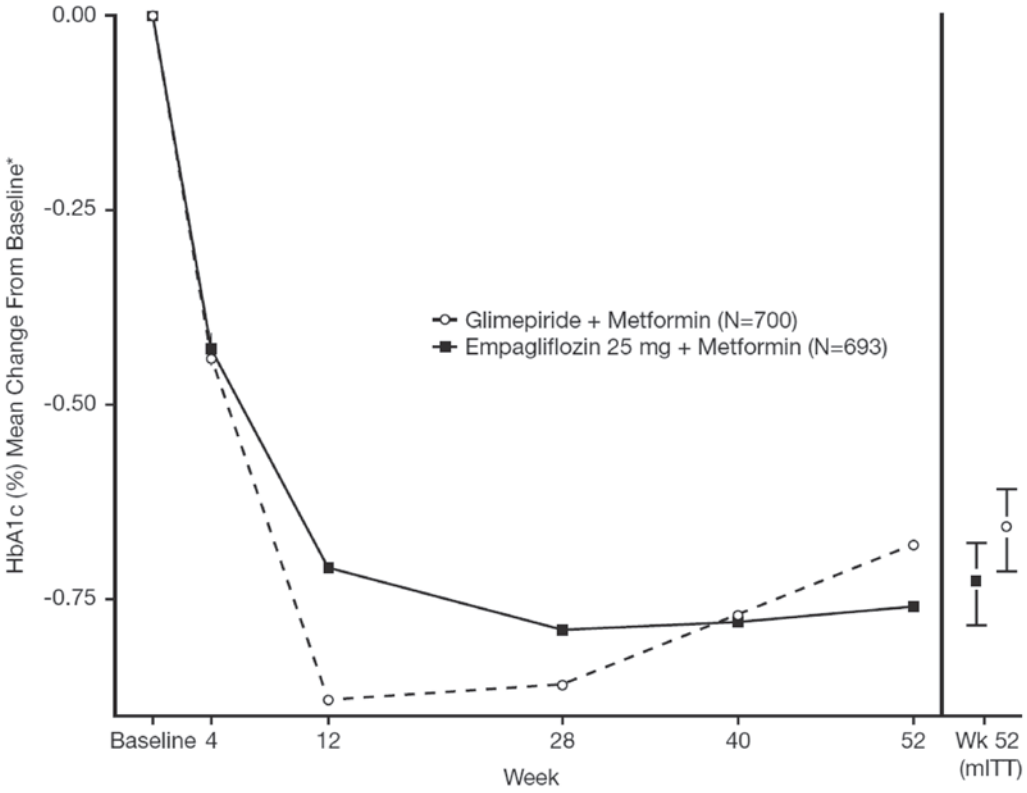
At Week 52, JARDIANCE 25 mg and glimepiride lowered HbA1c and FPG (see Table 8, Figure 4). The difference in observed effect size between JARDIANCE 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose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

Table 8 Results at Week 52 from an Active-Controlled Study Comparing JARDIANCE to Glimepiride as Add-On Therapy in Patients Inadequately Controlled on Metformin

	JARDIANCE 25 mg + Metformin N=765	Glimepiride + Metformin 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 study (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 JARDIANCE 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 JARDIANCE 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 JARDIANCE 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 dose of glimepiride was 2.7 mg and the maximal approved dose 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 JARDIANCE 25 mg and 12.9% for glimepiride.

At Week 104, JARDIANCE 25 mg daily resulted in a statistically significant difference in change from baseline for body weight compared to glimepiride (-3.1 kg for JARDIANCE 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 participated in a double-blind, placebo-controlled study to evaluate the efficacy and safety of JARDIANCE in combination with pioglitazone, with or without metformin.

Patients with inadequately controlled type 2 diabetes on metformin at a dose of at least 1500 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, JARDIANCE 10 mg, or JARDIANCE 25 mg.

Treatment with JARDIANCE 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 9).

Table 9 Results of Placebo-Controlled Study for JARDIANCE in Combination Therapy with Pioglitazone

	JARDIANCE 10 mg + Pioglitazone N=165	JARDIANCE 25 mg + Pioglitazone N=168	Placebo + Pioglitazone 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 study (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 JARDIANCE 10 mg, JARDIANCE 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 JARDIANCE 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 inadequately controlled on insulin, or insulin in combination with oral drugs participated in a double-blind, placebo-controlled study to evaluate the efficacy of JARDIANCE 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 JARDIANCE 10 mg, JARDIANCE 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 JARDIANCE 10 mg, 25 mg, and placebo was 45 IU, 48 IU, and 48 IU, respectively.

JARDIANCE 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 10). JARDIANCE 10 mg or 25 mg daily also resulted in statistically significantly greater percent body weight reduction compared to placebo.

Table 10 Results at Week 18 and 78 for a Placebo-Controlled Study for JARDIANCE in Combination with Insulin

	18 weeks (no insulin adjustment)			78 weeks (adjustable insulin dose after 18 weeks)		
	JARDIANCE 10 mg + Insulin N=169	JARDIANCE 25 mg + Insulin N=155	Placebo + Insulin N=170	JARDIANCE 10 mg + Insulin N=169	JARDIANCE 25 mg + Insulin N=155	Placebo + Insulin 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 study (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 JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo, respectively. At Week 78, 32.5%, 38.1% and 42.4% was imputed for patients randomized to JARDIANCE 10 mg, JARDIANCE 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 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 study to evaluate the efficacy of JARDIANCE 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 JARDIANCE 10 mg, JARDIANCE 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 JARDIANCE 10 mg, JARDIANCE 25 mg, and placebo was 88.6 IU, 90.4 IU, and 89.9 IU, respectively.

JARDIANCE 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 11).

Table 11 Results at Week 18 for a Placebo-Controlled Study for JARDIANCE in Combination with Insulin and with or without Metformin

	JARDIANCE 10 mg + Insulin +/- Metformin N=186	JARDIANCE 25 mg + Insulin +/- Metformin N=189	Placebo + Insulin +/- Metformin 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 study (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 JARDIANCE 10 mg, JARDIANCE 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 JARDIANCE 10 mg and 25 mg. After 52 weeks, JARDIANCE 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 JARDIANCE 10 mg, and -2.04 kg for JARDIANCE 25 mg.

Renal Impairment
A total of 738 patients with type 2 diabetes and a baseline eGFR less than 90 mL/min/1.73 m^2 participated in a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of JARDIANCE in patients with type 2 diabetes 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 a baseline eGFR of 45 to less than 60 mL/min/1.73 m^2.

At Week 24, JARDIANCE 25 mg provided statistically significant reduction in HbA1c relative to placebo in patients with mild to moderate renal impairment (see Table 12). A statistically significant reduction relative to

placebo was also observed with JARDIANCE 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 JARDIANCE 10 mg in patients with mild [-0.5 (95% CI: -0.7, -0.3)] renal impairment.

The glucose lowering efficacy of JARDIANCE 25 mg decreased with decreasing level of renal function in the mild to moderate range. Least square mean Hb1Ac 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 12 Results at Week 24 (LOCF) of Placebo-Controlled Study for JARDIANCE in Patients with Type 2 Diabetes and Renal Impairment

	Mild and Moderate Impairment[b]
	JARDIANCE 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 study (LOCF) was used to impute missing data at Week 24. At Week 24, 24.6% and 26.2% was imputed for patients randomized to JARDIANCE 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 JARDIANCE 25 mg compared to placebo *[see Indications and Usage (1), Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

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

The effect of JARDIANCE on cardiovascular risk in adult patients with type 2 diabetes and established, stable, atherosclerotic cardiovascular disease was evaluated in the EMPA-REG OUTCOME study, a multicenter, multi-national, randomized, double-blind parallel group trial. The study compared the risk of experiencing a major adverse cardiovascular event (MACE) between JARDIANCE and placebo when these were added to and used concomitantly with standard of care treatments for diabetes and atherosclerotic cardiovascular disease. Coadministered 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 7020 patients were treated (JARDIANCE 10 mg = 2345; JARDIANCE 25 mg = 2342; placebo = 2333) and followed for a median of 3.1 years. Approximately 72% of the study population was Caucasian, 22% was Asian, and 5% was Black. The mean age was 63 years and approximately 72% were male.

All patients in the study 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 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 cardiovascular 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 cardiovascular 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.

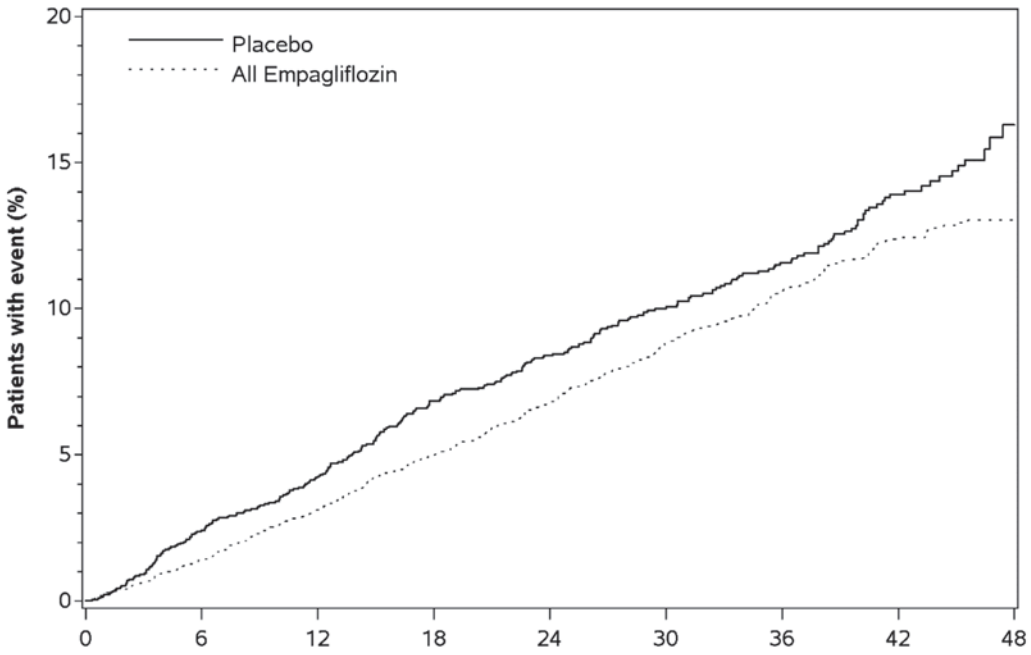
JARDIANCE significantly reduced the risk of first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI: 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects 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 13 and Figures 5 and 6). Results for the 10 mg and 25 mg empagliflozin doses were consistent with results for the combined dose groups.

Table 13 Treatment Effect for the Primary Composite Endpoint, and its Components[a]

	Placebo N=2333	**JARDIANCE N=4687**	**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)
Cardiovascular death[c]	137 (5.9%)	172 (3.7%)	0.62 (0.49, 0.77)

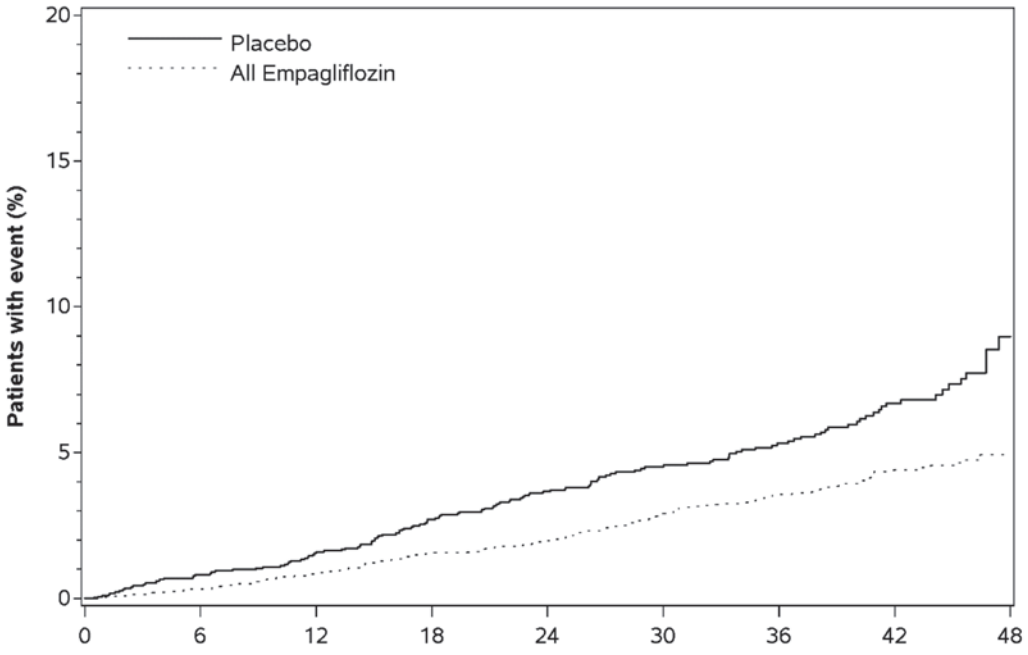
[a]Treated set (patients who had received at least one dose of study drug)
[b]p-value for superiority (2-sided) 0.04
[c]Total number of events

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 JARDIANCE on cardiovascular 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 cardiovascular deaths. The non-cardiovascular deaths were only a small proportion of deaths and were balanced between the treatment groups (2.1% in patients treated with JARDIANCE, and 2.4% of patients treated with placebo).

Heart Failure

EMPEROR-Reduced (NCT03057977) was a double-blind study 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 and safety of JARDIANCE as adjunct to standard of care heart failure therapy.

Of 3730 patients, 1863 were randomized to JARDIANCE 10 mg and 1867 to placebo and were followed for a median of 16 months. The mean age of the study 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 study 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 death (CV) or hospitalization for heart failure (HHF). First and recurrent HHF was assessed as a key secondary endpoint.

JARDIANCE 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. JARDIANCE reduced the risk of first and recurrent HHF (see Table 14 and Figures 7 and 8).

Table 14 Treatment Effect for the Primary Composite Endpoint, its Components, and Key Secondary Endpoints

	Placebo N=1867	JARDIANCE 10 mg N=1863	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 Cardiovascular Death or Hospitalization for Heart Failure

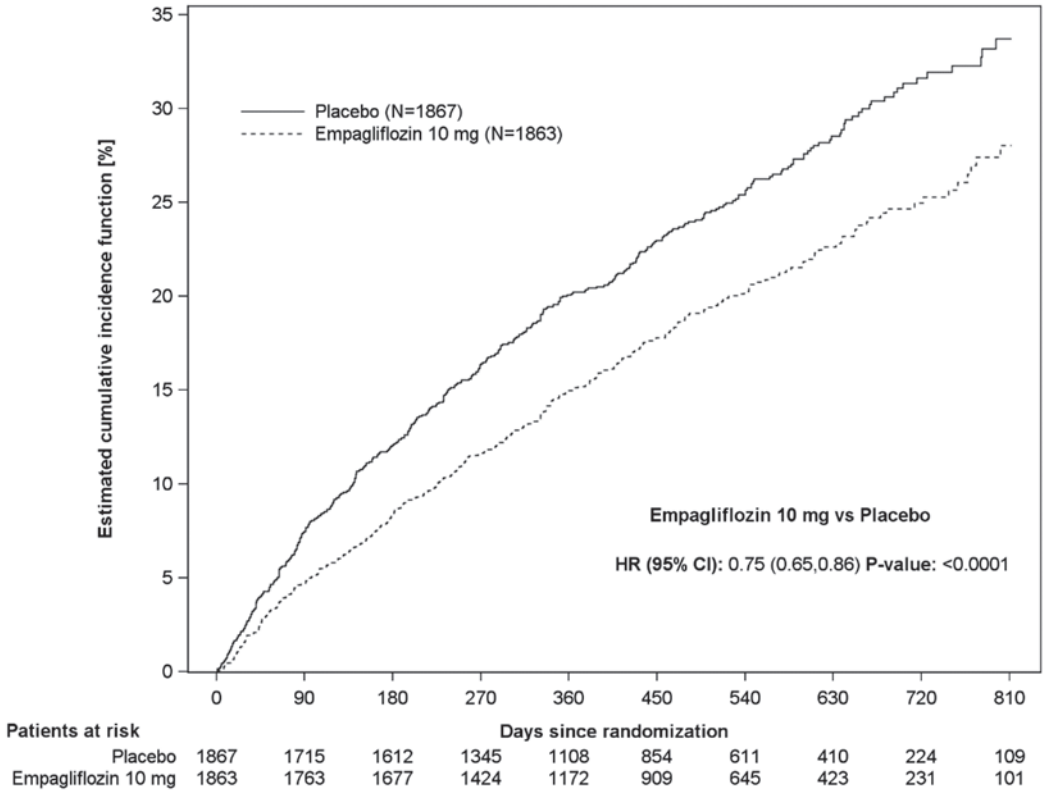
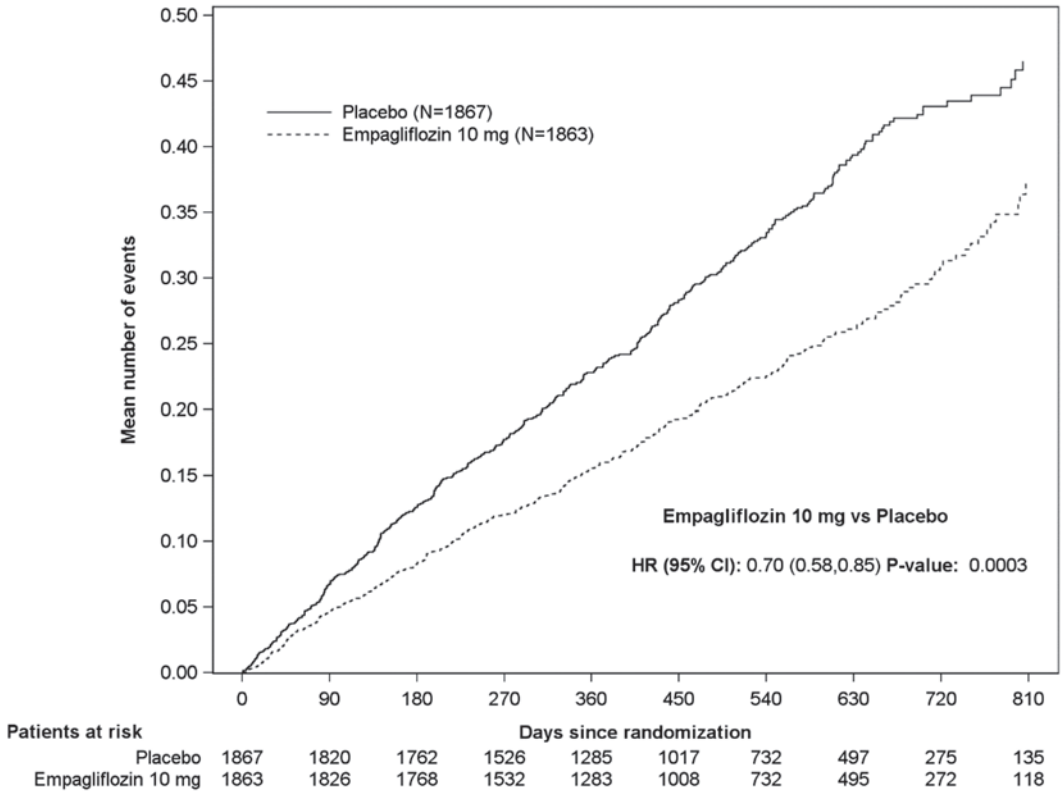
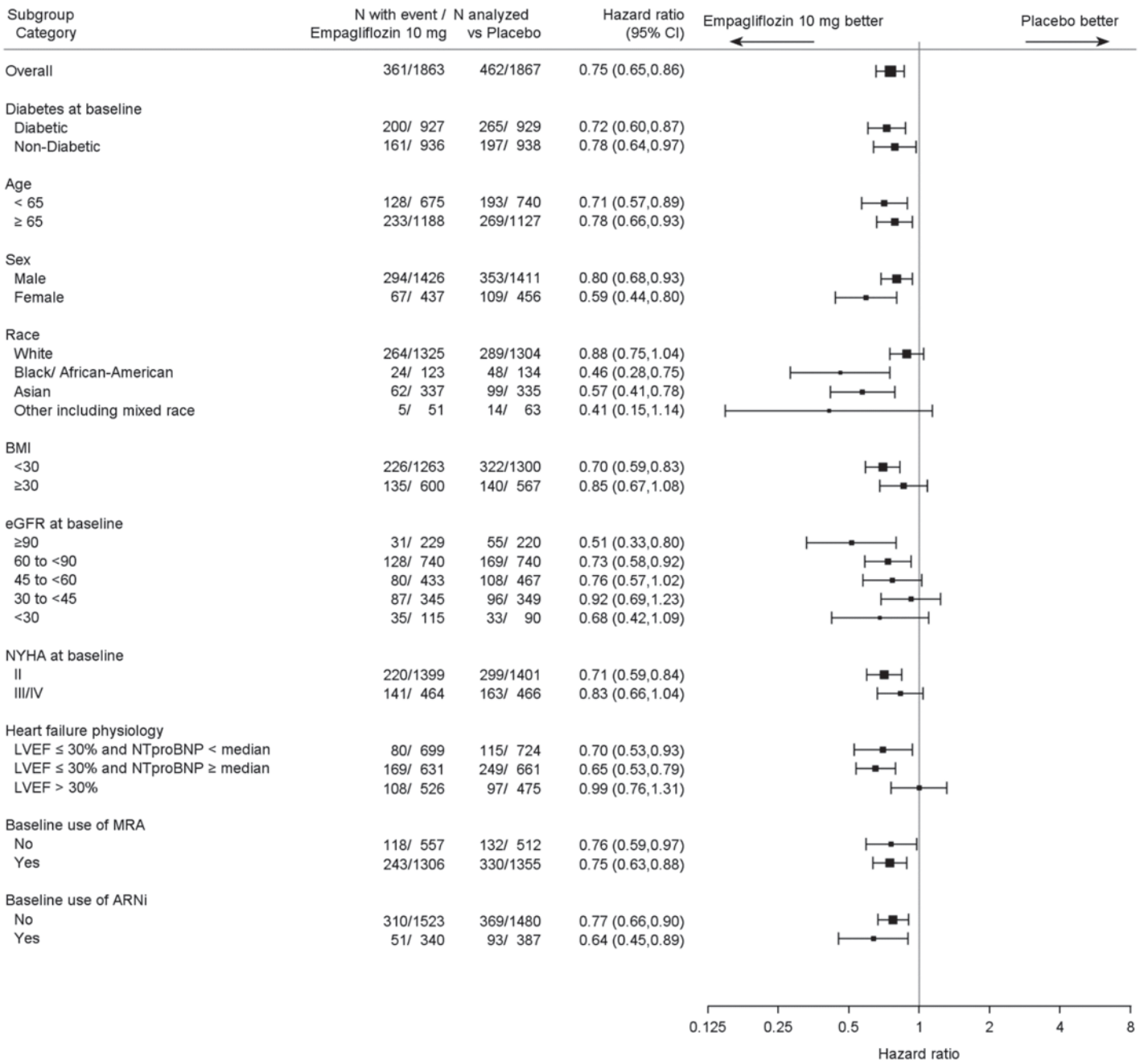


Figure 8 Time to Event of Hospitalization for Heart Failure (First and Recurrent)



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 (Cardiovascular 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 study conducted in patients with chronic heart failure NYHA Class II-IV with LVEF >40% to evaluate the efficacy and safety of JARDIANCE as adjunct to standard of care therapy.

Of 5988 patients, 2997 were randomized to JARDIANCE 10 mg and 2991 to placebo and were followed for a median of 26 months. The mean age of the study 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 study 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 study population included patients with a LVEF <50% (33.1%), with a LVEF 50 to <60% (34.4%) and a LVEF ≥60% (32.5%). At baseline, the mean eGFR was 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.

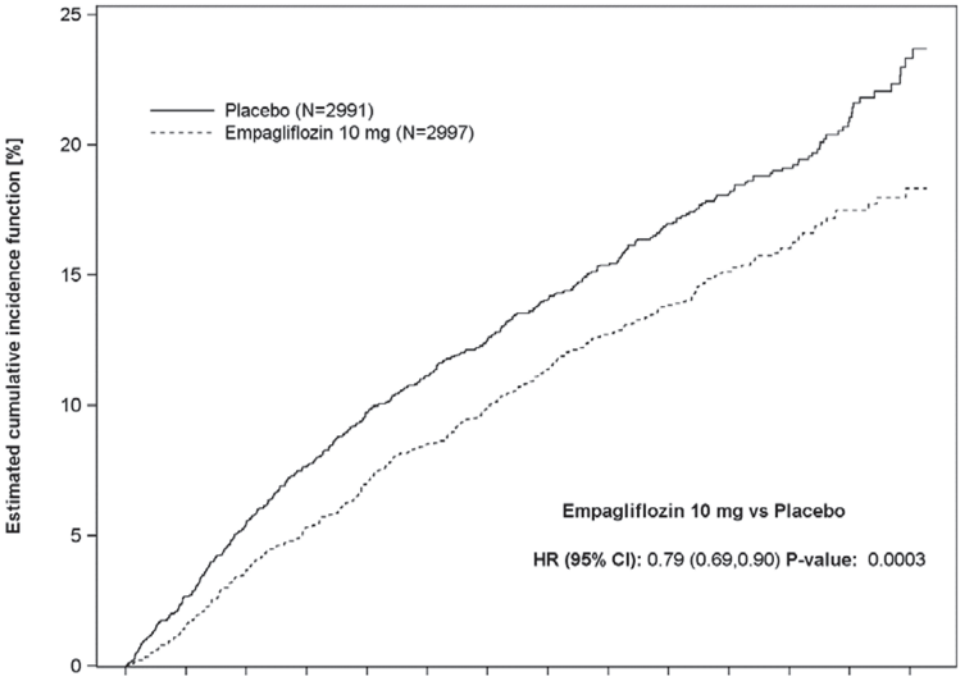
JARDIANCE was superior in reducing the risk of the primary composite endpoint compared with placebo, mostly through a reduction in hospitalization for heart failure. JARDIANCE reduced the risk of first and recurrent HHF (see Table 15 and Figures 10 and 11).

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

	Placebo N=2991	JARDIANCE 10 mg N=2997	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

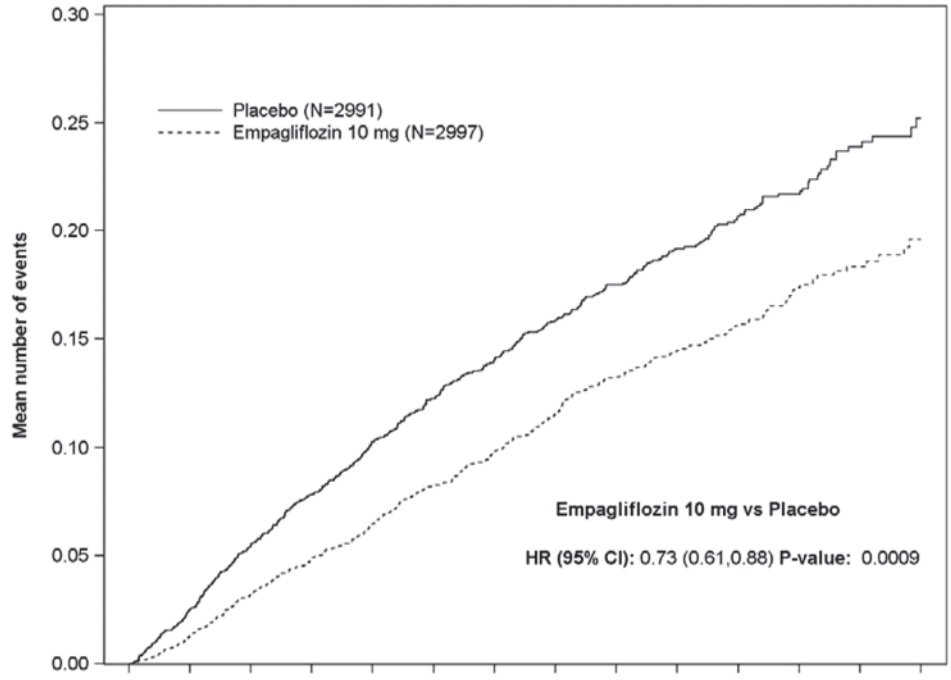
[a]Time to first event
[b]Includes deaths following hospitalization
[c]Joint frailty model accounting for CV death

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



Patients at risk														
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400	187
Empagliflozin 10 mg	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402	192

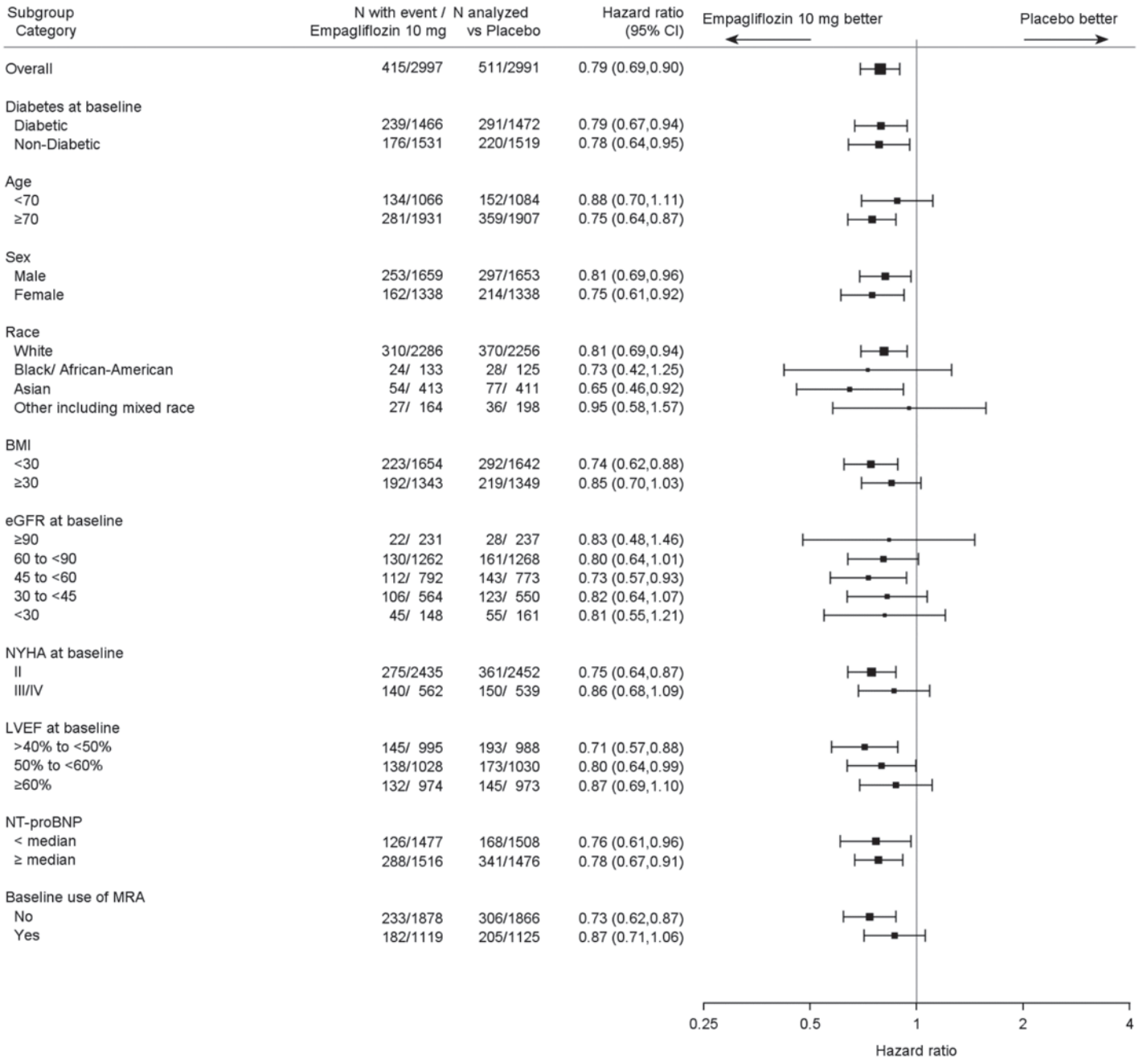
Figure 11 Time to Event of Hospitalization for Heart Failure (First and Recurrent)



Patients at risk														
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448	213
Empagliflozin 10 mg	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446	216

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 (Cardiovascular Death or Hospitalization for Heart Failure) Subgroup Analysis (EMPEROR-Preserved)



16 HOW SUPPLIED/STORAGE AND HANDLING

JARDIANCE tablets are available as follows:

10 mg tablets: 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.
Bottles of 30 (NDC 0597-0152-30)
Bottles of 90 (NDC 0597-0152-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0152-37), institutional pack.

25 mg tablets: pale yellow, oval, biconvex film-coated tablets, debossed with "S 25" on one side and the Boehringer Ingelheim company symbol on the other side.
Bottles of 30 (NDC 0597-0153-30)
Bottles of 90 (NDC 0597-0153-90)
Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0153-37), institutional pack.

Dispense in a well-closed container as defined in the USP.

Storage
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ketoacidosis
Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of JARDIANCE, 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 JARDIANCE and seek medical attention immediately *[see Warnings and Precautions (5.1)]*.

Volume Depletion
Inform patients that symptomatic hypotension may occur with JARDIANCE 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
Inform patients that the incidence of hypoglycemia is increased when JARDIANCE 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 JARDIANCE. 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)]*.

Hypersensitivity Reactions
Inform patients that serious hypersensitivity reactions, such as urticaria and angioedema, have been reported with JARDIANCE. 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 (5.7)]*.

Laboratory Tests
Inform patients that elevated glucose in urinalysis is expected when taking JARDIANCE.

Pregnancy
Advise pregnant patients, and patients of reproductive potential, of the potential risk to a fetus with treatment with JARDIANCE *[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 JARDIANCE *[see Use in Specific Populations (8.2)]*.

Missed Dose
Instruct patients to take JARDIANCE 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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MEDICATION GUIDE
JARDIANCE® (jar DEE ans)
(empagliflozin tablets)
for oral use

What is the most important information I should know about JARDIANCE?

JARDIANCE can cause serious side effects, including:

- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes,** during treatment with JARDIANCE. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with JARDIANCE. Ketoacidosis is a serious condition, which needs to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with JARDIANCE even if your blood sugar is less than 250 mg/dL. Stop taking JARDIANCE and call your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms**:
  - nausea
  - vomiting
  - stomach-area (abdominal) pain
  - tiredness
  - trouble breathing

  If you get any of these symptoms during treatment with JARDIANCE, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
- **Dehydration.** JARDIANCE can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up (orthostatic hypotension). There have been reports of sudden worsening of kidney function in people who are taking JARDIANCE.

  You may be at higher risk of dehydration if you:
  - take medicines to lower your blood pressure, including diuretics (water pills)
  - are on low sodium (salt) diet
  - have kidney problems
  - are 65 years of age or older

  Talk to your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

  Talk to your healthcare provider right away if you reduce the amount of food or liquid you drink, for example if you are sick or cannot eat, or start to lose liquids from your body, for example from vomiting, diarrhea or being in the sun too long.

What is JARDIANCE?

JARDIANCE is a prescription medicine used to:

- reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, when the heart cannot pump enough blood to the rest of your body.
- reduce the risk of cardiovascular death in adults with type 2 diabetes and who also have known cardiovascular disease.
- lower blood sugar along with diet and exercise in adults with type 2 diabetes.

JARDIANCE is not for people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in blood or urine).

JARDIANCE is not for use to lower blood sugar in adults with type 2 diabetes who have severe kidney problems, because it may not work.

It is not known if JARDIANCE is safe and effective in children.

Who should not take JARDIANCE?

Do not take JARDIANCE if you:

- are allergic to empagliflozin or any of the ingredients in JARDIANCE. See the end of this Medication Guide for a complete list of ingredients in JARDIANCE. Symptoms of a serious allergic reaction to JARDIANCE may include:
  - swelling of your face, lips, throat and other areas of your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

  If you have any of these symptoms, stop taking JARDIANCE and call your healthcare provider right away or go to the nearest hospital emergency room.
- are on dialysis.

What should I tell my healthcare provider before taking JARDIANCE?

Before taking JARDIANCE, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems.
- have liver problems.
- have a history of infection of the vagina or penis.
- have a history of urinary tract infections or problems with urination.
- are going to have surgery. Your healthcare provider may stop your JARDIANCE before you have surgery. Talk to your healthcare provider if you are having surgery about when to stop taking JARDIANCE and when to start it again.
- are eating less, or there is a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often or drink a lot of alcohol in the short term ("binge" drinking).
- have type 1 diabetes. JARDIANCE should not be used to treat people with type 1 diabetes.
- are pregnant or plan to become pregnant. JARDIANCE may harm your unborn baby. If you become pregnant while taking JARDIANCE, tell your healthcare provider as soon as possible. Talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. JARDIANCE may pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking JARDIANCE. Do not breastfeed while taking JARDIANCE.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

JARDIANCE may affect the way other medicines work, and other medicines may affect how JARDIANCE works.

Especially tell your healthcare provider if you take:

- diuretics (water pills)
- insulin or other medicines that can lower your blood sugar

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take JARDIANCE?

- Take JARDIANCE exactly as your healthcare provider tells you to take it.
- Take JARDIANCE by mouth 1 time in the morning each day, with or without food.
- Your healthcare provider may change your dose if needed.
- If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take two doses of JARDIANCE at the same time. Talk with your healthcare provider if you have questions about a missed dose.
- Your healthcare provider may tell you to take JARDIANCE along with other diabetes medicines. Low blood sugar can happen more often when JARDIANCE is taken with certain other diabetes medicines. See **"What are the possible side effects of JARDIANCE?"**
- If you take too much JARDIANCE, call your healthcare provider or go to the nearest hospital emergency room right away.
- When taking JARDIANCE, you may have sugar in your urine, which will show up on a urine test.
- Your healthcare provider may do blood tests to check how well your kidneys are working before and during your treatment with JARDIANCE.

What are the possible side effects of JARDIANCE?

JARDIANCE may cause serious side effects, including:

- See "**What is the most important information I should know about JARDIANCE?**"
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking JARDIANCE. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.
- **Low blood sugar (hypoglycemia).** If you take JARDIANCE with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take JARDIANCE. Signs and symptoms of low blood sugar may include:
  - headache
  - irritability
  - confusion
  - dizziness
  - drowsiness
  - hunger
  - shaking or feeling jittery
  - sweating
  - weakness
  - fast heartbeat
- **A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has

happened in women and men who take JARDIANCE. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. **Seek medical attention immediately if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:**

- pain or tenderness
- swelling
- redness of skin (erythema)

- **Vaginal yeast infection.** Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the penis (balanitis).** Swelling of an uncircumcised penis may develop that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around the penis

  Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions have happened in people who are taking JARDIANCE. Symptoms may include:
  - swelling of your face, lips, throat and other areas of your skin
  - difficulty with swallowing or breathing.
  - raised, red areas on your skin (hives)

  If you have any of these symptoms, stop taking JARDIANCE and call your healthcare provider right away or go to the nearest hospital emergency room.

The most common side effects of JARDIANCE include:

- urinary tract infections
- yeast infections in females

These are not all the possible side effects of JARDIANCE. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store JARDIANCE?

- Store JARDIANCE at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep JARDIANCE and all medicines out of the reach of children.**

General information about the safe and effective use of JARDIANCE.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use JARDIANCE for a condition for which it is not prescribed. Do not give JARDIANCE to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about JARDIANCE that is written for health professionals.

What are the ingredients in JARDIANCE?

Active Ingredient: empagliflozin

Inactive Ingredients: lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and yellow ferric oxide.

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For more information about JARDIANCE, including current prescribing information and Medication Guide, go to www.jardiance.com, scan the code, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration. Revised: February 2022

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s033

MULTI-DISCIPLINE REVIEW

Clinical Review
Statistical Review
Clinical Pharmacology Review

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	204629 S 33
Priority or standard	Priority
Submit date(s)	9/13/2021
Received date(s)	9/13/2021
PDUFA goal date	3/13/2022
Division/office	Division of Cardiovascular and Renal Products (DCaRP)
Review completion date	Click or tap to enter a date.
Established name	Empagliflozin
(Proposed) trade name	Jardiance
Pharmacologic class	SGLT2 Inhibitor
Code name	BI 10773
Applicant	Boehringer Ingelheim
Dose form/formulation(s)	Tablets
Dosing regimen	10 mg once daily
Applicant proposed indication(s)/population(s)	To reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction (b) (4) (b) (4)
Proposed SNOMED indication	Heart failure
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure.
Approved SNOMED indication	Heart failure

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Glossary

ACC	American College of Cardiology
ACEi	Angiotensin converting enzyme inhibitor
AE	adverse event
AESI	adverse event of special interest
AF	atrial flutter
AHA	American Heart Association
AKI	acute kidney injury
ALT	alanine aminotransferase
ARB	Angiotensin receptor blocker
ASE	American Society of Echocardiography
AST	aspartate aminotransferase
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customized MedDRA query
BMI	Body Mass Index
BNP	brain natriuretic peptide
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
CRF	case report form
CRO	contract research organization
CRT	clinical review template/cardiac resynchronization therapy
CSR	clinical study report
CTP	clinical trial protocol
CV	cardiovascular
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DMC	data monitoring committee
Empa	empagliflozin
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOT	end of treatment/trial
ExSC	Executive Steering Committee
FDA	Food and Drug Administration
FMQ	FDA medical query
GCP	good clinical practice
Hb	hemoglobin
HbA1c	hemoglobin A1c

HDL	high-density lipoprotein
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reserved ejection fraction
HHF	hospitalization for heart failure
IA	interim analysis
ICD	implantation of cardioverter defibrillator
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
iPSP	initial Pediatric Study Plan
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intention-to-treat
i.v.	intravenous
KA	ketoacidosis
LDL	low-density lipoprotein
LLA	low-limb amputation
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MRA	Mineralocorticoid receptor antagonist
NDA	new drug application
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
NYHA	New York Heart Association
PT	preferred term
RD	risk difference
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGLT2	sodium-glucose co-transporter 2
SMQ	standard MedDRA query
sNDA	supplemental new drug application
SOC	system organ class
SOP	standard operating procedure
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TSAP	Trial statistical analysis plan
ULN	upper limit of normal

UTI urinary tract infection

I. Executive Summary

1. Summary of Regulatory Action

Pursuant to §21 CFR 314.126, it can fairly and responsibly be concluded that the applicant provided substantial evidence to support approval of empagliflozin to reduce the risk of cardiovascular death and hospitalization for heart failure (HHF) in patients with heart failure (HF).

Evidence to support this indication was provided by EMPEROR-Preserved, a randomized, double-blind, multi-national, placebo-controlled trial comparing empagliflozin 10 mg once daily to placebo, in patients with HF and with left ventricular ejection fraction (LVEF) greater than 40%.

Empagliflozin is currently approved in the US to: 1) improve glycemic control in adults with type 2 diabetes mellitus (T2DM); 2) reduce the risk of cardiovascular death in adult patients with T2DM and established cardiovascular disease (*based on the EMPA-REG OUTCOME trial*); and 3) reduce the risk of cardiovascular death plus HHF in adults with HF and reduced LVEF (*based on the EMPEROR-Reduced trial*).

In literature and evolving guidelines, HF has been classified based on LVEF as heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), and more recently, heart failure with mildly reduced ejection fraction (HFmrEF). The definition of HFpEF has varied over different clinical trials (e.g., LVEF $\geq$ 40%, or $\geq$ 45% or $\geq$ 50%). The American Society of Echocardiography (ASE) defines a normal mean LVEF as 62% in males and 64% in females. Measurements of LVEF by echocardiography can have up to 5-10% inter and intra-observer and temporal variability. Hence, HFpEF is not clearly defined although it is considered to be a serious condition and an unmet medical need.

The Division of Cardiology and Nephrology (DCN) considers LVEF to be a continuous rather than a dichotomous variable. Despite phenotypic variances in cardiac morphology (i.e., dilated cardiomyopathy and systolic dysfunction in HFrEF .vs. hypertrophic cardiomyopathy and diastolic dysfunction in HFpEF), HF signs and symptoms (e.g., peripheral and/or pulmonary edema, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, arrhythmia, exercise intolerance) present similarly in clinical practice. Drugs approved for the reduction of clinical events in patients with HF based on the feel-function-survive paradigm would not be characterized in the indication by dichotomous definitions of LVEF.

Description of the LVEF range in which the drug demonstrates substantial evidence of efficacy would be placed in section 14 of the label. Sacubitril/valsartan was recently approved under this paradigm.

Empagliflozin, previously approved for HFrEF based on EMPEROR-Reduced, showed substantial evidence of efficacy for the same endpoints for an expanded range of LVEF based EMPEROR-Preserved. The expanded range of LVEF would be described in section 14 of the label.

EMPEROR-Preserve was an event-driven trial that randomized 5988 eligible subjects (2997 in the empagliflozin arm and 2991 in the placebo arm, each over standard of care) to achieve 841 confirmed primary events. Randomization was stratified by geographical region (North America, Latin America, Europe, Asia and "Other"), history of diabetes (diabetes, prediabetes, no diabetes), LVEF (<50%, ≥50%) and eGFR at screening (<60 mL/min/1.73m², ≥ 60mL/min/1.73m²).

Key inclusion criteria were patients with New York Heart Association (NYHA) class II-IV chronic heart failure with a LVEF > 40%, NT-pro BNP > 300 pg/mL (> 900 pg/mL for patients with atrial fibrillation/flutter), and either structural heart disease or documented HHF within 12 months from the start of the trial. Key exclusion criteria were myocardial infarction, bypass surgery, stroke, or transient ischemic attack within 90 days prior to the start of the trial, heart transplant recipient, implantation of cardioverter defibrillator within 3 months of study start, infiltrative cardiomyopathy, acute decompensated heart failure requiring intervention during screening, chronic pulmonary disease requiring oxygen or steroids, liver disease, and major surgery within 90 days prior to study start.

The primary efficacy endpoint was the composite of time to first event of adjudicated cardiovascular (CV) death or adjudicated HHF. Secondary efficacy endpoints were the occurrence of adjudicated HHF (first and recurrent), and eGFR slope of change from baseline whereby eGFR was estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement (CKD-EPI).

The prespecified analysis for the primary composite endpoint of time until first CV death or adjudicated HHF was a Cox regression model with treatment, region, baseline diabetes status, age, sex, LVEF, and baseline eGFR covariates. Following the intention-to-treat (ITT) principle, all available patient data for the randomized population were used in the analysis. The analysis for the second key secondary endpoint of change in eGFR slope was based on a random coefficient model with random intercepts and random slopes for patients. Model covariates included treatment, region, baseline diabetes status, age, sex, LVEF, baseline eGFR, time, and a time-by-treatment interaction. A hierarchical testing procedure was pre-specified to adjust for the multiple endpoints at the final analysis. The primary composite first event endpoint was first in the hierarchy. This was followed by the first and recurrent events analysis for HHF. The eGFR slope of change from baseline was the last key secondary endpoint in the hierarchy with an allocated alpha of 0.001.

Demographic and baseline characteristics were balanced between the two study arms. The ITT population included 55% male, and 76% white. The mean age was 72 years. Only 12% of the ITT population was from North America. Almost half of the study population was diabetic of which 99.8% had type 2 diabetes mellitus (0.2% with type 1 diabetes mellitus). The ITT population was evenly divided (approximately 33% each) in LVEF < 50%, 50% to < 60%, and at least 60%. The mean (standard deviation) baseline LVEF was 54.3 (8.8). The median (min, max) baseline LVEF was 54% (40, 80). The etiologies of HF were mostly hypertensive and ischemic. The mean (standard deviation) baseline eGFR was 60.6 (19.9) mL/min/1.73m^2. Concomitant use of drugs in HF, other anti-hypertensive drugs, lipid-lowering drugs, and anti-thrombotic drugs at baseline and during the planned treatment period were balanced across the treatment groups.

Of the 2997 subjects randomized to the empagliflozin arm, 2940 completed the trial; of the 2991 randomized to the placebo arm, 2929 completed the trial. Median observation time to the end of the planned treatment period was about 26 months in both treatment groups, with 94% of patients observed for at least 1 year. Most patients were compliant with treatment (93.0% within the overall compliance window of 80 to 120%).

For the primary efficacy endpoint, the results demonstrated substantial effectiveness of empagliflozin, showing a hazard ratio (HR) of 0.79 (95% CI 0.69-0.89, p 0.0003). This was driven by HHF (HR 0.71, 95% CI 0.60-0.83). There was no difference between empagliflozin and placebo for CV death (HR 0.90, 95% CI 0.75-1.08). Several sensitivity analyses for the primary endpoint, including analyses performed to explore the impact of COVID-19 outbreak, demonstrated generally consistent results. Subgroup analyses for the primary composite endpoint were aligned with the overall findings.

For the secondary efficacy endpoint of total number of HHF events (first and recurrent), the HR was 0.73 (95% CI 0.61- 0.88, p=0.0009). Results for the change in eGFR slope used days as the unit of time. The estimated difference between slopes for the treatment arms was 0.0037 (99.9% CI: 0.0024, 0.0051). Multiplying these results by 365 to change the units to be yearly resulted in a change of 1.36 (99.9% CI: 0.86, 1.86).

Subgroup analysis of the primary efficacy endpoint as a function of baseline LVEF suggested a diminishing treatment effect with increasing baseline LVEF. The point-estimate of the HR favored empagliflozin throughout the range of LVEF in this trial. Similarly, analysis of the secondary efficacy endpoint of total number of HHF events suggested a diminished treatment effect as a function of increasing LVEF.

In summary for efficacy, empagliflozin was shown to meet the evidentiary standard to support an indication to reduce the risk of cardiovascular death and HHF in patients with heart failure. The range of LVEF in which empagliflozin was effective has expanded from the EMPEROR-Reduced trial, but with a diminishing treatment effect at higher LVEF values.

The safety evaluation over a mean study drug exposure of 22.7 months (equal in both arms of EMPEROR-Preserved) showed a balance between the arms in overall treatment emergent adverse events (TEAEs). Broad FMQs displaying an unfavorable risk difference greater than

1% were hypotension (2%) and syncope1%, driven by hypotension), which were expected adverse events based on empagliflozin's mechanism of action. Broad SMQs showed similar results. Deaths, and their cause, were balanced between the arms. The common CV deaths were sudden death and HF. The common non-CV deaths were infections and malignancy. Serious adverse events (SAEs) were balanced between the arms. None of the preferred terms for SAEs had a risk difference greater than 1% based on an evaluation of FMQs and SMQs. Discontinuations of study drug were balanced between the arms. Preferred terms for AEs leading to discontinuation with an unfavorable risk difference greater than 0.2% were death (0.7%), urinary tract infection (0.3%), and COVID-19 pneumonia (0.2%). Adverse events of specific interest (AESI) for empagliflozin included hepatic injury, decreased renal function, ketoacidosis, lower limb amputation, hypoglycemic events, genital infection, urinary tract infection, increased urination, bone fracture, hypotension, volume depletion, hypersensitivity, and thirst. These events were balanced between the arms. A review of laboratory and vital sign-related AESIs, including liver enzymes (ALT, AST, bilirubin), renal function tests (serum creatinine and eGFR), lipid panels (HDL-cholesterol, LDL-cholesterol, and triglycerides), hematology (hemoglobin and hematocrit) and blood pressure (systolic and diastolic) showed no difference between the arms in liver enzymes, renal function, and lipid panel. There was an increase in hemoglobin / hematocrit in the empagliflozin arm compared to the placebo arm, due to a higher amount of outlier values for hemoglobin (6.2% vs 2.6%) and hematocrit (25.9% vs 12.9%). The empagliflozin group also had lower systolic blood pressure (1-3 mmHg) than the placebo group. These effects were likely due to the empagliflozin-mediated diuresis and consequent hemoconcentration.

In summary for safety, deaths, TEAEs, AESIs, and laboratory parameters were balanced between the arms. Broad FMQs with risk differences larger than 1%: hypotension (2.0%) and syncope (1.4%, driven by hypotension), were expected AEs based on empagliflozin's mechanism of action and are adequately addressed in the current label. There were no unexpected safety findings in the EMPERIOR-Preserved trial.

2. Benefit-Risk Assessment

EMPEROR-preserved provided substantial evidence of efficacy to support the conclusion that, compared to placebo and over standard of care treatment, empagliflozin reduced the primary efficacy composite endpoint of cardiovascular death and HHF in patients with heart failure and LVEF > 40%, regardless of type 2 diabetes mellitus status. The efficacy results were driven by HHF. The treatment effect diminished with increasing baseline LVEF. The hazard ratio of empagliflozin .vs. placebo (HR 0.79, 95% CI 0.69-0.89, p=0.0003) resembles the results from EMPEROR-Reduced for the same endpoints in chronic heart failure patients with reduced LVEF (HR 0.75, 95% CI 0.65-0.86, p < 0.0001). Hence, the EMPEROR-Preserved trial successfully confirmed the results from the EMPEROR-Reduced trial in a patient population with an expanded range of LVEF.

There were no new safety signals from EMPEROR-Preserved. All laboratory and vital sign changes were expected and are adequately addressed in the label.

In conclusion, the benefit / risk assessment of the datasets from EMPEROR-Preserved favors approval of empagliflozin for the indication to reduce the risk of cardiovascular death plus HHF in adults with heart failure.

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Heart Failure (HF) is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[1] HF is a chronic condition associated with premature mortality and significant morbidity, largely due to high rates of hospitalization for heart failure (HHF).[2] It afflicts 1 to 3% of the population worldwide, with annual incidence of > 650,000 in the United States (US). Historically, HF has been classified based on left ventricular ejection fraction (LVEF) as heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). The origin of the clinical entity "HFpEF" is arbitrary[3] and continues to evolve. HF trials have defined HFpEF as HF with LVEF ≥ 40% or ≥ 45% or ≥ 50%.[4] The American Society of Echocardiography (ASE)[5] defines normal mean LVEF ± SD (2-SD range) as 62 ± 5 % (52-72) in males and 64 ± 5 % (54-74) in females. Note that the Division considers patients with HF with LVEF of 41 to 51% in males and 41-53% in females to have mildly reduced LVEF. Hence, HFpEF is a heterogenous disease that includes patients with mildly reduced and normal LVEF. Approximately half of the total HF cases are attributed to HFpEF[6] and the incidence of HFpEF is increasing.[7,8]	HF, regardless of LVEF, is a chronic condition with significant morbidity and mortality. APPEARS THIS WAY ON ORIGINAL

[1] Piotr Ponikowski, Adriaan A Voors, Stefan D Anker, Héctor Bueno, John G F Cleland, Andrew J S Coats, Volkmar Falk, José Ramón González-Juanatey, Veli-Pekka Harjola, Ewa A Jankowska, Mariell Jessup, Cecilia Linde, Petros Nihoyannopoulos, John T Parissis, Burkert Pieske, Jillian P Riley, Giuseppe M C Rosano, Luis M Ruilope, Frank Ruschitzka, Frans H Rutten, Peter van der Meer, ESC Scientific Document Group, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200

[2] Dunlay, S., Roger, V. & Redfield, M. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 14, 591–602 (2017).

[3] Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011;32(6):670-679.

[4] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007 Aug 21;50(8):768-77.

[5] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Recently, the indication for sacubitril/valsartan (Entresto) was expanded to treat patients with HF with mildly reduced LVEF. Currently there is no FDA approved therapy to treat patients with HF with normal LVEF. Per ACC/AHA recommendations[9], patients with "HFpEF" are treated with diuretics for symptom relief, mineralocorticoid receptor antagonists and angiotensin receptor blockers.	Available treatment options for patients with HF with mildly reduced or normal LVEF are limited. There is a continued unmet need to reduce morbidity and mortality in this patient population.
Benefit	EMPEROR-Preserved was a phase 3 multicenter randomized trial in patients with chronic heart failure and LVEF > 40% that evaluated efficacy and safety of Jardiance 10 mg versus placebo. The primary endpoint was a composite of time to first event of adjudicated cardiovascular (CV) death or hospitalization for heart failure (HHF). EMPEROR-Preserved randomized 5988 patients in 1:1 ratio to Jardiance versus placebo. Jardiance reduced the primary endpoint compared to placebo with respective incidence rate of 6.86 versus 8.67 per 100 patients years; hazard ratio of 0.79 (95% CI 0.69, 0.90); p-value < 0.0003.	EMPEROR-Preserved provided substantial evidence of efficacy of Jardiance in reduction of HHF and CV death in patients with heart failure with LVEF > 40%, when used on top of standard of care, regardless of type 2 diabetes mellitus (T2DM) status.

[6] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.
[7] Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126:65–75.
[8] Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10:401-410.
[9] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137–e161.

Risk and Risk Management	The label for Jardiance tablets describes the following adverse events/reactions: 1) Warnings and Precautions: ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections and hypersensitivity reactions, 2) Adverse reactions reported in ≥ 2% of patients treated with Jardiance and greater than placebo: urinary tract infection, genital mycotic infections, upper respiratory tract infection, increased urination, dyslipidemia, arthralgia, and nausea, 3) Laboratory Tests: increase in Low-Density Lipoprotein Cholesterol (LDL-C) and increase in hematocrit. In addition, the label describes the following adverse reactions identified during post approval use of Jardiance: angioedema and skin reactions. The safety review of Jardiance focused on previously identified risks of SGLT2 inhibitors, including Jardiance; and included a review of data quality, adverse event (AE), laboratory and vital sign datasets. 1) Generally, the incidence of death, SAEs, AESIs and AEs leading to discontinuation was similar between Jardiance and placebo arm. 2) Generally, the incidence of specific adverse events was low and balanced between the two treatment arms except for a slightly higher number of AEs of genital and urinary tract infections, symptomatic hypotension and volume depletion in the Jardiance arm compared to placebo. 3) The incidence of urosepsis/acute pyelonephritis in placebo versus Jardiance arm was 0.6% and 0.8%, respectively. 4) Although there have been post-marketing reports of acute kidney injury (AKI), the incidence of AKI (FMQ) was lower in the Jardiance arm (3.2%) compared to the placebo arm (4.4%). The incidence of AE of renal impairment was similar in the Jardiance (7.0%) versus placebo (7.2%) arms. 5) The incidence of ketoacidosis was similar between the Jardiance (1.5%) and placebo (1.7%) arms.	No new Jardiance-associated risks were identified in the EMPEROR-Preserved trial. Consistent with the trials of Jardiance for glycemic control and heart failure with reduced ejection fraction, volume depletion, genital and urinary tract infections, and sepsis occurred more commonly in the Jardiance group. Labeling is considered sufficient to ensure that the benefits of Jardiance in the target population outweigh the risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Consistent with findings in other SGLT2 inhibitor trials, there was a slight increase in hematocrit, and a decrease in blood pressure and weight in the Jardiance versus placebo arms.	

Conclusions Regarding Benefit-Risk

Jardiance is a sodium-glucose co-transporter 2 (SGLT2) inhibitor approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, to reduce the risk of CV death in adult patients with type 2 diabetes mellitus and established CV disease, and to reduce the risk of CV death plus HHF in adults with heart failure and reduced ejection fraction (based on the EMPEROR-Reduced trial). On September 13, 2021, Boehringer Ingelheim submitted an efficacy supplement for Jardiance for the proposed indication to "reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction (b) (4) (b) (4)

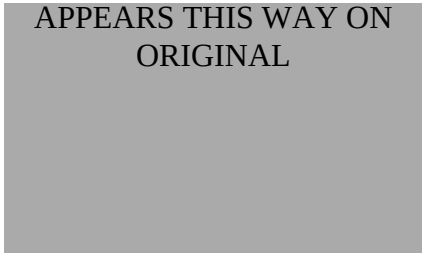
In support of the proposed indication, the Applicant conducted a single phase 3 randomized, double-blind trial to evaluate efficacy and safety of once daily Jardiance 10 mg compared to placebo, in patients with chronic heart failure with LVEF > 40%," referred to as "EMPEROR-Preserved." Jardiance was administered on top of standard of care therapy in adult patients with chronic heart failure with LVEF > 40% (NYHA class II-IV) and eGFR ≥ 20 ml/min/m^2.

EMPEROR-Preserved randomized 5988 eligible subjects, 2997 in the Jardiance arm and 2991 in the placebo arm. Baseline demographic and clinical characteristics, and concomitant CV medication use was balanced between the two treatment arms. Jardiance reduced the incidence of the primary composite endpoint of CV death or HHF compared to placebo with a HR of 0.79, 95% CI 0.69-0.89, p 0.0003, thus providing evidence of efficacy of Jardiance to reduced CV death and HHF in patients with HF with LVEF > 40%. The primary endpoint results were largely driven by a reduction in HHF (HR 0.71, 95% CI 0.60-0.83) with slightly favorable trend noted in the incidence of CV death (HR 0.90, 95% CI 0.75-1.08) with Jardiance versus placebo. Hence, the review team recommends the approval of Jardiance to reduce the risk of CV death and HHF in patients with HF with LVEF > 40%.

The first key secondary endpoint of total HHF (first and recurrent HHF) was also lower in Jardiance versus placebo arm with a HR of 0.73, 95% CI 0.61- 0.88, p=0.0009.

The second key secondary endpoint was eGFR Slope change from baseline with an allocated alpha of 0.001. All available alpha at the end of EMPEROR-Preserved, along with that from the EMPEROR-Reduced study was moved into a meta-analysis with the primary endpoint of time to first renal event. However, the meta-analysis failed in the first primary endpoint of first renal event. No evaluations of any of the meta-analyses endpoints were run for this review.

The submitted data provide substantial evidence of efficacy of Jardiance in reducing CV death and HHF in patients with HF with LVEF > 40%, with or without T2DM, when added to standard of care, and a compelling evidence that the clinical benefit outweighs potential risk with Jardiance. Hence, the review team recommends approval of the efficacy supplement.



II. Interdisciplinary Assessment

3. Introduction

The applicant has submitted a single, phase 3 trial (EMPEROR-preserved) in support of the supplemental new drug application (sNDA) for Jardiance (empagliflozin) for the following new indication:

"*JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction* (b) (4) (b) (4)

Jardiance is approved in the US for the following indications:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease (based on the EMPA-REG OUTCOME trial)
- to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction (based on the EMPEROR-Reduced trial)

Jardiance is a reversible, potent (IC_{50} of 1.3 nmol) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). SGLT2 is expressed in the kidney and is the predominant transporter for renal glucose reabsorption. Jardiance lowers both the saturation threshold and transport maximum of SGLT2 for glucose, resulting in glucosuria, insulin-independent reduction of plasma glucose levels, natriuresis, and weight and blood pressure reduction.

EMPA-REG OUTCOME, the cardiovascular outcomes trial of Jardiance, was a randomized, placebo-controlled trial that evaluated 10 and 25 mg of Jardiance in 7020 patients with type 2 diabetes mellitus (T2DM) and established cardiovascular disease. EMPA-REG OUTCOME demonstrated that Jardiance, on top of standard of care reduced the primary composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke, driven primarily by a 38% reduction in CV death. Jardiance also reduced the prespecified composite endpoint of CV death or hospitalization for heart failure (HHF) by 34% with a hazard ratio (HR) of 0.66; 95% CI 0.55, 0.79.

In addition to Jardiance, other FDA approved SGLT-2 inhibitors include Farxiga (dapagliflozin), Invokana (canagliflozin) and Steglatro (ertugliflozin). All SGLT2 inhibitors are approved for glycemic control and most have demonstrated efficacy in reduction of CV and renal events in

various patient populations, including heart failure with reduced ejection fraction (HFrEF).[10] The mechanism of CV benefit with SGLT2 inhibitors is not well understood but appears to be independent of glycemic control. Table 3 summarizes the approved CV and renal indications for SGLT2 inhibitors.

Table 3. FDA Approved Cardiovascular and Renal Indications of SGLT2 Inhibitors

SGLT2 Inhibitor	Cardiovascular and Renal Indications
Jardiance	To reduce the risk of cardiovascular death in adult patients with T2DM and established cardiovascular disease. To reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction
Dapagliflozin	To reduce the risk of hospitalization for heart failure in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors. To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV). To reduce the risk of sustained eGFR decline, end stage kidney disease cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.
Canagliflozin	To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria
All the SGLT2 inhibitors are approved as an adjunct to diet and exercise to improve glycemic control in patients with T2DM. Abbreviations: SGLT2, sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate	

Source: Reviewer compilation

Heart Failure (HF) is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[11] HF is a chronic condition associated with premature mortality and significant morbidity, largely due to high rates of hospitalization for heart failure (HHF).[12] It afflicts 1 to 3% of the population worldwide, with higher prevalence in the elderly, ≥10% in those age ≥65 years. The annual incidence of HF in the United States (US) is > 650,000 and continues to rise with the aging population. Approximately half of these cases are HFpEF[13] i.e., heart failure with LVEF > 40% and the incidence of HFpEF is increasing.[14,15]. In 2007, Fonarow

[10] Challenges of Cardio-Kidney Composite Outcomes in Large-Scale Clinical Trials. Ravi B. Patel, Jozine Magdalena ter Maaten, João Pedro Ferreira, Finnian R. Mc Causland, Sanjiv J. Shah, Patrick Rossignol, Scott D. Solomon, Muthiah Vaduganathan, Milton Packer, Aliza Thompson, Norman Stockbridge, and Faiez Zannad. 10.1161/CIRCULATIONAHA.120.049514.

[11] Piotr Ponikowski, Adriaan A Voors, Stefan D Anker, Héctor Bueno, John G F Cleland, Andrew J S Coats, Volkmar Falk, José Ramón González-Juanatey, Veli-Pekka Harjola, Ewa A Jankowska, Mariell Jessup, Cecilia Linde, Petros Nihoyannopoulos, John T Parissis, Burkert Pieske, Jillian P Riley, Giuseppe M C Rosano, Luis M Ruilope, Frank Ruschitzka, Frans H Rutten, Peter van der Meer, ESC Scientific Document Group, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200

[12] Dunlay, S., Roger, V. & Redfield, M. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 14, 591–602 (2017).

[13] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.

[14] Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126:65–75.

[15] Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10:401-410.

et al[16] reported that the mortality and re-admission rates during 60- to 90-day post discharge for patients with HFpEF and HFrEF were similar i.e., 9.5% vs. 9.8% and 29.2% vs. 29.9%, respectively.

Historically, HF has been classified based on LVEF as HFrEF or HFpEF. The origin of the clinical entity "HFpEF" is arbitrary[17] and continues to evolve. HF trials have defined HFpEF as HF with LVEF ≥ 40% or ≥ 45% or ≥ 50%.[18] LVEF is the proportion of blood ejected during LV systole. It is an indirect measure of global left ventricular systolic function. The most common modality used to measure LVEF is two-dimensional (2-D) echocardiography. The American Society of Echocardiography (ASE)[19] defines normal mean LVEF ± SD (2-SD range) as 62 ± 5 % (52-72) in males and 64 ± 5 % (54-74) in females. Echocardiography can have up to 5-10% inter and intra-observer and temporal variability in assessment of LVEF depending on the technique(s) used[20] and various patient factors. Hence, HFpEF is a heterogenous disease that is not well-defined. Nevertheless, it represents patients with a serious condition with significant unmet need.

Note that the Division considers patients with HF with LVEF of 41 to 51% in males and 41-53% in females to have mildly abnormal LVEF, i.e., mildly reduced LVEF or mild left ventricular systolic dysfunction. Patients with mildly abnormal LVEF are considered similar to patients with heart failure with reduced ejection fraction (HFrEF), defined as HF with LVEF ≤ 40%, in therapeutic response to candesartan, spironolactone and sacubitril/valsartan. Patients with HF with LVEF > 51% and 53% in males and females, respectively have normal LVEF and are considered to be distinct from those with HFrEF or HF with mildly reduced LVEF. Hence, the intended population for this sNDA is heterogenous and includes patients with mildly abnormal and normal LVEF.

Recently, the indication for sacubitril/valsartan was expanded to treat patients with HF with mildly abnormal LVEF.

Currently there is no FDA approved therapy to treat patients with HF with normal LVEF.

The 2017 ACC/AHA recommendations[21] to treat patients with HFpEF include the following:

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[16] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007 Aug 21;50(8):768-77.
[17] Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J. 2011;32(6):670-679.
[18] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007 Aug 21;50(8):768-77.
[19] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.
[20] Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013 Jan 8;61(1):77-84. doi: 10.1016/j.jacc.2012.09.035. Epub 2012 Nov 28.
[21] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137–e161.

- Class I recommendation to treat hypertension
- Class I recommendation to use of diuretics for symptomatic relief
- Class IIa recommendation for coronary revascularization for concomitant symptomatic (or evidence of significant myocardial ischemia) coronary artery disease; and guideline directed management of atrial fibrillation
- Class IIb recommendation to use MRA in appropriately selected patients with HFpEF with LVEF ≥45%, elevated brain natriuretic peptide (BNP) levels or HF admission within 1 year, estimated glomerular filtration rate (eGFR) >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L, based on the findings from the Treatment of Preserved Cardiac Function Heart Failure trial (TOPCAT).[4]
- Class IIb recommendation to use angiotensin receptor blockers (ARBs) to decrease hospitalizations for patients with HFpEF.

The applicant's evaluation of patients with chronic HF (EMPEROR program) included the previously conducted EMPEROR-Reduced trial in patients with HFrEF, and the EMPEROR-Preserved trial in patients with heart failure with preserved ejection fraction (HFpEF). The latter trial serves as the basis of this submission. The EMPEROR program also evaluated renal benefit in patients with HF.

In addition to EMPEROR-preserved, this submission also included a summary of EMPA-VISION trial and a pre-specified meta-analysis of efficacy endpoints based on EMPEROR-reduced and EMPEROR-preserved trials.

3.1. Approach to the Review

This is a joint clinical and statistical review. Charu Gandotra and Jennifer Clark focused on the data supporting efficacy, and Claire Ji focused on the data supporting safety. There were no relevant nonclinical or clinical pharmacology data for review.

This review focused on Study 1245.110 (EMPEROR-preserved) to evaluate efficacy and safety of Jardiance in the intended population. Findings from short-term (12 weeks) mechanistic Study 1245.148 (EMPA-VISION) and pre-specified meta-analysis of EMPEROR-reduced and EMPEROR-preserved were negative and did not contribute to the review of efficacy and safety of Jardiance in the intended population.

4. Evidence of Benefit (Assessment of Efficacy)

4.1. Design of Clinical Trial Intended to Demonstrate Benefit to Patients – EMPEROR-Preserved

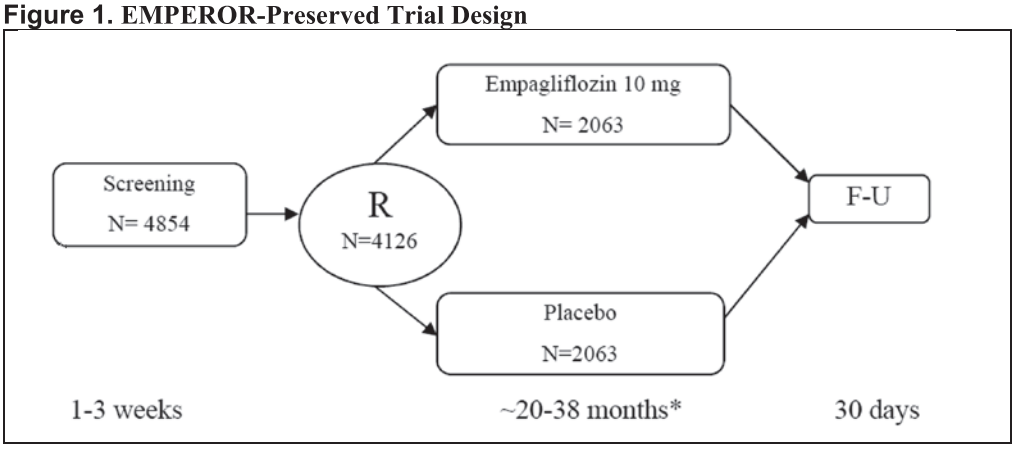
4.1.1. Trial Design

In support of the proposed indication, the applicant conducted a single phase 3 multicenter trial 1245.110 (EMPEROR-Preserved) titled, "a phase III randomized, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with

chronic Heart Failure with preserved Ejection Fraction (HFpEF).” EMPEROR-Preserved is described below according to Protocol Version 4.0, dated November 20, 2019. Relevant protocol amendments are described in the Section 4.1.4.

The primary objective of EMPEROR-Reduced was to demonstrate superiority of Jardiance 10 mg versus placebo in patients with symptomatic, chronic HF and LVEF > 40% under stable treatment of HF symptoms. Figure 1 displays the trial design and Table 4 summarizes the endpoints of EMPEROR-Preserved.

Figure 1. EMPEROR-Preserved Trial Design



Source: Sponsor material; Figure 3.1:1 of Appendices Section 16.1.1 titled Protocol and amendments

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Table 4. Endpoints of EMPEROR-Preserved

Primary Endpoint
Composite of time to first event of adjudicated CV death or adjudicated HHF in patients with HFpEF.
Key Secondary Endpoints (part of testing strategy)
1) Occurrence of adjudicated HHF (first and recurrent)
2) eGFR slope of change from baseline [glomerular filtration rate estimated by the chronic kidney disease epidemiology collaboration formula with serum creatinine measurement (CKD-EPI)]
Other Exploratory Secondary Endpoints (not part of testing strategy)
1) Time to first occurrence of events in composite renal endpoint - chronic dialysis^ or renal transplant or sustained* reduction of ≥40% eGFR or o sustained eGFR <15 mL/min/1.73 m^2 for patients with baseline eGFR ≥30 mL/min/1.73 m^2 o sustained eGFR <10 mL/min/1.73 m^2 for patients with baseline eGFR <30 mL/min/1.73 m^2 2) Time to first adjudicated HHF 3) Time to adjudicated CV death 4) Time to all-cause mortality 5) Time to onset of diabetes mellitus (DM) (defined as HbA1c ≥6.5% or as diagnosed by the investigator) in patients with pre-DM 6) Change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the KCCQ at Week 52 7) Occurrence of all-cause hospitalization (first and recurrent)
Safety Criteria
1) Adverse events (AE) 2) AE of special interest (AESI) 3) Incidence and intensity of AE including serious AE (SAE) 4) Withdrawal from trial medication due to AE 5) Clinically relevant new finding or worsening of existing condition on physical examination 6) Clinically relevant changes in laboratory measurements from baseline 7) Assessment of vital status
^ Chronic dialysis was defined as dialysis with a frequency of twice per week or more for at least 90 days * An eGFR reduction is considered sustained, if it is determined by two or more consecutive post-baseline central laboratory measurements separated by at least 30 days (first to last of the consecutive eGFR values). Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; CV, cardiovascular; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease - Epidemiology Collaboration Equation; cr, creatinine; KCCQ, Kansas City cardiomyopathy questionnaire

Source: Reviewer compilation

Eligible patients were randomized in 1:1 ratio to placebo versus Jardiance once a day to be taken without regard to food on top of standard of care. Randomization was stratified by geographical region (North America, Latin America, Europe, Asia and "Other"), history of diabetes (diabetes, prediabetes, no diabetes), LVEF (<50%, ≥50%) and eGFR at screening (<60 mL/min/1.73m², ≥ 60mL/min/1.73m²).

Interactive response technology (IRT) was used to ensure that a minimum of 35% of the trial population were patients with DM, a minimum of 15% were patients with pre-DM, and a minimum of 20% were patients without DM. DM was defined as active treatment with antidiabetic medication (for indication of DM), screening HbA1c ≥6.5%, or history of DM. Pre-DM was defined as screening HbA1c ≥5.7% and <6.5% without the intake of antidiabetic

medication (unless taken for a non-DM indication) and no history of DM. No DM was defined as screening HbA1c <5.7% without any intake of antidiabetic medication (unless taken for a non-DM indication) and no history of DM.

This was an event-driven trial with plan to randomize approximately 4126 patients to achieve 841 confirmed primary events within 18 months accrual and 20 additional months follow-up period to achieve a power of approximately 90%. The protocol allowed for extending the recruitment period by 6 months, adjusting the follow-up period, and increasing enrollment up to 6000 to achieve 841 confirmed primary endpoints. Table 17 in Section III.8 displays the Schedule of Assessments for EMPEROR-Preserved. A central laboratory service was used. When a patient permanently discontinued trial medication or when the required number of events had been reached for the trial, an end-of-treatment (EOT) visit was performed, followed by a follow-up Visit 30 days later.

The trial was monitored by an independent data-monitoring committee (DMC) and was responsible for unblinded safety and efficacy assessments at specified intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial. Measures were in place to ensure blinding of the Sponsor, Executive Steering Committee (ExSC), Scientific Excellence Committee (SEC), National Coordinator Committee (NCC), Contract Research Organization (CRO) and all other trial participants. The tasks and responsibilities of the DMC were specified in a charter. The DMC was provided with unblinded data to allow their review of efficacy and safety and to fulfil their tasks as outlined in the DMC charter. An independent team at (b) (4) which was otherwise not involved in the conduct of the trial, provided the unblinded results to the DMC.

An independent external Clinical Event Committee (CEC) adjudicated the pre-specified endpoints, centrally and in a blinded fashion, in accordance with the CEC charter. Independent external experts adjudicated certain hepatic events, metabolic acidosis, ketoacidosis (KA) and diabetic ketoacidosis (DKA) in a blinded fashion.

For patients who prematurely discontinued trial medication, all efforts were to be made to observe these patients and ask them to continue to attend the scheduled visits until the end of trial. If a patient who prematurely discontinued trial medication was not willing to return to the pre-defined trial visits, at minimum a telephone call every 24 weeks (preferably every 12 weeks) and a telephone call at trial end was required to document the occurrence of outcome events and vital status. Patients who prematurely discontinued trial medication were allowed to restart treatment at any time, if appropriate in the opinion of the investigator.

A patient had the right to withdraw informed consent for participation at any time for any reason. Patients who withdrew informed consent were not to be replaced. Vital status was to be collected at the end of trial for patients who had withdrawn consent from trial participation, if allowed by local regulations.

If a patient became pregnant during the trial, the trial medication was to be stopped, and the patient was to be followed up during the trial and until birth or termination of the pregnancy.

Dose selection: In the EMPA-REG-OUTCOME trial, both empagliflozin doses (10 and 25 mg) were administered to patients with T2DM and were shown to be equally effective in reducing CV death, HHF, and the composite of HHF or CV death in patients with HF at baseline. In subgroup analyses, empagliflozin improved the main outcome of CV death and HHF with a similar magnitude in patients with low or high levels of HbA1c at baseline. This suggested that risk reduction for HF outcome is independent of the degree of glycemic control at baseline, and that these benefits can be achieved with the 10 mg dose similar to the 25 mg dose in the non-diabetic population as well. The mechanism of action is supported by studies in healthy volunteers where both doses were associated with about 50 g glucosuria. Given the lower exposure with empagliflozin 10 mg as well as similar general safety and CV effects for both doses, empagliflozin 10 mg once daily was selected for this trial.

Empagliflozin can be taken with or without food. To ensure a dose interval of about 24 hours, the medication was to be taken in the morning at approximately the same time every day. If a dose was missed by more than 12 hours, that dose was to be skipped and the next dose was to be taken as scheduled. On days before the next visit, the dose was to be taken 22 to 26 h before the planned dose at the visit. No double doses were to be taken.

Treatment compliance: Patients were requested to bring all remaining trial medication including empty package material with them when attending visits. The investigator or designate counted the number of the returned tablets and calculated compliance as the number of tablets actually taken since last tablet count versus the number that should have been taken. Compliance was expected to range between 80% and 120%.

4.1.2. Eligibility Criteria

Relevant eligibility criteria are listed below.

Inclusion criteria

Patients with chronic HF with LVEF >40% (sponsor defines this as HFpEF).

- Age ≥18 years at screening. For Japan only: Age ≥20 years at screening.
- Male or female patients. Women of childbearing potential had to be ready and able to use highly effective methods of birth control that result in a low failure rate of less than 1% per year when used consistently and correctly.
- Patients with chronic HF diagnosed for at least 3 months before Visit 1, and currently in HF NYHA class II-IV
- Chronic HF with preserved EF defined as LVEF >40% per local reading (obtained by echocardiography, radionuclide ventriculography, invasive angiography, MRI, or CT), and no prior measurement of LVEF ≤40% under stable conditions (in the investigator's opinion). A historical LVEF measurement could be used if it had been measured within 6 months prior to Visit 1, and more than 90 days after any myocardial infarction, or the LVEF could be measured after study consent had been obtained. The LVEF had to be documented in an official report prior to randomization.

- Elevated N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) >300 pg/mL for patients without atrial fibrillation or atrial flutter (AF), or >900 pg/mL for patients with AF, analyzed at the central laboratory at Visit 1.
- Patients had to have at least one of the following evidence of HF:
    - Structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at Visit 1 or within 6 months prior to Visit 1
    - Documented HHF within 12 months prior to Visit 1 (the main reason for HHF had to be HF; documentation of HHF had to be provided)
- Oral diuretics, if prescribed to patient according to local guidelines and discretion of the investigator, should have been stable for at least 1 week prior to Visit 2 (randomization)
- Body Mass Index (BMI) <45 kg/m2 at Visit 1.
- Signed and dated written ICF in accordance with Good Clinical Practice (GCP) and local legislation prior to admission to the trial.

Exclusion criteria

- Myocardial infarction, coronary artery bypass graft surgery, or other major cardiovascular surgery, stroke, or transient ischemic attack (TIA) within 90 days prior to Visit 1.
- Heart transplant recipient or listed for heart transplant.
- Implantation of cardioverter defibrillator (ICD) within 3 months prior to Visit 1.
- Implanted cardiac resynchronization therapy (CRT)
- Cardiomyopathy based on infiltrative diseases (e.g., amyloidosis), accumulation diseases (e.g., haemochromatosis, Fabry disease), muscular dystrophies, cardiomyopathy with reversible causes (e.g., stress cardiomyopathy), hypertrophic obstructive cardiomyopathy or known pericardial constriction.
- Any severe (obstructive or regurgitant) valvular heart disease expected to lead to surgery during the trial in the investigator's opinion.
- Acute decompensated HF (exacerbation of chronic HF) requiring intravenous (i.v.) diuretics, i.v. inotropes or i.v. vasodilators, or left ventricular assist device within 1 week from discharge to Visit 1, and during screening period until Visit 2.
- Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm documented by ECG at Visit 1. In the original trial protocol, documentation by ECG was to be done at Visit 2; this was changed to Visit 1 by global protocol amendment 1.
- Systolic blood pressure (SBP) ≥180 mmHg at Visit 2. If SBP >150 mmHg and <180 mmHg at Visit 2, the patient was to be receiving at least 3 anti-hypertensive drugs.
- Symptomatic hypotension and/or SBP <100 mmHg at Visit 1 or Visit 2.
- Chronic pulmonary disease requiring home oxygen, oral steroid therapy, or hospitalization for exacerbation within 12 months, or significant chronic pulmonary disease in the opinion of the investigator, or primary pulmonary arterial hypertension.
- Indication of liver disease, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3x upper limit of normal (ULN) as determined at Visit 1.

- Impaired renal function, defined as eGFR <20 mL/min/1.73 m2 (CKD-EPI) or requiring dialysis, as determined at Visit 1.
- Hemoglobin (Hb) <9 g/dL at Visit 1.
- History of ketoacidosis.
- Major surgery (major according to the investigator's assessment) performed within 90 days prior to Visit 1, or scheduled major elective surgery (e.g., hip replacement) within 90 days after Visit 1.
- Gastrointestinal surgery or gastrointestinal disorder that could have interfered with trial medication absorption in the investigator's opinion.
- Any documented active or suspected malignancy or history of malignancy within 2 years prior to screening, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix, or low risk prostate cancer (patients with pretreatment PSA <10 ng/mL and biopsy Gleason score of ≤6 and clinical stage T1c or T2a).
- Presence of any other disease than heart failure with a life expectancy of <1 year in the opinion of the investigator.
- Current use or prior use of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor within 12 weeks prior to Visit 1 or during screening period until Visit 2. Discontinuation of a SGLT-2 inhibitor or combined SGLT-1 and 2 inhibitor for the purposes of study enrolment was not permitted.
- Women who were pregnant, nursing, or who planned to become pregnant while in the trial.

4.1.3. Statistical Analysis Plan

The prespecified analysis for the primary composite endpoint of time until first CV death or adjudicated HHF was a Cox regression model with treatment, region, baseline diabetes status, age, sex, LVEF, and baseline eGFR covariates. Following the recommended ITT principle, all available patient data for the randomized population was used in the analysis. For a first events analysis, this includes the time from randomization until the first composite event, or, for those without an event, the last follow-up for the patient within the planned treatment period (censored patients).

A joint frailty model was specified for the first and recurrent HHF events endpoint, this type of modeling accounts for the dependence between recurrent HHF and CV death. Covariates here included treatment, region, baseline diabetes status, age, sex, LVEF, and baseline eGFR. This analysis included all adjudicated HHF events that a patient may experience, not just the first event. The time used for this analysis includes all observed time until the last follow-up during the planned treatment period.

The SAS procedure (NLMIXED) for estimating this type of model requires specification of starting values for each of the parameters in order to obtain convergence for complex models such as the one specified in the protocol. In order to obtain reasonable starting parameters, the sponsor used a piecewise hazard based on percentiles within the data. They obtained starting values for the model parameters by running a Poisson regression for count data to model the

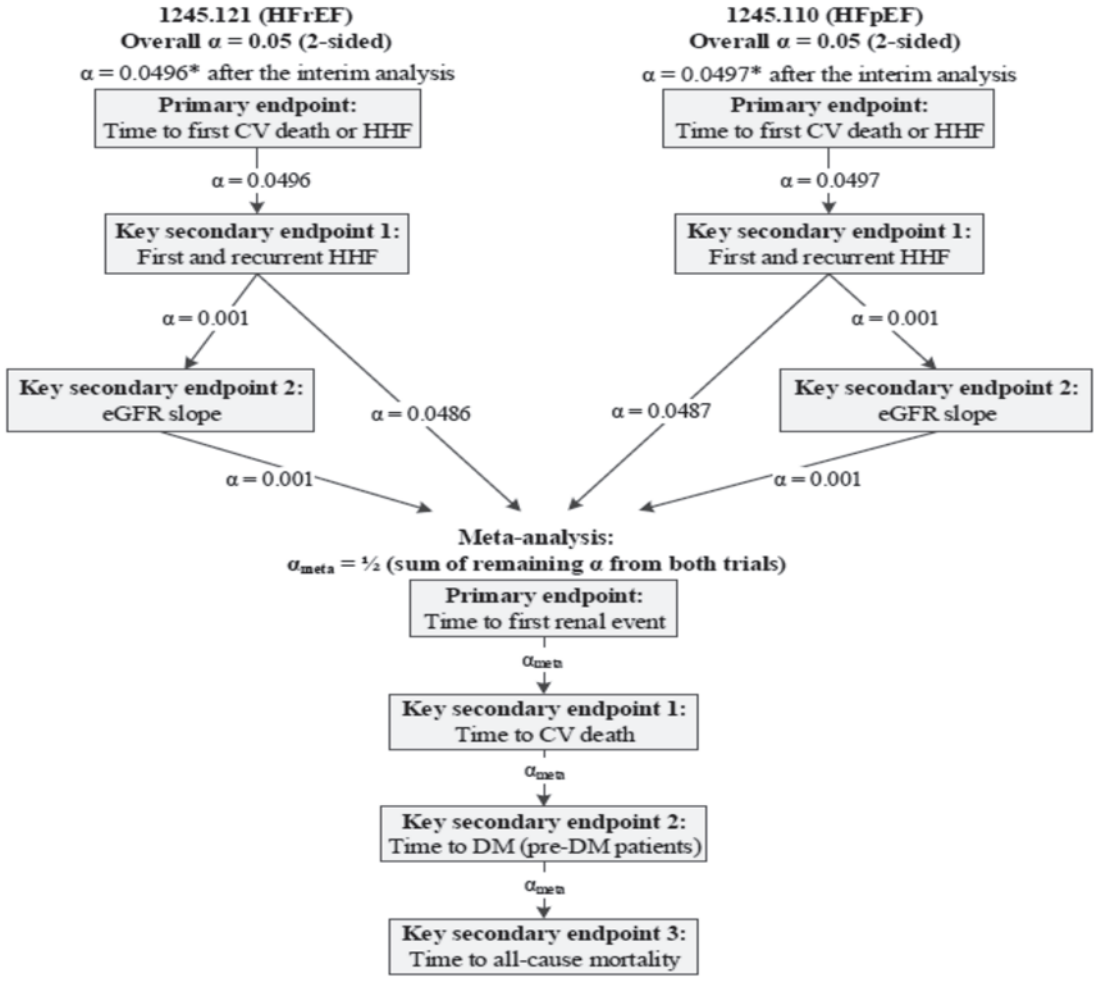
number of events. The applicant used these model estimates as starting values for the joint frailty model. We used empirical estimates for the starting value of the hazard. Andersen-Gill models for repeated events for HHF and HHF+CV Death were run to obtain starting values for model parameters. Due to review timeline constraints, further exploration of starting values could not be run. If convergence criteria for the complex full joint frailty model could not be met with these starting values, then a simpler unadjusted model was used. The unadjusted model would result in a treatment effect that would be close to the unadjusted one, but potentially with a smaller effect due to not adjusting for applicable covariates.

The analysis for the second key secondary endpoint of change in eGFR slope was a random coefficient model with random intercepts and random slopes for patients. Model covariates included treatment, region, baseline diabetes status, age, sex, LVEF, baseline eGFR, time, and a time-by-treatment interaction. For this analysis the applicant used an on-treatment analysis where only measurements taken up to one day after the last study medication was taken were used. This is different from the ITT based analyses specified for the primary and other key secondary endpoint. Based on using the change from baseline data, the model intercept is seen as the acute drop and the slope as the long-term effects.

An interim analysis (IA) was pre-specified to occur after approximately 500 events (60% of anticipated events). The IA was pre-specified in the Clinical Trial Protocol (CTP) to be conducted by the DMC which could stop the trial for overwhelming efficacy based on results from the primary endpoint. Events that occurred up to one day prior to the IA cut-off date would be considered with patients not experiencing an even at the time of the IA being censored at the cut-off date. The Hwang, Shih and De Cani alpha spending function with γ=-8 was specified to adjust for the IA. Alpha levels were expected to be 0.001 at the interim, and 0.0248 (one-sided) at the final analysis.

A hierarchical testing procedure was pre-specified to adjust for the multiple endpoints at the final analysis (Figure 2). The primary composite first event endpoint was first in the hierarchy. This was followed by the first and recurrent events analysis for HHF. The eGFR slope of change from baseline was the last key secondary endpoint in the hierarchy with an allocated alpha of 0.001. All available alpha at the end of this study, along with that from the EMPEROR-Reduced study was moved into a meta-analysis with a separate hierarchy of endpoints within the meta-analysis. The alpha allotment is shown in the applicant created figure 2 below.

Figure 2. Applicant created schematic of testing hierarchy



Multiple sensitivity analyses were specified by the applicant to assess underlying model assumptions along and missing data. Other models and methodology for the endpoints were also specified as supplementary analyses. Sensitivity analyses examining the impact of the COVID-19 pandemic were also run. Additionally, cumulative incidence function curves accounting for competing risks and Kaplan-Meier curves were also included as appropriate for these endpoints.

In addition to the usual subgroup analysis methods estimating contrasts with model interactions, we used shrinkage analyses to help resolve any random highs and lows in sample estimates of subgroup treatment effects due to small sample size and large variability. We used the same flat prior to derive shrinkage estimates for all subgroups. For $i = 1, 2\ldots$, Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 100)$, $1/\tau^2 \sim$ Half Cauchy(0, 25)

4.1.4. Protocol Amendments

There were three amendments to the original trial protocol. In addition, there were local amendments in Czech Republic, Japan, and UK. Relevant changes in the global amendments are summarized below.

1) Global Protocol Revision 1, dated 23 Nov 2017 (IEC/IRB approval required) (458 patients randomized, 7 confirmed primary endpoints accrued)
    a. The screening period was extended by 7 days.
    b. For laboratory analyses at screening, a hematology panel was added while urinalysis was removed.
    c. A national coordinator committee was set up to advise on the trial.
    d. Ketone monitoring strategy for patients with T1DM was added.
    e. Guidance to sites on the consent process for patients with T1DM was added.

2) Global Protocol Revision 2, dated 19 Jul 2018 (IEC/IRB approval not required) (2286 patients randomized, 80 confirmed primary endpoint events accrued)
    a. The changes involved logistical or administrative aspects only and did not require IEC/IRB approval (unless required by local regulations).

3) Global Protocol Revision 3, dated 20 Nov 2019 (IEC/IRB approval required in most countries) (5557 patients randomized, 502 confirmed primary endpoint events accrued)
    a. The use of any SGLT-2/1 inhibitors was allowed during the 30 day-period between the EOT and the follow-up visit occurring at study close-out.
    b. On recommendation of the ExSC, the Trial Statistical Analysis Plan (TSAP) was updated (prior to the interim database lock on 24 Jan 2020) so that the primary analysis would not include events after the planned end of treatment; events in the periods of unplanned treatment interruptions would be included (no change). Additional sensitivity analyses including all events after randomization were specified.
    c. In the random coefficient model used to estimate eGFR slope change from baseline, an additional fixed effect term “interaction of baseline eGFR (continuous) by time” was included.

On 12 Feb 2021, the final TSAP was amended to include additional analyses for assessing the impact of COVID-19 pandemic.

4.1.5. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

Baseline Characteristics

Baseline was defined as the last available measurement before the start of the trial medication, except for serum creatinine and related parameter of eGFR. Baseline for serum creatinine was the mean of all available measurements from screening until the start of randomized trial medication, to consider the variability of creatinine measurements.

Demographic and baseline characteristics appear to be balanced between the two study arms (Table 5). 55% of the patient population was male and a majority (76%) were white. Only 12% of the study population was from North America. Almost half of the study population was diabetic, which already has an approved indication for CV death which was primarily due to HF death reductions seen in the EMPA-REG trial. There were 10 patients (0.2%) with history of type 1 diabetes.

Table 5: Baseline Demographics

Characteristic	Category	Empagliflozin N=2997	Placebo N=2991
Age 65	<65	594 (19.8%)	605 (20.2%)
	at least 65	2403 (80.2%)	2386 (79.8%)
Sex	Male	1659 (55.4%)	1653 (55.3%)
	Female	1338 (44.6%)	1338 (44.7%)
Race	Missing	1 (0.0%)	1 (0.0%)
	Am. Indian or Alaska	90 (3.0%)	104 (3.5%)
	Asian	413 (13.8%)	411 (13.7%)
	Black	133 (4.4%)	125 (4.2%)
	White	2286 (76.3%)	2256 (75.4%)
	Other	74 (2.5%)	94 (3.1%)
Ethnicity	Missing	0 (0.0%)	1 (0.0%)
	Not Hispanic	2227 (74.3%)	2236 (74.8%)
	Hispanic	770 (25.7%)	754 (25.2%)
Region	N. America	360 (12.0%)	359 (12.0%)
	L. America	758 (25.3%)	757 (25.3%)
	W. Europe	390 (13.0%)	413 (13.8%)
	E. Europe	956 (31.9%)	930 (31.1%)
	Asia	343 (11.4%)	343 (11.5%)
	Other	190 (6.3%)	189 (6.3%)
LVEF	<50	995 (33.2%)	988 (33.0%)
	50 to <60	1028 (34.3%)	1030 (34.4%)
	at least 60	974 (32.5%)	973 (32.5%)
Baseline Diabetes	Diabetic	1466 (48.9%)	1472 (49.2%)
	Pre-Diabetes	1001 (33.4%)	979 (32.7%)
	Normal	530 (17.7%)	540 (18.1%)
NYHA	I	3 (0.1%)	1 (0.0%)

	II	2432 (81.1%)	2451 (81.9%)
	III	552 (18.4%)	531 (17.8%)
	IV	10 (0.3%)	8 (0.3%)
Cause of HF	Missing	1 (0.0%)	0 (0.0%)
	Ischemic	1079 (36.0%)	1038 (34.7%)
	Hypertensive	1066 (35.6%)	1120 (37.4%)
	Valvular Heart Disease	187 (6.2%)	168 (5.6%)
	Diabetic	67 (2.2%)	58 (1.9%)
	Alcoholism	6 (0.2%)	7 (0.2%)
	Idiopathic	289 (9.6%)	262 (8.8%)
	Cardiomyopathy	3 (0.1%)	5 (0.2%)
	Other	299 (10.0%)	333 (11.1%)
Age	N	2997	2991
	Mean (SD)	71.8 (9.3)	71.9 (9.6)
	Median (Min, Max)	73.0 (28.0, 100.0)	73.0 (22.0, 93.0)
Baseline LVEF	N	2997	2991
	Mean (SD)	54.3 (8.8)	54.3 (8.8)
	Median (Min, Max)	54.0 (40.0, 87.0)	54.0 (40.0, 88.0)
proBNP	N	2997	2989
	Mean (SD)	1443.2 (1785.7)	1479.2 (2115.2)
	Median (Min, Max)	994.0 (17.0, 31559)	946.0 (20.0, 48947)
BMI	N	2997	2991
	Mean (SD)	29.8 (5.8)	29.9 (5.9)
	Median (Min, Max)	29.2 (15.9, 47.3)	29.4 (15.5, 50.2)
SBP	N	2997	2991
	Mean (SD)	131.8 (15.6)	131.9 (15.7)
	Median (Min, Max)	132.0 (90.0, 194.0)	132.0 (86.0, 180.0)
DBP	N	2997	2991
	Mean (SD)	75.7 (10.6)	75.7 (10.5)
	Median (Min, Max)	76.0 (39.0, 115.0)	76.0 (43.0, 118.0)
eGFR	N	2997	2989
	Mean (SD)	60.6 (19.8)	60.6 (19.9)
	Median (Min, Max)	59.5 (18.0, 131.0)	60.0 (17.5, 145.5)

Source: adbasco SAS dataset
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic

HF related medical history was balanced across the treatment groups. Overall, most patients were in NYHA Class II (82%), 35% had ischemic HF, 37% had hypertensive HF, 77% of the patients met the inclusion criteria of evidence of structural heart disease only, 6% had HHF within 12 months of screening, and 16% had both structural heart disease and HHF within 12 months of screening. Table 18 in Section 10 under Appendices summarizes heart failure-related medical history in the randomized set.

Concomitant Medications

Concomitant use of drugs in HF, other anti-hypertensives, lipid-lowering drugs, or anti-thrombotic drugs at baseline and during the planned treatment period were balanced across the treatment groups. Overall, at baseline, a total of 79% patients were on ACEIs/ARBs, 86% were on beta-blockers, and 86% were on diuretics, including 38% on MRAs and 68% on loop or high ceiling diuretics. Table 19 in Section 10 under Appendices summarizes concomitant medications at baseline in the randomized set. Intensification of diuretic therapy after baseline was less frequent in Jardiance group vs placebo (16.1 vs 20.4% of patients), while decrease of diuretic therapy was more frequent in Jardiance group vs placebo (14.1 vs 12.0%).

Patient Disposition

We used a combination of last follow-up dates along with recorded completion status in the submitted datasets to create the patient disposition tables. Based on this criteria, slightly more patients were considered completers than what was in the applicant's report. The differences here are minimal and do not affect results for the primary or key secondary endpoints. The time observed in the study for each subject is defined as one plus the difference between randomization and last follow-up date.

Of the 11583 patients screened, 5988 patients (48%) were randomized. The most common reason for screen failure (37.6% of screened patients) was NT-proBNP levels being below the protocol-specified thresholds at screening. Approximately 67% of the randomized patients had an LVEF ≥ 50%. Of the 5988 randomized patients, 5816 patients (97.1%) had complete follow-up for the primary endpoint and the final vital status was known for 5952 patients (99.4%).

Of the 5985 patients treated with study medication, 1888 patients prematurely discontinued treatment (31.5%, including patients who died). The incidence of premature discontinuation of study medication was balanced between empagliflozin and placebo groups. The most common reason for premature discontinuation of study medication was an AE (10.6% of patients with non-fatal events and 8.2% with fatal events). The next most common reason was refusal to continue study medication, which was balanced across the placebo (10.2%) and empagliflozin (9.5%) groups. During this trial, the medication code was not broken at the investigational sites for any patients. Table 6 presents patients disposition in EMPEROR-Preserved trial.

Table 6: Patient Disposition

		Empagliflozin	Placebo	Total
Screened		.	.	11583
Randomized		2997	2991	5988
Completed		2940	2929	5869
	Censored	2354 (80.1%)	2270 (77.5%)	4624
	HHF	253 (8.6%)	340 (11.6%)	593
	All Cause Death	333 (11.3%)	319 (10.9%)	652
	CV Death Event	153 (46%)	156 (48.9%)	309
Discontinued		57	62	119
	Consent Withdrawn	33 (57.9%)	37 (59.7%)	70
	Lost to follow-up	21 (36.8%)	19 (30.7%)	40
	Missing	3 (5.3%)	6 (9.7%)	9
Median (Q1, Q3) time observed/subject		749 (516, 974)	734 (496, 969)	741 (504, 973)
	Completers	759.5 (526, 979.5)	739 (500, 973)	749 (512, 975)
	Discontinued	337 (118, 541)	231.5 (71, 671)	302 (85, 615)
Total Amount of observed time (days)		2,208,141	2,151,797	4,359,938

Source: adsl, adtte SAS datasets

Efficacy Analysis

Median observation time up to the end of the planned treatment period was about 26 months in both treatment groups, with 94% of patients observed for at least 1 year. Most patients were compliant with treatment (93.0% within the overall compliance window of 80 to 120%). Exposure to study treatment was balanced between arms (Table 7).

Table 7: Exposure to Study Treatment

	Empagliflozin N=2997	Placebo N-2991
<12 weeks	4.8%	5.4%
12 to 26 weeks	4.3%	4.4%
26 to 52 weeks	6.7%	6.3%
52 to 78 weeks	20.5%	19.4%
78 to 104 weeks	17.8%	18.1%
104 to 156 weeks	35.9%	36.1%
≥156 weeks	10.1%	10.3%

Source: adsl SAS dataset

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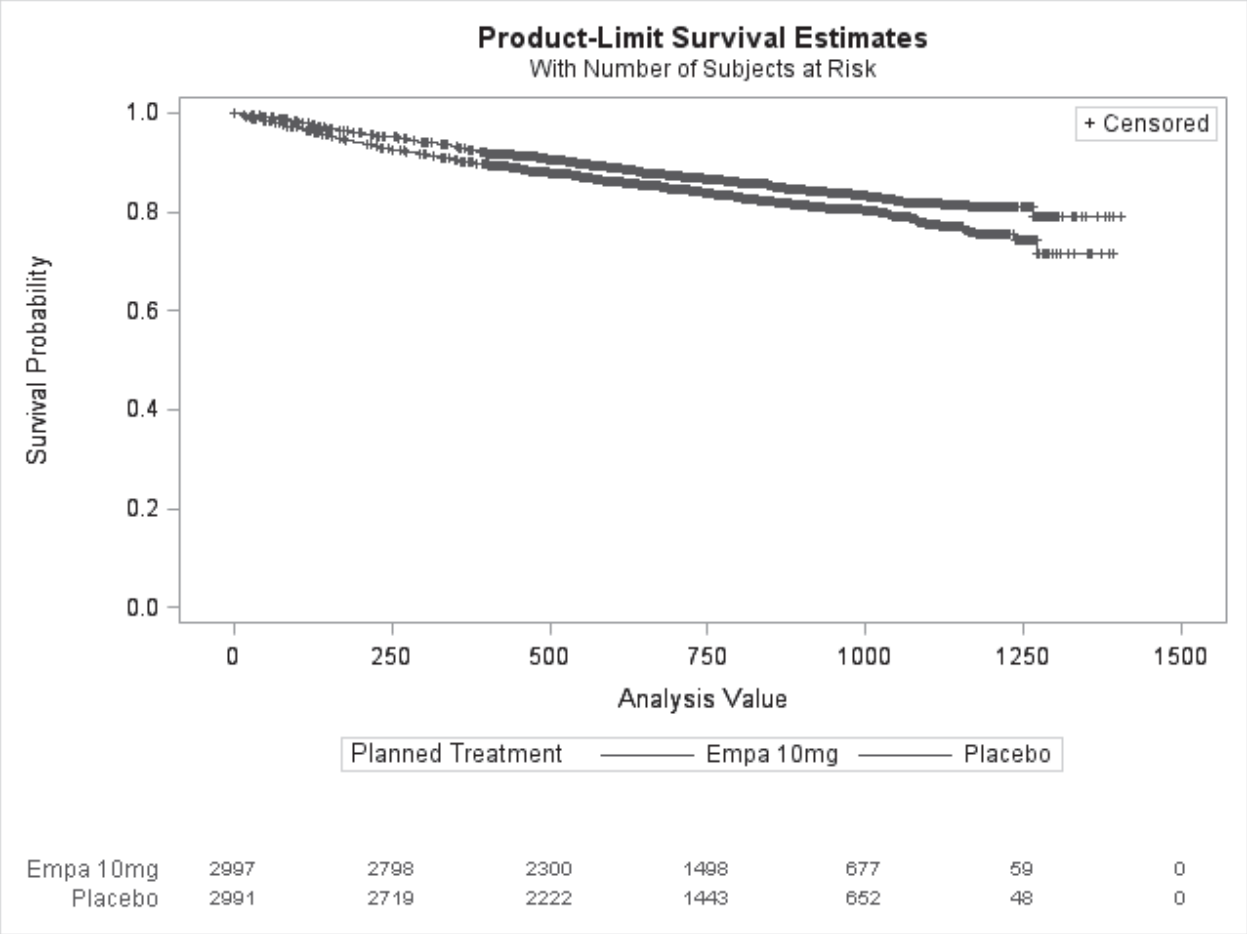
The trial protocol pre-specified approximately 841 adjudicated primary endpoint events of CV death or HHF. After 494 events, an interim analysis (IA) was performed by the independent DMC and DMC recommended the trial to continue as planned. An alpha adjustment for the IA was quite small with differences in confidence intervals (95% vs. 95.03%) being negligible. Results for the primary first event composite endpoint of HHF or CV death are shown below in

Table 8. A hazard ratio of 0.8 (0.7, 0.9) indicated a statistically significant reduction in the time until the first primary composite for those on empagliflozin when compared to placebo. This was driven largely by a reduction in HHF. The treatment effect of Jardiance on CV death was minimal but in favor of Jardiance with 25 fewer CV deaths in Jardiance versus placebo arm.

Table 8: First Events Results

Endpoint	Empagliflozin N=2997	Placebo N=2991	HR (95% CI)	p
First HHF or CV Death	415 (13.9%)	511 (17.1%)	0.79 (0.69, 0.89)	0.0003
CV Death	219 (7.3%)	244 (8.2%)	0.9 (0.75, 1.08)	
HHF	259 (8.6%)	352 (11.8%)	0.71 (0.6, 0.83)	

Figure 3: Kaplan-Meier Curves for Primary Composite Endpoint



There were a total of 407 first and recurrent HHF events in the empagliflozin arm, and 541 in the placebo arm. Results for this endpoint did not converge using Andersen-Gill model estimates as starting values with the full joint frailty model. The simplified unadjusted model did converge with an estimated treatment effect of 0.74 (0.62, 0.9). This is in line with the adjusted model

results the applicant had of 0.73 (0.61, 0.88). The applicant's code, along with the methodology they used to get reasonable starting values was executable and appeared valid. It is of note that nominal estimated treatment effect on the time until the first HHF (Table 8) was slightly stronger with tighter confidence intervals [point estimates: 0.71 (95% CI range of 0.21) vs. 0.73 (95% CI range of 0.27)].

The number of patients with a HHF or CV death during the 30 days after treatment discontinuation was similar in each treatment arm (empagliflozin: 147 patients, 5.1%; placebo: 153 patients, 5.3%).

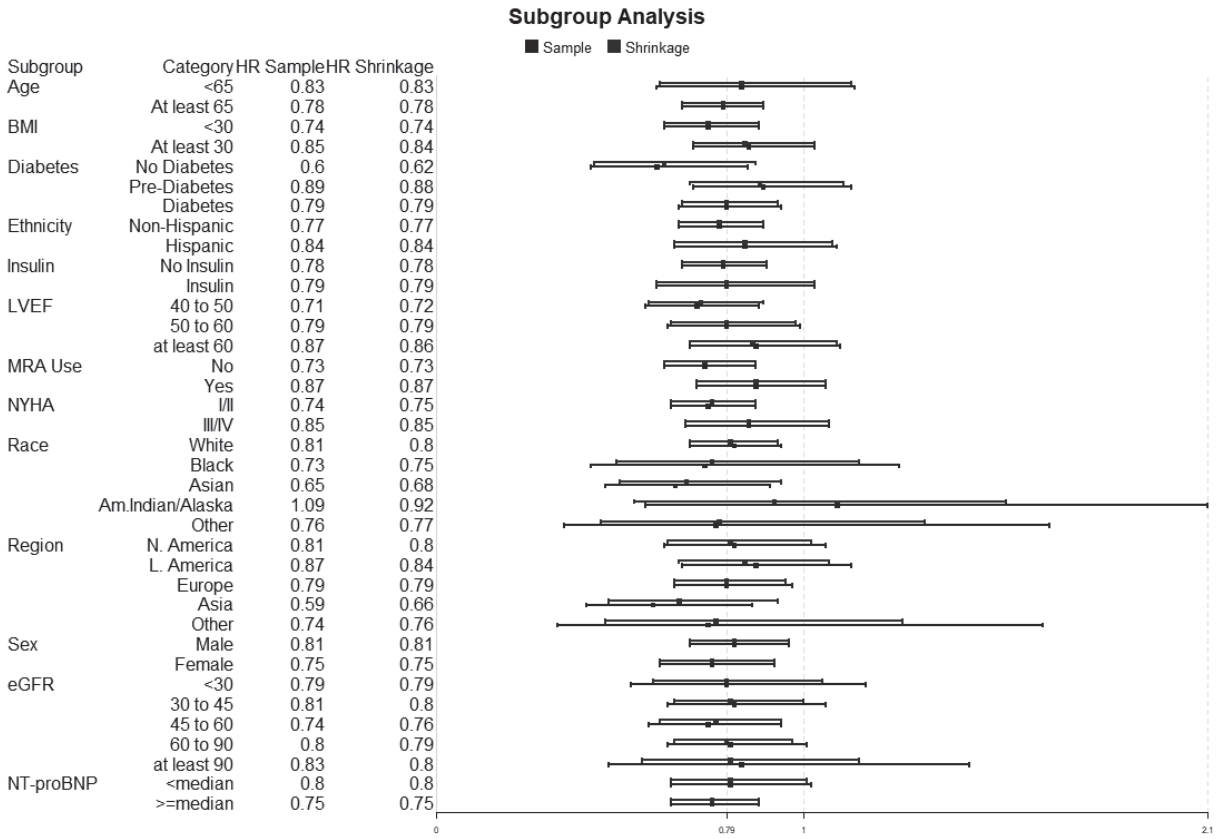
Several sensitivity analyses for the primary endpoint, including analyses done to explore impact of COVID-19 outbreak, demonstrated generally consistent results.

Results for the change in eGFR slope used days as the unit of time in the model. The estimated difference between slopes for the treatment arms was 0.0037 (99.9% CI: 0.0024, 0.0051). Multiplying these results by 365 to change the units to be yearly resulted in a change of 1.36 (99.9% CI: 0.86, 1.86). Results based on a yearly time unit are comparable to what was seen in the applicant's study report.

All alpha was available from both this and the HFrEF study. However, the meta-analysis failed in the first primary endpoint of first renal event. No evaluations of any of the meta-analyses endpoints were run for this review.

Subgroup analyses for the primary composite endpoint were in line with the overall findings. While some subgroups could be viewed as having little to no treatment effect, these results should be interpreted cautiously, recognizing that smaller subgroups are more sensitive to outliers.

Figure 4. Subgroup Analyses



Source: adtte and adbasco SAS datasets

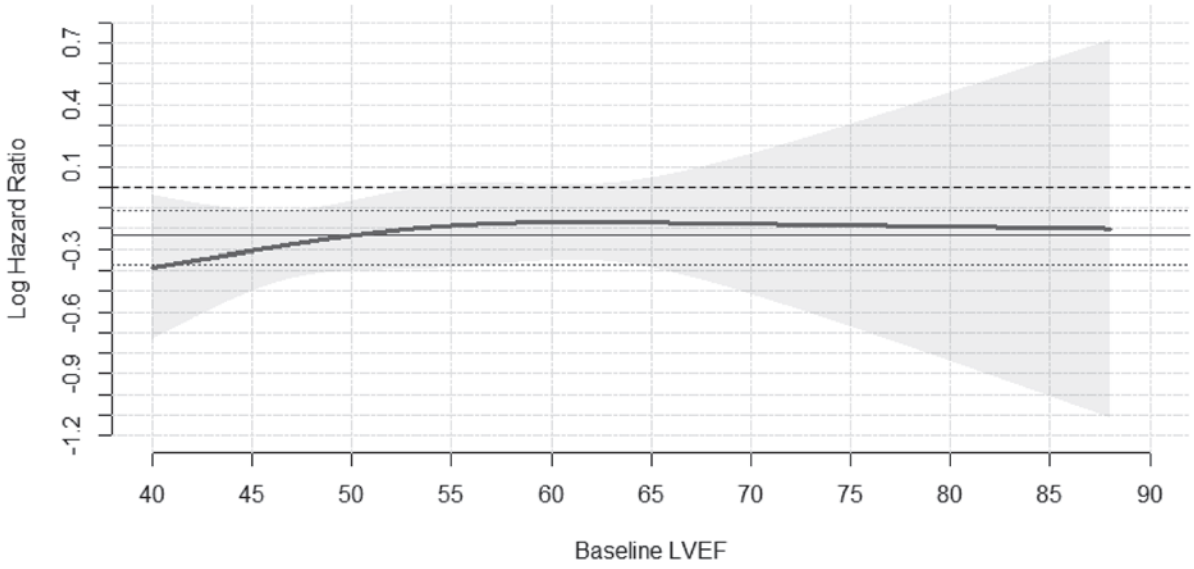
4.1.6. Review Issues Relevant to the Evaluation of Benefit

The main review issue was - subgroup analyses for the primary composite endpoint displayed in Figure 4 suggested diminishing treatment effect in patients with LVEF ≥ 60%.

We analyzed the hazard ratio for primary composite endpoint across the spectrum of LVEF as a continuous variable (Figure 5) using a cubic spline model. This analysis demonstrated that while the treatment effect appeared to be slightly lower in higher LVEF subgroups, the point estimate remained in favor of Jardiance. Reference lines are drawn where there is a null effect, and at the point estimates for the prespecified analysis treatment effect and confidence interval. While estimates for the treatment effect in higher LVEF patients, based on the cubic spline model, appear to be slightly higher than the overall estimate, it remains within a reasonable range of the overall estimated effect.

A potential reason for this finding may be lower event rate for HHF in patients with higher LVEF (Table 9), perhaps representing a healthier HF population, rather than a lack of efficacy of Jardiance in this subpopulation.

Figure 5. Hazard Ratio for time to first event of adjudicated HHF or CV death by LVEF



HHF: hospitalization for heart failure, CV: cardiovascular, LVEF: left ventricular ejection fraction

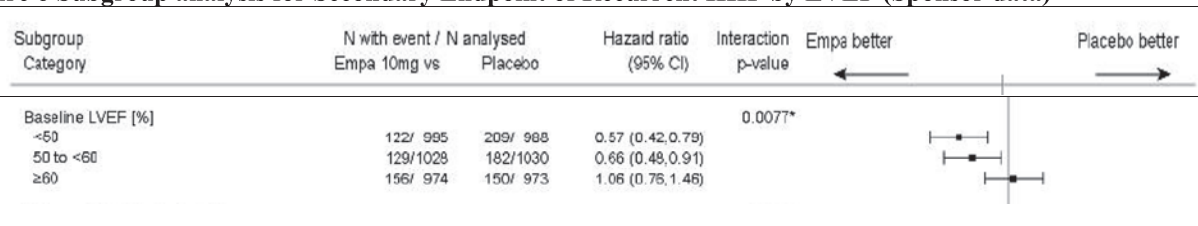
Table 9. Number of first HHF or CV Death events in LVEF categories

LVEF	Empagliflozin	Placebo
<50	145	193
50-60	138	173
≥60	132	145

LVEF: left ventricular ejection fraction

Similar to primary endpoint, subgroup analysis for the key secondary endpoint of occurrence of adjudicated HHF (first and recurrent) suggested a diminishing treatment effect in higher LVEF subgroups (Figure 6). In patients with LVEF ≥ 60%, there were 13 less first events but 6 more recurrent HHF events in Jardiance arm. While there is a noticeably smaller treatment effect in the higher LVEF population, this group also had the fewest number of events making interpretation about the point estimate difficult for those with LVEF ≥ 60%.

Figure 6 Subgroup analysis for Secondary Endpoint of Recurrent HHF by LVEF (Sponsor data)



HHF: hospitalization for heart failure, LVEF: left ventricular ejection fraction

The review team concludes that Jardiance is efficacious in reducing HHF and CV death in patients with heart failure with LVEF > 40% across the entire LVEF spectrum evaluated in EMPEROR-Preserved trial.

5. Risk and Risk Management

5.1. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Empagliflozin has been approved for adults with type 2 diabetes mellitus (T2DM) and adults with heart failure and reserved ejection fraction (HFrEF). Known risks of empagliflozin from the approved label include ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, hypersensitivity reactions, thirst, increased urination, and urinary tract infections.

5.2. FDA Approach to the Safety Review

There are no concerns regarding submission quality, conduct of the studies with respect to assessment of safety, or the Applicant's characterization of adverse events. Data issues identified had low impact due to the low number of records affected (<1%).

The safety review was based on the data collected in the phase 3 study 1245.110 (EMPEROR-Preserved). Furthermore, the Applicant submitted a meta-analysis of lower-limb amputation (LLA), which consisted of three randomized, placebo-controlled, double-blinded, parallel-grouped, and event-driven studies (1245.25, 1245.110, and 1245.121). The safety reviewer did not perform an independent analysis of the LLA meta-analysis.

The safety review focused on the safety population in study EMPEROR-Preserved and the results were presented for that population unless specified otherwise. Adverse events were presented as Risk Difference (RD) which was calculated as the difference in the percentage of subjects with adverse events between empagliflozin 10 mg and placebo groups: negative RD values favor empagliflozin and positive RD favor placebo.

Evaluation of safety signals consisted of using FDA Medical Query (FMQ), Standard MedDRA Query (SMQ, version 23.1), and Boehringer Ingelheim customized MedDRA Query (BIcMQ). BIcMQs were provided in Listing 6 of "Adverse Events Listings" (link). The safety reviewer has checked the preferred terms of BIcMQs associated with adverse events of special interest (AESIs) that do not have corresponding FMQs or SMQs and in general agree with the Sponsor. Subgroup analyses of baseline diabetes status, hypertension medical history, and sex were performed for AESIs.

5.3. Adequacy of the Clinical Safety Database

The mean and median exposure duration was 23 weeks in EMPEROR-Preserved. It was balanced between the empagliflozin and the placebo group (Table 10). The safety database is

considered adequate. Over 2500 subjects had exposure to empagliflozin longer than 12 months and over 1000 subjects had exposure longer than 24 months.

The LLA meta-analysis study included over 16,000 patients and the median exposure was 2.6 years.

Table 10. Duration of Exposure, Safety Population, EMPEROR-Preserved

Exposure	Empa 10mg N=2996 n(%)	Placebo N=2989 n(%)	Absolute Risk Difference (95.0% CI)[1]
Duration of treatment, months			
Mean (SD)	22.7 (10.7)	22.7 (10.8)	
Median (min, max)	23.3 (0.0, 46.8)	23.3 (0.0, 46.1)	
Patients treated, by duration, n(%)			
>= 12 weeks	2854 (95.3%)	2830 (94.7%)	0.6 (-0.5, 1.7)
>= 26 weeks	2726 (91.0%)	2699 (90.3%)	0.7 (-0.8, 2.2)
>= 52 weeks	2524 (84.2%)	2511 (84.0%)	0.2 (-1.6, 2.1)
>= 78 weeks	1911 (63.8%)	1930 (64.6%)	-0.8 (-3.2, 1.6)
>= 104 weeks	1379 (46.0%)	1389 (46.5%)	-0.4 (-3.0, 2.1)
>= 156 weeks	303 (10.1%)	308 (10.3%)	-0.2 (-1.7, 1.3)

Source: adsl, adexpo; **Software:** R
Abbreviations: N, number of patients in treatment arm; n, Number of patients with an event; CI, Confidence Interval
[1]Difference is shown between Empa 10mg and Placebo

5.4. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The safety profile of empagliflozin in the EMPEROR-Preserved study was similar to the known safety profile of empagliflozin. There were no unexpected safety findings.

5.4.1. Overall Adverse Event Summary

The overall treatment emergent adverse events (TEAEs) were balanced between empagliflozin and placebo (Table 11).

Broad FMQs with RD larger than 1% were hypotension (2%) and syncope (1%, driven by hypotension), which were expected AEs based on the mechanism of action. Broad SMQs showed similar results.

Table 11. Overview of Treatment Emergent Adverse Events, Safety Population, EMPEROR-Preserved.

Event	Empa 10mg N=2996 n(%)	Placebo N=2989 n(%)	Absolute Risk Difference (95.0% CI)[2]
Any AE	2574 (85.9%)	2585 (86.5%)	-0.6 (-2.3, 1.2)
Severe	786 (26.2%)	851 (28.5%)	-2.2 (-4.5, 0.0)
Moderate	1608 (53.7%)	1661 (55.6%)	-1.9 (-4.4, 0.6)

Event	Empa 10mg N=2996 n(%)	Placebo N=2989 n(%)	Absolute Risk Difference (95.0% CI)[2]
Mild	2133 (71.2%)	2140 (71.6%)	-0.4 (-2.7, 1.9)
SAE	1436 (47.9%)	1543 (51.6%)	-3.7 (-6.2, -1.2)
Death	287 (9.6%)	297 (9.9%)	-0.4 (-1.9, 1.1)
Life-threatening	127 (4.2%)	114 (3.8%)	0.4 (-0.6, 1.4)
Persistent or significant disability/incapacity	53 (1.8%)	43 (1.4%)	0.3 (-0.3, 1.0)
Requires or prolongs hospitalization	1106 (36.9%)	1182 (39.5%)	-2.6 (-5.1, -0.2)
Congenital anomaly or birth defect	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)
Other	645 (21.5%)	739 (24.7%)	-3.2 (-5.3, -1.1)
AE leading to permanent discontinuation	571 (19.1%)	551 (18.4%)	0.6 (-1.4, 2.6)
AE leading to interruption of study drug	396 (13.2%)	379 (12.7%)	0.5 (-1.2, 2.2)

Source: adsl, adae; **Software:** R
Abbreviations: N, number of patients in treatment arm; n, Number of patients with an event; CI, Confidence Interval; SAE, Serious Adverse Event
[1]Treatment-Emergent AEs defined as occurring after treatment start day and before the treatment end day
[2]Difference is shown between Empa 10mg and Placebo

5.4.2. Deaths

Death was balanced between empagliflozin and placebo in the randomized population (Table 12). In both groups, common cardiovascular deaths were sudden cardiac death and heart failure, and common non-cardiovascular deaths were infections and malignancy.

Table 12. Deaths in Randomized Population, EMPEROR-Preserved.

Event	Empa 10mg N=2997 n(%)	Placebo N=2991 n(%)	Absolute Risk Difference (95.0% CI)[2]
Cause of death	437 (14.6%)	445 (14.9%)	-0.3 (-2.1, 1.5)
Cardiovascular	190 (6.3%)	223 (7.5%)	-1.1 (-2.4, 0.2)
Non-Cardiovascular	213 (7.1%)	191 (6.4%)	0.7 (-0.5, 2.0)
Undetermined	34 (1.1%)	31 (1.0%)	0.1 (-0.4, 0.6)
Cardiovascular death	190 (6.3%)	223 (7.5%)	-1.1 (-2.4, 0.2)
Sudden Cardiac Death	103 (3.4%)	118 (3.9%)	-0.5 (-1.5, 0.4)
Heart Failure	40 (1.3%)	54 (1.8%)	-0.5 (-1.1, 0.2)
Stroke	19 (0.6%)	21 (0.7%)	-0.1 (-0.5, 0.3)
Other Cardiovascular causes	16 (0.5%)	22 (0.7%)	-0.2 (-0.6, 0.2)
Acute Myocardial Infarction	5 (0.2%)	5 (0.2%)	-0.0 (-0.2, 0.2)
Cardiovascular Procedures	7 (0.2%)	2 (0.1%)	0.2 (-0.0, 0.4)
Cardiovascular Hemorrhage	0 (0.0%)	1 (0.0%)	-0.0 (-0.1, 0.0)
Non-Cardiovascular death	213 (7.1%)	191 (6.4%)	0.7 (-0.5, 2.0)
Infection (includes sepsis)	98 (3.3%)	84 (2.8%)	0.5 (-0.4, 1.3)
Malignancy	40 (1.3%)	34 (1.1%)	0.2 (-0.4, 0.8)
Other Non-Cardiovascular causes	27 (0.9%)	41 (1.4%)	-0.5 (-1.0, 0.1)
Trauma	13 (0.4%)	2 (0.1%)	0.4 (0.1, 0.6)
Gastrointestinal causes	12 (0.4%)	4 (0.1%)	0.3 (0.0, 0.5)
Renal causes	4 (0.1%)	10 (0.3%)	-0.2 (-0.4, 0.0)

Event	Empa 10mg N=2997 n(%)	Placebo N=2991 n(%)	Absolute Risk Difference (95.0% CI)[2]
Pulmonary causes	6 (0.2%)	5 (0.2%)	0.0 (-0.2, 0.2)
Hemorrhage	3 (0.1%)	3 (0.1%)	-0.0 (-0.2, 0.2)
Hepatobiliary causes	2 (0.1%)	3 (0.1%)	-0.0 (-0.2, 0.1)
Non-CV procedure or surgery	3 (0.1%)	1 (0.0%)	0.1 (-0.1, 0.2)
Neurological (non-cardiovascular)	4 (0.1%)	0 (0.0%)	0.1 (0.0, 0.3)
Suicide	1 (0.0%)	3 (0.1%)	-0.1 (-0.2, 0.1)
Pancreatic causes	0 (0.0%)	1 (0.0%)	-0.0 (-0.1, 0.0)

Source: adsl, adadj; **Software:** R
Abbreviations: N, number of patients in treatment arm; n, Number of patients with an event; CI, Confidence Interval; SAE, Serious Adverse Event
[1]Randomized population
[2]Difference is shown between Empa 10mg and Placebo

5.4.3. Serious Adverse Events

Overall, more subjects in placebo (52%) had SAEs compared to empagliflozin (48%). However, none of the preferred terms (PTs) for SAEs had RD larger than 1% (Table 13). An evaluation of FMQs and SMQs showed similar results; indicating there were no imbalances in SAEs.

Table 13. Serious Adverse Events with Risk Difference > 0.2%, Safety Population, EMPEROR-Preserved.

Primary System Organ Class Preferred Term[3]	Empa 10mg N=2996 n(%)	Placebo N=2989 n(%)	Absolute Risk Difference (95.0% CI)[4]
Nervous system disorders	197 (6.6%)	184 (6.2%)	0.4 (-0.8, 1.7)
Ischemic stroke	42 (1.4%)	35 (1.2%)	0.2 (-0.3, 0.8)
General disorders and administration site conditions	116 (3.9%)	104 (3.5%)	0.4 (-0.6, 1.3)
Death	56 (1.9%)	38 (1.3%)	0.6 (-0.0, 1.2)
Reproductive system and breast disorders	15 (0.5%)	7 (0.2%)	0.3 (-0.0, 0.6)
Benign prostatic hyperplasia	8 (0.3%)	2 (0.1%)	0.2 (-0.0, 0.4)
Vascular disorders	130 (4.3%)	154 (5.2%)	-0.8 (-1.9, 0.3)
Hypotension	26 (0.9%)	19 (0.6%)	0.2 (-0.2, 0.7)
Infections and infestations	327 (10.9%)	355 (11.9%)	-1.0 (-2.6, 0.6)
Cellulitis	22 (0.7%)	8 (0.3%)	0.5 (0.1, 0.8)
COVID-19 pneumonia	25 (0.8%)	17 (0.6%)	0.3 (-0.2, 0.7)
Urinary tract infection	36 (1.2%)	28 (0.9%)	0.3 (-0.3, 0.8)
Respiratory, thoracic, and mediastinal disorders	113 (3.8%)	151 (5.1%)	-1.3 (-2.3, -0.2)
Dyspnea	9 (0.3%)	3 (0.1%)	0.2 (-0.0, 0.4)
Cardiac disorders	740 (24.7%)	882 (29.5%)	-4.8 (-7.1, -2.6)
Atrial fibrillation	92 (3.1%)	80 (2.7%)	0.4 (-0.5, 1.2)
Myocardial infarction	37 (1.2%)	27 (0.9%)	0.3 (-0.2, 0.9)
Sinus bradycardia	7 (0.2%)	1 (0.0%)	0.2 (0.0, 0.4)
Acute coronary syndrome	8 (0.3%)	2 (0.1%)	0.2 (-0.0, 0.4)

Source: adsl, adae; **Software:** R
Abbreviations: N, number of patients in treatment arm; n, Number of patients with an event; CI, Confidence Interval

Primary System Organ Class Preferred Term[3]	Empa 10mg N=2996 n(%)	Placebo N=2989 n(%)	Absolute Risk Difference (95.0% CI)[4]

[1]Risk Difference > 0.2%

[2]Treatment-Emergent AEs defined as occurring after treatment start day and before the treatment end day

[3]MedDRA version: 23.1

[4]Difference is shown between Empa 10mg and Placebo

5.4.4. Discontinuations Due to Adverse Events

Numerically more subjects had AEs leading to permanent discontinuation of study drug in empagliflozin (19%) than placebo (18%), but the difference was small. Preferred terms for AEs leading to discontinuation with risk difference larger than 0.2% between empagliflozin and placebo were death (0.7%), urinary tract infection (0.3%), and COVID-19 pneumonia (0.2%)

5.4.5. Adverse Events of Special Interest (AESI)

Adverse events of special interest for empagliflozin included hepatic injury, decreased renal function, ketoacidosis, lower limb amputation (LLA), hypoglycemic events, genital infection, urinary tract infection (UTI), increased urination, bone fracture, hypotension, volume depletion, hypersensitivity, and thirst. There were no concerning imbalances between empagliflozin and placebo in AESIs. Table 14 shows the AESIs with RD larger than 1%.

Table 14. Adverse Events of Special Interest with Risk Difference > 1% in Empagliflozin Arm than Placebo, Safety Population, EMPEROR-Preserved

AESI	QUERIES	MEAN AE RISK DIFFERENCE (95% CI)	MEAN SAE RISK DIFFERENCE (95% CI)
UTI	BIcMQ	1.8 (0.3, 3.2)	0.3 (-0.3, 0.9)
Genital infection	BIcMQ	1.5 (0.9, 2.1)	-0.1 (-0.3, 0.1)
Hypotension	FMQ	1.5 (0.1, 2.8)	0.3 (-0.1, 0.8)
Volume depletion (including hypotension)	BIcMQ	2.3 (0.7, 3.9)	0.4 (-0.4, 1.1)

Source: adsl, adae **; Software:** R
Abbreviations: FMQ, FDA Medical Query; BIcMQ, Boehringer Ingelheim customized MedDRA Query; CI, Confidence Interval; AE, Adverse Event; SAE, Serious Adverse Event; AESI, Adverse Events of Special Interest.

5.4.5.1. Urinary Tract Infection (UTI)

More subjects had UTI-related AEs (BIcMQ) following empagliflozin compared to placebo (Table 14). The most common PTs (empagliflozin vs. placebo) were urinary tract infection (7.9% vs 6.1%) and cystitis (1.2% vs 1.7%). Most AEs were mild to moderate in severity. Severe AEs occurred in 22 (0.7%) subjects following empagliflozin and 18 (0.6%) subjects following placebo. Numerically more subjects had UTI-related SAEs in empagliflozin than placebo, but the difference was not significant (Table 14).

Subgroup analysis showed more females had UTI-related AEs. In females, UTI-related AEs occurred in 15% subjects taking empagliflozin and 12% taking placebo. In males, UTI-related AEs occurred in 6.0% subjects taking empagliflozin and 4.8% taking placebo.

Numerically subjects taking empagliflozin had more pyelonephritis and urosepsis (0.8%) than those taking placebo (0.6%), but the differences were not significant. Most of these events were SAEs (0.7% vs. 0.6% for empagliflozin vs. placebo).

5.4.5.2. Genital Infection

More subjects had genital infection-related AEs (BIcMQ) following empagliflozin compared to placebo. Preferred terms with the highest risk difference between empagliflozin and placebo were fungal balanitis (0.3% vs. 0.0%) and vulvovaginal mycotic infection (0.4% vs. 0.1%). Most AEs were mild to moderate in severity. Severe AEs occurred in 4 (0.1%) subjects taking empagliflozin and 2 (0.1%) subjects taking placebo. Numerically more subjects had genital infection-related SAEs in placebo, but the difference was not significant (Table 14).

Subgroup analysis showed numerically more females had genital infection-related AEs. In females, genital infection-related AEs occurred in 2.6% subjects taking empagliflozin and 1.0% subjects taking placebo. In males, these AEs occurred in 1.9% subjects taking empagliflozin and 0.5% subjects taking placebo.

5.4.5.3. Hypotension

More subjects had hypotension-related AEs (FMQ) following empagliflozin compared to placebo (Table 14). Preferred terms with risk difference larger than 0% between empagliflozin and placebo were hypotension (7.7% vs. 6.3%) and blood pressure decreased (0.1% vs. 0.0%). Most AEs were mild to moderate in severity. Severe AEs occurred in 22 (0.7%) subjects following empagliflozin and 10 (0.3%) subjects following placebo. Numerically more subjects had hypotension-related SAEs in empagliflozin than placebo, but the difference was not significant (Table 14).

Subgroup analysis showed subjects taking empagliflozin without a history of hypertension had a higher risk difference (RD = 2.8%) of hypotension-related AEs compared to subjects with a history of hypertension (RD = 1.3%). Results from BIcMQ were similar to FMQ.

5.4.5.4. Volume Depletion

More subjects had volume depletion-related AEs (BIcMQ) following empagliflozin (12%) compared to placebo (10%). Most of the volume depletion events were driven by the PT hypotension (7.7% and 6.3% for empagliflozin and placebo, respectively).

5.4.5.5. Lower-Limb Amputation

In EMPEROR-Preserved study, numerically more subjects taking placebo (0.8%) had LLA events (defined by investigators) compared to empagliflozin (0.5%). The difference was not significant.

The meta-analysis of LLA consisted of three randomized, placebo-controlled, double-blinded, parallel-group, and event-driven studies (1245.25, 1245.110, and 1245.121).

- Study 1245.25 was conducted in patients with T2DM and increased cardiovascular risk. In total, 7020 patients were treated with empagliflozin 10 mg (2345), empagliflozin 25mg (2342), and placebo (2333), orally once daily. LLA-related events were not pre-specified in the protocol or specifically captured on eCRF pages. They were identified through a post-hoc search in SAE narratives, events reported as AEs, events reported as a 'medical procedure' under 'concomitant therapy', and investigator comments describing AEs.
- Study 1245.110 and 1245.121 were conducted in patients with chronic heart failure with preserved ejection fraction (1245.110) and reduced ejection fraction (1245.121). In study 1245.110, 5985 patients were treated with empagliflozin 10 mg (2996) and placebo (2989), orally once daily. In study 1245.121, 3726 patients were treated with empagliflozin 10 mg (1863) and placebo (1863), orally once daily. LLA-related events were specified as AESI in these two studies.

LLA events included any AE leading to a lower-limb procedure of amputation, auto-amputation, or disarticulation:

- Amputation was defined as a resection of a limb through a bone.
- Auto-amputation was a spontaneous separation of non-viable portion of the lower limb.
- Disarticulation was a resection of a limb through a joint.

LLA events were analyzed in two populations: M1, which included all three studies (1245.25, 1245.110, and 1245.121), and M2, which included the two heart failure studies (1245.110 and 1245.121). Table 15 and Table 16 summarize LLA events in the population of M1 and M2, respectively.

In the M1 population, the pooled empagliflozin group (including 10 mg and 25 mg) had numerically higher LLA incidence rate compared to placebo (Table 15), but the difference was not significant. The mean hazard ratio (95% CI) was 1.02 (0.73, 1.42). Subjects with diabetes had more LLA events compared to subjects without diabetes. In this population, discontinuation of medication, discontinuation due to AE, mean exposure, and baseline diabetes status were similar between empagliflozin 10 mg and placebo groups, while the empagliflozin 25 mg group had lower discontinuation, higher exposure, and more diabetic subjects (Table 15). This is most likely because all subjects receiving empagliflozin 25 mg came from study 1245.25.

In the M2 population, the placebo group had a numerically higher LLA incidence rate than empagliflozin (Table 16), but the difference was not significant. The mean hazard ratio (95% CI) was 0.85 (0.45, 1.60). Subjects with diabetes had more LLA events than subjects without diabetes. In this population, discontinuation of medication, discontinuation due to AE, mean exposure, and baseline diabetes status were balanced between empagliflozin 10 mg and placebo.

In summary, there were no significant differences in LLA incidence rates between empagliflozin and placebo. The data suggests that LLA events were more likely related to subjects having diabetes than related to empagliflozin treatment.

Table 15: Summary of Lower-limb Amputation Meta-analysis in M1 Population (Studies 1245.25, 1245.110, and 1245.121).

	EMPA 10 MG	EMPA 25 MG	ALL EMPA	PLACEBO
Treated patients	7204 (100%)	2342 (100%)	9546 (100%)	7185 (100%)
Discontinued medication	1982 (27.5%)	542 (23.1%)	2524 (26.4%)	2137 (29.7%)
Due to AE	1179 (16.4%)	273 (11.7%)	1452 (15.2%)	1199 (16.7%)
Mean exposure (SD) months	23.33 (12.29)	31.23 (12.72)	25.27 (12.85)	22.94 (12.22)
Baseline diabetes status: Yes	4737 (65.8%)	2342 (100%)	7079 (74.2%)	4730 (65.9%)
LLA Incidence rate (per 100 patient-years)			0.48 (0.39, 0.58)	0.40 (0.30, 0.52)
Diabetic (N with event/N analyzed)			94/7079 (1.3%)	53/4730 (1.1%)
Non-diabetic (N with event/N analyzed)			1/2467 (0.04%)	2/2455 (0.08%)

Table 16: Summary of Lower-limb Amputation Meta-analysis in M2 Population (Studies 1245.110 and 1245.121).

	EMPA 10 MG	PLACEBO
Treated patients	4859 (100%)	4852 (100%)
Discontinued medication	1427 (29.4%)	1454 (30.0%)
Due to AE	912 (18.8%)	896 (18.5%)
Mean exposure (SD) months	19.63 (10.36)	19.55 (10.46)
Baseline diabetes status: Yes	2392 (49.2%)	2397 (49.4%)
Incidence rate (per 100 pt-yrs)	0.23 (0.13, 0.34)	0.27 (0.17, 0.39)
Diabetic (N with event/N analyzed)	17/2392 (0.71%)	19/2397 (0.79%)
Non-diabetic (N with event/N analyzed)	1/2467 (0.04%)	2/2455 (0.08%)

5.4.6. Laboratory and Vital Sign Findings

Laboratory- and vital sign-related AESIs were reviewed, which included liver enzymes (ALT, AST, and Bilirubin), renal function tests (serum creatinine and eGFR), lipid panels (HDL-cholesterol, LDL-cholesterol, and triglycerides), hematology (hemoglobin and hematocrit), and blood pressure (systolic and diastolic).

Liver Enzymes: There were no relevant differences in the time course of mean alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin between empagliflozin and placebo. Outliers (≥ ULN, ≥3xULN, and ≥5xULN) were balanced between the two treatment groups.

Renal Function: In the empagliflozin group, mean serum creatinine increased and eGFR decreased acutely after the start of the treatment and remained steady through the study. In contrast, in the placebo group, serum creatinine steadily increased and eGFR decreased throughout the study (Figure 7). Outliers (≥ULN, ≥3xULN, and ≥5xULN for creatinine; ≤LLN for eGFR) were balanced between the two treatment groups.

Lipid Panel: There was little change in mean high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels over time in the empagliflozin group; in contrast, HDL and LDL levels decreased in the placebo group. Both treatment groups had mean triglycerides increase from baseline to week 52. There were no significant differences in mean HDL, LDL, and triglycerides between the two treatment groups and the numbers of outliers (≥ULN, ≥2xULN, and ≥3xULN) were balanced.

Hematology: Both hemoglobin and hematocrit increased following empagliflozin compared to placebo (Figure 8), and more subjects taking empagliflozin had outlier values (≥ULN) for hemoglobin (6.2% vs 2.6%) and for hematocrit (25.9% vs 12.9%). For subjects with valid baseline, last value on-treatment and follow-up values, at the follow-up visit after about 30 days post-treatment, hemoglobin and hematocrit values partially returned to baseline in the empagliflozin group (change from baseline at follow-up visit was 1.4 g/L for hemoglobin and 0.43% for hematocrit in the empagliflozin group).

Blood Pressure: Empagliflozin group had lower diastolic and systolic blood pressure compared to placebo, and the difference was more pronounced in systolic blood pressure (Figure 9). Lowing blood pressure is expected from empagliflozin as a mechanism of action.

In summary, all lab and vital sign changes were within expectation and were addressed adequately described in product labeling.

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Figure 7: Time Course of Serum Creatine, Safety Population, EMPEROR-Preserved.

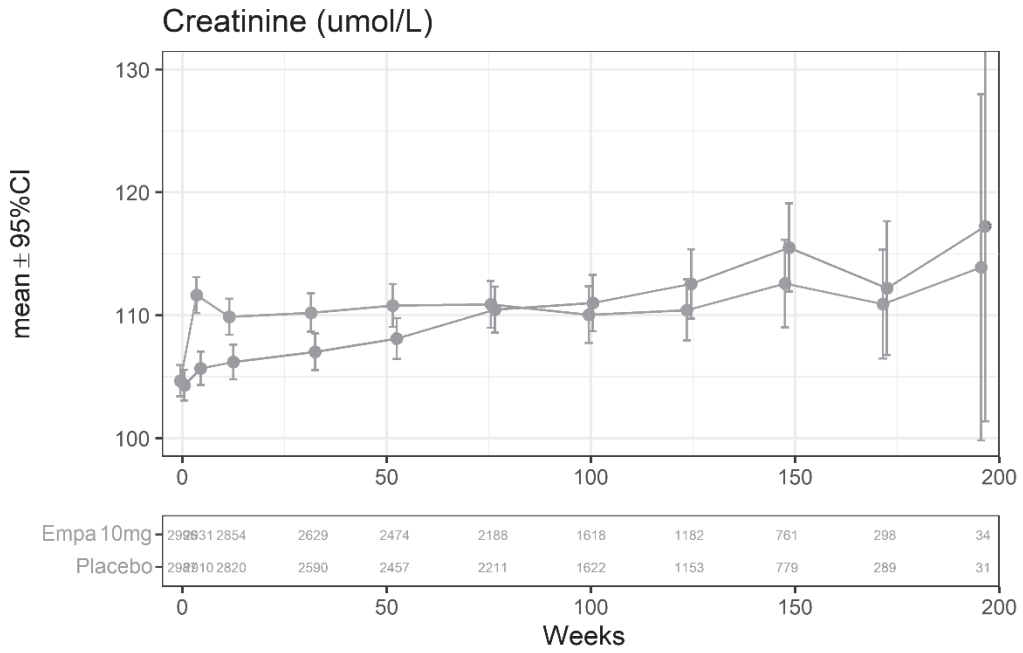
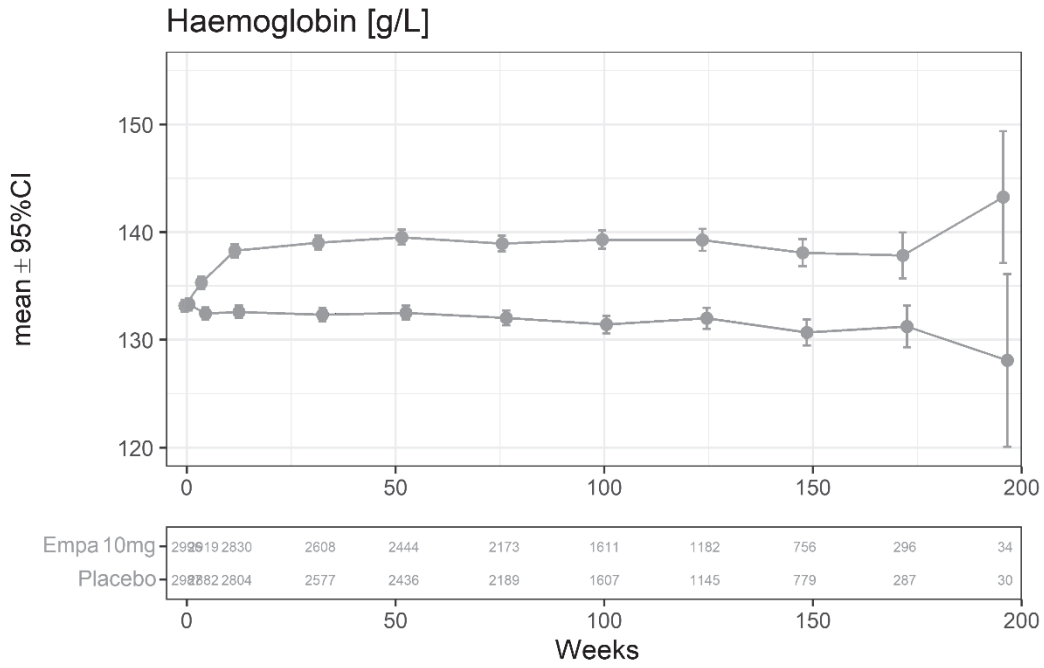


Figure 8: Time Course of Hemoglobin and Hematocrit, Safety Population, EMPEROR-Preserved.



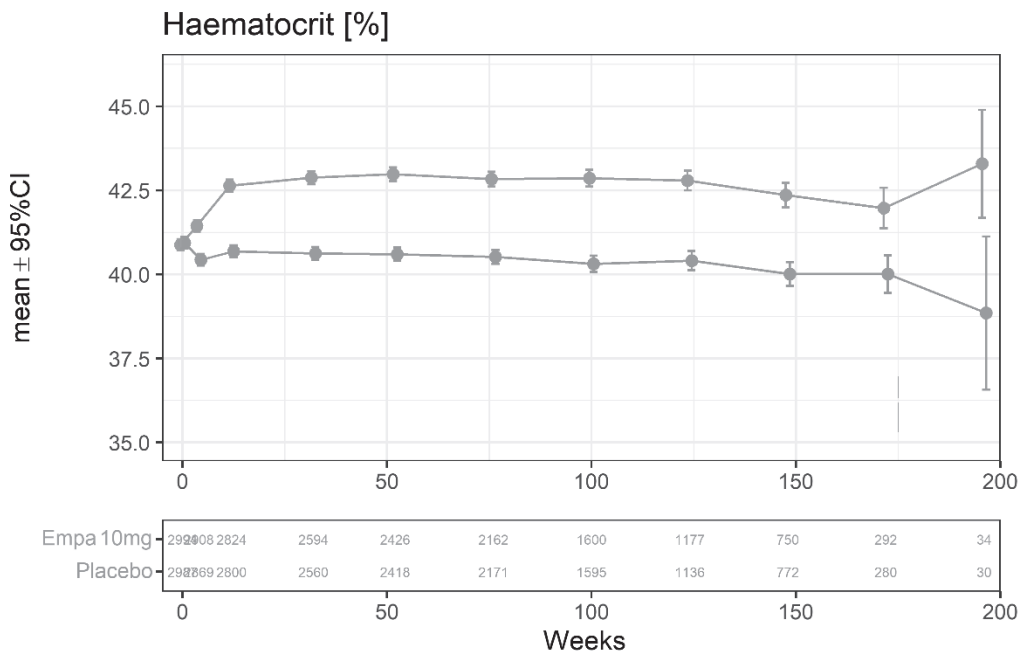
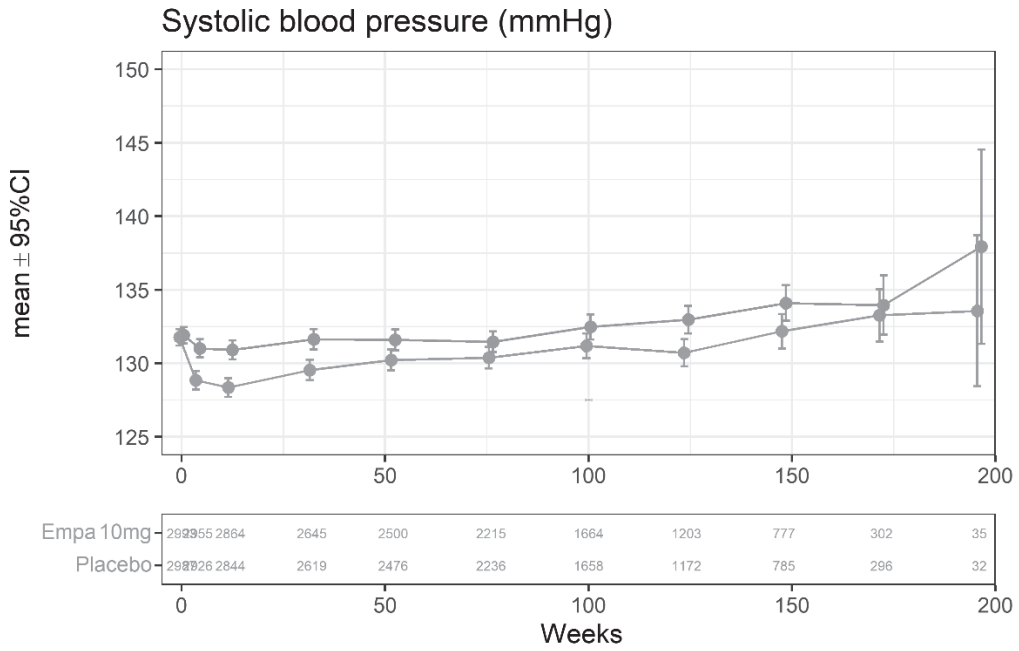


Figure 9: Time Course of Systolic Blood Pressure, Safety Population, EMPEROR-Preserved.



5.4.7. Summary of Safety Findings

Overall, there are no unexpected safety findings in this study.

- Death was balanced between empagliflozin (14.6%) and placebo (14.9%).

- Risk Difference were small and favored empagliflozin for TEAE (-0.6%), serious adverse events (-3.7%), and severe adverse events (-2.2%). The RD for AE leading to permanent drug discontinuations was 0.6%.
- Broad FMQs with RD larger than 1% were hypotension (2.0%) and syncope (1.4%, driven by hypotension), which were expected AEs based on the mechanism of action.
- Adverse events of special interest with RD larger than 1% were urinary tract infection (1.8%), genital infection (1.5%), hypotension (1.5%), and volume depletion (2.3%, driven by hypotension). There were no concerning imbalances in AESIs.
- There were no significant differences in LLA incidence rates between empagliflozin and placebo in the meta-analysis. The analysis suggests that LLA events are more likely to be related to diabetes than empagliflozin treatment.
- All laboratory and vital sign changes were within expectation and were addressed adequately in product labeling.

6. Therapeutic Individualization

6.1. Pediatric Labeling/Plans for Pediatric Drug Development

The Applicant has requested a full waiver for pediatric studies according to the agreed initial Pediatric Study Plan (iPSP) for pediatric patients with heart failure from birth to less than 18 years on the grounds that necessary studies are impossible or highly impractical.

7. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

The trial was carried out in compliance with the Clinical Trial Protocol, in accordance with the principles of the Declaration of Helsinki, in accordance with the ICH GCP, and in accordance with applicable regulatory requirements and Boehringer Ingelheim (BI) standard operating procedures (SOPs), and applicable IQVIA SOPs.

III. Appendices

8. Trial Design: Additional Information and Assessment – EMPEROR-Preserved

Table 17. Schedule of Assessments for EMPEROR-Preserved

Schedule of Assessments for EMPEROR-Preserved

Trial Period	Screening[1]	Randomised Treatment Period[2]															Follow Up Period [3]		Relevant CTP section
Visit	1	2	3	4	5 Phone call	6	7 Phone call	8	9 Phone call	10	11 Phone call	12	13 Phone call	14	15 Phone call	16	EOT Visit	FU Visit[3]	
Trial week	-3	1	4	12	22	32	42	52	64	76	88	100	112	124	136	148	EOT Visit	EOT + 30 days	
Days from Randomisation Visit window[4]	-28 to -4	1	29±7	85 ±7	155 ±7	225 ±7	295 ±7	365 ±7	449 ±7	533 ±7	617 ±7	701 ±7	785 ±7	869 ±7	953 ±7	1037 ±7	---	--- ±7	
Fasting status[5]	NF	F	NF	NF	-	NF		NF	-	NF	-	NF	-	NF	-	NF	F	F	
Informed Consent [6]	X																		2.8
In-/exclusion criteria	X	X																	2.3
Medical History/ Concomitant diagnoses	X																		8.3.1
Screening (register in IRT)	X																		6.2.1
Randomisation (via IRT)		X																	6.2.2
Demographics[7]	X																		-
NYHA classification	X	X	X	X		X		X		X		X		X		X	X	X	5.2.2 10.3
Physical exam		X				X		X		X		X		X		X	X		5.3.1
Clinical routine exam[8]		X	X	X		X		X		X		X		X		X	X		5.3.2
Vital signs [9]	X	X	X	X		X		X		X		X		X		X	X	X	5.3.3
Height	X																		-

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Schedule of Assessments for EMPEROR-Preserved

Trial Period	Screening[1]	Randomised Treatment Period[2]															Follow Up Period[3]		Relevant CTP section
Visit	1	2	3	4	5 Phone call	6	7 Phone call	8	9 Phone call	10	11 Phone call	12	13 Phone call	14	15 Phone call	16	EOT Visit	FU Visit[3]	
Trial week	-3	1	4	12	22	32	42	52	64	76	88	100	112	124	136	148	EOT Visit	EOT + 30 days	
Days from Randomisation Visit window[4]	-28 to -4	1	29±7	85 ±7	155 ±7	225 ±7	295±7	365 ±7	449 ±7	533 ±7	617 ±7	701 ±7	785 ±7	869 ±7	953 ±7	1037 ±7	---	--- ±7	
Fasting status[5]	NF	F	NF	NF	-	NF		NF	-	NF	-	NF	-	NF	-	NF	F	F	
Weight	X	X	X	X		X		X		X		X		X		X	X	X	5.2.4
Concomitant Therapy	X	X	X	X		X		X		X		X		X		X	X	X	4.2
Assessment of Endpoints[10, 11]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2, 5.3
12-lead-ECG[12]	X																X		5.3.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.3.7
KCCQ		X		X		X		X									X	X	5.2.1
EQ-5D		X		X		X		X				X				X	X	X	5.6.1
HCRU		X	X	X		X		X		X		X		X		X	X		5.6.2
Urine Pregnancy Test[13]	X	X	X	X		X		X		X		X		X		X	X		5.3.4.2
Safety lab Tests	X[14]	X	X	X		X		X		X		X		X		X	X	X	5.3.4
NT-proBNP	X	X	X	X				X				X					X	X	5.5
High-sensitivity TroponinT		X																	5.5
HbA1c[15]	X	X		X		X		X		X		X		X		X	X		-

Trial Period	Screening[1]	Randomised Treatment Period[2]															Follow Up Period[3]		Relevant CTP section
Visit	1	2	3	4	5 Phone call	6	7 Phone call	8	9 Phone call	10	11 Phone call	12	13 Phone call	14	15 Phone call	16	EOT Visit	FU Visit[3]	
Trial week	-3	1	4	12	22	32	42	52	64	76	88	100	112	124	136	148	EOT Visit	EOT + 30 days	
Days from Randomisation Visit window[4]	-28 to -4	1	29±7	85 ±7	155 ±7	225 ±7	295±7	365 ±7	449 ±7	533 ±7	617 ±7	701 ±7	785 ±7	869 ±7	953 ±7	1037 ±7	---	--- ±7	
Fasting status[5]	NF	F	NF	NF	-	NF		NF	-	NF	-	NF	-	NF	-	NF	F	F	
Lipid profile panel		X						X				X					X	X	5.3.4
eGFR (CKD-EPI$_{cr}$ formula)	X	X	X	X		X		X		X		X		X		X	X	X	5.3.4.1
UACR	X	X	X	X		X		X		X		X		X		X	X	X	5.3.4
PK sampling (substudy)[16]				X															5.4.1
Sampling for biobanking of serum/plasma/urine/ DNA (optional, requires separate informed consent)[17]		X[18]		X				X											5.5.1
Dispense trial medication[19]		X	X	X		X		X		X		X		X		X			4.1.4 6.2.1
Return Medication/ medication compliance check			X	X		X		X		X		X		X		X	X		4.3

Schedule of Assessments for EMPEROR-Preserved

1. The screening procedures can be done on different days within the time window.
2. From Visit 8 and onwards, on-site visits will be scheduled every 24 weeks until end of trial.
   Patients who prematurely discontinue trial medication will perform EOT visit and Follow Up visit, and then continue with scheduled visits until the trial is stopped.
   For patients not willing to attend scheduled visits, telephone calls must be made regularly (ref. Section 3.3.4.1) to document any occurrence of outcome events and vital status.
   If the trial continues beyond 148 weeks, visits are to be repeated with same intervals as from week 64 and onwards.
3. Timepoint for the EOT will be communicated via an Investigator letter when the Sponsor is confident that required number of events will be reached within a reasonable timeframe (ref. Section 3.1 and 6.2.3). All patients will have a follow up visit 30 days following regular or premature completion of the treatment period.
4. Visit dates are determined per the date of randomisation. If a visit is missed, the patient should be returned to the original visit schedule at the next visit.
5. NF = non fasting, F=fasting. Fasting means no food or liquid intake except for water the last 10-16 hours
6. All visit 1 procedures should be performed within 28 days of signing the informed consent form (ICF).
7. If accepted by local authorities or ethic committees, demographics to be collected in this trial are gender, year of birth, ethnicity and race.
8. The Investigator will be asked to record results from clinical routine examinations like ECG, echocardiography or similar procedures (MRI, CT-scan, etc.), and if applicable information gathered from interrogations of the ICD in the eCRF.
9. Vital signs measurements in this trial are blood pressure and pulse rate.
10. Protocol specified outcome events should be collected on the appropriate eCRF page. Exemptions from reporting on the SAE form are specified in Section 5.3.7.
11. For patients with non-fatal stroke the Modified Rankin Scale (MRS) should be scored by the investigator based on an interview at the next regular on-site visit after the onset of the stroke. In those cases where MRS assessment occurred within 90 days after the stroke, a repeat MRS-assessment should be performed at the next on-site visit. For patients who experience a non-fatal stroke less than 90 days prior to the study closure date, the final MRS assessment will occur at the final study visit for that patient.
12. For the 12-lead ECG done at screening and EOT visit, the interpretation of the tracing must be made locally by a qualified physician or appropriately qualified designee and documented on the ECG section of the eCRF. In case of any cardiac symptoms (indicating rhythm disorders or cardiac ischaemia), additional 12-lead ECG(s) should be done to document a potential outcome event.
13. For female patients of child-bearing potential, local urine pregnancy test should be performed according to the Flow Chart. More frequent testing should be performed if required by local regulations/authorities.
14. For the screening Visit 1, the safety laboratory is limited to liver transaminases, alkaline phosphatase, serum creatinine and haematology panel. Patients do not have to be fasting.
15. HbA1c to be analysed in all patients, e.g. diabetics and non-diabetics.
16. For PK analysis, one blood sample will be collected prior to the next scheduled dose of trial medication at Visit 4 and between 22 to 26 h after the most recent drug intake.
17. Collection of biobanking samples (plasma, serum, urine, DNA) is optional. Participating patients are required to give informed consent specifically for biobanking. Samples will be stored at a biobanking facility for future research.
18. DNA biobanking requires only one blood sample to be taken, preferably at Visit 2 (Randomisation). However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.
19. At all visits; the respective kit number has to be allocated to the patient via IRT. Trial medication should be taken after all trial related procedures are completed at an on-site visit.

Source: Flow Chart on Page 106 of Appendices titled Protocol and amendments

Pharmacokinetic endpoints: Sampling for pharmacokinetic (PK) endpoints was performed as part of a sub study in a limited number of patients (approximately 1140 patients planned) and at sites in pre-selected countries only. The pre-dose blood samples were collected at Week 12 (Day 85, Visit 4) to determine plasma empagliflozin trough concentrations. These samples served to determine steady state trough concentrations of empagliflozin. The effect of demographic and baseline characteristics, including sex, age, body weight, BMI, geographical region, investigator country, race, ethnicity, renal impairment, NYHA classification, heart failure physiology (based on NT-proBNP and LVEF%), and diabetes status on empagliflozin trough concentrations were to be investigated descriptively.

9. Efficacy Assessment Additional Information and Assessment – EMPEROR-Preserved

Table 18 Heart Failure-related medical history – Randomized Set (Sponsor material)

	Placebo	Empa 10 mg	Total
Number of patients, N (%)	2991 (100.0)	2997 (100.0)	5988 (100.0)
NYHA class at baseline, N (%)			
I	1 (<0.1)	3 (0.1)	4 (0.1)
II	2451 (81.9)	2432 (81.1)	4883 (81.5)
III	531 (17.8)	552 (18.4)	1083 (18.1)
IV	8 (0.3)	10 (0.3)	18 (0.3)
Time since diagnosis of HF [years], mean (SD)	4.3 (5.0)	4.5 (5.2)	4.4 (5.1)
≤1, N (%)	782 (26.1)	730 (24.4)	1512 (25.3)
>1 to 5, N (%)	1325 (44.3)	1368 (45.6)	2693 (45.0)
>5 to 10, N (%)	553 (18.5)	550 (18.4)	1103 (18.4)
>10, N (%)	331 (11.1)	349 (11.6)	680 (11.4)
Cause of HF, N (%)			
Ischaemic	1038 (34.7)	1079 (36.0)	2117 (35.4)
Hypertensive	1120 (37.4)	1066 (35.6)	2186 (36.5)
Valvular heart disease	168 (5.6)	187 (6.2)	355 (5.9)
Diabetic	58 (1.9)	67 (2.2)	125 (2.1)
Alcoholism	7 (0.2)	6 (0.2)	13 (0.2)
Idiopathic	262 (8.8)	289 (9.6)	551 (9.2)
Other	338 (11.3)	302 (10.1)	640 (10.7)
HHF within 12 months before screening and/or structural heart disease[1], N (%)			
HHF within 12 months before screening only	187 (6.3)	199 (6.6)	386 (6.4)
Structural heart disease only	2317 (77.5)	2297 (76.6)	4614 (77.1)
Both	482 (16.1)	499 (16.6)	981 (16.4)

Sponsor Table 10.4.3: 1 of Clinical Trial Report for 1245.110

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Table 19 Baseline Concomitant Medications in Randomized Set (Sponsor material)

	Placebo N (%)	Empa 10 mg N (%)	Total N (%)
Number of patients	2991 (100.0)	2997 (100.0)	5988 (100.0)
Drugs used in heart failure	2972 (99.4)	2985 (99.6)	5957 (99.5)
ACE inhibitors/ARBs/ARNi	2404 (80.4)	2428 (81.0)	4832 (80.7)
ACE inhibitors/ARBs	2338 (78.2)	2367 (79.0)	4705 (78.6)
ARNi	69 (2.3)	65 (2.2)	134 (2.2)
Beta-blockers	2569 (85.9)	2598 (86.7)	5167 (86.3)
Diuretics	2600 (86.9)	2563 (85.5)	5163 (86.2)
Mineralocorticoid receptor antagonists (MRAs)	1125 (37.6)	1119 (37.3)	2244 (37.5)
Loop or high ceiling diuretics	2024 (67.7)	2030 (67.7)	4054 (67.7)
Ivabradine	31 (1.0)	40 (1.3)	71 (1.2)
Cardiac glycosides	263 (8.8)	293 (9.8)	556 (9.3)
Nitrates	338 (11.3)	408 (13.6)	746 (12.5)
Hydralazine	74 (2.5)	82 (2.7)	156 (2.6)
Other anti-hypertensives	883 (29.5)	943 (31.5)	1826 (30.5)
Lipid-lowering drugs	2139 (71.5)	2103 (70.2)	4242 (70.8)
Anti-thrombotic drugs	2609 (87.2)	2631 (87.8)	5240 (87.5)

ARB: excluding valsartan when taken with sacubitril, because sacubitril/valsartan is shown as ARNi.

Sponsor Table 10.4.4.1: 1 of Clinical Trial Report for 1245.110

Adjudication of Efficacy Endpoints

HHF and CV death events were adjudicated by the CEC.

Mortality in EMPEROR-Preserved

Table 20 summarizes time to all-cause mortality, CV death, and non-CV death in randomized set. Number of patients with all-cause mortality and CV death were less in Jardiance compared to placebo arm. Overall, there were 20 more patients with non-CV death in Jardiance (n= 203) arm versus placebo (n=183). Table 21 displays the CEC-defined categories of non-CV death. The higher incidence of non-CV mortality in Jardiance arm appears to be largely driven by deaths due to infection including sepsis (91 vs 78, Jardiance vs placebo), followed by malignancy (39 vs 34), trauma (13 vs 2) and gastrointestinal causes (12 vs 4).

Since, overall mortality favors Jardiance, sepsis is an identified safety risk, and there is no clear mechanism for increase in non-CV mortality due to other causes, a higher incidence of overall non-CV death in Jardiance versus placebo arm (3.17 versus 2.86 per 100 patient years) is not considered to constitute a significant safety signal.

Table 20 Time to all-cause mortality, CV death, and non-CV death, Cox regression – Randomized Set (Sponsor analysis)

	Placebo	Empa 10 mg
Analysed patients, N (%)	2991 (100.0)	2997 (100.0)
Patients with all-cause mortality, N (%)	427 (14.3)	422 (14.1)
Incidence rate per 100 years at risk	6.67	6.60
Hazard ratio vs placebo (95% CI)		1.00 (0.87, 1.15)
Nominal p-value		0.9893
Patients with CV death, N (%)	244 (8.2)	219 (7.3)
Incidence rate per 100 years at risk	3.81	3.42
Hazard ratio vs placebo (95% CI)		0.91 (0.76, 1.09)
Nominal p-value		0.2951
Patients with non-CV death, N (%)	183 (6.1)	203 (6.8)
Incidence rate per 100 years at risk	2.86	3.17
Hazard ratio vs placebo (95% CI)		1.13 (0.92, 1.38)
Nominal p-value		0.2434

Cox regression model included factors age, baseline eGFR $(CKD\text{-}EPI)_{cr}$, region, baseline diabetes status, sex, baseline LVEF, and treatment

Sponsor Table 11.1.2.4:1 of Clinical Trial Report for 1245.110

Table 21 CEC-defined categories of non-CV death – RS (Sponsor analysis)

	Placebo N (%)	Empa 10 mg N (%)
Analysed patients	2991 (100.0)	2997 (100.0)
All with non-CV death	183 (6.1)	203 (6.8)
Infection (including sepsis)	78 (2.6)	91 (3.0)
Malignancy	34 (1.1)	39 (1.3)
Other non-CV causes	39 (1.3)	25 (0.8)
Trauma	2 (0.1)	13 (0.4)
Gastrointestinal causes	4 (0.1)	12 (0.4)
Pulmonary causes	5 (0.2)	6 (0.2)
Renal causes	10 (0.3)	4 (0.1)
Neurological (non-CV)	0	4 (0.1)
Haemorrhage	3 (0.1)	3 (0.1)
Non-CV procedure or surgery	1 (<0.1)	3 (0.1)
Hepatobiliary causes	3 (0.1)	2 (0.1)
Suicide	3 (0.1)	1 (<0.1)
Pancreatic causes	1 (<0.1)	0

CEC: Clinical Events Committee, CV: cardiovascular, RS: randomized set

Measures taken due to COVID-19 pandemic

The sponsor provided the following guidance to the investigators and study coordinators via guidance letters:

a. If a planned clinic visit on-site was not feasible, remote visit (telephone contact) could be performed.

b. Per investigator's decision, the follow-up visit could be completed as early as 7 days instead of between 23 and 37 days after the EOT visit.
c. Per investigator's discretion, local laboratory could be used for safety laboratory tests as required by the protocol.
d. Patients with a remote visit instead of on-site visit could have the study medication shipped to them by courier upon their consent. The study kits could be arranged to be returned by courier.
e. Any protocol deviation and/or missing protocol-required data was to be documented including that this was COVID-19 related.
   Information on temporary or permanent treatment discontinuation due to COVID-19 was collected on the eCRF and summarized.

Effect of COVID-19 pandemic

The cut-off date for the start of the pandemic was 01 Dec 2019 for China and 01 Jan 2020 for all other countries. Before the onset of the COVID-19 outbreak, 5896 patients (98.5%) had been randomized, and 92 patients were randomized thereafter.

a. The start of the end-of-treatment visit period in the trial was 11 Jan 2021. Due to the pandemic, 0.9% (1815 of 204 394) of forms could not undergo source data verification (SDV) as planned. Remote SDV was performed at 10 trial sites in 3 countries (Brazil, Canada, and United States) and documented in the Data Handling Report in TMF.

b. Prior to database lock, following analyses on the impact of COVID-19 were planned in the TSAP:
    a. The number of patients screened, randomized, or completed before and after the outbreak of the pandemic
    b. The frequency of patients impacted by COVID-19 regarding clinical visits and study medication supply (Table 22)
    c. Sensitivity analyses for the primary endpoint (CV death or HHF) and the first key secondary endpoint (first and recurrent HHF) that included only events that were thought to occur before the pandemic, and using the same model as for the respective primary analysis
    d. Sensitivity analyses for the primary endpoint: Cox regression models including the COVID-19 outbreak as a binary time-dependent covariate with or without outbreak by-treatment interaction term
    e. Sensitivity analyses for the primary endpoint, the first key secondary endpoint, and CV death that included only events up to 7 days prior to a reported SARS-CoV-2 infection (based on BIcMQ SARS-CoV-2 infections including PT suspected Covid-19 (broad scope))
    f. Frequency of patients with and rate of AEs before and after the outbreak
    g. For patients who had SARS-CoV-2 infections (based on the BIcMQ SARS-CoV-2 infections (narrow scope) and additionally by including the PT suspected Covid-19 (broad scope)): overall summary of AEs, AEs by SOC and PT, AEs

leading to treatment discontinuation by SOC and PT, SAEs by SOC and PT, and a listing for these patients. Only AEs with an onset date 7 days before SARS-CoV-2 infection until the end of the on-treatment period were shown for these patients.

Table 22. Frequency of Patients with COVID-19 impact on visits or medication supply – Randomized Set (Source: Sponsor material, Clinical Study Report Table 15.1.3)

Table 15.1.3: 2 Frequency [N(%)] of patients with COVID-19 impact on visits or medication supply - RS

	Placebo N (%)	Empa 10mg N (%)	Total N (%)
Number of patients	2991 (100.0)	2997 (100.0)	5988 (100.0)
Patients without documented impact of COVID-19	1974 (66.0)	1961 (65.4)	3935 (65.7)
Patients with any documented impact of COVID-19	1017 (34.0)	1036 (34.6)	2053 (34.3)
Patients with at least one visit affected by COVID-19	936 (31.3)	967 (32.3)	1903 (31.8)
Patients with at least one visit not performed	25 (0.8)	28 (0.9)	53 (0.9)
Patients with at least one visit performed via phone instead of on site	763 (25.5)	773 (25.8)	1536 (25.7)
Patients with at least one visit performed outside of protocol window	127 (4.2)	151 (5.0)	278 (4.6)
Patients with at least one on-site visit with missed assessment(s)	71 (2.4)	81 (2.7)	152 (2.5)
Patients with impact of COVID-19 on medication intake	75 (2.5)	72 (2.4)	147 (2.5)
Patients with drug interruption	48 (1.6)	42 (1.4)	90 (1.5)
Patients with drug interruption for more than 7 days	45 (1.5)	37 (1.2)	82 (1.4)
Patients with drug interruption for no more than 7 days	5 (0.2)	6 (0.2)	11 (0.2)
Patients with permanent treatment discontinuation	27 (0.9)	30 (1.0)	57 (1.0)
Due to AE SARS-CoV-2 infection	22 (0.7)	23 (0.8)	45 (0.8)
Not due to AE SARS-CoV-2 infection	5 (0.2)	7 (0.2)	12 (0.2)
Patients with at least one drug delivery to patient´s home	274 (9.2)	263 (8.8)	537 (9.0)
Patients with at least one study drug returned from patient´s home to site	50 (1.7)	61 (2.0)	111 (1.9)
Patients with other impact (not listed above) observed due to COVID-19	45 (1.5)	37 (1.2)	82 (1.4)
Missing	7 (0.2)	5 (0.2)	12 (0.2)

SARS-CoV-2 infection defined by broad scope: BIcMQ SARS-CoV-2 infections including preferred term "Suspected

Reviewer Comments: *There were 34 % patients with any documented impact of COVID-19. The most common impact was at least one visit was performed via phone instead of on-site (~ 26%). A total of 1.4% of patients had interruption of trial medication for more than 7 days due to COVID-19 and 0.8% had permanent treatment discontinuation due to COVID-19 infection The categories of impact of COVID-19 shown above are unlikely to negatively impact evaluation of efficacy or safety of Jardiance in EMPEROR-Preserved trial.*

Applicability of EMPEROR-Preserved Results to US Population

Only 719 out of 5988 (12%) patients were randomized from North America. Patients were mostly enrolled from Europe (2689/5988, 45%) and Latin America (1515/5988, 25%). The use of concomitant medications to treat HF and other cardiovascular co-morbidities was similar in

US versus ex-US patient populations. Hence, EMPEROR-Preserved results are thought to apply to US population.

Pharmacokinetic Sampling

Limited pharmacokinetic (PK) sampling was done in 519/5988 (8%) patients in EMPEROR-Preserved trial. Pre-dose blood samples were collected at Week 12 (Day 85) in a subset of patients to determine steady state plasma trough concentrations. A total of 1657 pre-dose samples were collected with 841 in the placebo group and 813 in the Jardiance 10 mg group. The effect of demographic and baseline characteristics, including sex, age, body weight, BMI, geographical region, investigator country, race, ethnicity, renal impairment (eGFR calculated by CKD-EPI formula), NYHA classification, and diabetes status on Jardiance trough concentrations were also investigated descriptively.

There were no major differences in Jardiance exposure by sex, race (comparison Asian vs White or Black vs White), NYHA classification, or diabetes status. Jardiance exposure increased with an increase in age, and it decreased with an increase in body weight or body mass index. Jardiance exposure increased with a decrease in renal function. Slight differences in Jardiance exposures were observed among different groups of geographic region or investigator country. Per clinical pharmacology review, no labelling changes are indicated based on these data.

Protocol Deviations

The proportion of patients with at least one important protocol deviations (pre-defined in TSAP) were balanced between the two treatment arms. The most common deviation was entrance criteria not met.

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10. Financial Disclosure

Table 23. Covered Clinical Studies: [Insert Names]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 3451		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator: 2 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3):0		
Is an attachment provided with the reason:	Yes ☒	No ☒ (Request explanation from Applicant) All clinical investigators are listed on Form 3454.

11. Review Team Acknowledgements

Table 24. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Alexis Childers
Nonclinical Reviewer	N/A
Nonclinical Team Leader	N/A
Office of Clinical Pharmacology Reviewer(s)	Li Wang
Office of Clinical Pharmacology Team Leader(s)	Doahn Tran
Clinical Reviewer	Charu Gandotra
Clinical Team Leader	Fred Senatore
Statistical Reviewer	Jennifer Clark
Statistical Team Leader	Jialu Zhang
Cross-Disciplinary Team Leader	Fred Senatore
Division Director (DHOT)	N/A
Division Director (OCP)	N/A
Division Director (OB)	N/A
Division Director (OHOP)	N/A
Division Director (or designated signatory authority)	Norman Stockbridge

Table 25. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Daneli LopezPerez
Microbiology	N/A
OPDP	David Foss
OSI	N/A
OSE/DEPI	N/A
OSE/DMEPA	Devin Kane
OSE/DRISK	N/A
Patient Labeling	Susan Redwood

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Table 26. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Choose discipline	Enter name.	Choose office or center/Enter division	Enter sections. ☐ Authored ☐ Approved
Choose title/role	**Signature:**		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary.

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JENNIFER J CLARK
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JIALU ZHANG
02/18/2022 12:54:26 PM

FORTUNATO F SENATORE
02/18/2022 02:57:20 PM

NORMAN L STOCKBRIDGE
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s033

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	204629 /S-33 (Efficacy Supplement)
Submission Date:	9/13/2021
Sponsor:	Boehringer Ingelheim
Drug:	Jardiance (empagliflozin)
Reviewer:	Li Wang, Ph.D.
Secondary Reviewer:	Doanh Tran, Ph.D.
OCP Division:	Division of Cardiometabolic and Endocrine Pharmacology
OND Division:	Division of Cardiology and Nephrology

Background

The applicant (Boehringer Ingelheim) submitted this supplemental NDA seeking the indication for reduction of the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction. The proposed dose of empagliflozin for the claimed indication is 10 mg once daily. The applicant's claims are based on the results of the EMPEROR-preserved trial (1245.110). The EMPEROR-preserved trial was a phase III randomized, double-blind trial to evaluate efficacy and safety of once daily empagliflozin 10 mg compared to placebo, in patients with chronic heart failure with preserved ejection fraction (HFpEF). This review discusses the clinical pharmacology information from trial 1245.110.

Recommendation

The Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology has reviewed the clinical pharmacology information in this supplement and found it acceptable. There are no changes to the clinical pharmacology sections of the label.

Summary

In the EMPEROR-preserved trial (1245.110), pre-dose blood samples were collected at Week 12 to determine steady state plasma trough concentrations in a subset of randomized patients (n=519). The effect of demographic and baseline characteristics, including sex, age, body weight, BMI, geographical region, investigator country, race, ethnicity, renal impairment, NYHA classification, heart failure physiology (based on NT-proBNP and LVEF%), and diabetes status on empagliflozin steady state trough concentration was investigated.

Key Clinical Pharmacology Findings:

- Increased empagliflozin exposure in trial 1245.110 was observed in mild, moderate and severe impaired renal function groups with eGFR as 60-90 mL/min/1.73m^2, 30-60 mL/min/1.73m^2, 15-30 mL/min/1.73m^2, respectively, compared with subject with normal renal function (eGFR: ≥90 mL/min/1.73m^2). The greatest difference (3.01-fold difference in geometric mean (gMean)) was observed between subjects with severe renal impairment and ones with normal renal function. Though this

difference appears to be larger than the findings described in the current label for empagliflozin, no changes to the clinical pharmacology sections of the label is recommendation because of the limitation in this analysis including small sample size (n=30 and 25 for subjects with normal renal function and severe renal impairment, respectively) and large variability in trough plasma concentration of empagliflozin (coefficient of variation (CV) as 109% and 75.9% for subjects with normal renal function and severe renal impairment, respectively).

- Empagliflozin exposure in trial 1245.110 was increased with increasing age, based on the results from four age groups (<50 yrs, 50-65 yrs, 65-75 yrs, and ≥75 yrs), with greatest difference (1.38-fold difference in gMean) observed between subject with age <50 yrs and ≥75 yrs.
- Empagliflozin exposure in trial 1245.110 was increased with increasing body weight, based on the results from four body weight groups (<50 kg, 50-70 kg, 70-90 kg, and ≥90 kg), with greatest difference (1.54-fold difference in gMean) observed between subject with body weight <50 kg and ≥90 kg.
- Empagliflozin exposure in trial 1245.110 was increased with increasing BMI, based on the results from four BMI groups (<25 kg/m^2, 25-<30 kg/m^2, 30-<35 kg/m^2, and ≥35 kg/m^2), with greatest difference (1.25-fold difference in gMean) observed between subject with BMI <25 kg/m^2 and ≥35 kg/m^2.
- There were no differences (<1.25-fold difference in gMean) in empagliflozin exposure by sex, race (comparison Asian versus White or Black versus White), NYHA classification, diabetes status or use of angiotensin receptor-neprilysin inhibitor at baseline.
- Small differences in empagliflozin exposures were observed among different groups of geographic regions (up to 1.38-fold difference in gMean) or investigator country (up to 1.44-fold difference in gMean). To be specific, empagliflozin exposure appeared to be comparable in patients from Canada, China, and Japan and lower in patients from Germany, Mexico, and the Netherlands, whereas empaglifozin exposure in patients from the United States was in between the two groups.
- When correlating steady state trough concentration of empagliflozin with a heart failure biomarker, NT-proBNP, a weak positive correlation was observed (Pearson correlation r =0.19 for NT-proBNP at Week 12 versus empagliflozin steady state trough concentration).

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LI WANG
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s033

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

sNDA: 204629 S033
Drug: Jardiance (empagliflozin) 10 mg tablet
Class: SGLT2 inhibitor

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Proposed Indication: to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced independent of left ventricular ejection fraction.

(b) (4)

Final indication: to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure

Date of submission: September 13, 2021
PDUFA date: March 13, 2022
Action date: February 24, 2022

❖ **REVIEW TEAM**

- Office of Cardiology, Hematology, Endocrinology, and Nephrology, Division of Cardiology and Nephrology
  - Cross Discipline Team Leader (CDTL)
    - Fortunato Senatore
  - Medical Reviewer
    - Charu Gandotra
- Office of Regulatory Operations Cardiology, Hematology, Endocrinology, and Nephrology
  - Regulatory Health Project Manager
    - Alexis Childers
- Office of Clinical Pharmacology
    - Li Wang
- Office of Biostatistics, Division of Biometrics I
    - Jennifer Clark
- Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis
    - Devin Kane
- Office of Pharmaceutical Quality
  Daneli Lopez Perez

BACKGROUND

Empagliflozin is a sodium glucose co-transporter-2 (SGLT2) inhibitor approved in 2014 for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). In 2016 Jardiance was also approved to reduce the risk of cardiovascular (CV) death in adult patients with T2DM and established CV disease based on results of a cardiovascular safety study, EMPA-REG OUTCOME. In 2021, Jardiance was approved to reduce the risk of cardiovascular (CV) death plus hospitalization for heart failure (HHF) in adults with heart failure and reduced ejection fraction (LVEF).

This efficacy supplement proposed an update to the prescribing information to add new clinical information based on results from pivotal trial 1245.110 (EMPEROR-Preserved) and proposed an expanded indication to include patients with preserved ejection fraction. Fast Track designation was granted for the program On April 15, 2019.

Upon review of the supplement, it was determined that the indication statement would be modified to be less specific but was not dependent on the information submitted in the supplement. However, changes elsewhere e.g. section 14, were dependent on the results of the trial (see clinical review).

A combined review was completed by statistical and clinical reviewers. The CDTL and Signatory also provided their concurrence in the document. The aforementioned group signed a single document in DARRTS.

User Fee

No user fee required.

Pediatric Review Committee (PeRC) (March 31, 2020)

An agreed iPSP, for a full waiver, was issued under IND 131597 on October 23, 2018 to include both reduced and preserved ejection fraction patients. During the review of s26 (EMPEROR-reduced), the Division noted that the results for the primary efficacy endpoint of trial demonstrated efficacy in patients who had both ischemic ad non-ischemic heart failure with reduced ejection fraction. Also, the ongoing evaluation of heart failure across the adult and pediatric cohorts has revealed that the etiology, pathophysiology and symptoms of dilated cardiomyopathy generally overlap between these two populations. The Division asked the Applicant to propose a strategy to bridge the evidence of effectiveness between the adult and pediatric populations. We suggested that they consider a biomarker or a combination of biomarkers that may be used as a predictor of efficacy in pediatric patients with dilated cardiomyopathy. The Applicant performed a careful evaluation in order to identify a biomarker or a combination of biomarkers to be used as a predictor of efficacy due to empagliflozin treatment in pediatric patients with dilated cardiomyopathy. They were unable to identify a biomarker and provided their reasons, and therefore continued to request a waiver. In the case of empaglifozin, the precise mechanisms through which its beneficial effect in HFrEF are exerted are not defined. The Division agreed with the Applicant's assessment. PeRC agreed to the waiver on June 15, 2021 for S26. On January 18, and 25, 2022 PeRC discussed the same iPSP and request for full waiver. Based on previous minutes stating that there is not a biomarker developed to devise a pediatric plan at this time and PeRC agreed to a full waiver.

Advisory Committee
There was no Advisory Committee meeting for this NDA because this drug does not raise significant safety or efficacy issues.

Trade name
No trade name was submitted as this is a supplement.

Facilities Inspection
There were no facility inspections as no new CMC information was submitted and all sites were acceptable based on previous information.

Division of Scientific Investigations
No clinical sites were inspected. The Division did not feel an inspection was needed since the drug is approved and the study results seemed straight forward.

❖ REVIEWS

Below are the conclusions reached by the Jardiance team members, organized by role or discipline.

Divisional Concurrence, Cross-Discipline Team Leader (CDTL) Review, and Medical/ Biostatistics Review (August 15, 2021)
A joint collaborative review was written by the clinical and statistical teams. Dr.'s Gandotra (clinical) and Clark (statistics) focused on efficacy and safety data. Dr. Senatore, CDTL, provided the Executive Summary within the review. Dr. Stockbridge, signatory, signed the review in concurrence.

Results of EMPEROR-Preserved showed that empagliflozin reduced the primary efficacy composite endpoint of cardiovascular death and HHF in patients with heart failure, regardless of type 2 diabetes mellitus status, and LVEF > 40%. The primary endpoint results were largely driven by a reduction in HHF with slightly favorable trend noted in the incidence of CV death with Jardiance versus placebo. The patient population included patients with mildly reduced and normal LVEF. The review continued to state that although EMPEROR-Preserved expanded the LVEF range from the previously approved supplement based on EMPEROR-Reduced, there was a diminishing effect at higher LVEF levels.

There were no unexpected safety findings in the EMPERIOR-Preserved trial.

Although the indication language changed with this supplement, the change in the indication was not dependent on data provided in this supplement, however, changes elsewhere, e.g. Section 14, were dependent based on EMPEROR-Preserved. The change in indication provided for clarity of language rather than an expansion of the indication.

The review team recommended approval of this supplement

See review for full details.

CMC Review (dated October 20, 2021)

Dr. LopezPerez provided a brief review stating that no new information or labeling changes were submitted from a CMC perspective. The review stated that Environmental Assessment was submitted and the request for Categorical Exclusion is acceptable.

Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology (dated January 28, 2022)
Dr. Li reviewed clinical pharmacology data from study report for trial the EMPEROR-preserved trial (1245.110). He found the data acceptable and indicated no changes were needed to the clinical pharmacology section of the label. The review states that notable findings are:

- increased exposures with increasing age, increasing body weight, and increasing BMI.
- No differences in exposure by sex race, NYHA classification, diabetes status or use of angiotensin receptor-neprilysin inhibitor at baseline.
- A weak positive correlation was observed for NT-proBNP at Week 12 versus empagliflozin steady state trough concentration.
- Increased exposure in was observed in mild, moderate and severe impaired renal function groups. Dr. Wang stated that the findings were larger than findings described in current labeling, but no changes are needed to the label because of the limitations in the analysis.

Division of Medication Error Prevention and Analysis DMEPA (dated November 11, 2021)
Dr. Kane reviewed the prescribing information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors. He concluded that the proposed PI and MG are acceptable from a medication error perspective and had no recommendations for either document.

CONSULTS

Office of Medical Policy Initiatives, Division of Medical Policy Programs (dated February 1, 2022)
Ms. Redwood conducted a combined review with Dr. Foss evaluating the MG They concluded that the document is acceptable with no additional comments.

Office of Prescription Drug Promotions, Division of Professional Drug Promotion (dated January 31, 2022)
Dr. Foss conducted a review of the PI, and a combined review with Ms. Redwood evaluating the MG, and determined no additional edits were needed.

Labeling
Labeling discussions occurred with the applicant. The final agreed upon labeling will be attached to the approval letter. Major changes were updates to the indication for heart failure and updates to section 14. See the attached, red-lined label for exact revisions.

CONCLUSION: The review team recommended approval of the supplement providing for inclusion of new clinical data and a simplification to the indication statement to read: “to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure”. Dr. Stockbridge signed the approval letter on February 24, 2022.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	February 1, 2022
To:	Alexis Childers Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	JARDIANCE (empagliflozin)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 204629
Supplement Number:	S-033
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On September 10, 2021, Boehringer Ingelheim Pharmaceuticals, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their New Drug Application (NDA) 204629/S-033 for JARDIANCE (empagliflozin) tablets. This supplement proposes a new indication to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction.

On September 30, 2021, the Division of Cardiology and Nephrology (DCN) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for JARDIANCE (empagliflozin) tablets.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed MG for JARDIANCE (empagliflozin) tablets.

2 MATERIAL REVIEWED

- Draft JARDIANCE (empagliflozin) tablets MG received on September 10, 2021, and received by DMPP on January 27, 2022.
- Draft JARDIANCE (empagliflozin) tablets Prescribing Information (PI) received on September 10, 2021, revised by the Review Division throughout the review cycle, and received by DMPP on January 27, 2022.
- Draft JARDIANCE (empagliflozin) tablets MG approved August 18, 2021.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 31, 2022

To: Michael Oyewole, Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for JARDIANCE (empagliflozin tablets), for oral use

NDA: 204629/Supplement 33

In response to DCN's consult request dated September 30, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide for Jardiance. This supplement (S33) proposed a new indication to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN on January 27, 2022, and have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
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SUSAN W REDWOOD
02/01/2022 09:33:19 AM

SHAWNA L HUTCHINS
02/01/2022 09:39:13 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 23, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 204629/S-033
Product Name, Dosage Form, and Strength:	Jardiance (empagliflozin) tablets, 10 mg and 25 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc. (BI)
FDA Received Date:	September 13, 2021
OSE RCM #:	2021-1820
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Boehringer Ingelheim Pharmaceuticals, Inc. submitted an efficacy supplement on September 13, 2021 under NDA 204629/S-033 for Jardiance (empagliflozin) tablets. This efficacy supplement proposes a new indication "to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction [redacted (b) (4)]." We reviewed the proposed Jardiance prescribing information (PI) and medication guide for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

Jardiance is a 505(b)(1) drug product that was approved on August 1, 2014 under NDA 204629 as a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. On December 2, 2016, an additional indication was approved for Jardiance to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. On August 18, 2021, an additional indication was approved for Jardiance to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction. Jardiance is available as tablets in strengths of 10 mg and 25 mg.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI) and medication guide for Jardiance to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed PI and medication guide for Jardiance did not identify any unique areas of vulnerability that may lead to medications errors. Thus, we have no concerns or recommendations for the PI or the medication guide. We defer to the Division of Cardiology and Nephrology (DCN) for the acceptability of the proposed indication for Jardiance.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Jardiance prescribing information (PI) and medication guide did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jardiance received on September 13, 2021 from Boehringer Ingelheim Pharmaceuticals, Inc..

Table 2. Relevant Product Information for Jardiance	
Initial Approval Date	August 1, 2014
Active Ingredient	empagliflozin
Indication	JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated: • as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. • ***Proposed:*** to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure independent of left ventricular ejection fraction. (b) (4)
Route of Administration	Oral
Dosage Form	tablets
Strength	10 mg and 25 mg
Dose and Frequency	• The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food • For additional glycemic control, dose may be increased to 25 mg in patients tolerating JARDIANCE
How Supplied	10 mg tablets: 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. • Bottles of 30 (NDC 0597-0152-30) • Bottles of 90 (NDC 0597-0152-90) • Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0152-37), institutional pack. 25 mg tablets: pale yellow, oval, biconvex film-coated tablets, debossed with “S 25” on one side and the Boehringer Ingelheim company symbol on the other side. • Bottles of 30 (NDC 0597-0153-30) • Bottles of 90 (NDC 0597-0153-90)

	• Cartons containing 3 blister cards of 10 tablets each (3 x 10) (NDC 0597-0153-37), institutional pack.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 19, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Jardiance. Our search identified 4 previous reviews[a,b,c,d], and we considered our previous recommendations to see if they are applicable for this current review.

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[a] Agustin R. Label, Labeling, and Packaging Review for Jardiance, NDA 204629. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Nov 25. RCM No.: 2013-655.

[b] Conrad, A. Label and Labeling Review for Jardiance (NDA 204629/S-019). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 05. RCM No.: 2018-2249.

[c] Conrad, A. Label and Labeling Review for Jardiance (NDA 204629/S-019). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 19. RCM No.: 2018-2249-1.

[d] Straka, M. Label and Labeling Review for Jardiance (NDA 204629/S-026). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 17. RCM No.: 2020-2247.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Jardiance labels and labeling submitted by Boehringer Ingelheim Pharmaceuticals, Inc..

- Medication Guide received on September 13, 2021, available from \\CDSESUB1\evsprod\nda204629\0332\m1\us\proposed.doc
- Prescribing Information (Image not shown) received on September 13, 2021, available from \\CDSESUB1\evsprod\nda204629\0332\m1\us\proposed.doc

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[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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