CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204629Orig1s008

Trade Name:	JARDIANCE
Generic or Proper Name:	empagliflozin
Sponsor:	Boehringer Ingelheim
Approval Date:	December 2, 2016
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 events in adults with type 2 diabetes mellitus and established cardiovascular disease . Limitations of Use**:** • Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204629/S-008

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Daniel T. Coleman, Ph.D.
Sr. Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Coleman:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 4, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jardiance (empagliflozin) tablets.

We acknowledge receipt of your major amendment dated May 18, 2016, which extended the goal date by three months.

This Prior Approval supplemental new drug application proposes a new indication for Jardiance based on results of the cardiovascular safety study 1245.25, the EMPA-REG OUTCOME trial. It also updates the PI to comply with the Pregnancy and Lactation Labeling Rule (PLLR).

APPROVAL & LABELING

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

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert), 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.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this supplemental application because necessary studies are impossible or highly impracticable. This was determined because macrovascular complications of diabetes mellitus require years to develop, and they are very rare in pediatric patients with diabetes mellitus. For a meaningful study to be conducted, the population would require a diagnosis of type 2 diabetes mellitus AND high cardiovascular risk. The number of pediatric patients fitting these criteria is small, and the required length of follow-up would likely result in patients exceeding the pediatric age range. A clinical trial for the new proposed indication is therefore not feasible.

FULFILLMENT OF POSTMARKETING REQUIREMENT

This supplemental application contained the final report for the following postmarketing requirement listed in the August 1, 2014, approval letter.

2755-4 A randomized, double-blind, placebo-controlled trial evaluating the effect of empagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with empagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of empagliflozin on the incidence of liver toxicity, bone fractures,

nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. Estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening renal function.

We have reviewed your supplemental application, as amended, and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements listed in the August 1, 2014, approval letter for NDA 204629 and a postapproval postmarketing requirement listed in the December 4, 2015, approval letter for NDA 204629/S-007 that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), 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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, call Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
12/02/2016

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)	12/2016
Warnings and Precautions (5)	12/2016

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

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 adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)

Limitations of Use: Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1)

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

- The recommended dose of JARDIANCE is 10 mg once daily, taken in the morning, with or without food (2.1)
- Dose may be increased to 25 mg once daily (2.1)
- Assess renal function before initiating JARDIANCE. Do not initiate JARDIANCE if eGFR is below 45 mL/min/1.73 m^2 (2.2)
- Discontinue JARDIANCE if eGFR falls below 45 mL/min/1.73 m^2 (2 2)

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

Tablets: 10 mg, 25 mg (3)

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

- History of serious hypersensitivity reaction to JARDIANCE (4)
- Severe renal impairment, end-stage renal disease, or dialysis (4)

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

- *Hypotension* Before initiating JARDIANCE assess and correct volume status in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.1)
- *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. (5.2)
- *Acute kidney injury and impairment in renal function* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy. (5.3)
- *Urosepsis and Pyelonephritis* Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (5.4)
- *Hypoglycemia* Consider lowering the dose of insulin secretagogue or insulin to reduce the risk of hypoglycemia when initiating JARDIANCE (5.5)
- *Genital mycotic infections* Monitor and treat as appropriate (5.6)
- *Increased LDL-C* Monitor and treat as appropriate (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 1-800-459-9906 TTY, 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 (5.1, 5.3, 8.5)
- *Patients with renal impairment* Higher incidence of adverse reactions related to reduced renal function (2.2, 5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2016

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:

- 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.

Limitations of Use

JARDIANCE is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food. In patients tolerating JARDIANCE, the dose may be increased to 25 mg *[see Clinical Studies (14)]*.

In patients with volume depletion, correcting this condition prior to initiation of JARDIANCE is recommended *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5), and Patient Counseling Information (17)]*.

2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of JARDIANCE and periodically thereafter.

JARDIANCE should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

JARDIANCE should be discontinued if eGFR is less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.1, 5.3), and Use in Specific Populations (8.6)]*.

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

- History of serious hypersensitivity reaction to JARDIANCE.
- Severe renal impairment, end-stage renal disease, or dialysis *[see Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

JARDIANCE causes intravascular volume contraction. Symptomatic hypotension may occur after initiating JARDIANCE *[see Adverse Reactions (6.1)]* particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating JARDIANCE, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension

after initiating therapy and increase monitoring in clinical situations where volume contraction is expected *[see Use in Specific Populations (8.5)]*.

5.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in 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. 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 due to illness or 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. In patients treated with JARDIANCE consider monitoring for ketoacidosis and temporarily discontinuing JARDIANCE in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.3 Acute Kidney Injury and Impairment in Renal Function

JARDIANCE causes intravascular volume contraction *[see Warnings and Precautions (5.1)]* and can cause renal impairment *[see Adverse Reactions (6.1)]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving SGLT2 inhibitors, including JARDIANCE; some reports involved patients younger than 65 years of age.

Before initiating JARDIANCE, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing JARDIANCE in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue JARDIANCE promptly and institute treatment.

JARDIANCE increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating JARDIANCE *[see Adverse Reactions (6.1)]*. Renal function should be evaluated prior to initiation of JARDIANCE and monitored periodically thereafter. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of JARDIANCE is not recommended when eGFR is persistently less than 45

mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.2), Contraindications (4), Use in Specific Populations (8.6)]*.

5.4 Urosepsis and Pyelonephritis
There have been postmarketing 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)]*.

5.5 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.

5.6 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 mycotic genital infections. Monitor and treat as appropriate.

5.7 Increased Low-Density Lipoprotein Cholesterol (LDL-C)
Increases in LDL-C can occur with JARDIANCE *[see Adverse Reactions (6.1)]*. Monitor and treat as appropriate.

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

- Hypotension *[see Warnings and Precautions (5.1)]*
- Ketoacidosis *[see Warnings and Precautions (5.2)]*
- Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions (5.3)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6)]*
- Increased Low-Density Lipoprotein Cholesterol (LDL-C) *[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.

Pool of Placebo-Controlled Trials evaluating JARDIANCE 10 and 25 mg
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. 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

	Number (%) of Patients		
	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 Warnings and Precautions (5.1) and 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.

Acute Impairment in Renal Function
Treatment with JARDIANCE was associated with increases in serum creatinine and decreases in eGFR (see Table 2). Patients with moderate renal impairment at baseline had larger mean changes *[see Warnings and Precautions (5.3)* and *Use in Specific Populations (8.5, 8.6)]*.

In a long-term cardiovascular outcome trial, the acute impairment in renal function was observed to reverse after treatment discontinuation suggesting acute hemodynamic changes play a role in the renal function changes observed with empagliflozin.

Table 2 Changes from Baseline in Serum Creatinine and eGFR[a] in the Pool of Four 24-week Placebo-Controlled Studies and Renal Impairment Study

		Pool of 24-Week Placebo-Controlled Studies		
		Placebo	**JARDIANCE 10 mg**	**JARDIANCE 25 mg**
Baseline Mean	N	825	830	822
	Creatinine (mg/dL)	0.84	0.85	0.85
	eGFR (mL/min/1.73 m^2)	87.3	87.1	87.8
Week 12 Change	N	771	797	783
	Creatinine (mg/dL)	0.00	0.02	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-1.3	-1.4
Week 24 Change	N	708	769	754
	Creatinine (mg/dL)	0.00	0.01	0.01
	eGFR (mL/min/1.73 m^2)	-0.3	-0.6	-1.4
		Moderate Renal Impairment[b]		
		Placebo		**JARDIANCE 25 mg**
Baseline Mean	N	187	--	187
	Creatinine (mg/dL)	1.49	--	1.46
	eGFR (mL/min/1.73 m^2)	44.3	--	45.4
Week 12 Change	N	176	--	179
	Creatinine (mg/dL)	0.01	--	0.12
	eGFR (mL/min/1.73 m^2)	0.1	--	-3.8
Week 24 Change	N	170	--	171
	Creatinine (mg/dL)	0.01	--	0.10
	eGFR (mL/min/1.73 m^2)	0.2	--	-3.2
Week 52 Change	N	164	--	162
	Creatinine (mg/dL)	0.02	--	0.11
	eGFR (mL/min/1.73 m^2)	-0.3	--	-2.8
Post-treatment Change[c]	N	98	--	103
	Creatinine (mg/dL)	0.03	--	0.02
	eGFR (mL/min/1.73 m^2)	0.16	--	1.48

[a]Observed cases on treatment.
[b]Subset of patients from renal impairment study with eGFR 30 to less than 60 mL/min/1.73 m^2
[c]Approximately 3 weeks after end of treatment.

Hypoglycemia
The incidence of hypoglycemia by study is shown in Table 3. The incidence of hypoglycemia increased when JARDIANCE was administered with insulin or sulfonylurea *[see Warnings and Precautions (5.5)]*.

Table 3 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 Warnings and Precautions (5.4) and Use in Specific Populations (8.5)]*.

Laboratory Tests
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 *[see Warnings and Precautions (5.7)]*. 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 *[see Warnings and Precautions (5.2)]*
- Urosepsis and pyelonephritis *[see Warnings and Precautions (5.4)]*

7 DRUG INTERACTIONS
7.1 Diuretics
Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion *[see Warnings and Precautions (5.1)]*.

7.2 Insulin or Insulin Secretagogues
Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia *[see Warnings and Precautions (5.5)]*.

7.3 Positive Urine Glucose Test
Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

7.4 Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

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.

Limited data available 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. Empagliflozin was not teratogenic in rats and rabbits up to 300 mg/kg/day, which approximates 48-times and 128-times, respectively, the maximum clinical dose of 25 mg when administered during organogenesis *[see Data]*.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% 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 2-4% and 15-20%, 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, stillbirth, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, 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. 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 no 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, advise women 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 -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 in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No JARDIANCE dosage change is recommended based on age *[see Dosage and Administration (2)]*. In studies assessing the efficacy of empagliflozin in improving glycemic control in patients with type 2 diabetes, a total of 2721 (32%) patients treated with empagliflozin 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 (5.1) and Adverse Reactions (6.1)]*.

8.6 Renal Impairment

The efficacy and safety of JARDIANCE were evaluated in a study of patients with mild and moderate renal impairment *[see Clinical Studies (14.1)]*. 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 *[see Warnings and Precautions (5.3)]*, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function.

In a large cardiovascular outcomes study, 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 (14.2)]*.

The efficacy and safety of JARDIANCE have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. JARDIANCE is not expected to be effective in these patient populations *[see Dosage and Administration (2.2), Contraindications (4) and Warnings and Precautions (5.1, 5.3)]*.

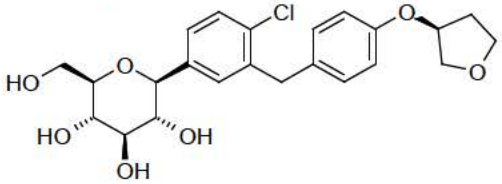
8.7 Hepatic Impairment
JARDIANCE may be used in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE
In the event of an overdose with JARDIANCE, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied.

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

12.2 Pharmacodynamics

Urinary Glucose Excretion

In patients with type 2 diabetes, urinary glucose excretion increased immediately following a dose of JARDIANCE 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 JARDIANCE once daily *[see Clinical Studies (14)]*.

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 JARDIANCE 25 mg, JARDIANCE 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%.

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.

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. 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 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 subjects with kidney failure/end stage renal disease (ESRD) patients, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in subjects with moderate renal impairment and kidney failure/ESRD compared to patients with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in subjects with mild and severe renal impairment as compared to subjects with normal renal function. 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 subjects 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)]*.

Pediatric

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

Drug Interactions

In vitro Assessment of Drug Interactions

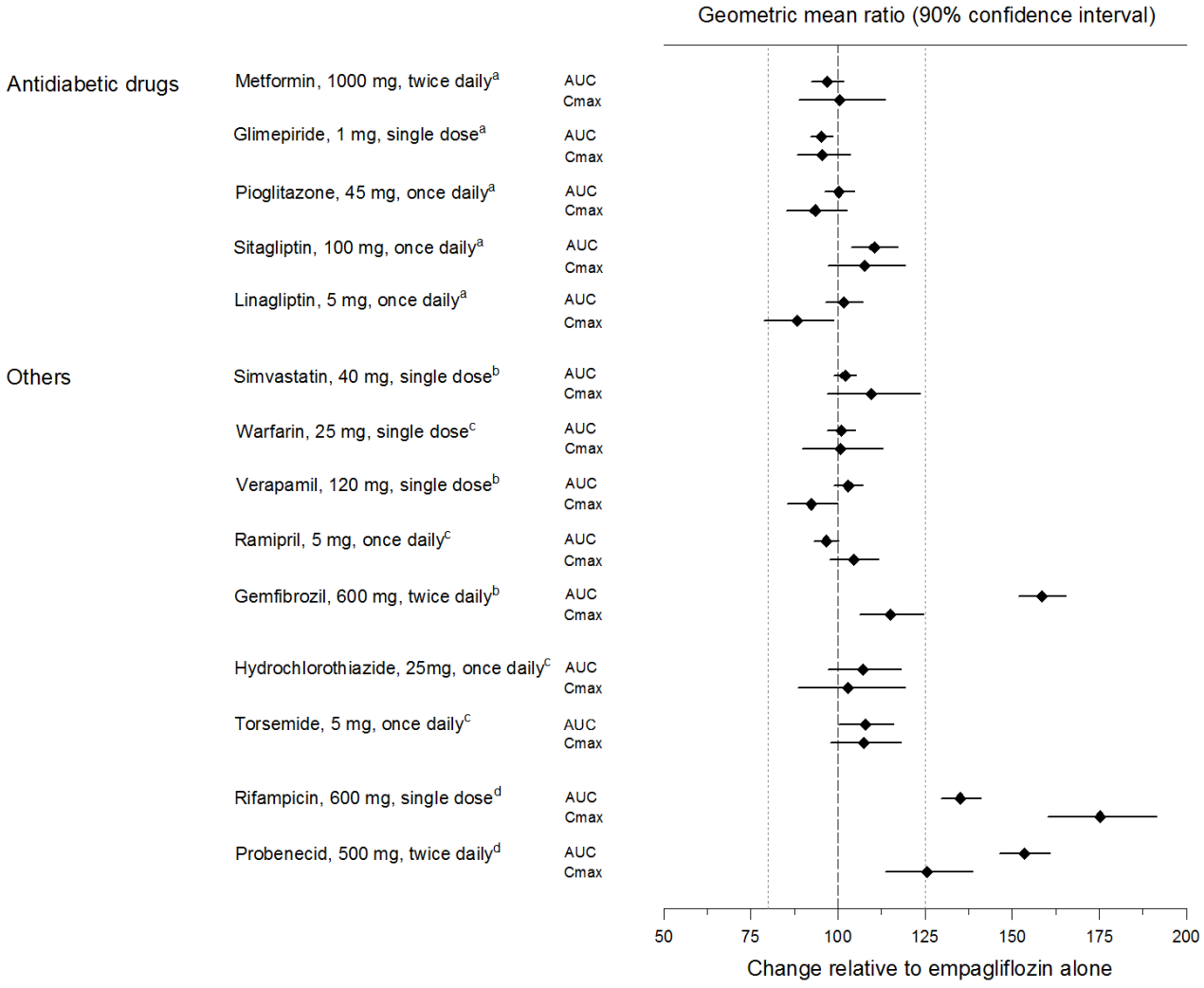
Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. *In vitro* data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT1A3, UGT1A8, UGT1A9, and UGT2B7. Empagliflozin does not inhibit UGT1A1,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

No dose adjustment of JARDIANCE is recommended when coadministered with commonly prescribed medicinal products based on results of the described pharmacokinetic studies. 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). The observed increases in overall exposure (AUC) of empagliflozin following coadministration with gemfibrozil, rifampicin, or probenecid are not clinically relevant. 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.

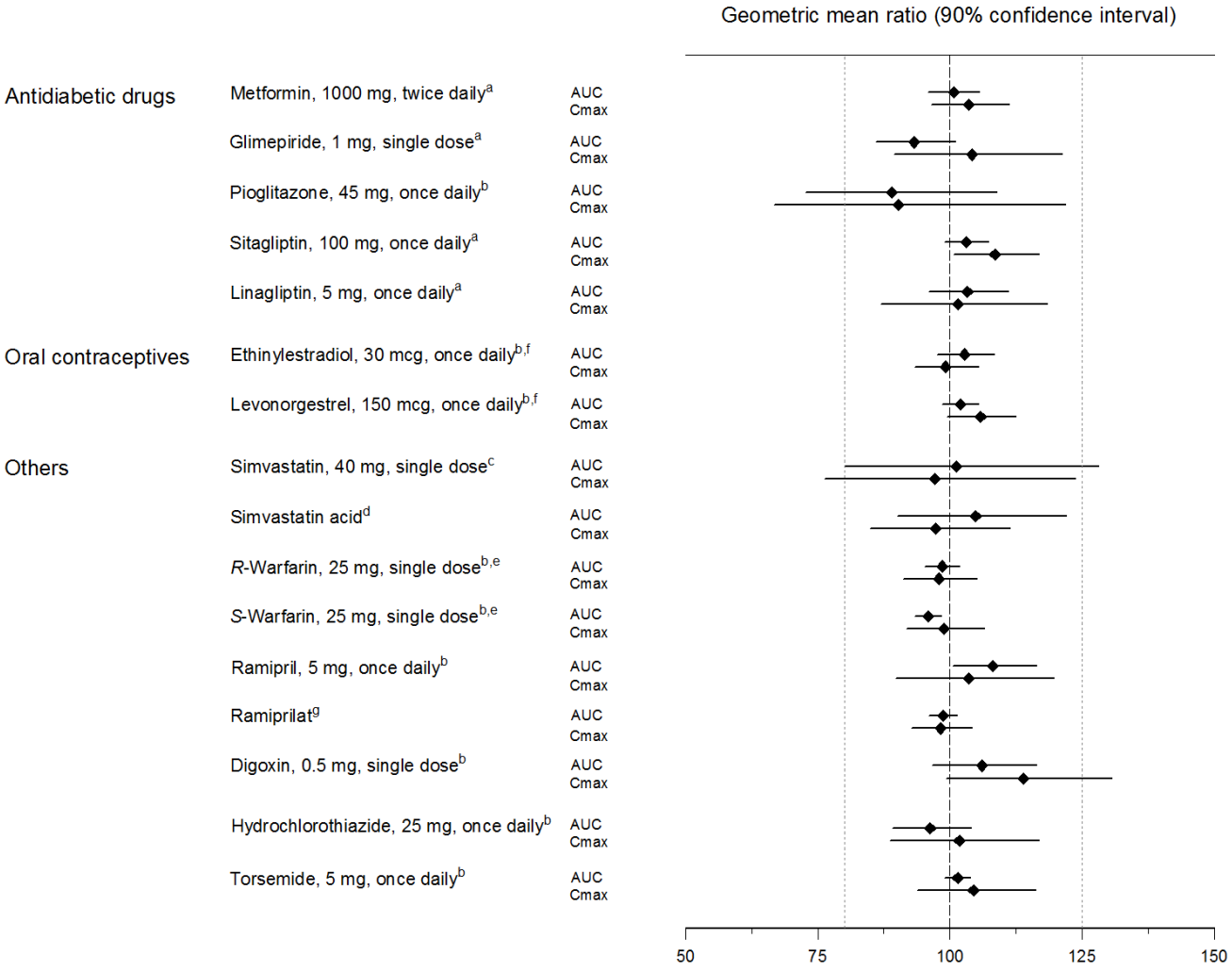
Figure 1 Effect of Various Medications on the Pharmacokinetics of Empagliflozin as Displayed as 90% Confidence Interval of Geometric Mean AUC and C_{max} Ratios [reference lines indicate 100% (80% - 125%)]



[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

14.1 Glycemic Control

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.

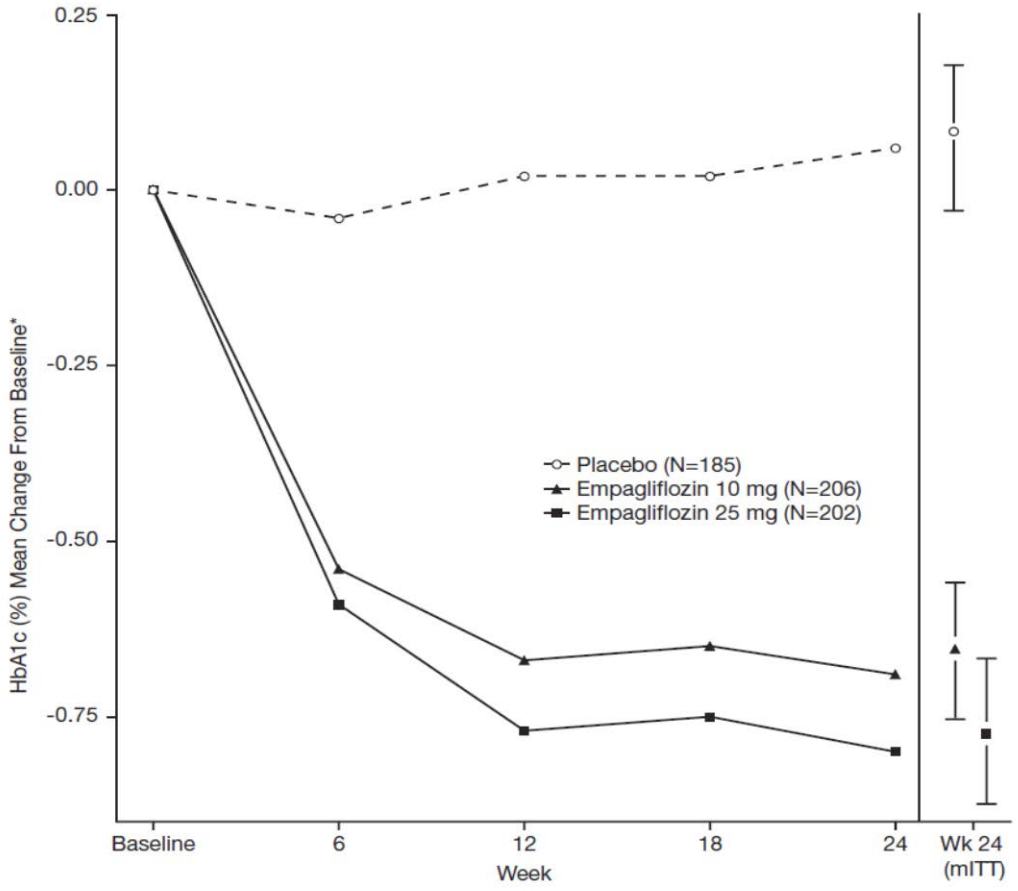
At Week 24, treatment with JARDIANCE 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (p-value <0.0001), fasting plasma glucose (FPG), and body weight compared with placebo (see Table 4 and Figure 3).

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.

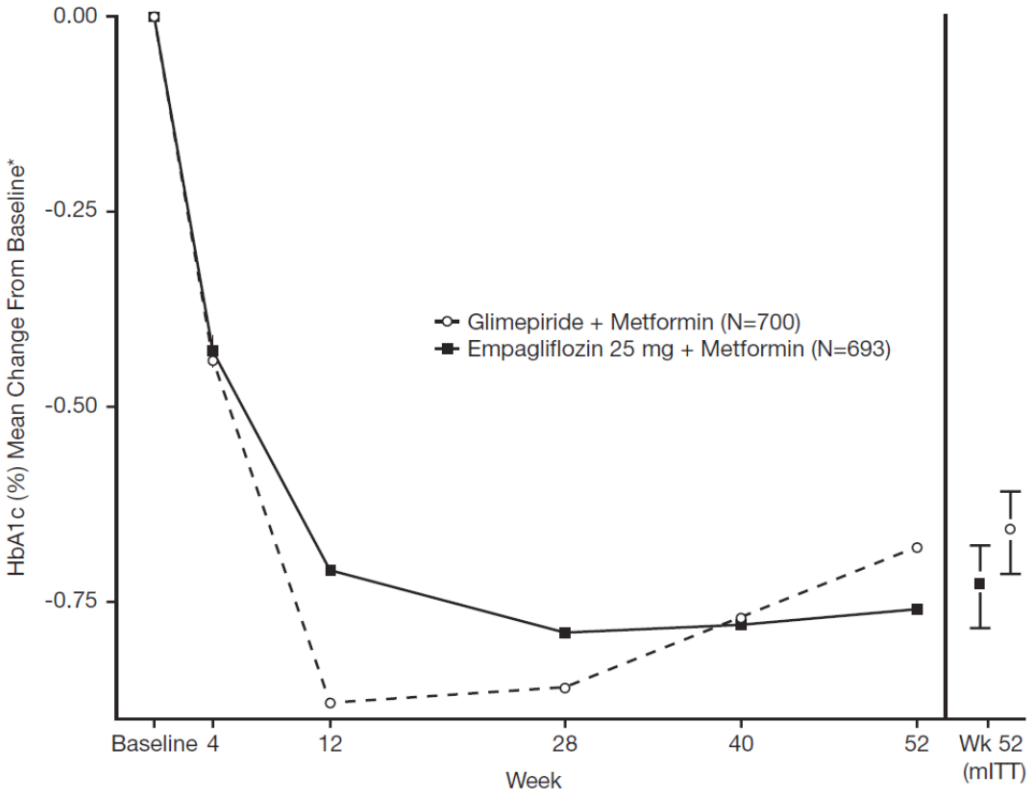
At Week 52, JARDIANCE 25 mg and glimepiride lowered HbA1c and FPG (see Table 8, Figure 4). The difference in observed effect size between JARDIANCE 25 mg and glimepiride excluded the pre-specified non-inferiority margin of 0.3%. The mean daily dose of glimepiride was 2.7 mg and the maximal approved dose 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 placebo, 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 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 Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

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

The effect of 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 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 nonfatal myocardial infarction (MI) or a nonfatal 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.

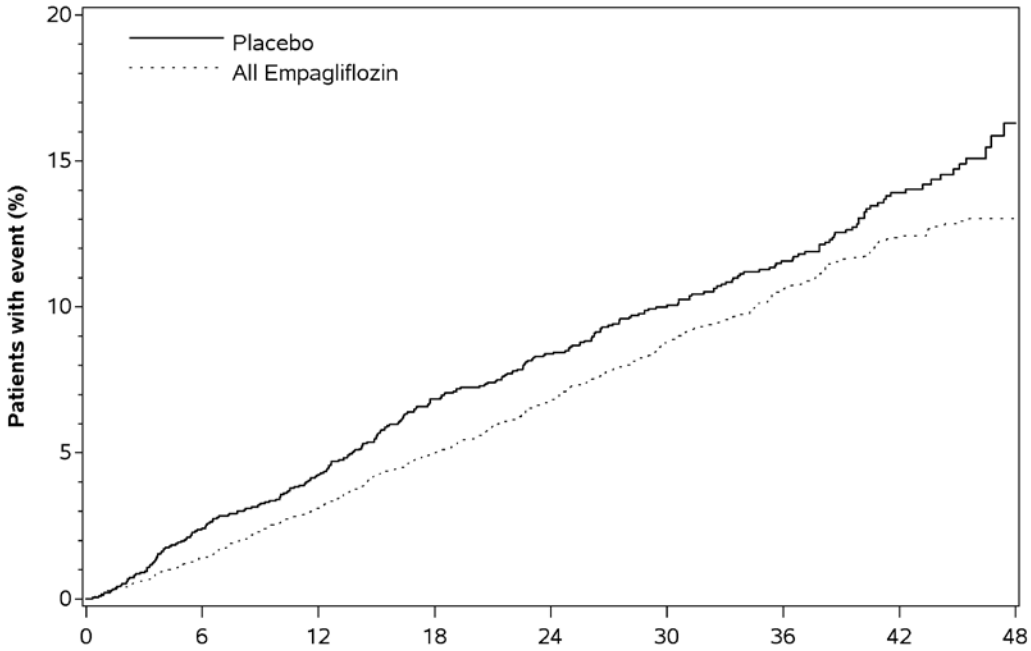
JARDIANCE significantly reduced the time to first occurrence of primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (HR: 0.86; 95% CI 0.74, 0.99). The treatment effect was due to a significant reduction in the risk of cardiovascular death in subjects 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 Figure 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)

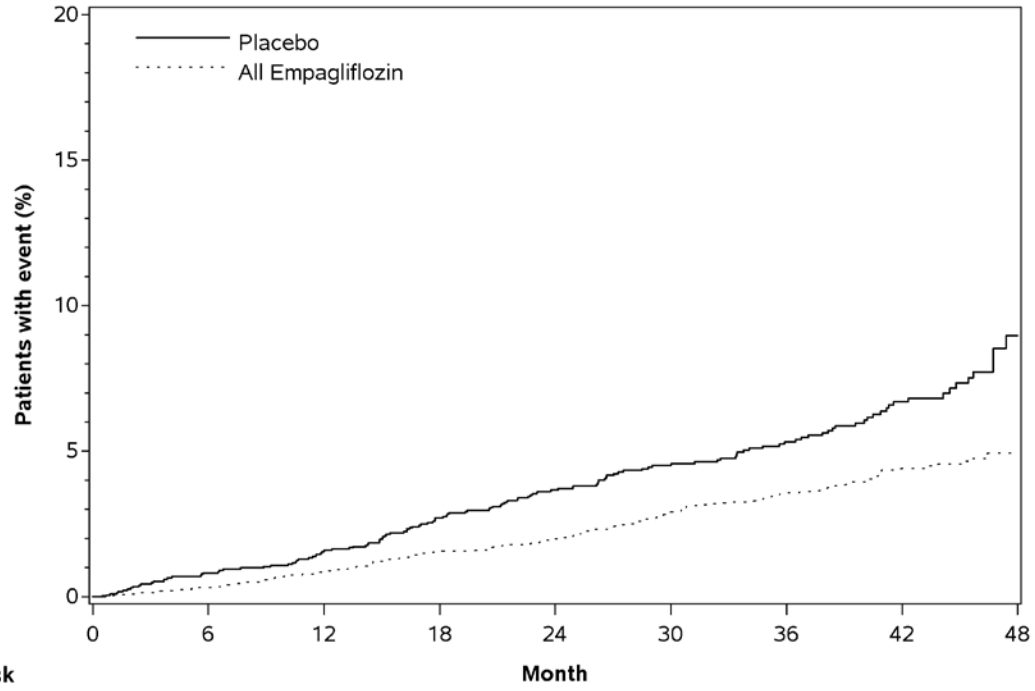
[a]Treated set (patients who had received at least one dose of study drug)
[b]p−value for superiority (2−sided) 0.04
[c]Total number of events

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).

16 HOW SUPPLIED/STORAGE AND HANDLING

JARDIANCE tablets are available in 10 mg and 25 mg strengths 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 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Instructions
Instruct patients to read the Patient Information before starting JARDIANCE therapy and to reread it each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens.

Inform patients of the potential risks and benefits of JARDIANCE and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

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.

Inform patients that the most common adverse reactions associated with the use of JARDIANCE are urinary tract infections and mycotic genital infections.

Inform female patients of reproductive potential that the use of JARDIANCE during pregnancy has not been studied in humans, and that JARDIANCE should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal data, JARDIANCE may cause fetal harm in the second and third trimesters. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue JARDIANCE or nursing, taking into account the importance of the drug to the mother. It is not known if JARDIANCE is excreted in breast milk; however, based on animal data, JARDIANCE may cause harm to nursing infants.

Hypotension

Inform patients that hypotension may occur with JARDIANCE and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.1)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of JARDIANCE. 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 advice immediately *[see Warnings and Precautions (5.2)]*.

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of JARDIANCE. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue JARDIANCE use in those settings *[see Warnings and Precautions (5.3)]*.

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 (5.4)]*.

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 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)]*.

Laboratory Tests

Inform patients that renal function should be assessed prior to initiation of JARDIANCE and monitored periodically thereafter.

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

Inform patients that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and HbA1c levels, with a goal of decreasing these levels toward the normal range. Hemoglobin A1c monitoring is especially useful for evaluating long-term glycemic control.

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PATIENT INFORMATION
JARDIANCE® (jar DEE ans)
(empagliflozin)
Tablets

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

JARDIANCE can cause serious side effects, including:

- **Dehydration.** JARDIANCE can cause some people to have dehydration (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).

  You may be at higher risk of dehydration if you:
  - have low blood pressure
  - take medicines to lower your blood pressure, including diuretics (water pill)
  - are on low sodium (salt) diet
  - have kidney problems
  - are 65 years of age or older
- **Vaginal yeast infection.** Women who take JARDIANCE may get vaginal yeast infections. 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 or balanoposthitis).** Men who take JARDIANCE may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis 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 penis

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis. Your doctor may suggest you use an over-the-counter antifungal medicine. Talk to your doctor right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

What is JARDIANCE?

- JARDIANCE is a prescription medicine used:
  - along with diet and exercise to lower blood sugar in adults with type 2 diabetes.
  - to reduce the risk of cardiovascular death in adults with type 2 diabetes who have known cardiovascular disease.
- JARDIANCE is not for people with type 1 diabetes.
- JARDIANCE is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- It is not known if JARDIANCE is safe and effective in children under 18 years of age.

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 leaflet for a list of ingredients in JARDIANCE.
- have severe kidney problems or are on dialysis

What should I tell my doctor before using JARDIANCE?

Before you take JARDIANCE, tell your doctor if you:

- have kidney problems
- have liver problems
- have a history of urinary tract infections or problems with urination
- are going to have surgery
- are eating less due to illness, surgery, or 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 any other medical conditions
- are pregnant or planning to become pregnant. It is not known if JARDIANCE will harm your unborn baby. If you are pregnant, talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if JARDIANCE passes into your breast milk. Talk with your

doctor about the best way to feed your baby if you take JARDIANCE.

Tell your doctor 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 doctor if you take:

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

Ask your doctor or pharmacist for a list of these medicines if you are not sure if your medicine is listed above.

How should I take JARDIANCE?

- Take JARDIANCE exactly as your doctor tells you to take it.
- Take JARDIANCE by mouth 1 time in the morning each day, with or without food.
- Your doctor 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 doctor if you have questions about a missed dose.
- Your doctor 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 doctor or go to the nearest hospital emergency room right away.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine that you need may change. Tell your doctor right away if you have any of these conditions and follow your doctor's instructions.
- Check your blood sugar as your doctor tells you to.
- Stay on your prescribed diet and exercise program while taking JARDIANCE.
- Talk to your doctor about how to prevent, recognize and manage low blood sugar (hypoglycemia), high blood sugar (hyperglycemia), and complications of diabetes.
- Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your hemoglobin HbA1c.
- When taking JARDIANCE, you may have sugar in your urine, which will show up on a urine test.

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?**"
- **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 is a serious condition, which may need 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 doctor right away if you get any of the following symptoms**:
  - o nausea
  - o vomiting
  - o stomach-area (abdominal) pain
  - o tiredness
  - o 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.
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking JARDIANCE. Tell your doctor 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:
  - o headache
  - o drowsiness
  - o weakness
  - o irritability
  - o hunger
  - o fast heartbeat
  - o confusion
  - o shaking or feeling jittery
  - o dizziness
  - o sweating
- **Kidney problems.** Sudden kidney injury has happened to people taking JARDIANCE. Talk to your doctor right

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

- **Increased fats in your blood (cholesterol)**

These are not all the possible side effects of JARDIANCE. For more information, ask your doctor 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 68°F to 77°F (20°C to 25°C).

General information about the safe and effective use of JARDIANCE.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. 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.

This Patient Information summarizes the most important information about JARDIANCE. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about JARDIANCE that is written for health professionals.

For more information about JARDIANCE, go to www.jardiance.com, scan the code below, or call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

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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IT5728QL012016

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: December 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s008

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MDCM
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	204629 #008
Applicant Name	Boehringer Ingelheim
Date of Submission	November 4, 2015
PDUFA Goal Date	December 4, 2016 (clock extended by 3 months)
Proprietary Name / Established (USAN) Name	Jardiance/ Empagliflozin
Dosage Forms / Strength	Jardiance; Tablet: 10 mg and 25 mg
Proposed Indication(s)	*In adult patients with type 2 diabetes mellitus and high cardiovascular risk to reduce the risk of all-cause mortality by reducing the incidence of cardiovascular death or hospitalization for heart failure*
Action/Recommended Action for NME:	Approval
Indications Granted	*to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ondina Lungu, MD
Statistical Review	Jennifer Clarck, PhD
Clinical Pharmacology Review	Sang Chung, PhD
Safety Stats Review (DB-7)	Sherman Xia, PhD
DSI	Cynthia Kleppinger, MD
CDTL Review	William Chong, MD
Medical Officer Consult Review	Karen, Hicks, MD
Medical Officer Consult Review	Kimberly, Smith, MD
Medical Officer Consult Review	Jody, Green, MD

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

On November 4, 2015 Boehringer Ingelheim submitted an efficacy supplement to new drug application 204629 for Jardiance (empagliflozin) pursuant to Section 505(b)(1) of the Food Drug and Cosmetic Act. Jardiance is a sodium glucose co-transporter 2 (SGLT-2) inhibitor approved in 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

In this supplement, the applicant is seeking to add data from a new clinical investigation (i.e., the EMPA-REG OUTCOME study also referred to as Study 1245.25) to the product label. Specifically, the applicant believes the findings from the EMPA-REG OUTCOME study support the new indication that empagliflozin*…reduces the risk of all-cause mortality by reducing the incidence of cardiovascular death or hospitalization for heart failure* in adult patients with type 2 diabetes at high risk of cardiovascular disease.

The memorandum serves as the decisional summary memorandum for the application and will focus specifically on whether the data from the EMPA-REG OUTCOME study are sufficient to support a new claim.

The EMPA-REG OUTCOME study was a cardiovascular outcomes trial (CVOT) required by FDA under PMR 2755-4 and conducted to *exclude* the possibility that use of empagliflozin for the treatment of adults with type 2 diabetes mellitus would result in an unacceptable increase in the risk of atherosclerotic cardiovascular disease[1]. The trial has a long regulatory history which is summarized in Section 2.4 of Dr. Lungu's clinical review (see this review for details).

The applicant also sought to add data from exploratory analyses in the EMPA-REG OUTCOME study to imply another clinical benefit of empagliflozin, namely that empagliflozin has renal protective effects. These data were discussed at the 28 June Advisory Committee and in detail in Dr. Smith's nephrology consult review, Dr. Lungu's primary clinical review and Dr. Chong's cross discipline team leader review. I am in full agreement with the conclusions reached by these reviewers and the Committee that these data do not conclusively establish that empagliflozin has a lasting beneficial effect on renal outcomes in this population. The implicit renal efficacy claim will not be allowed in labeling. I will not discuss this issue in my memorandum and refer the reader to each of the above reviews for detailed discussions related to this specific topic.

2. Background

[1] Refer to Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

Diabetes and Cardiovascular Disease

Cardiovascular disease is a major cause of morbidity and mortality in patients with diabetes. Large observational studies have demonstrated that diabetes is an independent risk factor for cardiovascular disease and cardiovascular death[2]. Patients with diabetes have an approximately 2-fold higher lifetime risk of atherosclerotic cardiovascular disease and heart failure, and are more likely to die from cardiovascular causes than patients without diabetes.

Hyperglycemia and Cardiovascular Disease

Although observational data suggests hyperglycemia could contribute to the excess cardiovascular disease burden in patients with type 2 diabetes, to date, no individual, large, prospectively conducted trial has provided conclusive evidence of a beneficial effect of intensive glucose control on macrovascular disease outcomes (i.e., cardiovascular outcomes from heron in) in individuals with type 2 diabetes.

No difference in cardiovascular outcomes between intensive and conventional glucose control groups [between group Hemoglobin A1c (HbA1c) difference; 7.0% versus 7.9% respectively over ~10 years] was observed in patients **with newly diagnosed** type 2 diabetes enrolled United Kingdom Prospective Diabetes Study[3]. In contrast, a strong association between blood pressure reduction and CV risk reduction was observed in UKPDS[4]. In the study, each 10 mm Hg decrease in mean systolic blood pressure was associated with a 15% (12% to 18%, P<0.0001) reduction in the risk of death and an 11% (7% to 14%, P<0.0001) reduction in the risk of myocardial infarction.

Better glucose control was also not associated with improvement in cardiovascular outcomes in patients **with long standing diabetes** in the ACCORD trial[5] (Hb1Ac difference; 6.4% versus 7.5% for a median follow-up of 3.4 years), ADVANCE trial[6] (HbA1c difference; 6.5% versus 7.3% for a median follow-up of 5 years) or Veterans Affairs Diabetes trial[7] (HbA1c difference; 6.6% versus 8.4% for a median follow-up of 5.6 years) trials. The ACCORD trial was, in fact, terminated early because intensive glucose control led to a significant increase in cardiovascular and all-cause mortality (i.e., a 35 and 22 percent excess in all cause and cardiovascular death respectively, relative to conventional glucose control).

Multiple reasons[8] have been put forward to explain the neutral or adverse findings in the above cited trials. For example, it is possible that hyperglycemia per se may be associated with CV risk but not be in the causal pathway, or that glucose only contributes a small amount to excess CV risk in the range of HbA1c examined in these trials, or that the duration

[2] Am J Cardiol. 1974;34(1):29, Circulation 59, No. 1, 1979, Diabetes Care 1993; 16(2):434 and Lancet 2010; 375(9733):2215.
[3] Lancet. 1998;352(9131):837.
[4] BMJ. 2000;321(7258):412.
[5] N Engl J Med 2008; 358:2545-2559
[6] N Engl J Med 2008; 358:2560-2572
[7] N Engl J Med 2009; 360:129-139
[8] Diabetes Care 2009 Jan; 32(1): 187-192.

of follow-up in these studies was insufficient, or that the population in the later studies had disease that was too advanced, or that harm (i.e., hypoglycemia) from too aggressive glucose lowering could have outweighed potential benefits gained or that harm from the specific cocktail of drugs used to lower glucose could have outweighed benefits. The actual reason(s) is (are) at present unknown.

Specific Glucose Lowering Drugs and Cardiovascular Disease Benefit

Similarly, no data have conclusively established that a specific antidiabetic drug could improve cardiovascular outcomes. Up until the publication of the EMPA-REG OUTCOME trial, no large, randomized, controlled trials designed to evaluate the effect of correcting glucose abnormalities with a specific glucose lowering drug on cardiovascular outcomes, for glucose abnormalities spanning the pre-diabetes to diabetes range, have conclusively demonstrated benefits. These trials have examined the following specific glucose lowering drugs; pioglitazone[9] (diabetes), nateglinide[10] (prediabetes), insulin glargine[11] (diabetes and prediabetes), saxagliptin[12] (diabetes) and sitagliptin[13] (diabetes).

There are 13 broad classes of drugs indicated to improve glucose control in adults with type 2 diabetes mellitus in the United States. These classes differ widely in the mechanisms by which they lower glucose and many have pleiotropic effects. Empagliflozin, the specific drug product in this supplement, belongs to the sodium glucose co-transporter 2 (SGLT-2) inhibitor class of drugs. Products in this class lower circulating glucose but also have diuretic, natriuretic, uricosuric, and ketogenic effects. These effects are not shared by other glucose lowering drug classes.

Treatment of Cardiovascular Disease in Diabetes

The approach to treating atherosclerotic cardiovascular disease in diabetes consists in aggressive management of modifiable risk factors. Smoking cessation, treatment of hypertension and dyslipidemia and use of aspirin or other antiplatelet agents for secondary prevention are the cornerstone of therapy.

3. CMC/Device

[9] Lancet 2005; 366, 1279–1289. In the PROactive study no difference was observed in the primary composite endpoint between placebo and pioglitazone (Hazard Ratio 0.90, 95% CI 0.80-1.02, p=0.095). The most frequent events in the composite endpoint were deaths and the majority of deaths were cardiovascular deaths. No trend suggestive of a benefit was apparent in the mortality assessment (Hazard Ratio 0.96, 95% CI 0.78–1.18). One of the key secondary composite endpoint [non-fatal stroke, non-fatal MI (specifically excluding silent MI) and all cause death] suggested pioglitazone could potentially reduce risk (0.84, 0.72-0.98) but the findings could have been the result of chance. No trials to evaluate the veracity of the hypothesis that pioglitazone could have beneficial effect on the secondary three-point composite endpoint was ever carried out.

[10] N Engl J Med 2010; 362:1463-1476

[11] N Engl J Med 2012; 367:319-328

[12] N Engl J Med 2013; 369:1317-1326

[13] N Engl J Med 2015; 373:232-242

No new information is included with the supplement.

4. Nonclinical Pharmacology/Toxicology

No new information is included with the supplement.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The evidence and clinical data submitted to support the cardiovascular benefit claim has been reviewed by Drs. Lungu, Clark, Hicks and Chong in details. My review will briefly summarize the findings but readers should refer to these reviews for a comprehensive assessment of the evidence.

The evidence to support the applicant's new claim is provided by the EMPA-REG OUTCOME trial. The EMPA-REG OUTCOME study was a 7065 subject, randomized, double-blind, parallel group, placebo-controlled trial carried out in adult patients with type 2 diabetes at high risk for an ischemic cardiovascular event.

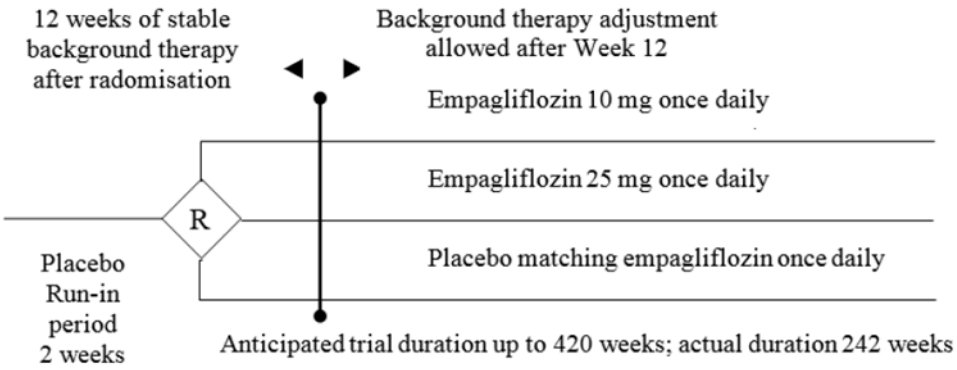
Patients with diabetes whose glycemia was not optimally controlled on diet and exercise alone (HbA1c between 7% and 9%) or on standard of care treatment for diabetes (HbA1c between 7% and 10%) and who had evidence of stable atherosclerotic cardiovascular disease (i.e., coronary heart disease, stroke or peripheral arterial disease > 2 months prior to trial entry) at baseline were eligible to participate. Patients with unstable diabetes, atherosclerotic cardiovascular disease, liver disease and renal disease at baseline were excluded from participation.

The trial included a two-week run-in period to confirm participant eligibility and ensure patients were clinically stable.

A total of 7065 patients were randomized 1:1:1 to empagliflozin 10 mg, empagliflozin 25 mg or placebo. Randomization was stratified by HbA1c, BMI, geographic regions and renal function. Study visits occurred at Weeks 4, 8, 12, 16, 28, 40, 52, and every 14 weeks until a

minimum of 691 3-Point major adverse cardiovascular events[14] (MACE) had occurred. Figure 1 provides a schematic representation of the EMPA-REG OUTCOME study.

Figure 1: Schematic Representation of the EMPA-REG OUTCOME Study



Patients in the trial were to receive standard of care treatment for the management of diabetes and atherosclerotic cardiovascular disease for the duration of the trial. Co-administered antidiabetic medications were to be kept stable for the first 12 weeks of the trial to minimize the risk of hypoglycemia. Thereafter, antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were receiving optimal standard local care for these diseases. Patients in the trial were not eligible to receive rescue treatment with metformin or with other SGLT-2 inhibitors.

End of study visits were to occur when the required number of outcome events was anticipated to have been reached. The end of study visit was to occur within 7 days after permanent discontinuation from study medication. A final follow-up visit was to occur 30 days after the end of study visit. Abnormalities which occurred within 7 days of the last intake of study medication were considered "on-treatment" for the purpose of analyses. Patients who discontinued prematurely were to remain in the study and follow-trial the protocol schedule until study completion unless they withdrew consent.

The primary endpoint for this trial was the time to first occurrence of adjudicated CV death (including fatal stroke and fatal MI), non-fatal myocardial infarction (excluding silent MI), and non-fatal stroke (3-Point MACE). The key secondary endpoint was the time to first occurrence of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction, or hospitalization for unstable angina pectoris (4-Point MACE).

Type-1 error was controlled across the four pre-specified hypotheses to be tested using a hierarchical testing strategy (see below). Non-inferiority refers to the non-inferiority hypothesis to rule out a 30% or greater risk relative to placebo. Superiority refers to the

[14] Cardiovascular death, Non-fatal myocardial infarction, Non-fatal stroke

superiority hypotheses to test whether empagliflozin conferred a benefit on MACE or MACE+ over placebo.

Pre-specified Testing Hierarchy

1. Non-inferiority: 3-Point MACE
2. Non-inferiority: 4-Point MACE
3. Superiority: 3-Point MACE
4. Superiority: 4-Point MACE

For the analyses, the applicant had pre-specified that the 10 mg and 25 mg empagliflozin treatment arms would be combined into a single group. A cox proportional hazards model with factors for treatment (pooled empagliflozin vs. placebo), age, sex, geographical region (*North America [including Australia and New Zealand], Latin America, Europe, Africa, and Asia*), baseline values for BMI (*less than vs. greater than or equal to 30*), HbA1c *(less than vs. greater than or equal to 8.5%*), and eGFR (*normal: eGFR ≥ 90 ml/min, mild impairment: 60 ml/min ≤ eGFR ≤ 89 ml/min, and moderate impairment: 30 ml/min ≤ eGFR ≤ 59 ml/min*) was used to test for non-inferiority of the primary and secondary endpoints against a margin of 1.3 using a 1 sided alpha of 0.0249 (corresponding to 95.02% confidence intervals). The alpha had been adjusted by 0.0001 based on a Haybittle-Peto method to account for a single interim analysis to preserve the overall alpha-level level at 0.025. If non-inferiority was established for both 3-Point and 4-Point MACE, then testing for superiority was to occur in sequence for 3 and 4-Point MACE respectively.

RESULTS

The trial started on August 26, 2010, first randomization occurred on September 15, 2010 and the last study visit for the last subject occurred on April 21, 2015. Subjects with a study visit on or after December 15, 2014 were considered to be completers. Final database lock occurred on June 22, 2015.

Approximately 11,000 individuals were screened. Screening failures were predominantly due to not meeting HbA1c entry criteria. A total of 7065 subjects were randomized at 607 study sites (mean ~ 12 subjects/site) across 42 countries in North (20% of randomized subjects) and South (15% of randomized subjects) America, Eastern and Western Europe (41% of randomized subjects), Asia (19% of randomized subjects), and Africa (4.4% of randomized subjects). The three countries with the largest enrollment were the United States (17%), Brazil (7%), South Africa (4.4%) and Korea (4.0%).

The primary analysis was to follow the intent to treat principle and all subjects who were randomized and received at least one dose of empagliflozin or placebo were to be included in the analysis population (i.e., treated set). Of the 7065 subjects randomized, 7020 were included in the analysis population. The 45 patients who were excluded, were excluded on the grounds that they never started treatment (n=8) or because significant good clinical

practice violations were identified at the clinical site during site monitoring (n=37). Dr. Lungu reviewed the reasons why the eight patient who were randomized never received treatment and found them to be justified (refer to page 57 of her review).

More than 85% of all participants were observed for at least 2 years, and more than half for at least 3 years. The mean observation time was 2.91 years for placebo, and 2.96 years for the pooled empagliflozin group. The median observation time was 3.07 years for placebo and 3.15 years for empagliflozin.

Two hundred eleven patients were missing follow-up data for MACE [i.e., 67 on placebo (2.87%), 81 on empagliflozin 10 mg (3.45%), and 63 on empagliflozin 25 mg (2.69%)]. These patients had prematurely discontinued follow-up for MACE during the study without having experienced a MACE event. When pooling the empagliflozin arms, this translates to 3.07% of patients treated with empagliflozin versus 2.87% with placebo. Follow-up for vital status was essentially complete. Vital status was available for all but 53 patients [i.e., 17 (0.73%) on placebo and 36 (0.77%) in empagliflozin].

The demographic characteristics, baseline disease characteristics, and baseline concomitant drugs are shown in various tables in Dr. Lungu's review between pages 46 to 54. Baseline characteristics were balanced across the three arms. The majority of participants were male (72%), and White (72%). Black and Asian participants accounted for 5% and 22% of the population respectively. The mean age was 63 years. Overall, 82% of participants had had diabetes for more than 5 years and the mean HbA1c at baseline was 8.1%. Approximately 31%, 22% and 20% reported a past history of neuropathy, retinopathy and nephropathy respectively. Moderate and severe renal impairment based on eGFR criteria was present in 25% and 0.4% of trial participants respectively. In the trial population, 76% had coronary artery disease and 23% had a history of cerebrovascular disease at baseline (see Table 1 below for cardiovascular disease characteristics across groups at baseline).

Table 1: Baseline Cardiovascular Disease Characteristics in EMPA-REG OUTCOME (excerpted from Table 4 in Dr. Lungu's Review)

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342	All Empa N=4687
	N (%)	N (%)	N (%)	N (%)
Any CV high-risk factor	2307 (98.9)	2333 (99.5)	2324 (99.2)	4657 (99.4)
Coronary artery disease (CAD)[1]	1763 (75.6)	1782 (76.0)	1763 (75.3)	3545 (75.6)
Multi-vessel CAD	1100 (47.1)	1078 (46.0)	1101 (47.0)	2179 (46.5)
History of MI	1083 (46.4)	1107 (47.2)	1083 (46.2)	2190 (46.7)
Coronary artery bypass graft	563 (24.1)	594 (25.3)	581 (24.8)	1175 (25.1)
Single-vessel CAD	238 (10.2)	258 (11.0)	240 (10.2)	498 (10.6)
History of stroke	553 (23.7)	535 (22.8)	549 (23.4)	1084 (23.1)
Peripheral artery disease	479 (20.5)	465 (19.8)	517 (22.1)	982 (21.0)

[1] CAD defined as any of the following: history of MI, coronary artery bypass graft, multi-vessel CAD, single-vessel CAD
Source: Adapted from Table 10.4.2:1 of the study report for study 1245.25

Treatments for diabetes and atherosclerotic cardiovascular disease were balanced between groups as shown in Tables 2 and 3 excerpted from Dr. Lungu's review. These tables also show that the population was receiving expected common standard of care therapies for used in the management of type 2 diabetes, dyslipidemia, hypertension and atherosclerotic cardiovascular disease.

Table 2: Baseline Antidiabetic and Cardiovascular Disease Treatments in EMPA-REG OUTCOME (excerpted from Table 8 and 9 in Dr. Lungu's Review)

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342	All Empa N=4687
	N (%)	N (%)	N (%)	N (%)
Any antidiabetic	2297 (98.5)	2299 (98.0)	2295 (98.0)	4594 (98.0)
– Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)	3459 (73.8)
– Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)	2252 (48.0)
– Sulfonylurea	992 (42.5)	985 (42.0)	1029 (43.9)	2014 (43.0)
– DPP-4 inhibitor	267 (11.4)	282 (12.0)	247 (10.5)	529 (11.3)
One antidiabetic medication	691 (29.6)	704 (30.0)	676 (28.9)	1380 (29.4)
Two antidiabetic medications	1148 (49.2)	1110 (47.3)	1149 (49.1)	2259 (48.2)
Three antidiabetic medications	387 (16.6)	419 (17.9)	411 (17.5)	830 (17.7)
Four or more antidiabetic medications	71 (3.0)	66 (2.8)	59 (2.5)	125 (2.7)
Any antihypertensive	2221 (95.2)	2227 (95.0)	2219 (94.7)	4446 (94.9)
– ACE inhibitor/ARB	1868 (80.1)	1896 (80.9)	1902 (81.2)	3798 (81.0)
– β-blocker	1498 (64.2)	1530 (65.2)	1526 (65.2)	3056 (65.2)
– Diuretics	988 (42.3)	1036 (44.2)	1011 (43.2)	2047 (43.7)
– Calcium channel blockers	788 (33.8)	781 (33.3)	748 (31.9)	1529 (32.6)
– Mineralocorticoid receptor antagonists	136 (5.8)	157 (6.7)	148 (6.3)	305 (6.5)
– Renin inhibitors	19 (0.8)	16 (0.7)	11 (0.5)	27 (0.6)
– Other	191 (8.2)	193 (8.2)	190 (8.1)	383 (8.2)
Anticoagulants	2090 (89.6)	2098 (89.5)	2064 (88.1)	4162 (88.8)
– Platelet aggregation inhibitors, excluding heparin	2003 (85.9)	2016 (86.0)	2003 (85.5)	4019 (85.7)
– Vitamin K antagonists	156 (6.7)	141 (6.0)	125 (5.3)	266 (5.7)
– Heparin group	16 (0.7)	7 (0.3)	8 (0.3)	15 (0.3)
– Direct thrombin inhibitors	8 (0.3)	6 (0.3)	5 (0.2)	11 (0.2)
– Direct factor Ax inhibitors	5 (0.2)	0	1 (<0.1)	1 (<0.1)
Lipid lowering drugs	1864 (79.9)	1926 (82.1)	1894 (80.9)	3820 (81.5)
– Statins	1773 (76.0)	1827 (77.9)	1803 (77.0)	3630 (77.4)
– Fibrates	199 (8.5)	214 (9.1)	217 (9.3)	431 (9.2)
– Ezetimibe	81 (3.5)	95 (4.1)	94 (4.0)	189 (4.0)
– Niacin	35 (1.5)	56 (2.4)	35 (1.5)	91 (1.9)

DPP-4 = dipeptidyl peptidase 4; ACE inhibitor = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker

Source: Adapted from Table 10.4.6.1: 1 and 10.4.6.1: 2 of the study report for study 1245.25

Patients who were randomized to empagliflozin were observed to have a lower risk of 3-Point MACE in the EMPAREG OUTCOME study. A total of 490 patients (10.6%) experienced a first 3-Point MACE event in the two empagliflozin arms and 282 patients (12.1%) experienced a first 3-Point MACE event in the placebo arm. The hazard ratio for 3-Point MACE based on the Cox proportional model was 0.86 [95.02% confidence interval (CI); 0.74; 0.99, p-value = 0.032].

Table 3: Results of Primary and Secondary Analyses (excerpted from Table 3 in Dr. Clark's review).

	Pooled Empa vs. Placebo	
	HR (95.02% CI)	p-value
3-Point MACE	0.86 (0.74, 0.99)	0.0382
4-Point MACE	0.89 (0.78, 1.01)	0.0795

Each component of 3-Point MACE was examined. While non-fatal MI made up a majority of first events in the three treatment arms, the biggest difference between empagliflozin groups and placebo was observed for the CV death component. Table 5 shows the breakdown of first events in the primary analysis.

Table 4: Breakdown of first events contributing to 3-Point MACE analysis

MACE First Event	Placebo N=2333	Empa 10* N=2345	Empa 25** N=2342
Total number of patients with a MACE	**282 (12.09%)**	**243 (10.36%)**	**247 (10.55%)**
CV Death	107 (4.59%)	78 (3.33%)	65 (2.78%)
Non-fatal MI	120 (5.14%)	92 (3.92%)	116 (4.95%)
Non-fatal Stroke	55 (2.36%)	75 (3.20%)	67 (2.86%)

*Two patients had non-fatal MI and non-fatal stroke as first events; **One patient had non-fatal MI and CV death as first events

Dr. Clark reviewed the number of subjects who experienced at least one of each component outcomes of MACE and who died for any reason in the trial. These analyses confirmed that differences in major adverse cardiovascular events in the EMPA-REG OUTCOME study were primarily driven by a large difference in occurrence of CV deaths between groups [i.e., 3.7% versus 5.9% (p-value<0.0001)]. This is shown in the following table and figures excerpted from Dr. Clark's review.

Table 5: Number of Subjects Experiencing Composite and Individual MACE Outcomes in EMPA-REG Study (the category Stroke and MI combine fatal and non-fatal events)

	Placebo N=2333	Empa 10 mg N=2345	Empa 25 mg N=2342
3-Point MACE	282 (12.09%)	243 (10.36%)	247 (10.55%)
4-Point MACE	333 (14.27%)	300 (12.79%)	299 (12.77%)
CV Death	137 (5.87%)	90 (3.84%)	82 (3.50%)
Non-fatal Stroke	60 (2.57%)	77 (3.28%)	73 (3.12%)
Non-fatal MI	121 (5.19%)	96 (4.09%)	117 (5.00%)
UA	66 (2.83%)	69 (2.94%)	64 (2.73%)
Stroke	69 (2.96%)	85 (3.62%)	79 (3.37%)
MI	126 (5.40%)	101 (4.31%)	122 (5.21%)
All-Cause Death	194 (8.32%)	137 (5.84%)	132 (5.64%)

Table 6: Cox Model Results for 3-Point MACE and Component Outcomes

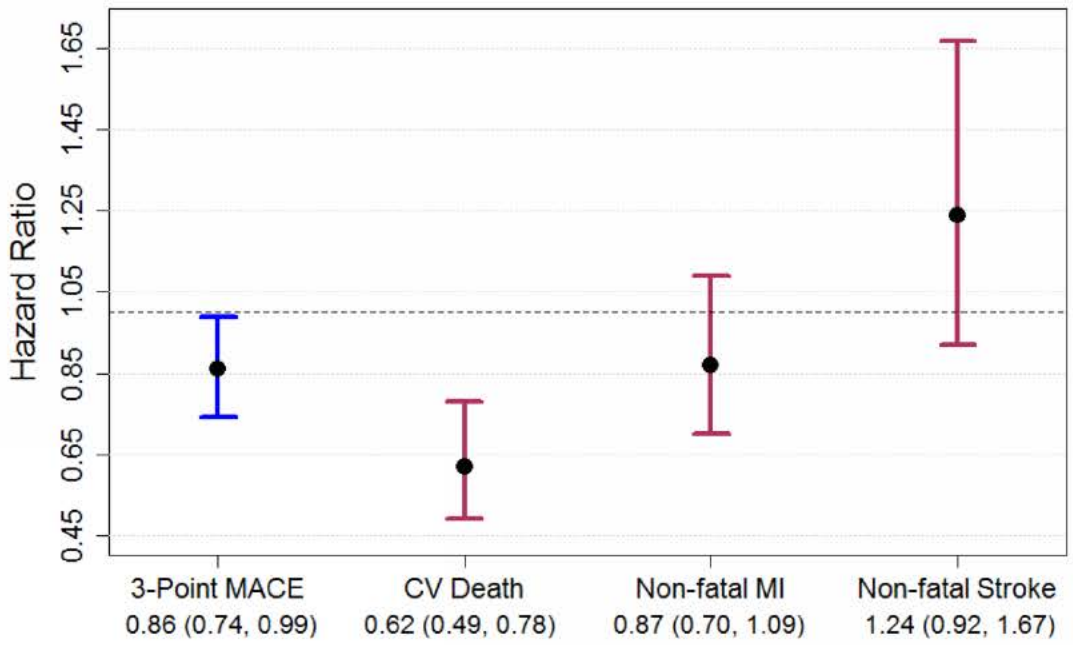
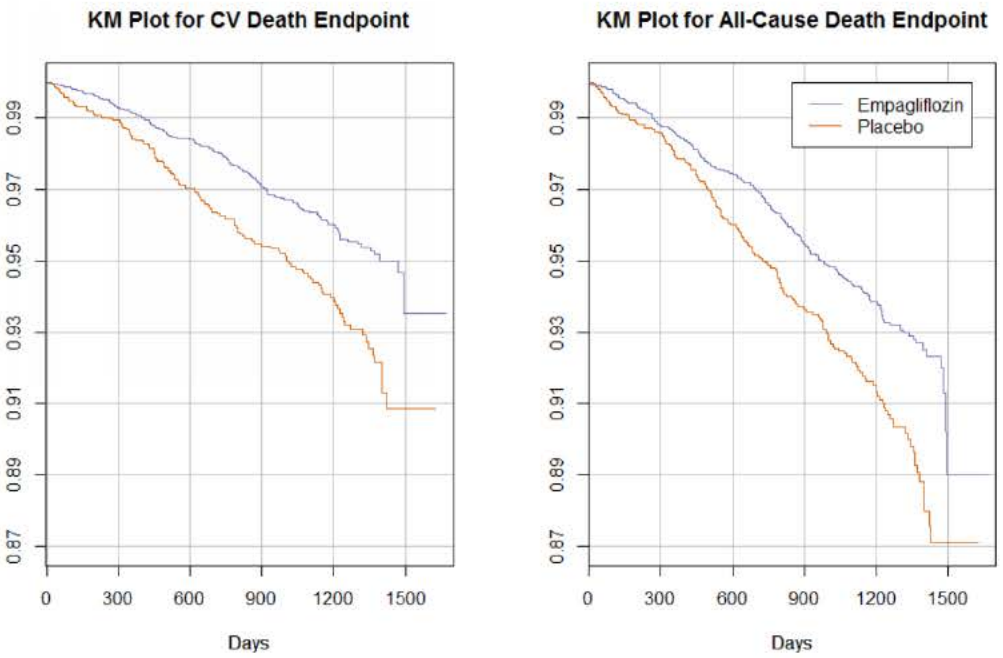


Figure 2: Kaplan Meier Plots for CV Death and All-Cause Death in EMPA-REG OUTCOME study



Dr. Clark concludes that the difference in CV deaths between groups is of such magnitude that it likely represents a true effect and is not the product of chance. She notes, however, that the point estimate could be an overestimate of the true effect because it is difficult to obtain an accurate measure from a single trial. In her review she paraphrases a statistician on the Advisory Committee who stated that even if the 38% hazard reduction for cardiovascular death was of only 20% (i.e., the upper confidence limit) the results would still be impressive.

The applicant explored other endpoints, including the endpoint of hospitalization for heart failure, in prospective and post-hoc analyses. Drs. Hicks, Lungu and Chong have reviewed the limitations around these data in their reviews. I concur with these reviewers that the EMPA-REG OUTCOME study was not designed to robustly evaluate these outcomes. The findings on heart failure are interesting and hypothesis generating but do not establish that the drug is effective at treating heart failure or that the cardiovascular benefit of empagliflozin is definitively and solely mediated through an effect on heart failure. The preliminary findings on heart failure should be confirmed in dedicated trials that address the limitations identified in EMPA-REG OUTCOME.

8. Safety

The EMPA-REG OUTCOME study was also used to address signals of potential serious risks that were identified based on review of the integrated safety data in the original NDA. These

issues were listed in the PMR and included: liver toxicity, bone fractures, renal function over time, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections pyelonephritis, urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions. Drs. Lungu and Chong have reviewed the findings for each of these issues in EMPA-REG OUTCOME. Both reviewers conclude that the study either allays concerns for the above listed issues or serve to confirm risks that are already adequately labeled. I concur with their assessment that the safety findings in EMPA-REG OUTCOME do not support the need for further regulatory action on the above issues. Refer to the memoranda by Drs. Lungu and Chong for a detailed discussion of the safety findings in EMPA-REG OUTCOME and for the recommended regulatory course of action on each of these issues.

The Division of Neurology Products was consulted to provide further interpretation of the stroke findings in EMPA-REG OUTCOME study. Dr. Green notes that the study was limited with regard to the type of information collected on stroke. She points to the lack of information on baseline disability, the lack of a requirement for baseline and on-trial neurologic examinations and the lack of baseline imaging as specific examples. She believes that the observation of the unfavorable non-significant lean for non-fatal strokes [HR (95% CI) of 1.24 (0.92, 1.67)] and fatal + non-fatal strokes [HR (95% CI); 1.18 (0.89, 1.56)] in EMPA-REG OUTCOME is a chance finding. To support her conclusion, she states that; the increased risk is not consistently observed across regions (the increased risk is seen in Europe, due to what appears to be a low stroke incidence in placebo in this region, but not in other regions), there is no clear temporal relationship between stroke occurrence and drug initiation, there is no clear dose response relationship, and that empagliflozin-induced hypotension or hemoconcentration are not very plausible mechanisms to explain the findings.

The findings related to strokes were also discussed at the 28 June 2016 Advisory Committee meeting. The Committee reviewed analyses on stroke fatalities, disabling strokes, types of stroke (> 90% ischemic) and on the sub-classification of ischemic strokes [large artery arteriosclerosis, small vessel (lacunar strokes) and cardio-embolic strokes] in EMPA-REG OUTCOME. Committee members commented that while they could not exclude the possibility of a slight increase in stroke from the data in EMPA-REG OUTCOME they did not regard the stroke findings to be of substantial concern. I concur with this interpretation of the stroke findings in EMPA-REG OUTCOME and recommend no further regulatory action at this time.

On 17 March 2016, Janssen Pharmaceuticals, Inc. informed the FDA that the independent data monitoring committee overseeing the CANVAS cardiovascular outcomes trial had made them aware of an emerging potential serious risk of increased risk of lower-limb amputations in subjects receiving canagliflozin in that trial. To assess whether this risk could be germane to empagliflozin, a member of the same drug class, a retrospective review of amputation data in EMPA-REG OUTCOME was undertaken and a major amendment extending the review clock was issued on 1 August 2016.

DMEP worked in collaboration with the Office of Surveillance and Epidemiology and the Office of Biostatistics to devise a search strategy to identify all potential events representing amputations in the EMPA-REG OUTCOME data. Extensive searches across datasets and narratives were carried out. Dr. Lungu manually reviewed 963 available narratives for cases identified as having at least one trigger term used in the search strategy. A total of 139 amputation events were identified from this search, these events were distributed evenly between the empaglifozin and placebo arms and the odds ratio (95% CI) for amputation was estimated to be 1.01 (0.70, 1.44). The number of cases identified by FDA were compared to the applicant's findings and found to be similar (refer to Tables 2 and 3 in Dr. Xia's review). Although the reviewers acknowledge that there are limitations to this retrospective assessment, both reviewers conclude that the data in EMPA-REG OUTCOME do not suggest empagliflozin increases the risk of amputations. I concur with this assessment and in the absence of an identified signal in EMPA-REG OUTCOME, do not recommend further regulatory action on this issue at this time for empagliflozin products.

9. Advisory Committee Meeting

An Advisory Committee meeting was held on June 28, 2016 to discuss the results of the EMPA-REG OUTCOME study and the proposed new indication refer to transcript and materials for details. At that meeting, two voting questions were asked:

For the first voting question (i.e., did the EMPA-REG OUTCOME study satisfy the 2008 Guidance for Industry), the vote was as follows:

Yes: 23	**No: 0**	**Abstain: 0**

The committee unanimously voted "Yes, agreeing that the EMPA-REG OUTCOME study fulfilled the recommendations laid out in the 2008 Guidance for Industry and demonstrated no increased risk for major adverse cardiovascular events.

For the second voting question (i.e., did the EMPA-REG OUTCOME study provide substantial evidence to establish a reduction in cardiovascular mortality), the vote was as follows:

Yes: 12	**No: 11**	**Abstain: 0**

The committee members who voted "Yes" found the results of the EMPA-REG study provided substantial evidence to establish that empagliflozin will be effective at reducing cardiovascular mortality in the population studied. These members stated that although the p-value for 3-Point MACE was marginal, they found the p-value for the individual component of CV death to be very persuasive. They cited the clinical importance of the findings (mortality) and sensitivity analyses demonstrating the robustness of the results to substantiate their vote. The committee members who voted "No" were not comfortable using this single trial to establish the product's effectiveness for reducing cardiovascular

mortality and recommended the study findings be confirmed. Several members cited the lack of a mechanism as a reason to explain their vote.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Jardiance will be indicated to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. A description of the evidence forming the basis for this new claim will be included in Section 14 of labeling. Data that imply clinical benefits not supported by substantial evidence will be removed from labeling. Specifically, data on heart failure outcomes are too preliminary and limited to support a claim that the drug has efficacy in heart failure or to definitively establish that the drug exerts its salutary effect on cardiovascular death through an effect on heart failure. Similarly, data suggesting that empagliflozin may have a renal protective effect are also too limited to support a new claim. Safety section of labeling was reviewed to ensure accuracy in light of new information from EMPA-REG and to include recent safety labeling changes for the class.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

In the EMPA-REG OUTCOME study, patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease treated with empagliflozin were less likely to die than patients treated with standard of care antidiabetic therapies. The benefit was attributable to a reduction in cardiovascular deaths. In Table 5, Dr. Clark provides the adjusted raw incidence for CV death in the EMPA-REG OUTCOME study. In the trial 20.2 and 12.4 deaths per 1000 patient years were observed on placebo and empagliflozin respectively. Empagliflozin in the study thus prevented 7.8 cardiovascular deaths for every 1000 patients treated for a year (i.e., 7800 deaths per million patients treated for a year). No risks that outweighed this benefit were identified in the safety review.

It is important to recall that the impact on the population is dependent on the accuracy of the estimate (i.e., closeness to the true value) and on the absolute background cardiovascular

mortality risk in the population. If for example, the estimated relative risk reduction in EMPA-REG was overestimated by two-fold and background cardiovascular mortality risk in the US population of patients with type 2 diabetes and cardiovascular disease is truly equal to the risk observed in the EMPA-REG OUTCOME study; empagliflozin would prevent 3.9 deaths per 1000 patients treated for a year. If a population with a lower background risk of cardiovascular death than the population studied in EMPA-REG OUTCOME is considered, let's say one with an absolute risk of cardiovascular death of 5 deaths per 1000 patient years, and the relative risk reduction is constant at 40%; empagliflozin would prevent 2 deaths for every 1000 patients treated for year etc. All this to say that the absolute benefit, and thus the benefit risk, will change depending on the true benefit of empagliflozin and the background risk in the population studied.

The evidentiary standard used by FDA to establish that a new drug is effective under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) is "substantial evidence" of effectiveness [21 U.S.C. § 355(d)]. Section 505(d) defines substantial evidence as evidence consisting ordinarily of "adequate and well-controlled investigations." FDA has interpreted the plural "investigations" in section 505(d) to mean two or more clinical trials. Replication of trial results is regarded as necessary to rule out chance, bias, and other problems that might undermine the integrity and reliability of trial results. In 1997, Congress amended section 505(d) to authorize FDA to find "substantial evidence" of effectiveness without requiring data from two trials if FDA determines, "…*based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness*".

FDA has issued guidance[15] on the characteristics of an adequate and well-controlled trial that could be used to support a determination of effectiveness based on a single trial under section 505(d). One characteristic is that the study is sufficiently large to demonstrate that the effect is not driven by a few clinical sites and that it is consistent across a majority of participating study sites. A second characteristic is that the study demonstrates consistency of the effect across study subsets (subgroups). A third characteristic is that the study design allows for independent confirmation of the effect within the trial (e.g., replication of the effect). A fourth characteristic is that multiple endpoints provide statistically persuasive evidence of a beneficial effect. The fifth characteristic is that the trial show a statistically very persuasive finding.

FDA has relied on only a single adequate and well controlled efficacy study to support approval of a new claim generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and where a confirmatory study would have been difficult to conduct on ethical grounds. In the guidance, FDA emphasizes that reliance on data from a single trial to find effectiveness is appropriate only for a drug with an effect on

[15] http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&ie=UTF-8&access=p&oe=UTF-8.

mortality, irreversible morbidity, or a disease with potentially serious outcomes, so that confirmation of the results in an additional trial would be practically or ethically impossible.

I concur with the review team's assessment that the EMPA-REG OUTCOME trial provides the substantial evidence necessary to establish that empagliflozin reduces cardiovascular death in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease for each of the following reasons discussed in details below;

1. **The trial was large and adequately designed to minimize bias**

The trial was large and carried out at more than 607 sites worldwide (i.e., an average of 11 patients enrolled per site). This design feature minimizes the impact of a single site or single investigator on overall results and makes the results more generalizable. In the trial, randomization was used to allocate participants to intervention. This minimizes selection bias and the risk that differences in baseline characteristics between groups, rather than the intervention itself, affected the outcomes. In addition, blinding of personnel involved in trial operations and data management, steering committee, investigators and patient participants was used to minimize performance/ascertainment bias and the risk that knowledge[16] of intervention received, rather than the intervention itself, affected the outcomes. The trial also relied on a Clinical Event Committee blinded to treatment allocation to determine outcomes. This is expected to have had the effect of minimizing detection bias and the risks that differences in outcomes would be driven by systematic differences between groups in how outcomes are determined. The plan detailing statistical methods to be used in the primary analysis was pre-specified prior to data unblinding to ensure sources of analytical biases were minimized (e.g., the primary analysis was conducted using the intent to treat principle). The primary analysis was to be carried out at an appropriately adjusted alpha-level that ensured type 1 error was controlled.

2. **No issues related to trial conduct susceptible to impacting reliability of the primary results were identified**

The trial has a complex history. Key aspects of the history are summarized in Section 2.4 of Dr. Lungu's review. Dr. Lungu reviewed changes made to the protocol, clinical event committee charter, endpoint definitions and statistical analysis plan[17] during trial conduct. She found that the reasons for changes to these documents were adequately documented, justified and reasonable. Overall, no temporal association between changes to the protocol, clinical event committee charter, endpoint definitions and statistical analysis plan and DMC analyses or interim analysis was noted to suggest that these changes were based on, or informed by, knowledge of interim results.

[16] Knowledge of the intervention could lead to systemic differences in how one group is treated, to systemic differences in the reporting of endpoint events for adjudication or to biased analytical methods.
[17] This included handling of silent MI issues. Refer to Drs. Lungu and Hicks' reviews for details.

Specifically, a change to the sample size and trial duration was made in 2011 in response to guidance received from FDA. The FDA's recommendation to increase sample size and trial duration was meant to facilitate and expedite the post-marketing CV-risk assessment. This specific change was implemented prior to any data unblinding and was agreed to by FDA.

Several changes were also made to definitions used for endpoint adjudication. This resulted in some definitions being "loosened" over the course of the trial. These changes make definitions for certain endpoints (e.g., unstable angina, hospitalization for heart failure) less specific and this change would be expected to lead to more rapid accrual of events but to add noise to the estimate by increasing variability. This latter effect could bias the results of analyses which include these endpoints towards the null. Nothing in the review of trial records suggest that changes were motivated by knowledge of interim results.

The issue of silent MI is covered in detail in Dr. Hicks and Lungu's review. Silent MI was one of the many pre-specified secondary endpoints. The applicant in 2011, after trial initiation but prior to data unblinding, clarified that events of "silent MI" would not be included in the primary endpoint. Although silent MI could be referred for adjudication, the definition for MI in the clinical endpoint committee charter required symptoms and the option to adjudicate an event as a silent MI on the adjudication case report form was not available to adjudicators. The applicant explicitly clarified that this endpoint would not be included in the primary endpoint since it was not an adjudicated outcome.

Although silent MIs are clinically important events, full ascertainment and analyses of these clinically *silent* events in trials is challenging. Full ascertainment requires scheduling electrocardiographic recordings at regular timed intervals in the trial, having these recording centrally read for trigger ECG abnormalities and having case histories for all ECG abnormalities identified reviewed to distinguish occurrence of a silent MI from other events (i.e., changes due to an antecedent symptomatic event). In addition, since these events are by definition clinically silent, the exact time to silent MI event is difficult to accurately capture and this may pose a problem in time to event analyses. Finally, in patients who have specific ECG abnormalities at baseline, occurrence of silent MI events cannot be ascertained. The applicant defined "Silent MI" events in EMPA-REG OUTCOME using ECG based criteria only and did not require that these events be reviewed or undergo adjudication. In addition analyses of Silent MI data in EMPA-REG OUTCOME were based on a subgroup of patients (n=3589) who had no baseline ECG abnormalities and had at least one ECG post-baseline. It is not clear that randomization was preserved in this subgroup. Analyses using the applicant's definition for "silent MI" and population are thus severely limited in this study and in my opinion provide little to no useful additional CV-risk information. Silent MI has not been consistently included as part of the primary endpoint in cardiovascular outcomes trials (refer to the PLATO, SAVOR, EXAMINE, TECOS, and ELIXA trials).

Dr. Lungu also reviewed trial records including case report forms, datasets, line listings for adverse events, steering committee minutes, data monitoring committee minutes and the clinical endpoint committee minutes. No conduct or operational issues susceptible to affecting reliability of the results were found in the review of these documents.

Finally Dr. Lungu examined trends of concomitant medication changes (i.e., antidiabetic drugs, antihypertensive drugs, platelet inhibitor drugs and lipid lowering drugs) over the trial period to determine whether one group received differentially better treatment for their diabetes or cardiovascular disease than the other, either due to unblinding or due to an inherent property of the intervention (i.e., LDL raising property of empagliflozin). These analyses revealed that the placebo arm had more frequent addition of glucose lowering, antihypertensive, antihyperlipidemic and aspirin than the empagliflozin group. Review of the trends in medication changes revealed that intensification of therapies in the trial did not favor the empagliflozin group and this should have biased to unity.

The Office of Scientific Investigation (OSI) inspected 3 domestic clinical sites and the sponsor of this supplement. No regulatory violations were found at 1 site, and minor regulatory violations were found at 2 sites for failure to follow the investigational plan. OSI deemed all 3 sites acceptable to support the supplement, and considered the violations at the clinical sites unlikely to affect the quality or the integrity of the data. OSI also inspected the sponsor of this application and in their inspections reviewed among other things adequacy of; monitoring, randomization, clinical endpoint collection, clinical endpoint adjudication and data management procedures. Firewall procedures in place to protect integrity of the data after interim database lock were also audited and found to be compliant. The sponsor inspection did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data in the supplemental NDA and OSI concludes that data supporting this supplement are acceptable. A summary of the inspectional findings can be found in Dr. Cynthia Kleppinger's review.

Dr. Clark examined whether the interim analyses had an impact on the types of patients enrolled in the trial by comparing effect sizes observed at trial end in the subgroup of patients enrolled before and after the 2012 interim analysis. Effect sizes (Hazard Ratios) for these two subgroups were comparable as shown in Table 6 of her review (recopied below). Incidence rates are higher in the subgroup of patients who were already enrolled at interim because this subgroup was followed for longer. These analyses suggest the population was similar before and after interim analysis and indirectly suggest the blind was adequately maintained post interim.

Table 6: Results before and after Interim Analysis

	Pooled Empa Events / N	Placebo Events / N	HR (95% CI)
Included in Interim Analysis	358 / 3027 (11.8%)	207 / 1499 (13.8%)	0.85 (0.72, 1.01)
After Interim Analysis	132 / 1660 (8%)	75 / 834 (9%)	0.86 (0.65, 1.15)

3. The results of the primary analysis were statistically significant and no issues related to the robustness of the results were identified.

Alpha-level was appropriately adjusted and Type-1 error was controlled

The analysis was carried out according to the pre-specified analysis plan. The alpha-level used for the primary analysis was appropriately adjusted to account for all interim looks and a closed testing procedure was used to control type-1 error across multiple tests.

The probability that missing data could have altered overall conclusions was determined to be low

The missing data for 3-Point MACE in the trial were determined to have a low likelihood of affecting the robustness of the primary results. Specifically, 211 subjects discontinued the trial prematurely and did not have follow-up data on 3-Point MACE. Dr. Clark used multiple imputations to examine the likelihood that this missing information could have altered overall study conclusions. Information from patients who discontinued study treatment but continued to be followed in the study (i.e., retrieved dropouts) was used to calculate the MACE incidence rate in the placebo group (8.28 events per 100 patient years), empagliflozin group (7.95 events per 100 patients years) and pooled intervention groups (8.08 events per 100 patient years) for patient with missing follow-up data. These rates were then used in the model to impute missing follow-up time (i.e., MACE events) for the 211 subjects who discontinued prematurely and were missing follow-up data on MACE. Dr. Clark performed 2000 imputations and the average number of imputed events was ~ 10 events in placebo and 20 events in the two empagliflozin arms. Sensitivity analyses which took into account these additional imputed events, did not alter the conclusion that empaglifozin reduced the 3-Point MACE primary endpoint (refer to Table 8 of her review reproduced below). These sensitivity analyses, based on reasonable assumptions, showed that missing data on 3-Point MACE are not likely to impact overall conclusions in this trial.

Table 8: Sensitivity Analyses for 3-Point MACE

Estimated Incidence Used for Imputation	Hazard / 100 Patient Years		Average Number of Imputed Events		P-value based on observed + imputed data	HR (95% CI) based on observed + imputed data
	Placebo	Empa	Placebo	Empa		
Retrieved Dropouts - Pooled	8.08	8.08	9	20	0.046	0.86 (0.745, 0.998)
Retrieved Dropouts by Arm	8.28	7.95	10	20	0.044	0.86 (0.744, 0.996)

Censoring of non-CVD in the 3-Point MACE time to event analysis tended to bias the results slightly in favor of placebo

Patients who died from a non-cardiovascular cause (non-CVD) in the trial and did not experience a 3-Point MACE event prior to dying were censored (N= 135). For the purpose of the primary analysis these patients were considered to still be "at risk[18]" and had a time to event imputed based on the assumption that they would have the same time to a 3-Point MACE event as those who were censored alive. Dr. Clark evaluated the impact that this unreasonable assumption had on the results by including non-CVD events as an endpoint in a sensitivity analysis (i.e., time to all-cause mortality, non-fatal MI and non-fatal stroke). In this

[18] In essence, for the purpose of the primary analysis, these patients were still considered to be alive! This assumption is necessary for the statistical method but is obviously not anchored in or compatible with reality.

analysis, the time to event for people who died from non-cardiovascular causes prior to experiencing a non-fatal MACE event does not require imputation. In Table 7, Dr. Clark shows that the handling of non-CVD data in the primary analysis resulted in a slight bias in favor of placebo (i.e., more benefit was seen in the sensitivity analysis than in the primary 3-Point MACE analysis). This shows that the method of analysis likely underestimated the benefit and provides further evidence that the overall conclusion based on 3-Point MACE is robust.

Table 7: Effect of non-CVD death handling in primary analysis on effect size and 95% CI (Adapted from Table 7 in Dr. Clark's review)

Analysis	Endpoint	Hazard Ratio (95% CI)
Primary Analysis	3-Point MACE	0.86 (0.74, 0.99)
Sensitivity Analysis	3-Point MACE + non CVD	0.85 (0.74, 0.97)

4. **The major effect of empagliflozin on 3-Point MACE was due to a large effect on cardiovascular mortality**

The benefit on 3 point MACE was due to an extreme difference in the risk of cardiovascular death between intervention groups in the trial. There were ~ 300 cardiovascular deaths (CVD) in the trial. A 38% relative reduction (i.e., HR 0.62; 95% CI 0.49-0.79; P<0.001) in cardiovascular mortality favoring empagliflozin with a persuasive p-value was observed in the EMPA-REG OUTCOME trial. Cardiovascular mortality was a component of the pre-specified primary endpoint (i.e., not an unrelated secondary endpoint selected post-hoc), is an irreversible outcome and arguably the most important of the three components. The benefit on CV death was not counterbalanced by an increased risk of stroke (fatal and non-fatal) or myocardial infarction (fatal and non-fatal) in the overall trial.

The most common categories of CVD were "presumed CV deaths", sudden cardiac deaths and heart failure related deaths in this order. The magnitude of benefit for each CVD category was qualitatively similar (i.e., overlapping 95% CI) and these analyses do not establish a definitive mechanism to explain the salutary effect of empagliflozin on CVD. "Presumed CV deaths" were deaths that did not meet the strict definition of a cardiovascular (fatal MI, fatal stroke, Sudden death or death due to heart failure) or non-CV death category. Exclusion of "presumed CV deaths" from the CV death analysis did not affect the estimate (i.e., HR for CV-death excluding presumed CV death was 0.59; 95% CI 0.44, 0.79; P< 0.001).

5. **Vital status was almost fully ascertained in the trial and results based on overall mortality were similar to results based CVD mortality.**

Results based on overall mortality were consistent with results based on cardiovascular mortality (HR 0.68; 95% CI 0.57-0.82; P<0.001; number needed to treat 38). Overall mortality

encompasses the totality of benefits and risks and is less susceptible to ascertainment and detection biases than other outcomes because it can be easily and fully ascertained and because determining whether the endpoint occurred, or not, is not subject to interpretation. In the trial, there were almost no missing data for overall mortality as vital status was available for 99.25% of randomized individuals. The risk of dying, in EMPA-REG OUTCOME, was observed to be very different in subjects on placebo and empagliflozin and driven by CVD. While the estimate on the risk of death between groups could be overestimated, it is highly unlikely that if the trial were to be repeated no difference between empagliflozin and placebo on risk of death would be observed. I also believe that the mortality finding would make it practically and ethically difficult to carry out a confirmatory study.

6. **The results of the trial were consistent for each of the two empagliflozin dose groups evaluated (i.e., 10 mg and 25 mg)**

The results for the primary endpoint, cardiovascular death, and overall mortality were consistent across two doses of empagliflozin. The risk of cardiovascular death was reduced by 35% [HR 0.65; 95% CI 0.50-0.85 (P-value=0.0016)] and 41% [HR 0.59; 95% CI 0.45-0.77 (P-value=0.001)] for the 10 and 25 mg doses of empagliflozin respectively. The risk of overall mortality was reduced by 30% [HR 0.70; 95% CI 0.56-0.87 (P-value=0.0013)] and 33% [HR 0.67; 95% CI 0.54-0.83 (P-value=0.0003)] for the 10 and 25 mg doses of empagliflozin respectively. The fact that both doses confirm a difference in effect between empaglifozin and placebo and that the magnitude of the difference for each dose is in keeping with the overall effect, suggests the effect on CV death is real and not a product of chance.

The small dose response observed for CV death in the intent to treat population appeared larger in sensitivity analyses examining CVD and all-cause mortality in the on-treatment population. Acknowledging these analyses have inherent limitations, the risk of cardiovascular death for patients on treatment was reduced by 34% [HR 0.66; 95% CI 0.48-0.91] and 48% [HR 0.52; 95% CI 0.37-0.74] for the 10 and 25 mg doses of empagliflozin respectively (refer to Table 27 in Dr. Lungu's review).

7. **The cardiovascular death and overall death results were consistent across all subgroups examined**

The applicant and Dr. Clark (refer to Table 9 in her review) performed a number of subgroup analyses based on age, sex race, HbA1c, geographic region and medications used at baseline. These analyses revealed consistent benefit across all major subgroups considered for these two endpoints. The internal consistency in subgroup analyses suggests the findings are not attributable to chance.

8. **The cardiovascular death findings for EMPA-REG OUTCOME are mechanistically plausible and supported by exploratory analyses of secondary endpoints**

Empagliflozin, the specific drug product in this supplement, belongs to the sodium glucose co-transporter 2 (SGLT-2) inhibitor class of drugs. Products in this class lower circulating

glucose but also have non-glycemic effects including diuretic, natriuretic, uricosuric, and ketogenic effects. While the exact mechanism(s) responsible for empagliflozin's effect on cardiovascular death is unknown some interesting preliminary findings, suggesting potential favorable effects, on heart failure were made in EMPA-REG OUTCOME. These findings are hypothesis generating, as the trial was not adequately designed to robustly assess heart failure outcomes, but this lead could be explored to determine whether effects on heart failure related outcome do or do not explain the benefits seen in EMPA-REG OUTCOME.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

No issues were identified that require use of Postmarketing Risk Evaluation and Mitigation Strategies.

- Recommendation for other Postmarketing Requirements and Commitments

This supplemental application contained the final report for postmarketing requirement PMR 2755-4 issued on 1 August 2014 and fulfills this requirement. No new issues were identified in the review of the supplemental application that require issuance of new Postmarketing Requirements and Commitments.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
12/02/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s008

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H. Chong, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 204629 (Suppl-8)
Applicant	Boehringer Ingelheim
Date of Submission	November 4, 2015
PDUFA Goal Date	December 4, 2016
Proprietary Name / Established (USAN) names	JARDIANCE (empagliflozin)
Dosage forms / Strength	10 mg and 25 mg tablets
Proposed Indication(s)	"in adult patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the incidence of cardiovascular death"
Recommendation:	*Approval, pending agreement on labeling*

1. Introduction

Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor. By inhibiting renal glucose reabsorption, empagliflozin leads to glucosuria which in turn contributes to lowering of plasma glucose. Empagliflozin was approved with the proprietary name of JARDIANCE on August 1, 2014 for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. As part of the approval for JARDIANCE, an assessment of cardiovascular risk was required as a post-marketing requirement (PMR). To fulfill this PMR, Boehringer Ingelheim (hereafter referred to as "the applicant") has completed the EMPA-REG OUTCOME study.

In this supplement (NDA-204629, Suppl-8) the applicant has submitted the results of the EMPA-REG OUTCOME study. The applicant also proposes labeling changes and a new indication based upon the results of this study. The proposed new indication is "in adult patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the incidence of cardiovascular death."

This cross-discipline team leader (CDTL) review will discuss the results of the study as they pertain to the PMR, interpretation of the results in the context of the "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" [1], and recommended labeling changes.

2. Background

Diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia. There are two main types of diabetes mellitus: type 1 diabetes mellitus (T1DM; characterized by autoimmune destruction of pancreatic β-cells and loss of insulin secretion) and type 2 diabetes mellitus (T2DM; characterized by resistance to insulin activity with inadequate insulin production to maintain euglycemia). As a result of chronic hyperglycemia, patients with diabetes mellitus are at an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. Based on the results of the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes study (UKPDS), improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes (i.e., microvascular complications).

In part as a result of a 2007 meta-analysis of studies with the antidiabetic drug rosiglitazone which raised concerns that use of rosiglitazone may increase the risk for myocardial infarction, the Food and Drug Administration (FDA) issued a Guidance document [2] outlining the need to

[1] 1998 Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products at:
http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078749.pdf
[2] 2008 Guidance for Industry: Diabetes mellitus – Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes at:
http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

demonstrate that new antidiabetic therapies do not increase the risk for major adverse cardiovascular events (MACE). The EMPA-REG OUTCOME study was conducted to address the guidance.

At the time of approval, the applicant had already initiated the EMPA-REG OUTCOME study and interim data from the study was included in support of the New Drug Application (NDA). A meta-analysis of phase 3 studies including the interim data from the EMPA-REG OUTCOME study excluded the pre-approval risk margin of 1.8 (see Table 24 of Dr. Janelle Charles' statistical review from NDA 204629, excerpted below).

Table 24 Summary of Meta-analysis Findings for MACE and MACE+ Individual Components

Outcome	Number of Patients with Events		HR (95% CI)
	Empagliflozin[1] (N=6206)	Comparator[2] (N=3830)	
MACE+	141	103	0.74 (0.57, 0.96)
MACE	111	85	0.71 (0.54, 0.95)
CV Death	30	30	0.54 (0.33, 0.90)
Non-fatal MI	46	39	0.62 (0.40, 0.96)
Non-fatal Stroke	40	20	1.15 (0.67, 1.98)
Hospitalization for UA	33	20	0.86 (0.49, 1.50)

[1]Pooled 10mg and 25 mg empagliflozin doses
[2]Pooled active and placebo comparators
CV=cardiovascular, MI=myocardial infarction, UA=unstable angina
Source: Created by the reviewer using dataset "adttecv.xpt"

MACE = 3-point MACE = composite of cardiovascular (CV) death, non-fatal stroke, and non-fatal myocardial infarction (MI); MACE+ = 4-point MACE = composite of CV death, non-fatal stroke, non-fatal MI, and hospitalization for unstable angina (UA)

To support this interim analysis, unblinded information was made available to approximately 230 individuals. These individuals signed confidentiality agreements.

The risk margin of 1.3 could not be excluded based on the 142 events that had accrued in the EMPA-REG OUTCOME study (Hazard Ratio [HR]: 0.74; 99.98% confidence interval [CI]: 0.39, 1.39), thus the study continued and completion of the study was included as a post-marketing requirement.

The applicant has now submitted the results of the completed EMPA-REG OUTCOME study and proposed a new indication. In 1962, the Federal Food, Drug, and Cosmetic (FDC) Act added a requirement for manufacturers of drug products to provide substantial evidence to establish a drugs' effectiveness. The term "substantial evidence" was defined in section 505(d) of the FDC Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the

labeling or proposed labeling thereof." This has generally been interpreted as requiring at least two adequate and well-controlled trials each convincing on its own to establish effectiveness (i.e., independent substantiation). This is relevant as there is only a single study to support the proposed new indication. However, the FDA has recognized that there are times when evidence from a single study may be sufficient. One such situation when evidence from a single study may be adequate is when the results come from a large multicenter study with no single site providing an unusually large fraction of subjects or being disproportionately responsible for the results, with internal consistency, and with very statistically persuasive results for a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation with a second study would be ethically and practically difficult.

3. CMC/Device

Not applicable. No new manufacturing information is included with the supplement.

4. Nonclinical Pharmacology/Toxicology

Not applicable. No new nonclinical information is included with the supplement.

5. Clinical Pharmacology/Biopharmaceutics

As noted in Dr. Sang Chung's clinical pharmacology review, the pharmacokinetic data from the EMPA-REG OUTCOMES study were similar to those submitted in the original NDA. Steady-state trough concentrations (C_{trough}) of empagliflozin were collected at week 12 and week 52 in a subset of subjects, and the means of C_{trough} were dose proportional though there was a large amount of overlap between the individual concentrations.

Dr. Chung also comments on the applicant's proposal to (b) (4) (b) (4) . His commentary is limited to consideration of the data to support this change with respect to the glycemic effects of empagliflozin. The effect of empagliflozin on HbA1c is notably reduced in subjects with an eGFR < 45 mL/min/1.73 m^2 compared to the effect seen in subjects with an eGFR of 45 to < 60 mL/min/1.73 m^2 (Table 1). (b) (4) Dr. Chung does not believe that the data (b) (4) support (b) (4) (b) (4) .

Table 1: Adjusted mean change in HbA1c from baseline to week 12 in subjects with moderate renal impairment

	N	Placebo-adjusted mean change from baseline (SE)	95% CI	p-value
Subjects with eGFR 45 to < 60 mL/min/1.73 m^2				
Empa 10	364	-0.39% (0.05)	-0.5, -0.29	< 0.0001
Empa 25	351	-0.41% (0.05)	-0.51, -0.31	< 0.0001
Subjects with eGFR < 45 ml/min/1.73 m^2				
Empa 10	141	-0.16 (0.08)	-0.31, 0	0.0492
Empa 25	146	-0.2 (0.08)	-0.35, -0.04	0.0136

SE = standard error; CI = confidence interval; eGFR = estimated glomerular filtration rate
Source: Adapted from Table 2 of Dr. Sang Chung's clinical pharmacology review

For a detailed discussion of the clinical pharmacology data and recommendations, see Dr. Sang Chung's review.

6. Clinical Microbiology

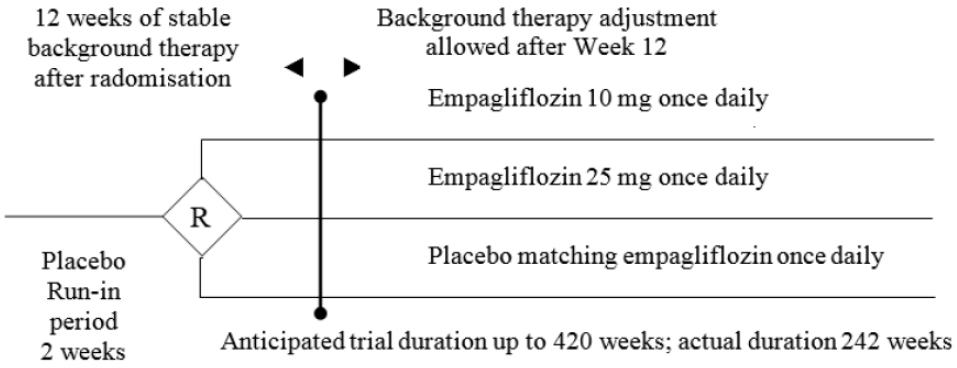
Not applicable.

7. Clinical/Statistical- Efficacy

The discussion of efficacy will focus on the cardiovascular endpoints from the EMPA-REG OUTCOME study and on the 'nephropathy' endpoints. The statistical analysis of the EMPA-REG OUTCOME study was conducted by Dr. Jennifer Clark. Findings from the statistical review will be incorporated into the discussion here. For detailed discussion of the statistical analysis, see Dr. Clark's statistical review.

The EMPA-REG OUTCOME study was a randomized, double-blind study of empagliflozin (10 mg once daily and 25 mg once daily) vs. placebo as add-on to local standard of care in patients with type 2 diabetes mellitus and cardiovascular disease. The schematic of the trial design is presented below in Figure 1.

Figure 1: Trial Design



Source: Excerpted from Figure 9.1: 1 of the clinical study report for study 1245.25

The study enrolled patients with T2DM who were drug-naïve or pretreated with any background therapy, with HbA1c of ≥7.0% and ≤10% for patients on background therapy or ≥7.0% and ≤9.0% for drug-naïve patients. The patient population was enriched for cardiovascular events by enrolling patients with high cardiovascular risk. High cardiovascular risk was defined as:

- Confirmed history of MI
- Evidence of multi-vessel CAD, irrespective of the revascularization status
- Evidence of single vessel CAD with:
  - Stenosis of at least 50% of one major coronary artery in patients not subsequently successfully revascularized, and
  - At least one of the following: positive non-invasive stress test, or a hospital discharge diagnosis of unstable angina within 12 months prior to selection
- Unstable angina with evidence of multi-vessel, or single vessel CAD
- History of ischemic or hemorrhagic stroke
- Presence of peripheral artery disease

The primary endpoint was time to first occurrence of any component of the primary composite endpoint (i.e., 3-point MACE [CV death, non-fatal MI, or non-fatal stroke]). An independent external Clinical Event Committee (CEC) was established to adjudicate centrally and in a blinded fashion suspected events of stroke, myocardial ischemia (including myocardial infarction), all deaths, and other relevant events, including heart failure.

The pre-specified testing hierarchy included four steps:

1. Non-inferiority for 3-point MACE
2. Non-inferiority for 4-point MACE
3. Superiority for 3-point MACE
4. Superiority for 4-point MACE

Testing was based on a 95.02% confidence interval as an interim analysis was previously conducted to support the original NDA. Non-inferiority was concluded if the upper-bound of this confidence interval was below 1.3. Superiority was concluded if the upper-bound of this confidence interval was below 1.

A total of 772 3-point MACE and 932 4-point MACE were accrued and included in the analysis (see Table 4 of Dr. Jennifer Clark's statistical review, excerpted below).

Table 4: Number of Subjects Experiencing Outcomes			
	Placebo N=2333	Empa 10 mg N=2345	Empa 25 mg N=2342
3-Point MACE	282 (12.09%)	243 (10.36%)	247 (10.55%)
4-Point MACE	333 (14.27%)	300 (12.79%)	299 (12.77%)
CV Death	137 (5.87%)	90 (3.84%)	82 (3.50%)
Non-fatal Stroke	60 (2.57%)	77 (3.28%)	73 (3.12%)
Non-fatal MI	121 (5.19%)	96 (4.09%)	117 (5.00%)
UA	66 (2.83%)	69 (2.94%)	64 (2.73%)
Stroke	69 (2.96%)	85 (3.62%)	79 (3.37%)
MI	126 (5.40%)	101 (4.31%)	122 (5.21%)
All-Cause Death	194 (8.32%)	137 (5.84%)	132 (5.64%)

Based on a Cox proportional hazard model analysis for 3-point MACE and for 4-point MACE, the EMPA-REG OUTCOME study demonstrated non-inferiority of empagliflozin for 3-point MACE and 4-point MACE (see Table 2 of Dr. Clark's statistical review, excerpted below).

Table 2: 3 and 4-Point MACE Cox Model Results		
	Pooled Empa vs. Placebo	
	HR (95.02% CI)	P
3-Point MACE	0.86 (0.74, 0.99)	0.0382
4-Point MACE	0.89 (0.78, 1.01)	0.0795

p-value for superiority

Superiority was demonstrated for 3-point MACE but not for 4-point MACE. As a result, had there been any further hypotheses there would no longer be any control for type 1 error and they would be considered as exploratory.

Dr. Clark also examined whether the unblinding that occurred at interim could have impacted the final results. Based on her analysis, there was no apparent difference between the occurrence of MACE in subjects enrolled before or after interim unblinding (see Table 6 of Dr. Clark's statistical review, excerpted below).

Table 6: Results before and after Interim Analysis			
	Pooled Empa Events / N	Placebo Events / N	HR (95% CI)
Included in Interim Analysis	358 / 3027 (11.8%)	207 / 1499 (13.8%)	0.85 (0.72, 1.01)
After Interim Analysis	132 / 1660 (8%)	75 / 834 (9%)	0.86 (0.65, 1.15)

Delving further into the components of the MACE composites, it becomes clear that there are differences between the components (see Table 5 of the Statistical Summary from the FDA Briefing Document for the June 28, 2016 Endocrine and Metabolic Drug Advisory Committee Meeting, excerpted below). Cardiovascular (CV) death appears to be the only one of the components where there is a clinical benefit.

Table 5: Cox Model Results for Composite, Component, and Related Endpoints

		Pooled Empa vs. Placebo	
		HR (95% CI)	P
Primary Endpoint	3-Point MACE	0.86 (0.74, 0.99)	0.0382
Secondary Endpoint	4-Point MACE	0.89 (0.78, 1.01)	0.0795
Endpoint Components	CV Death	0.62 (0.49, 0.78)	<.0001
	Non-fatal Stroke	1.24 (0.92, 1.67)	0.1638
	Non-fatal MI	0.87 (0.70, 1.09)	0.2189
	UA	0.99 (0.74, 1.34)	0.9706
Related Endpoints	Stroke	1.18 (0.89, 1.56)	0.2567
	MI	0.87 (0.70, 1.09)	0.2302
	All-Cause Death	0.68 (0.57, 0.82)	<.0001

While the results for 3-point MACE are marginally statistically significant, it is worth mentioning that the observed risk reduction for cardiovascular death is highly statistically significant. The reason for this is unclear, but it does not appear to be due to a reduction in ischemic events as there is no clear benefit on stroke or MI.

While noting that there are some issues with the study, Dr. Clark concludes based on her analysis of the data that the study results support a conclusion of a reduction in the risk of CV death. With regard to the 3-point MACE composite, Dr. Clark does not believe that the results are sufficiently robust to conclude a risk reduction for the composite. Dr. Clark does note some issues that could affect the conclusions (i.e., unclear mechanism, true treatment effect, changes in event definitions and protocol, and unblinding at interim analysis). However, Dr. Clark concludes that these issues would be unlikely to alter conclusions for CV death.

In Dr. Ondina Lungu's Clinical Review, she also considers this question. Dr. Lungu reaches conclusions similar to Dr. Clark. While the 3-point MACE findings are not particularly convincing, Dr. Lungu believes the findings on CV death to provide sufficiently substantial evidence that there is a reduction in cardiovascular death with empagliflozin. Dr. Lungu does note some potential differences between treatment arms, such as differences in medication added during the study, but does not believe that these differences impacted the results. Though Dr. Lungu notes that a large proportion of the CV deaths were deaths where the cause of death was determined to be "not assessable" (Table 2), she notes that the majority of these (if not all) are likely to be due to cardiovascular reasons in this patient population and that removing these events does not change the apparent benefit for CV death (estimated HR 0.61). Further, Dr. Lungu notes that there is internal consistency for this finding as the observed risk reduction for CV death is seen with empagliflozin 10 mg and empagliflozin 25 mg, as well as across sub-groups (Table 3 below, and Table 9 of Dr. Clark's statistical review [excerpted below]).

Table 2: Further break down of CV death

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342	All Empa N=4687
Patients with CV death	137	90	82	172
- Not assessable, n (% of CV deaths)	53 (38.7)	34 (37.7)	37 (45.1)	71 (41.3)
CV deaths excluding not assessable, n (% of treatment arm)	84 (3.6)	56 (2.4)	45 (1.9)	101 (2.2)

Source: Adapted from Table 24 of Dr. Lungu's clinical review

Table 3: CV death by individual empagliflozin dose

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342
Patients with CV death	137 (5.9)	90 (3.8)	82 (3.5)
- HR vs. placebo (95% CI)		0.65 (0.5, 0.85)	0.59 (0.45, 0.77)

Source: Adapted from Table 11.1.2.2: 1 of the study report for study 1245.25

Table 9: Subgroup Analyses HR (95% CI)

Group	Category	N	MACE	CV Death	Death
Age	Under 65	3893	1.04 (0.84, 1.29)	0.72 (0.51, 1.00)	0.71 (0.53, 0.95)
	65 and Over	3127	0.72 (0.59, 0.88)	0.56 (0.41, 0.75)	0.67 (0.53, 0.86)
Sex	Female	2004	0.83 (0.62, 1.11)	0.74 (0.47, 1.17)	0.91 (0.63, 1.32)
	Male	5016	0.86 (0.73, 1.02)	0.58 (0.45, 0.75)	0.62 (0.50, 0.77)
Race	White	5081	0.87 (0.73, 1.03)	0.64 (0.50, 0.83)	0.66 (0.54, 0.82)
	Black or African American	357	1.51 (0.82, 2.80)	0.81 (0.34, 1.90)	1.32 (0.60, 2.87)
	Asian	1517	0.68 (0.48, 0.96)	0.44 (0.25, 0.78)	0.63 (0.40, 1.00)
	Other	64	0.53 (0.15, 1.89)	.	.
HbA1c	At or above 8.5	2201	1.14 (0.87, 1.50)	0.70 (0.47, 1.04)	0.82 (0.59, 1.13)
	Under 8.5	4819	0.76 (0.64, 0.90)	0.59 (0.45, 0.77)	0.63 (0.50, 0.79)
Geographic Region	Outside of USA	5800	0.84 (0.71, 0.98)	0.58 (0.45, 0.74)	0.64 (0.52, 0.79)
	USA	1220	0.91 (0.66, 1.27)	0.80 (0.47, 1.36)	0.86 (0.57, 1.31)
Weight in kg	70 or less	1438	0.63 (0.46, 0.87)	0.45 (0.28, 0.72)	0.67 (0.46, 0.98)
	>70 to ≤80	1402	1.26 (0.88, 1.81)	0.94 (0.53, 1.68)	0.93 (0.59, 1.47)
	>80 to ≤90	1415	0.56 (0.41, 0.76)	0.42 (0.26, 0.68)	0.48 (0.32, 0.71)
	≥90	2765	1.06 (0.83, 1.34)	0.77 (0.54, 1.11)	0.74 (0.54, 0.99)

The Division of Cardiovascular and Renal Products (DCRP) was consulted for their opinion on the quality and sufficiency of the data to support the proposed new indication. For a detailed discussion, see Dr. Karen Hicks' consult review.

Based on review of the data, Dr. Hicks has concluded that the EMPA-REG OUTCOME study does not provide substantial evidence that empagliflozin reduces the risk for MACE (specifically strokes and MIs), but that there is evidence that empagliflozin reduces the risk of cardiovascular death. While Dr. Hicks also concludes that the finding of a reduced risk for CV death is reliable, she notes that the underlying mechanism remains unclear. One possible

explanation is through the diuretic effect of empagliflozin and an effect on heart failure. The applicant reports a reduction in the risk for heart failure related endpoints (Table 4).

Table 4: Heart failure related endpoints

	Estimated Hazard Ratio [1]	95% CI
Heart failure requiring heart failure	0.65	0.5, 0.85
Heart failure requiring hospitalization or CV death (excluding stroke)	0.66	0.55, 0.79

[1] estimated hazard ratio for All Empa vs. Placebo
Source: Adapted from the Executive Summary of Dr. Hick's consult

Of note, the overall proportion of subjects with congestive heart failure at baseline was low (10.1%) which raises questions as to whether this small proportion of subjects could be so substantially impacted by treatment with empagliflozin to yield the observed results. The study was not designed with an interest in heart failure, and collection of baseline conditions was based on subjects reporting known medical conditions. It is possible that there were subjects with undiagnosed heart failure at the time of randomization. It is impossible to say how many (if any) subjects had undiagnosed heart failure.

While Dr. Hicks acknowledges that the reported effect of empagliflozin on these heart failure related endpoints is plausible due to the diuretic effect, she notes several limitations of the study to provide substantial evidence of any heart failure related claims. Neither hospitalization for heart failure nor other heart failure related endpoints were included in the plan to control for overall type 1 error. As noted above, the last step of the testing hierarchy did not yield a statistically significant finding, thus all subsequent analyses are best considered exploratory. Changes to the definitions of heart failure events occurred over the course of the trial may have resulted in less clinically significant events that may not truly reflect heart failure events being captured (i.e., made the endpoint a "soft" endpoint). For subjects with heart failure at baseline, little information is known in terms of the type of heart failure or the severity of heart failure. Additionally, it is unclear whether patients with heart failure were receiving optimal guideline-directed therapy for heart failure. These all limit the ability to make confident conclusions with respect to heart failure. This finding would be most appropriately considered hypothesis-generating and should be confirmed in a dedicated trial.

Overall, I agree with the conclusions reached by Drs. Clark, Lungu, and Hicks. The results of the EMPA-REG OUTCOME study have demonstrated no increased cardiovascular risk. The use of empagliflozin appears to be associated with a reduction in the risk for macrovascular events though the results are insufficient to accept this conclusion based on this single study. In considering the components of the 3-point MACE composite, the findings for reducing the risk of CV death are sufficiently persuasive to accept that empagliflozin reduces the risk of CV death in patients with T2DM and established cardiovascular disease. This endpoint is clinically meaningful, highly statistically significant, and supported by consistent findings across both doses and across sub-groups. I also agree with Dr. Hicks that while the results suggest a reduction in heart failure events with empagliflozin, the data are not sufficient to conclude that there is substantial evidence of a benefit for this endpoint. While the diuretic effect of empagliflozin may plausibly lead to a benefit on heart failure, the definition used in the study may have captured events that were not clinically significant. Additionally, information on the type and severity of heart failure was not captured nor was information on

the adequacy of heart-failure related therapies. As a result, I believe that additional study of empagliflozin in heart failure is needed before concluding that there is a benefit on heart failure related events.

8. Safety

The review of safety was completed by Dr. Andreea Lungu. Based on her review, Dr. Lungu has concluded that the safety findings from the EMPA-REG OUTCOME study are generally consistent with the known safety profile of empagliflozin. For a detailed discussion of non-cardiovascular safety, see Dr. Lungu's clinical review.

In this CDTL review I will focus on selected adverse events which merit further discussion. These are:

- Stroke
- Renal events
- Amputations
- Malignancies
- Fractures

Stroke:
While stroke was a component of the composite endpoint for the EMPA-REG OUTCOME study, I will be discussing the findings for stroke as part of the safety discussion.

In considering fatal and nonfatal stroke events, the results of the EMPA-REG OUTCOME study suggest a possible increased risk for stroke (Table 5).

Table 5: Stroke results from EMPA-REG OUTCOME

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342	All Empa N=4687
Fatal/Nonfatal Stroke, n (%)	69 (3)	85 (3.6)	79 (3.4)	164 (3.5)
- HR vs. placebo (95% CI)		1.22 (0.89, 1.68)	1.13 (0.82, 1.56)	1.18 (0.89, 1.56)
Nonfatal Stroke, n (%)	60 (2.6)	77 (3.3)	73 (3.1)	150 (3.2)
- HR vs. placebo (95% CI)		1.27 (0.91, 1.79)	1.2 (0.85, 1.69)	1.24 (0.92, 1.67)

Source: Adapted from Table 37 of Dr. Lungu's clinical review

The Division of Neurology Products (Dr. Jody Green) was consulted for an opinion of these results and whether this suggests a risk due to treatment. Dr. Green notes that there were some limitations with regard to the type of information collected (e.g., disability, baseline neurologic examination or imaging), but believes that the observation of an increased hazard ratio for stroke events to be a chance findings. The increased risk for stroke appeared to be driven by subjects from Europe where the estimated hazard ratio was 2.04 and the 95% confidence interval excluded 1 (95% CI: 1.26, 3.29). Exclusion of this population (which accounts for 41.1% of the study population) results in no difference between treatment arms for stroke. It is unclear why there appears to be an increased risk in the European subjects.

The topic of strokes was also discussed at the June 28, 2016 Advisory Committee meeting. Committee members commented that while the data could reflect a small signal of risk, the events covered the entire spectrum of stroke pathophysiologies. Thus, a unifying mechanism cannot be identified. Ultimately the committee did not view the results of stroke to be a substantial safety concern.

I recognize that the stroke findings are not statistically different with empagliflozin vs. control from the EMPA-REG OUTCOME study and that the diverse types of stroke do not support a unifying mechanism for the observed difference. While Dr. Green concludes that this is a chance observation and the Advisory Committee did not feel this to be a substantial safety concern, I remain concerned that this may be a drug-related effect. However, my level of concern and degree of certainty that this is drug-related are not so substantial that I would recommend including stroke as a Warning and Precaution. Given the amount of uncertainty, I believe that describing the results for stroke as part of the description of the EMPA-REG OUTCOME study is sufficient to communicate that there may be an increase in strokes with empagliflozin.

Renal Events:
In the postmarketing requirement (PMR 2755-4) the applicant was required to assess "[t]he long-term effects of empagliflozin on the incidence of […] nephrotoxicity/acute kidney injury […]. Estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening renal function." Serum creatinine and urine albumin-to-creatinine ratio (UACR) were measured routinely and centrally. Estimated glomerular filtration rate was calculated based on these tests. In addition, adverse events were reviewed for renal-related adverse events. The applicant also evaluated what they have referred to as "renal safety endpoints". These were:

- New onset of albuminuria defined as UACR ≥30 mg/g
- New onset of macroalbuminuria defined as UACR >300 mg/g
- A composite microvascular outcome defined as:
    - Initiation of retinal photocoagulation,
    - Vitreous hemorrhage,
    - Diabetes-related blindness, or
    - New or worsening nephropathy, defined as:
        - New onset of macroalbuminuria,
        - Doubling of serum creatinine with an eGFR (MDRD) ≤45 mL/min/1.73m^2,
        - Initiation of continuous renal replacement therapy, or
        - Death due to renal disease.

Consistent with previous reviews of empagliflozin, there was an acute increase in serum creatinine (and thus decrease in eGFR) in the EMPA-REG OUTCOME study (see Figure 23 and Figure 24 of Dr. Lungu's clinical review, excerpted below). This acute change did not appear to persist or progress with longer term treatment.

Figure 23 Descriptive Statistics for Creatinine (mg/dL) MMRM Results Over Time by Treatment– TS (OC)

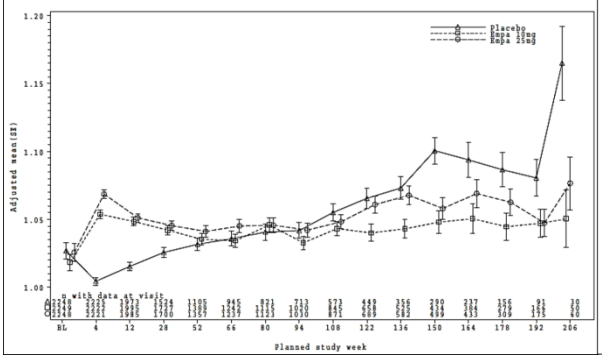
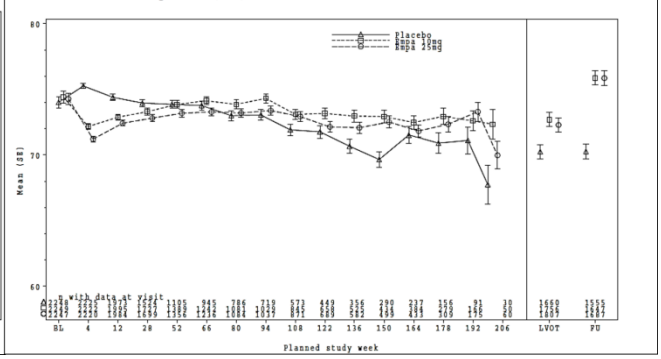


Figure 24 eGFR [mL/min/1.73m2] MMRM results over time (OC), with unadjusted last value on treatment and follow-up value (OR) – TS



The analysis of renal related adverse events conducted by the applicant utilized a standardized MedDRA query (SMQ) and did not identify an increased risk of renal adverse events with empagliflozin (Table 6). Dr. Lungu has considered this analysis as well as an analysis which included additional terms and also concludes that there is no increased risk for renal adverse events with empagliflozin. She does however note that there is an early imbalance in the reported renal adverse events. This imbalance appears to be reflective of the acute change in renal function observed with use of empagliflozin.

Table 6: Renal adverse events based on applicant defined SMQ

	Placebo N=2333	All Empa N=4687
	N (%)	N (%)
Patients with renal adverse event	155 (6.6%)	245 (5.2%)
- In first 30 days	16 (0.7%)	41 (0.9%)
- In first 90 days	29 (1.2%)	70 (1.5%)
Preferred terms		
– Renal impairment	77 (3.3%)	146 (3.1%)
– Renal failure	42 (1.8%)	54 (1.2%)
– Acute kidney injury	37 (1.6%)	45 (1%)
– Azotemia	1 (< 0.1%)	5 (0.1%)
– Prerenal failure	0 (0%)	1 (< 0.1%)
– Anuria	1 (< 0.1%)	1 (< 0.1%)
– Acute prerenal failure	2 (0.1%)	1 (< 0.1%)
– Oliguria	1 (<0.1)	0 (0)

Source: Adapted from Table 50 of Dr. Lungu's clinical review

The applicant has concluded based on the analysis of the EMPA-REG OUTCOME study that use of empagliflozin results in a reduction in "nephropathy" (Table 7) primarily based on an effect on albuminuria. The DCRP (Dr. Kimberly Smith) was consulted for an opinion on this conclusion and for an interpretation of the "renal safety endpoints".

Table 7: Summary of results of "renal endpoints"

	Placebo	All Empa	Hazard Ratio (95% CI; p-value)
New onset albuminuria [1]	703/1374 (51.2)	1430/2779 (51.5)	0.95 (0.87, 1.04; 0.25)
New onset macroalbuminuria [2]	330/2033 (16.2)	459/4091 (11.2)	0.62 (0.54, 0.72; < 0.01)

	Placebo	All Empa	Hazard Ratio (95% CI; p-value)
Sustained improvements to normo- or micro-albuminuria [3]	74/257 (28.8)	248/499 (49.7)	1.82 (1.4, 2.37; < 0.01)
Microvascular Composite	424/2068 (20.5)	577/4132 (14)	0.62 (0.54, 0.7; < 0.01)
• Retinal photocoagulation	29/2333 (1.2)	41/4687 (0.9)	0.69 (0.43, 1.12; 0.13)
• Vitreous hemorrhage	16/2333 (0.7)	30/4687 (0.1)	0.93 (0.51, 1.71; 0.81)
• Diabetes related blindness	2/2333 (0.3)	4/4687 (0.1)	-----
• New or worsening nephropathy	388/2061 (18.8)	525/4124 (12.7)	0.61 (0.53, 0.7; < 0.01)
○ New onset macroalbuminuria	330/2033 (16.2)	459/4091 (11.2)	0.62 (0.54, 0.72; < 0.01)
○ Doubling of serum creatinine [4]	60/2323 (2.6)	70/4645 (1.5)	0.56 (0.39, 0.79; < 0.01)
○ Continuous renal replacement therapy	14/2333 (0.6)	13/4687 (0.3)	0.45 (0.21, 0.97; 0.04)
○ Renal death	0/4687 (0)	3/4687 (0.1)	-----

[1] analysis includes only subjects without albuminuria at baseline; [2] analysis includes only subjects without macroalbuminuria at baseline; [3] not a specified secondary endpoint, analysis includes subjects with macroalbuminuria at baseline; [4] also with eGFR ≤ 45 mL/min/1.73 m^2 on same date
Source: Adapted from Table 2 of Dr. Kimberly Smith's consult review and Table 11.1.2.7: 1 of the study report for study 1245.25

Dr. Smith has reviewed the endpoints and the results, and has noted several issues with this data. One is that the laboratory changes (i.e., albuminuria, serum creatinine) could include small, transient, and/or reversible changes. These would not necessarily be clinically relevant. Another is that the definition of "continuous renal replacement therapy" is not clear and could include cases of reversible acute kidney injury that would not be representative of progression to end-stage disease requiring chronic dialysis. Additionally, Dr. Smith notes that the endpoints were re-defined throughout the trial and that some aspects were defined after trial completion.

In considering the data, Dr. Smith does not believe that these results represent a clinically meaningful endpoint. In her review of the data, she believes that the findings reflect a hemodynamic effect rather than a direct effect on the underlying disease process. Further, she notes that a reduction in albuminuria has not been validated or accepted as a surrogate for clinical outcomes in diabetic nephropathy. This is in part because therapies may have an acute, reversible pharmacologic effect on albuminuria (which appears to be the case with empagliflozin) that may differ from the long-term effects on irreversible loss of renal function and/or on the underlying disease progression. Dr. Smith's assessment is that the data does not support a conclusion that empagliflozin reduces "nephropathy" and that these be considered exploratory.

Based on my review of Dr. Lungu's review and Dr. Smith's consult review, I agree that there appears to be a risk for an acute impairment in renal function but that this does not necessarily result in long-term kidney injury. Thus, I would not remove the current Warning and Precaution of acute kidney injury. I also agree with Dr. Smith's assessment that the data do not clearly demonstrate a benefit in reducing renal complications of diabetes or progression of renal disease. As with the data on heart failure, I do not conclude that the data from EMPA-REG OUTCOME substantial evidence for this endpoint and I do not recommend including any of these endpoints in the label.

Amputations:
Amputations were identified as a safety concern for the class due to a signal identified with another SGLT2 inhibitor [3]. As a result, the applicant was asked to provide an analysis of amputations. Dr. Lungu, with the assistance of Dr. Changming Xia from the Office of Biostatistics, has also separately reviewed the data from the EMPA-REG OUTCOME study for a potential risk of amputation with empagliflozin.

In the applicant's analysis, they report that there is no evidence of increased risk for amputations (Table 8). Dr. Lungu and Dr. Xia found similar results to the applicant analysis.

Table 8: Incidence of lower limb amputations from EMPA-REG OUTCOME

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342	All Empa N=4687
	N (%)	N (%)	N (%)	N (%)
Applicant analysis	44 (1.89)	42 (1.79)	47(2.01)	89 (1.9)
Level of first amputation				
- Toe	22 (0.94)	30 (1.28)	30 (1.28)	60 (1.28)
- Above toe	22 (0.94)	12 (0.51)	17 (0.73)	29 (0.62)
FDA analysis	46 (1.97)	44 (1.87)	49 (2.09)	93 (1.98)

Source: Adapted from Table 5: 2 and Table 5: 3 of the Clinical Information submitted to NDA 204629 (SD 632, eCTD 0140) on May 16, 2016 and from Table 3 of Dr. Changming Xia's statistical review

The results of both the applicant's analysis and the FDA analysis do not reveal an increased risk for amputations with empagliflozin, but it is important to note that amputations were not collected in a standard fashion and that amputations were not considered adverse events. As a result, identification of cases required review of available narratives, comments, and reports of concomitant therapies. This may have led to missed events of amputation and likely contributed to the small numerical discrepancy between the applicant's analysis and the FDA analysis. While this is a major limitation, I agree with Dr. Lungu's conclusion that there does not appear to be a signal of increased risk for amputation from EMPA-REG OUTCOME. I would not add amputation as a labeled risk with empagliflozin at this time.

Malignancies:
The PMR included a requirement to assess malignancies (specifically breast cancer, bladder cancer, lung cancer, and melanoma). This was based on imbalances seen during the NDA review for empagliflozin and for other SGLT2 inhibitors.

Malignancies were adjudicated in this study by an oncologic assessment and adjudication committee (oncAAC). Adjudication results for malignancies by the oncAAC could be reported as 'possibly related to study medication', 'not related to study medication', or 'not assessable'. The WHO causality categories were to be used as a guide in assessing the relationship.

Out of the 83 patients (3.78%) in the placebo group that were reported with a malignancy after at least 6 months exposure to study drug, 79 (3.6%) had the events sent for adjudication. In the empagliflozin pool, out of the 179 patients (4.05%) with malignancy events after at least 6

[3] http://www.fda.gov/Drugs/DrugSafety/ucm500965.htm

months of exposure to study drug, 169 (3.83%) had events sent for adjudication. Of those, 16 (0.73%) events in the placebo group and 31 (0.70%) events in the empagliflozin pool were adjudicated as possibly related. The events that were not sent for adjudication were hematologic malignancies in all treatment groups. The overall occurrence of malignancy was not different between treatment arms.

Dr. Lungu provides additional discussion on selected malignancies. Some of these (i.e., bladder cancer, breast cancer, lung cancer, and melanoma) were specifically mentioned in the PMR (PMR 2755-4). Others (i.e., pancreatic cancer and renal cancer) were examined due to a small imbalance or concerns from other members of the class. A detailed breakdown for these malignancies is presented in Table 9.

Table 9: Malignancies of Interest after 6 Months of Exposure by HLT and PT

Malignancy of interest High level term – Preferred Term	**Placebo** **N=2333** **N (%)**	**All Empa** **N=4687** **N (%)**
Breast cancer	3 (0.1)	7 (0.1)
Breast and nipple neoplasms malignant	3 (0.1)	7 (0.1)
– Breast cancer	2 (0.1)	5 (0.1)
– Intraductal proliferative breast lesion	0	1 (< 0.1)
– Invasive ductal breast carcinoma	1 (< 0.1)	1 (< 0.1)
Bladder cancer	4 (0.2)	10 (0.2)
Bladder neoplasms malignant	1 (< 0.1)	8 (0.2)
– Bladder cancer	1 (< 0.1)	6 (0.1)
– Bladder transitional cell carcinoma	0	2 (< 0.1)
Urinary tract neoplasms malignant NEC	3 (0.1)	2 (< 0.1)
– Transitional cell carcinoma	3 (0.1)	2 (< 0.1)
Pancreatic cancer	1 (< 0.1)	8 (0.2)
Pancreatic neoplasms malignant (excl islet cell and carcinoid)	1 (< 0.1)	8 (0.2)
– Adenocarcinoma pancreas	1 (< 0.1)	3 (0.1)
– Pancreatic carcinoma	0	4 (0.1)
– Pancreatic carcinoma metastatic	0	1 (< 0.1)
Melanoma	2 (0.1)	7 (0.1)
Skin melanomas (excl ocular)	3 (0.1)	7 (0.1)
– Malignant melanoma	2 (0.1)	5 (0.1)
– Malignant melanoma in situ	0	2 (< 0.1)
– Metastatic malignant melanoma	1 (< 0.1)	0
Lung cancer	11 (0.5)	19 (0.4)
Non-small cell neoplasms malignant of the respiratory tract cell type specified	5 (0.2)	11 (0.2)
– Large cell lung cancer	1 (< 0.1)	0
– Lung adenocarcinoma	2 (0.1)	7 (0.1)
– Lung adenocarcinoma metastatic	0	1 (< 0.1)
– Lung squamous cell carcinoma .stage III	1 (< 0.1)	0
– Non-small cell lung cancer stage IV	1 (< 0.1)	0
– Squamous cell carcinoma of lung	0	3 (0.1)
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	6 (0.3)	7 (0.1)
– Bronchial carcinoma	0	1 (< 0.1)
– Lung cancer metastatic	1 (< 0.1)	1 (< 0.1)
– Lung neoplasm malignant	5 (0.2)	5 (0.1)
Respiratory tract small cell carcinomas	0	1 (< 0.1)
– Small cell lung cancer	0	1 (< 0.1)

Malignancy of interest High level term – Preferred Term	**Placebo** **N=2333** **N (%)**	**All Empa** **N=4687** **N (%)**
Renal cancer	5 (0.2)	9 (0.2)
Renal neoplasms malignant	5 (0.2)	9 (0.2)
– Clear cell renal cell carcinoma	3 (0.1)	3 (0.1)
– Renal cancer	0	2 (< 0.1)
– Renal cancer metastatic	0	1 (< 0.1)
– Renal cell carcinoma	1 (< 0.1)	2 (< 0.1)
– Renal cell carcinoma stage I	0	1 (< 0.1)
– Renal cell carcinoma stage II	1 (< 0.1)	0

Source: Adapted from Table 75 of Dr. Lungu's clinical review

Of these malignancies, only pancreatic cancer was seen at a higher incidence with empagliflozin (0.2% with empagliflozin vs. <0.1% with placebo) though the overall number of events was small and the overall incidence was <1% in either treatment group. Additionally, most of the pancreatic cancers were adjudicated as 'not related' by the oncAAC (Table 10) and many of these cases also had other confounding factors.

Table 10: Patient Characteristics for the Patients with Pancreatic Cancer Events

Treatment	**Subject ID**	**Days post rand.**	**DPP4 or GLP-1**	**Alcohol or smoking?**	**Fatal?**	**Fam Hx of Malignancy**	**Adjudication Opinion**
Placebo	(b) (6)	463	No	Not available	No	Not available	Not related
Empa 10		946	DPP4	Yes both	Yes	Not available	Not related
Empa 10		642	No	Smoker	No	Pancreatic cancer (sister)	Not related
Empa 10		~4 yrs.	No	Not available	No	Not available	Not assessable
Empa 10		1269	No	Not available	Yes	Not available	Possibly related
Empa 10		225	No	No	Yes	No	Not related
Empa 25		637	No	4-3 beers/day	No	Not available	Not related
Empa 25		1470	No	Not available	No	Not available	Possibly related
Empa 25		244	No	Ex-smoker	Yes	Gastric cancer (mother), and pharyngeal cancer (sister)	Not related

Days post rand. = days after randomization; DPP4 = dipeptidyl peptidase 4 inhibitor; GLP-1 = glucagon like peptide-1 receptor agonist; Fam Hx = family history
Source: Adapted from Table 76 of Dr. Lungu's clinical review

The data from the EMPA-REG OUTCOME study do not demonstrate a clear increased risk for malignancy with empagliflozin. I would not add malignancy as a labeled risk for empagliflozin.

Fractures:
Canagliflozin, another SGLT2 inhibitor, carries a Warning & Precaution for Bone Fracture. As a result, fractures were identified as adverse events of interest and were included in the required assessments in the PMR.

Fracture events were analyzed using a BIcMQ. The overall incidence of fractures was comparable in the empagliflozin and the placebo treatment groups (3.9% with placebo vs. 3.8% with empagliflozin; Table 11). The incidence of serious adverse fracture events and fracture events leading to discontinuation was slightly higher in the placebo group, while there was a slightly higher incidence of fractures in the upper limb in the empagliflozin group.

Table 11: Incidence of fractures

	Placebo N=2333	All Empa N=4687
	N (%)	N (%)
Overall fractures	**91 (3.9)**	**179 (3.8)**
– Upper limb [1]	12 (0.5)	45 (1)
– Lower limb [2]	25 (1.1)	33 (0.7)
Serious AE	**35 (1.5)**	**57 (1.2)**
Leading to discontinuation	**16 (0.6)**	**12 (0.3)**
Preferred Term		
– Rib fracture	14 (0.6)	31 (0.7)
– Foot fracture	11 (0.5)	24 (0.5)
– Humerus fracture	4 (0.2)	14 (0.3)
– Ankle fracture	5 (0.2)	12 (0.3)
– Pathological fracture	7 (0.3)	13 (0.3)
– Upper limb fracture	3 (0.1)	12 (0.3)
– Hip fracture	2 (0.1)	8 (0.2)
– Radius fracture	4 (0.2)	8 (0.2)
– Tooth fracture	4 (0.2)	9 (0.2)
– Wrist fracture	1 (< 0.1)	9 (0.2)
– Tibia fracture	7 (0.3)	3 (0.1)
– Facial bones fracture	5 (0.2)	6 (0.1)
– Hand fracture	4 (0.2)	5 (0.1)
– Spinal compression fracture	4 (0.2)	5 (0.1)
– Femoral neck fracture	2 (0.1)	3 (0.1)
– Femur fracture	3 (0.1)	3 (0.1)
– Fibula fracture	3 (0.1)	3 (0.1)
– Pelvic fracture	0	3 (0.1)
– Acetabulum fracture	0	2 (< 0.1)
– Lumbar vertebral fracture	3 (0.1)	2 (< 0.1)
– Osteoporotic fracture	2 (0.1)	2 (< 0.1)
– Patella fracture	0	2 (< 0.1)
– Clavicle fracture	1 (< 0.1)	2 (< 0.1)
– Forearm fracture	0	2 (< 0.1)
– Jaw fracture	0	2 (< 0.1)
– Ulna fracture	1 (< 0.1)	2 (< 0.1)
– Fractured coccyx	2 (0.1)	1 (< 0.1)
– Lower limb fracture	3 (0.1)	1 (< 0.1)
– Open fracture	2 (0.1)	1 (< 0.1)
– Periprosthetic fracture	1 (< 0.1)	1 (< 0.1)
– Pubis fracture	3 (0.1)	1 (< 0.1)
– Avulsion fracture	0	1 (< 0.1)
– Cervical vertebral fracture	0	1 (< 0.1)
– Scapula fracture	1 (< 0.1)	1 (< 0.1)
– Skull fractured base	1 (< 0.1)	1 (< 0.1)
– Spinal fracture	0	1 (< 0.1)
– Multiple fractures	1 (< 0.1)	0
– Thoracic vertebral fracture	1 (< 0.1)	0
– Traumatic fracture	1 (< 0.1)	0

[1] includes 'humerus fracture', 'radius fracture', 'upper limb fracture', 'wrist fracture', and 'forearm fracture'; [2] includes 'ankle fracture', 'hip fracture', 'tibia fracture', 'femoral neck fracture', 'femur fracture', 'fibula fracture', and 'lower limb fracture'

Source: Adapted from Table 15.3.1.14: 1, Table 15.3.1.14: 2, and Table 15.3.1.14: 3 of the study report for study 1245.25

In an associated analysis, it was noted that adverse event terms potentially associated with osteoporosis were reported at a higher incidence in the empagliflozin group compared to the placebo group (Table 12). Though bone mineral density was not assessed in a standardized fashion as part of this study, this difference is notable as there are concerns regarding fractures and effects on bone mineral density with another SGLT2 inhibitor. Though the incidence of fractures was not markedly different between treatment arms, it is possible that longer exposures may be needed to see a difference in fracture events.

Table 12 Osteoporosis Analysis by PT and Treatment Arm

	Placebo N=2333	All Empa N=4687
	N (%)	N (%)
Total	**13 (0.56%)**	**41 (0.87%)**
Preferred Term		
– Bone density decreased	0 (0.00%)	1 (0.02%)
– Bone loss	1 (0.04%)	1 (0.02%)
– Osteopenia	7 (0.30%)	13 (0.28%)
– Osteoporosis	2 (0.09%)	25 (0.53%)
– Osteoporosis postmenopausal	1 (0.04%)	0 (0.00%)
– Osteoporotic fracture	2 (0.09%)	2 (0.04%)

Source: Adapted from Table 71 or Dr. Lungu's clinical review

Based on review of the data from the EMPA-REG OUTCOME study, there does not appear to be an increased risk for fracture. However, it is notable that there were more upper limb fractures with empagliflozin compared to placebo. Similarly, terms associated with osteoporosis (a risk for fractures) were more common with empagliflozin. The overall incidence of both of these is low, and it is not clear that either of these observations is clinically relevant. I would not include fractures as a safety concern in labeling at this time.

9. Advisory Committee Meeting

An Advisory Committee meeting was held on June 28, 2016 to discuss the results of the EMPA-REG OUTCOME study and the proposed new indication. At that meeting, the following questions were asked:

1. **DISCUSSION:** Discuss your interpretation of the EMPA-REG OUTCOME study conduct. Please comment on whether interim unblinding or changes made to the protocol, endpoint definitions, and analyses plan (e.g., specific exclusion of silent MI from the primary endpoint) during the course of the EMPA-REG OUTCOME study alter or do not alter your level of confidence in a conclusion that excess CV-risk was excluded and CV-benefit was established.

2. **DISCUSSION:** Please discuss the persuasiveness of the statistical results for the primary analysis. Please also comment on how results for the individual components in the primary composite endpoint impact your level of confidence in the study findings. Finally, comment on concerns you may have related to potentially incomplete ascertainment of some myocardial infarction events (i.e., silent MI) in this trial and whether these concerns, if any, alter your level of confidence in the results for the primary analysis.

3. **DISCUSSION:** Discuss the persuasiveness of the mortality findings in the EMPA-REG OUTCOME study. In your discussion, please address any potential limitations of these data including but not limited to:

    - Issues raised in Discussion Point #2
    - The proportion of deaths that were determined "non-assessable" by adjudicators
    - The lack of granular data on potentially important information such as baseline heart failure history and dose of relevant baseline and concomitant medications
    - The lack of pre-specified alpha-adjustment for this endpoint

4. **DISCUSSION:** Discuss the heart failure findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on heart failure and heart-failure related outcomes.

5. **DISCUSSION:** Discuss the renal findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on kidney disease related to diabetes.

6. **VOTE:** Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results have fulfilled the recommendations laid out in the 2008 Guidance for Industry by demonstrating that use of empagliflozin to improve glycemic control would not result in an unacceptable increase in cardiovascular risk?

    a. If yes, please provide the rationale for your vote.

    b. If no, please provide the rationale for your vote and comment on what additional data would be needed.

7. **VOTE:** Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results provide substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied?

    a. If yes, please provide the rationale for your vote.

    b. If no, please provide the rationale for your vote and comment on what additional data would be needed.

During the discussion period, committee members were in general satisfied that the EMPA-REG OUTCOME study demonstrated that there was no increased cardiovascular risk with empagliflozin. There was some uncertainty with regard to the superiority conclusion for 3-

point MACE with several committee members commenting that the finding was statistically persuasive. This was due to the multiple changes during the study, marginal p-value, and minor changes leading to no longer concluding superiority for 3-point MACE. For some, this impacted the ability to consider further endpoints while for others this was not a concern. Committee members commented that the mortality findings from the EMPA-REG OUTCOME study were the most interesting finding and the most clinically important though there was some disagreement as to whether the results could be considered substantial evidence due to concerns with respect to the robustness of the primary endpoint. Some members were persuaded by the highly statistically significant p-value and consistency of the cardiovascular mortality and all-cause mortality endpoints. Examples of cases where single studies were the basis of an indication were cited, as well as cases where findings from exploratory endpoints were not replicated. It was commented that similar data from another member of the class would be reassuring, though that type of data is not available. The absence of a clear mechanism of action (MOA) for the apparent benefit on cardiovascular mortality was a concern for some committee members as well. The concern was also raised that differences in co-management could be contributing to the apparent benefit.

Results for other endpoints such as heart failure and nephropathy were viewed as interesting but not conclusive. For these endpoints, committee members generally felt that additional studies were needed.

For the first voting question (i.e., did the EMPA-REG OUTCOME study satisfy the 2008 Guidance for Industry), the vote was as follows:

Yes: 23	No: 0	Abstain: 0

The committee unanimously voted "Yes", agreeing that the EMPA-REG OUTCOME study fulfilled the recommendations laid out in the 2008 Guidance for Industry and demonstrated no increased risk for major adverse cardiovascular events.

For the second voting question (i.e., did the EMPA-REG OUTCOME study provide substantial evidence to establish a reduction in cardiovascular mortality), the vote was as follows:

Yes: 12	No: 11	Abstain: 0

The committee members who voted "Yes" felt that the results provide substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied. The committee members voting "Yes" were convinced of the CV mortality endpoint findings due to its ability to withstand all sensitivity analysis, even missing data. One member noted that a 38% reduction may be an overstatement; however, a 20% endpoint may be more likely and is still considered a good benefit.

The committee members who voted "No" were intrigued by the CV mortality reduction endpoint but argued that more data would be needed to conclude that there was substantial evidence to support the observed benefit. Acknowledging that there is a need for therapies that

provide a benefit on cardiovascular outcomes, some committee members found it difficult to vote "Yes" for an additional indication without a better understanding of the mechanism or a second trial producing similar results. One committee member expressed low confidence in adding empagliflozin to a patient's regimen since it would be difficult to express to patients the need for the drug without understanding its MOA. Other committee members expressed their concurrence with the Agency's standard for approval, in which two well controlled trials are encouraged prior to the approval of any new indication.

10. Pediatrics

A full waiver was requested for study of the newly proposed indication. The basis of this waiver request is that the studies would be impossible or highly impracticable to perform. I agree with this waiver request, and the request was reviewed by the Pediatric Review Committee on July 27, 2016 who also agreed.

11. Other Relevant Regulatory Issues

None.

12. Labeling

I recommend approval of the proposed new indication for reducing the risk of cardiovascular death in patients with T2DM and established cardiovascular disease. I believe that the EMPA-REG OUTCOME study supports the addition of this indication. The applicant has also proposed removing the Warning and Precaution for Macrovascular Outcomes which states that there is no conclusive evidence of macrovascular risk reduction. Given acceptance of the conclusion that empagliflozin reduces the risk of cardiovascular death in patients with T2DM and established cardiovascular disease, removing this seems appropriate.

In addition to the proposed new indication, the applicant has proposed many other additions. The applicant has proposed to (b) (4) (b) (4) I do not agree with this as I do not believe there is sufficient information to support this change.

The applicant has proposed removing the Warning and Precaution for Impairment in Renal Function. I do not agree. The data suggest that there is a risk for acute kidney injury with initiation of empagliflozin. This Warning and Precaution should be retained and updated to be consistent with the other SGLT2 inhibitors.

The applicant has proposed the addition of a description of the results of the EMPA-REG OUTCOME study in section 14. The original proposed presentation included discussion of endpoints for which I do not believe there is sufficient evidence to conclude a benefit (e.g., heart failure, "nephropathy"). Discussion of these endpoints should be removed. Presenting the results for the primary composite endpoint (i.e., 3-point MACE) and the components

would be acceptable though presentation of p-values for endpoints other than 3-point MACE would not be appropriate. As the endpoint with evidence for benefit is cardiovascular death, additional discussion of the mortality findings is warranted, as is inclusion of a proposed Kaplan-Meier plot.

Labeling language to conform to the Pregnancy and Lactation Labeling Rule has also been submitted.

Labeling negotiations are ongoing, and final labeling language has yet to be agreed upon.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval of these supplements. I also recommend that PMR 2744-5 be recognized as "fulfilled".

- Risk Benefit Assessment

The results of the EMPA-REG OUTCOME study have not altered previous conclusions of a favorable risk-benefit for patients being treated with empagliflozin for glycemic control. In addition, the results of the EMPA-REG OUTCOME study support concluding that in patients with T2DM and established cardiovascular disease that there is evidence of a further benefit for reducing the risk of cardiovascular death in this population.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I do not recommend a Risk Evaluation and Management Strategy.

- Recommendation for other Postmarketing Requirements and Commitments

I do not recommend any Postmarketing Requirements or Postmarketing Commitments.

- Recommended Comments to Applicant

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H CHONG
12/01/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s008

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	NDA 204629, SDN 406/ NDA 206111, SDN 81
Priority or Standard	Standard
Received Date(s)	November 4, 2015, and December 4, 2015
PDUFA Goal Date	December 2, 2016
Division / Office	DMEP
Reviewer Name(s)	Andreea O. Lungu
Review Completion Date	November 3, 2016
Established Name	Empagliflozin / Empagliflozin and metformin hydrochloride
Trade Name	Jardiance (NDA 204629) / Synjardy (NDA 206111)
Therapeutic Class	Sodium-dependent glucose co-transporter-2 inhibitor
Applicant	Boehringer Ingelheim Pharmaceuticals Inc.
Formulation(s)	Tablet
Dosing Regimen	NDA 204629: Once daily: 10 mg and 25 mg empagliflozin NDA 206111: Twice daily: (mg empagliflozin / mg metformin hydrochloride) 5/500; 5/1000; 12.5/500; 12.5/1000
Indication(s)	Adjunct to diet and exercise to improve glycemic control (Proposed) In adult patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the incidence of cardiovascular death
Intended Population(s)	Adults with Type 2 Diabetes Mellitus
Team Leader	William H. Chong
Division Director	Jean-Marc Guettier
Statistical Reviewer - Efficacy	Jennifer Clark
Project Manager	Michael G. White

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Abbreviations

ADA	American Diabetes Association
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
CEC	Clinical events committee
CHF	Congestive heart failure
CI	Confidence interval
CMQ	Customized MedDRA query
CV	Cardiovascular
CVOT	Cardiovascular outcomes trial
CTD	Common technical document
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DPP-4	Dipeptidyl peptidase-4
eCTD	Electronic Common Technical Document
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
Empa	Empagliflozin
FAS	Full analysis set
FAS (OC)	Full analysis set, observed cases
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c/glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HLT	Medical Dictionary for Regulatory Activities High Level Term

ICH	International Conference on Harmonisation
ICH E3	International Conference on Harmonisation: Structure and content of clinical study reports
IND	Investigational new drug
LDL	Low density lipoprotein cholesterol
LL	Lower limit
LLRR	Lower limit of the reference range
LOCF	Last observation carried forward
LVOT	Last value on treatment
MACE	Major adverse cardiovascular event
MAED	MedDRA Adverse Event Diagnostics
MDI	Multiple daily injections (insulin)
Mdn	Median
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory activities
Met	Metformin
MI	Myocardial infarction
MMRM	Mixed-effects model repeated measures
NA	Not applicable
NCF	Noncompleters considered failure
NDA	New Drug Application
Non-HDL	Non-high density lipoprotein cholesterol
NR	Not reported
PG	Plasma glucose
PI	Principal investigator
PK	Pharmacokinetics
PPS	Per-protocol set
PT	Medical Dictionary for Regulatory Activities Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-dependent glucose co-transporter-2
SMQ	Standardized Medical Dictionary for

	Regulatory Activities Query
SOC	Medical Dictionary for Regulatory Activities System Organ Class
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TIA	Transient ischemic attack
TS	Treated set
TZD	Thiazolidinedione
ULN	Upper limit of normal
ULRR	Upper limit of reference range
WRR	Within the reference range

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant has submitted efficacy supplements with data from the completed cardiovascular outcomes study (1245.25) providing information regarding the treatment effect of empagliflozin on ischemic cardiovascular risk in patients with type 2 diabetes mellitus (T2DM) at high risk for cardiovascular disease. This study has been conducted as a post marketing requirement (PMR), based on the 2008 Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. The purpose of the study was to demonstrate that empagliflozin therapy is not associated with an increased risk for major adverse cardiovascular events (MACE).

The Applicant is also proposing the addition of a new indication for empagliflozin based on the results of the study as follows: "In adult patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the incidence of cardiovascular death."

Based on my review of the data, I believe that excess cardiovascular risk has been ruled out with empagliflozin per the postmarketing requirement. In addition, the study shows that treatment with empagliflozin results in a statistically significant reduction in cardiovascular (CV) mortality compared to placebo in the selected patient population. This finding was robust to multiple sensitivity analyses, and was consistent between the two empagliflozin doses and subgroup analyses. In this context, I believe that the new indication for reduction in cardiovascular mortality as proposed by the applicant for NDA 204629 (empagliflozin) is supported by the submitted data. While I am recommending approval of both these efficacy supplements, I do not believe that the proposed new indication for NDA 206111 (empagliflozin-metformin fixsed dose combination) is supported by the data. Inclusion of a description of the results in the label for NDA 206111 is currently under discussion.

1.2 Risk Benefit Assessment

Study 1245.25, which was a randomized, double-blind, event-driven trial comparing two doses of empagliflozin to placebo, both added to local standard of care antidiabetic treatments, in patients with T2DM at increased risk for atherosclerotic cardiovascular disease (ASCVD). As mentioned previously, the primary objective of the trial was to exclude the possibility that use of empagliflozin to treat diabetes results in increased cardiovascular risk (predominantly ASCVD risk) by 30% or more compared to use of alternate, standard of care, glycemic lowering

therapies. The same study results were submitted for both NDA 204629 (empagliflozin) and NDA 206111 (empagliflozin-metformin fixed-dose combination).

Empagliflozin is approved for treatment of adults with T2DM at the doses of 10 mg and 25 mg daily. The risk-benefit assessment was discussed at the time of the original NDA approval in the comprehensive clinical review by Dr. Chong. In the original NDA submission, empagliflozin was shown to be effective in reducing glycosylated hemoglobin (HbA1c) in patients with T2DM as monotherapy, and as add-on to a variety of antidiabetic regimens (including metformin, metformin plus sulfonylureas, pioglitazone, and basal insulin).

Metformin is an oral biguanide, which decreases production of hepatic glucose, intestinal glucose absorption and improves insulin sensitivity. It was approved for the treatment of T2DM in US as Glucophage (NDA 20357) on March 3, 1995.

The empagliflozin-metformin combination was approved for use in adults with T2DM at the following twice daily doses: 5 mg empagliflozin/500 mg metformin hydrochloride 5 mg empagliflozin/1000 mg metformin hydrochloride 12.5 mg empagliflozin/500 mg metformin hydrochloride 12.5 mg empagliflozin/1000 mg metformin hydrochloride.

In this submission, the Applicant has shown that empagliflozin added to standard of care therapy in patients with T2DM and increased risk of ASCVD resulted in a statistically significant reduction in the risk of 3-point major adverse cardiovascular event (MACE) defined as an incident event of either: cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke. This result is almost exclusively due to the benefit observed with empagliflozin on the CV death component of the primary outcome, while no clear benefit was observed for MI and a numerical imbalance not favoring empagliflozin was seen for stroke. This raises questions regarding the mechanism responsible for the observed reduction in the risk of MACE with empagliflozin, as it does not appear to be ischemic in nature. As a result, it is not clear whether empagliflozin reduces the risk of the ischemic cardiovascular events that resulted in the 2008 Guidance for Industry: Diabetes mellitus – Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes.

In considering the new proposed indications, a few other issues are notable regarding the EMPA-REG study and results:

- This is a single study designed as a cardiovascular safety study sized to show non-inferiority compared to the standard of care using a non-inferiority margin of 1.3. The 95.02% confidence intervals used to establish non-inferiority with upper bounds also showed a reduction in 3-point MACE. However, an efficacy claim usually

requires more than one adequate and well-controlled study, though there are situations in which a single adequate and well-controlled study has served as the basis for a claim.

- A large proportion of CV deaths were deemed not assessable, meaning there was missing information and the cause of death could not be ascertained. When these deaths were excluded from the primary endpoint, the results no longer showed superiority for 3-point MACE, however it did not change the CV death results.
- Silent MI was not included in the primary composite endpoint and including this in the primary analysis the primary MACE endpoint still demonstrates non-inferiority but no longer shows superiority. However, due to poor definition and ascertainment of silent MI events in this study, I do not believe that an analysis of the primary endpoint including these events is meaningful.
- A pre-specified interim analysis (IA) was conducted in conjunction with a meta-analysis to rule out excess 80% cardiovascular risk with empagliflozin at the time of the FDA submission, and a significant number of applicant employees were unblinded at that time. However, IA does not appear to be a concern as analyses looking at patients enrolled before IA and after IA yielded similar results.

The safety findings from this study are generally consistent with the current prescribing information for empagliflozin. However, we became aware during this review of issues related to lower extremity amputations from the canagliflozin cardiovascular outcomes trial interim analysis, and amputations were designated as a tracked safety issue for the drug class. We performed an analysis of amputations in EMPA-REG, and did not detect any significant imbalance between the treatment arms. However, the analysis is not completely reliable as amputation events were not systematically collected during the study, and this safety signal will have to be followed in future studies.

Regardless of the above-mentioned issues, I believe that the overall findings from study 1245.25 demonstrate that empagliflozin is not associated with increased CV risk in this patient population, therefore satisfying the PMR. In addition, the results of EMPA-REG demonstrate a statistically significant reduction in CV mortality, and all-cause mortality (due to the CV death component) with empagliflozin in the studied patient population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

Empagliflozin is a sodium-dependent glucose co-transporter-2 (SGLT2) inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, a disease of impaired glucose regulation due to impaired insulin action and insulin resistance. SGLT2 is a transporter found in the proximal renal tubule, and is responsible for renal glucose reabsorption. Inhibition of this transporter increases glucosuria, which in turn results in improved glycemic control.

2.1 Currently Available Treatments for Proposed Indications

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes include:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 (GLP-1) analogues
- SGLT2 inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colesevelam hydrochloride)

Despite the relatively large number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug. Further, some drug classes may be poorly tolerated by some patients or have limited usefulness in certain populations. For example, sulfonylureas (SU) and insulin are associated with a high risk for hypoglycemia, thiazolidinedione's (TZDs) may be associated with edema and are not for use in many patients with congestive heart failure, while metformin and sodium-glucose co-transporter 2 (SGLT2) inhibitors are contraindicated in patients with severe renal dysfunction.

TZDs, SUs, and insulin are all associated with significant weight gain. Additionally, progressive β-cell dysfunction may lead to secondary treatment failure to the anti-diabetic therapy over time requiring the addition of other agents. For these reasons, and because T2DM is a disease that is heterogeneous in both pathogenesis and clinical manifestation, there is an unmet need for new anti-diabetic therapies and concomitant treatment options for T2DM in patients who are not adequately controlled on monotherapy.

Most importantly, no antidiabetic medication has yet been able to demonstrate an improvement in diabetic macrovascular complications. EMPA-REG Outcome is the first study where there is a suggestion of improvement in specific cardiovascular outcomes.

2.2 Availability of Proposed Active Ingredient in the United States

Empagliflozin and the empagliflozin + metformin fixed-dose combination drug product are approved for marketing in the United States, and are available by prescription. Empagliflozin is also a component of a fixed-dose combination product with linagliptin.

2.3 Important Safety Issues with Consideration to Related Drugs

There are three SGLT2 inhibitors currently approved by the FDA: empagliflozin, dapagliflozin, and canagliflozin.

Safety concerns believed to be related to the drug class include hypotension, diabetic ketoacidosis (DKA), urosepsis and urinary tract infections, genital mycotic infections, decreases in renal function, and increases in hematocrit and cholesterol. Recently, serious concerns regarding a potential for ketoacidosis and serious urinary tract infections have been identified, resulting in a safety labeling change for all approved SGLT2 inhibitors on December 4, 2015

A numerical increase in stroke events was also seen with all members of the class, however not statistically significant.

A few safety signals are ongoing evaluation: fractures and amputations. An increase in the incidence of upper extremity fractures was seen with canagliflozin. Also, recently, canagliflozin was found to result in an increase in lower extremity amputations in patients at risk. It is not clear whether these signals will withstand time and whether they are a class effect. A safety label communication for canagliflozin regarding amputations was issued on May 18, 2016.

Canagliflozin was approved by the FDA on March 29, 2013. Issues discussed at the Advisory Committee for canagliflozin included reduced efficacy with impaired renal function, development of decreased renal function and renal adverse events (including hyperkalemia),

volume depletion events, changes in bone turnover markers, an imbalance in fractures (especially in upper limb fractures), increased risk of genital mycotic infections, effects on lipids (i.e. increases in low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and non-HDL), and an imbalance in early cardiovascular (CV) events. Post-marketing requirements for canagliflozin include a cardiovascular outcomes study, a bone safety study, and an enhanced pharmacovigilance program for reports of malignancy (pheochromocytoma, Leydig cell tumor, and renal cell carcinoma), fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy.

A Complete Response was issued for dapagliflozin on January 17, 2012 due to concerns that included malignancy (specifically bladder cancer) and liver toxicity. On July 11, 2013, the NDA was re-submitted, and dapagliflozin was approved by the FDA on January 8, 2014 following an Advisory Committee meeting that discussed cardiovascular risk, malignancy risk, and liver toxicity issues. Post-marketing requirements include a cardiovascular outcome study (with the protocol amended to include additional evaluation of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections [e.g. pyelonephritis, urosepsis], serious events related to hypovolemia and serious hypersensitivity reactions).

Empagliflozin was approved on August 1, 2014. Post-marketing requirements include a cardiovascular outcomes trial including evaluation of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast cancer, bladder cancer, lung cancer, melanoma, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions.

2.4 Summary of Presubmission Regulatory Activity Related to Submission

No signal of an increase in CV risk, as defined by the FDA guidance, was identified in the pre-market empagliflozin development program. For empagliflozin, the preplanned method for evaluation of cardiovascular safety was a meta-analysis of data from eight Phase II and III trials, one of which was study 1245.25. Interim data (142 MACE events) from Study 1245.25 were used in the CV meta-analysis, where they represented the majority of the events. The primary endpoint for the premarketing meta-analysis for cardiovascular safety was 4-point MACE, which is a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. The hazard ratio for 4-point MACE from the overall meta-analysis was estimated as 0.74 (95% CI 0.57, 0.96). The interim analysis (IA)was also used to independently test for the pre-market 1.3 risk margin, however the analysis did not exclude 1.3 at

that time likely due to a small number of events (HR for 3-point MACE was 0.74 (99.98% CI 0.4, 1.4).

The Applicant reported that the interim analysis was performed by a team independent of the trial team. To maintain the integrity of the trial, access to the unblinded data was only provided to the independent data team responsible for the interim database lock, statistical analyses, and reporting of the interim data, and this was controlled by a confidentiality agreement. Notably, approximately 230 applicant employees were unblinded at the time of the interim analysis, and signed confidentiality agreements. While it is unclear what level of unblinding is appropriate, the numbers of individuals unblinded seems large. However, we did not find any evidence that this unblinding at interim impacted the results of the study.

It is also important to note that there have been many changes that impacted the design and conduct of the trial, which occurred while the trial was ongoing. These changes are summarized below.

EMPA-REG OUTCOME Key Milestone Dates

April 1, 2010	Clinical Event Committee (CEC) charter changed to include definitions for events outlined in the 2009 Standardized Definitions for Cardiovascular Outcomes Trials: Draft Recommendations, and consistent with FDA advice at the time
May 10, 2010	Original trial protocol finalized
August 26, 2010	First subject enrolled
September 15, 2010	First subject randomized
September 22,2010	Protocol amendment 1: - Exempted cardiovascular outcomes from expedited reporting - Cardiovascular events occurring during screening/run-in to be considered as serious adverse events, not outcome events - Hepatic injury added to list of significant adverse events
February 11, 2011	Protocol first submitted to FDA
April 22, 2011	Protocol amendment 2: - Changes to inclusion/exclusion criteria and duration of follow-up - Changes made to endpoints - Changes made to planned analysis - Clarification that no interim analysis at the trial level planned, but unblinded data to be included in a pre-specified

	cardiovascular meta-analysis
June 9, 2011	Amended protocol submitted to FDA
December 29, 2011	Protocol amendment 3: - Based on discussion and feedback received from FDA at the End-of-Phase 2 meeting, an interim analysis was added to support the empagliflozin NDA submission. The sample size, and trial duration were increased. Empa-Reg would be used alone for 1.3 and it was determined that a total of 691 events would be required. - Clarification that silent MI would not be included in the primary endpoint - Endpoint definitions moved to the CEC Charter
January 9, 2012	Amended protocol submitted to FDA
February 18 2012	CEC Charter Version 6 Endpoint definitions modified - Criteria for Acute MI: Cardiac Biomarker Elevation: removed language which stated "with at least one value above the 99th percentile of the upper reference limit." Refers now to "upper reference limit." - Diagnosis of Stroke: Removed "amaurosis fugax (transient complete/partial loss of vision of one eye)" - Classification of Stroke: o Moved the following language previously under Hemorrhagic Stroke to Ischemic Stroke (Non-hemorrhagic): "this category includes ischemic strokes with hemorrhagic transformation (i.e., no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan") o Changed "Not assessable stroke" to "unknown" - Hospitalization for Unstable Angina: Changed the requirement for an "unscheduled visit to a healthcare facility and overnight admission [does not include chest pain observation units] to: "the date of this event will be the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit" - Heart Failure requiring Hospitalization: Changed the definition from "requires hospitalization defined as an

	admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available)" to "the date of this event will be the day of hospitalization of the patient including any overnight stay at an emergency room or chest pain unit."
August 24, 2012	Trial statistical analysis plans for 1.8 and 1.3 assessment were finalized
June 22, 2012	Data cut-off for the interim analysis and meta-analysis
August 31, 2012	Database lock for interim analysis and meta-analysis - Data for 4,874 subjects (1619 placebo, 1623 empagliflozin 10 mg, 1632 empagliflozin 25 mg) unblinded to firewalled team
March 19, 2013	Original NDA submission
April 19, 2013	Last subject randomized
October 15, 2013	Protocol amendment 4 - Minor changes to the language for exploratory endpoints - Description of the adjudication and assessment of hepatic events and cases of cancer - Clarification of the minimum number of primary endpoint events to be collected
January 7, 2014	Amended protocol submitted to FDA
April 4, 2014	CEC Charter Version 8a Updated "Hospitalization for Heart Failure" definition to include: - Initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy - Uptitration of oral diuretic or intravenous therapy, if already on therapy
December 12, 2014	CEC Charter Version 9 - Revised Hemorrhagic Stroke definition to remove "Subdural Hematoma".
April 13, 2015	Last subject's last visit
June 22, 2015	Final database lock - Database unblinded
November 4, 2015	sNDA submission to the FDA

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Based on review of the submitted study report, there are no apparent issues with data integrity or with the integrity of study conduct. While many changes occurred during the conduct of the study, it appears that they were motivated by recommendations from the FDA, Steering Committee, changes in event definition guidelines, and we found no evidence that any of the changes was made in response to unblinding at the IA. .

3.2 Compliance with Good Clinical Practices

The Applicant states that the trial was conducted in compliance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), and conformed to the Declaration of Helsinki, as well as applicable regulatory requirements, and relevant local guidelines.

3.3 Financial Disclosures

While a number of investigators disclosed significant compensation or equity interest in the company, it is unlikely that this had an impact on the findings from the study. See 10.2 for the completed Financial Disclosure Review Template.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no new CMC information included in this supplement.

4.2 Clinical Microbiology

There is no information related to clinical microbiology included in this supplement.

4.3 Preclinical Pharmacology/Toxicology

There is no new pharmacology/toxicology information included in this supplement.

4.4 Clinical Pharmacology

There is no new clinical pharmacology information included in this supplement.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

For this efficacy supplement, the Applicant has submitted a complete study report for study 1245.25 to support a new indication (prevention of cardiovascular events) for empagliflozin, and empagliflozin-metformin fixed dose combination drug product. As only a single study was submitted to support these supplements, it will not be presented as a table.

5.2 Review Strategy

This review is based on the 1245.25 efficacy supplement submission for NDA 204629, and NDA 206111, as well as the multiple responses to information requests.

Randomly selected narratives for deaths and nonfatal serious adverse events (SAEs) were reviewed. For review of the adverse events (AEs), the information presented in the study report was also compared to tabulations generated using the included datasets and using MedDRA Adverse Event Diagnostics (MAED), and JReview.

5.3 Discussion of Individual Studies/Clinical Trials

The Applicant submitted only one study report (Study 1245.25) in support of the two efficacy supplements for NDA 204629, and NDA 206111. This is a phase III, event-driven trial, intended to demonstrate non-inferiority (with a non-inferiority margin of 1.3) of the treatment with two pooled doses of empagliflozin (10 mg and 25 mg) versus placebo on the composite of three major adverse cardiovascular events (MACE): cardiovascular death, non-fatal stroke, or non-fatal MI in patients with T2DM and increased cardiovascular risk. If non-inferiority of empagliflozin was established for the primary endpoint and for the key secondary endpoint (cardiovascular death [including fatal stroke and fatal MI], non-fatal MI [excluding silent MI], non-fatal stroke, and hospitalization for unstable angina pectoris), the hierarchical statistical analysis was to continue to evaluate the superiority of empagliflozin vs. placebo for the primary endpoint and thereafter for the key secondary endpoint.

Study Title: A phase III, multicenter, international, randomized, parallel group, double blind cardiovascular safety study of BI 10773 (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk.

Study Design:

This was a randomized, double-blind, multinational, parallel group, event-driven study with 3 treatment groups (empagliflozin 10 mg once daily, empagliflozin 25 mg once daily, or placebo), as add-on to standard of care treatment, with the aim to investigate the safety of empagliflozin treatment in patients with T2DM and high cardiovascular risk. This study is part of the ongoing cardiovascular safety assessment for empagliflozin, and was a post marketing requirement.

This study was conducted in 607 centers in 42 countries worldwide (Argentina, Australia, Austria, Belgium, Brazil, Canada, Columbia, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Greece, Hong Kong, Hungary, India, Indonesia, Israel, Italy, Japan, Korea, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Portugal, Romania, Russia, Singapore, South Africa, Spain, Sri Lanka, Taiwan, Thailand, Ukraine, United Kingdom, and United States). The Coordinating Investigator was Dr Bernard Zinman, Toronto, Canada, nominated to coordinate investigators at different sites participating in this multicenter trial. There was a change in Coordinating Investigator during the conduct of this trial: Dr Silvio Inzucchi (New Haven, CT, USA) was initially appointed as Coordinating Investigator; Dr Zinman took over on 17 Jan 2012. Dr Inzucchi remained a member of the trial Steering Committee.

The primary objective of this study was to exclude excess CV risk with empagliflozin vs placebo added on top of standard of care in patients with T2DM at increased risk for atherosclerotic cardiovascular disease.

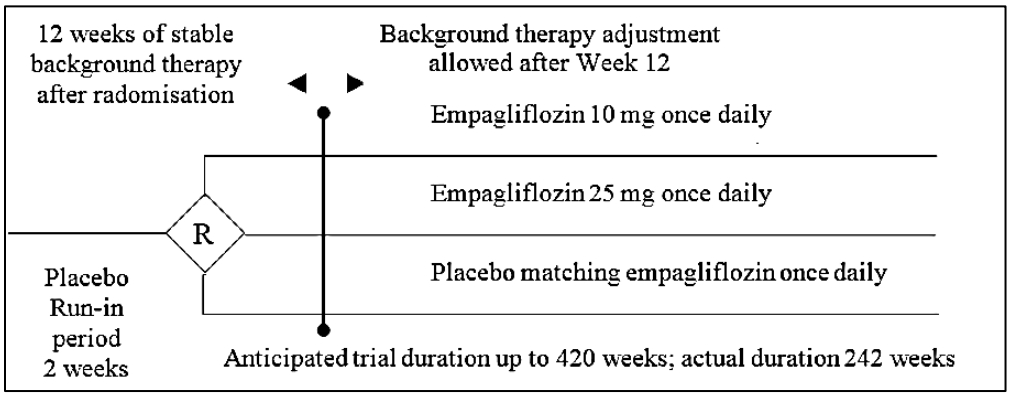
In total, approximately 7000 patients were planned to be included and randomized 1:1:1 per treatment group. Randomization was performed via an IXRS system and was stratified in a balanced ratio for HbA1c at screening, BMI at randomization, geographical region, and renal function at screening. The trial was event driven, and the anticipated duration of this trial was up to 420 weeks. The actual duration of treatment was dependent on recruitment rates and the occurrence of primary outcome events; the primary analysis was to occur after a minimum of 691 patients had experienced adjudicated primary outcome events.

The actual individual treatment duration for patients in this study was between approximately 2 and 5 years (approximately 104 to 242 weeks). Visits occurred at 4, 8, 12, 16, 28, 40, and 52 weeks and thereafter at 14 week intervals until the final visit (end of study [EOS] visit). Note that during the study treatment period, patients were allowed to go off-treatment and subsequently re-start treatment. The EOS visit was to occur ±7 days after permanent discontinuation from study medication, or when the required number of outcome events was reached, for patients ongoing in the trial at trial close out. A final follow-up visit was planned

for individual patients 30 days after the EOS visit. Patients who discontinued or withdrew from trial medication after randomization (Visit 3 and beyond) were to be followed up using the same visit schedule until the end of the trial.

As presented in Figure 1 below, after screening, all eligible patients were to undergo a 2-week, open-label, placebo run-in period before randomization. Patients who successfully completed this period and still met the inclusion/exclusion criteria were randomized to treatment with study medication in addition to the background therapy (if applicable) they were receiving at the time they signed the informed consent. After randomization, background antidiabetic therapy was to remain unchanged for 12 weeks, unless required for medical reasons; rescue medication could be added if needed. Individual patient participation was concluded when the patient had undergone the last planned visit, after the necessary number of events had accumulated in the trial, or when a fatal event occurred.

Figure 1 Trial Design



Source: Figure 9.1: 1 study report NDA 204629, SDN 406

The time period for which AEs were still to be considered on treatment was 7 days following last intake of study medication for AEs, 3 days for laboratory values and 1 day for pulse rate.

Data up to 7 days after last treatment intake was considered as on-treatment for glycosylated hemoglobin (HbA1c) and waist circumference and up to 1 day for all other endpoints.

The applicant efficacy analyses followed the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e. patients were analyzed as randomized. Safety analyses also assigned patients to the treatment group as randomized.

Table 1 Endpoint specific follow-up period for the assignment to active treatment

Endpoint	Last day of assignment to treatment phase (days after study drug stop date)
Safety	
Adverse events	7
Safety laboratory measurements	3
Pulse rate	1
Efficacy	
HbA_{1c}	7
FPG	1
Body weight	1
Blood pressure	1
Waist circumference	7

Source: Table 6.7:1 appendix 16.1.9 study report NDA 204629, SDN 406

The end of the trial was defined as 'last patient out', i.e. the last visit completed by the last patient in the trial. After the EOS visit, all AEs (including those persisting) were to be followed-up to the end of the 30-day follow-up period and it was to be confirmed if they had resolved or were sufficiently characterized. Additionally, to ensure that all available follow-up information was available for specific cases of malignancy, details of treatment and status of the cancer and its treatment were to be requested as follow-up data at trial close out (urogenital cancers, malignant melanomas, and lung cancers). Investigators were asked to provide a comment on the SAE narrative for each of these cases to include an update or to advise if no further information had been obtained. The 30-day follow-up period was considered by the applicant to be sufficient because previous studies with empagliflozin had shown that the pharmacodynamic effect of empagliflozin only extended to about 3 days after the last dose.

Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to 1 of the 3 treatment groups (empagliflozin 10 mg; empagliflozin 25 mg; placebo) in a 1:1:1 ratio. Randomization was performed at the randomization visit (Visit 3), and was stratified in a balanced ratio for HbA1c (<8.5 or ≥8.5% at screening), BMI (<30 or ≥30 kg/m^2 at randomization), geographical regions (North America, Latin America, Europe, Africa, and Asia), and renal function at screening (normal: eGFR ≥ 90 $mL/min/1.73m^2$; mild impairment: 60 $mL/min/1.73m^2$ ≤ eGFR ≤89 $mL/min/1.73m^2$; moderate impairment: 30 $mL/min/1.73m^2$≤ eGFR ≤59 $mL/min/1.73m^2$). To prevent unequal treatment allocation, blocks of 6 were used for randomization, and the blocks were assigned to strata.

The EMPA-REG study was conducted under the supervision of a Steering Committee and a Data Monitoring Committee.

- Steering Committee: A Steering Committee (SC) provided scientific leadership for the design and conduct of the study, and for interpretation of data. It was composed of experts in metabolic, cardiovascular, and renal diseases, and in biostatistics and epidemiology. The Coordinating Investigator was a member of the SC. Additionally, the Applicant had 3 voting representatives (clinicians) and 2 nonvoting representatives (statistician and trial monitor) on the SC.
- Data Monitoring Committee (DMC): An independent DMC was formed to monitor patient safety across several phase IIb/III empagliflozin trials. At database lock, the DMC for the 1245.25 study had met 16 times between 01 Feb 2011 and 27 Apr 2015. Based on monitoring of safety data, the DMC provided the Applicant with advice regarding whether the trial should continue as planned, be modified, or be discontinued. The DMC was composed of 5 members independent of the Applicant (4 physicians and 1 statistician); further support was provided by a statistician independent of the Applicant. The DMC chairperson was Dr Francine Welty, Department of Medicine, Division of Cardiology, Beth Israel Deaconness Medical Center, Boston, USA. Representatives of the Applicant were allowed to participate in the open sessions, e.g. for the discussion of recruitment issues. The DMC was allowed to perform its safety monitoring responsibilities with unblinded treatment group assignments, if necessary to ensure patient safety.

Other committees associated with this trial were as follows:

- Clinical Event Committee (CEC) established to adjudicate centrally and in a blinded fashion events suspect of stroke, myocardial ischemia (including myocardial infarction), all deaths, and other relevant events, including heart failure. The CEC was composed of 11 members (6 cardiologists and 5 neurologists). It was administratively supported by an independent research organization (b) (4) (b) (4) CEC members were reimbursed for their services. For all phase III empagliflozin trials, the CEC reviewed all reported fatal events, and any events suspected of stroke, transient ischemic attack (TIA), myocardial ischemia, hospitalization for unstable angina or heart failure, and stent thrombosis and revascularization procedures. Adjudication was blinded, and criteria for a trigger event to be sent for adjudication were defined in the trial protocol, and additional details were specified in the CEC charter. The CEC charter further defined the review process and the definitions of cardiovascular endpoints. Notably, the CEC charter was initially drawn for the linagliptin drug product, and empagliflozin was a later addition. Also, multiple changes were made to the CEC charter during the EMPA-REG Outcome trial, impacting specific event definitions.

- Hepatic External Adjudication Committee (hepEAC) consisted of up to 5 members, including the Chair, who was chosen based on his/her expertise and experience with the adjudication of cases of suspected liver damage. The hepEAC was administratively supported by (b) (4) All reported treatment-emergent events suspected of being DILIs or hepatic injuries were reviewed in a blinded fashion by the hepEAC. Based on clinical documentation provided by the investigators, compiled by the Applicant and organized by (b) (4) the hepEAC adjudicated cases with regard to causal relationship with study medication. See also Section 9.5.3.2.1 for the adjudication process. Events qualifying for adjudication were selected based on the SMQs, PTs, and by manual review. Note, laboratory results could also trigger hepatic adjudications. hepEAC panel meetings were held as needed and organized by (b) (4) A quorum for the panel meetings required a minimum of 3 hepEAC members, including the Chair. (b) (4) documented and archived the minutes, which were made available to the Applicant upon request.
- Oncologic Assessment and Adjudication Committee (oncAAC) was established to review all cases of suspected solid tumors. The oncAAC consisted of up to 6 members, including the Chair (determined by the oncAAC members). The members of the oncAAC were oncologists with specialization for lung cancer, malignant melanoma, and urological tumors and have general expertise for solid cancers; they were chosen based on their expertise and experience in these indications and with the adjudication of malignancy cases. An external safety advisor (ESA) case manager defined the kind of cancer specialization to which the case was allocated, based on a list of all trigger events provided by the Applicant. Lung, skin, and urologic cancer assessment cases were assigned to a specialist for that tumor location whenever possible. All other tumor types were randomly assigned to any oncAAC member. The oncAAC was administratively supported by (b) (4) All reported events suspect of solid cancer cases were independently reviewed in a blinded fashion by the oncAAC. The oncAAC evaluated the provided data and assessed whether the cancer case was drug related or not. Adjudication was performed for cancer cases in the 1245.25 trial only. Adjudication was based on the consensus of at least 2 oncAAC members. If the 2 reviewers did not agree on a case, the case was reviewed by the oncAAC during a panel meeting in order to reach a decision. (b) (4) reviewed the vote of each oncAAC member and completed the oncAAC decision form documenting the final oncAAC decision (whether from the two assigned reviewers or from the oncAAC panel meeting). The oncAAC communicated the adjudication results via an electronic portal to the Applicant. The Applicant was responsible for entry of these data into the trial database.

Duration of Main Study:

As previously mentioned, the duration of the study was dependent on accumulating a certain number of MACE events. In this case, less than 5 years were needed to accumulate the prespecified number of events.

Inclusion criteria included:

Male and female with T2DM on diet and exercise regimen who were drug-naïve or pretreated with any background therapy (for Japan, without pioglitazone), with HbA1c of ≥7.0% and ≤10% for patients on background therapy or ≥7.0% and ≤ 9.0% for drug-naïve patients, and with high cardiovascular risk defined as at least one of the following:

- Confirmed history of myocardial infarction (>2 months prior to informed consent)
- Evidence of multivessel coronary artery disease, in 2 or more major coronary arteries, irrespective of the revascularization status, i.e.

    a. Either the presence of a significant stenosis (imaging evidence of at least 50% narrowing of the luminal diameter measured during coronary angiography or multi-sliced computed tomography [CT] angiography), in 2 or more major coronary arteries

    b. Or a previous revascularization (percutaneous transluminal coronary angioplasty [PTCA] with or without stent, or coronary artery bypass grafting [CABG]) at least 2 months ago, in 2 or more major coronary arteries

    c. Or the combination of previous revascularization in 1 major coronary artery at least 2 months ago (PTCA with or without stent, or CABG), and the presence of a significant stenosis in another major coronary artery (imaging evidence of at least 50% narrowing of the luminal diameter measured during a coronary angiography or a multi-sliced CT angiography)

    Note: A disease affecting the left main coronary artery was considered as 2-vessel disease.

- Evidence of a single vessel coronary artery disease with:

    a. The presence of a significant stenosis i.e. the imaging evidence of at least 50% narrowing of the luminal diameter of 1 major coronary artery in patients not

subsequently successfully revascularized (measured during coronary angiography or multi-sliced CT angiography)

b. And at least 1 of the following (either i or ii):

i. A positive noninvasive stress test, confirmed by either:

1. A positive exercise tolerance test in patients without a complete left bundle branch block, Wolff-Parkinson-White syndrome, or paced ventricular rhythm, or

2. A positive stress echocardiography showing regional systolic wall motion abnormalities, or

3. A positive scintigraphic test showing stress-induced ischemia, i.e. the development of transient perfusion defects during myocardial perfusion imaging

ii. Patient discharged from hospital with a documented diagnosis of unstable angina within 12 months prior to selection

- Last episode of unstable angina >2 months prior to informed consent with confirmed evidence of coronary multivessel or single vessel disease as defined above
- History of ischemic or hemorrhagic stroke (>2 months prior to informed consent)
- Presence of peripheral artery disease (symptomatic or not) documented by either: previous limb angioplasty, stenting, or bypass surgery; or previous limb or foot amputation due to circulatory insufficiency; or angiographic evidence of significant (>50%) peripheral artery stenosis in at least 1 limb; or evidence from a non-invasive measurement of significant (>50% or as reported as hemodynamically significant) peripheral artery stenosis in at least 1 limb; or ankle brachial index of <0.9 in at least 1 limb

Exclusion criteria included:

- Uncontrolled hyperglycemia with a glucose level >240 mg/dl (>13.3 mmol/l) after an overnight fast and confirmed by a second measurement (not on the same day)
- Planned cardiac surgery or angioplasty within 3 months
- Acute coronary syndrome, stroke or TIA within 2 months prior to informed consent

- Liver disease, defined by serum levels of either alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase above three times upper limit of normal (ULN) as determined during screening or run-in period
- Impaired renal function, defined as GFR <30 ml/min (MDRD formula) as determined during the screening period and/or during the run-in period
- Bariatric surgery within the past 2 years and other gastrointestinal surgeries that can induce chronic malabsorption
- Blood dyscrasias or any disorders causing hemolysis or unstable red blood cell (e.g. malaria, babesiosis, hemolytic anemia)
- Treatment with anti-obesity drugs 3 months prior to informed consent or any other treatment at the time of screening (i.e. surgery, aggressive diet regimen, etc.) leading to unstable body weight
- Current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM
- For Canada only: active history of genito-urinary infection within 2 weeks prior to the informed consent
- For South Africa, uncontrolled hypertension (patients with blood pressure >160/100 mmHg at the screening visit)

For full inclusion and exclusion criteria, refer to the study protocol.

Reviewer Comment: The inclusion/exclusion criteria are generally acceptable for this type of study. It is notable that the inclusion and exclusion criteria were modified in version 3 of the clinical trial protocol (more than a year after trial start), at the advice of the Steering Committee, to allow for a broader enrollment including patients with single vessel coronary artery disease. However, we found no differences between treatment arms, and the proportion of patients with single vessel disease at enrollment was small.

Investigational drug dosing:

Empagliflozin was administered in 10 mg or 25 mg doses once daily. No dose escalation was applied for empagliflozin dosing. Patients assigned to treatment with empagliflozin initiated at the assigned dose.

Medication was dispensed in a double-blind manner. All patients received placebo matching empagliflozin during the 2-week, open-label, run-in period. The timing and dosing schedule of the run-in period (2 tablets, once daily) mirrored the dosing schedule of the randomized

treatment period. During the double-blind treatment period, each patient was to take two tablets daily in the morning.

Concomitant Medications

Concomitant medications (such as blood pressure lowering and lipid-lowering medications) could be added or changed at the discretion of the investigator throughout the trial to achieve best standard of care according to local guidelines. Details regarding the dosing of such medications were not collected during the EMPA-REG trial.

Glycemic Rescue:

Background antidiabetic medication was to be kept stable in the first 12 weeks (from visit 3 to visit 6) but could be changed thereafter to achieve standard of care according to investigator's discretion and local guidelines. For Japan, pioglitazone was not to be used as background therapy.

During the first 12 weeks, rescue medication could be initiated only if the patient had a glucose level >240 mg/dL (for France, the specified glucose level was >200 mg/dL) after an overnight fast. This result for FPG, which could be obtained from the home blood glucose monitoring (HBGM) device, had to be confirmed, i.e. there had to be a minimum of two measurements, at least one of which was performed after an overnight fast at the investigational site, and on a different day to the initial (overnight fast) measurement.

If the above criteria were met, the initiation of rescue medication, the choice of rescue medication, and its dosage, was at the investigator's discretion, based on the patient's current clinical condition (e.g. ongoing illness, etc), and dependent upon existing background medication. Rescue medication could also include up titration of background therapy. If insulin was part of the background therapy, changes by more than 10% of the total daily prescribed dose were to be considered rescue therapy. Other SGLT-2 inhibitors (for Japan: also pioglitazone) (if available) were not to be used as rescue medication. Regardless of the choice made, rescue medication was to be taken in accordance with the local prescribing information of that respective medication, taking into account potential contraindications. Samples for the assessment of FPG and HbA1c were to be collected before initiation of rescue therapy and sent to central laboratory for analysis. The HbA1c sample was not required if a sample had been collected and sent to the central laboratory for analysis within the last 4 weeks.

In the case of symptomatic or severe hypoglycemia, appropriate adjustment of antidiabetic therapy, such as a dose reduction/discontinuation of ongoing rescue medication or existing

background therapy could be initiated. Reduction or discontinuation of ongoing rescue medication was to be considered before a reduction in the dose of existing background therapy.

Any rescue medication or any change in dose of antidiabetic medication was recorded in the source documents and on the appropriate pages of the eCRF. Rescue medication was not provided as part of the clinical trial supplies, unless required by local laws and regulations. Any additional treatment that did not qualify as a rescue medication and was considered necessary for the patient's welfare could be given at the discretion of the investigator.

Subjects were identified as "rescued" if one of the following occurred:

- additional antidiabetic medication used for ≥7 consecutive days or until premature discontinuation of trial medication;
- the patient discontinued trial medication prematurely due to lack of efficacy (including hyperglycemia reported as AE) and the patient started an additional antidiabetic medication on the next day

Patients continued participation in the trial if rescue medication was required, and rescue medication could be used from when it was initiated until the end of the trial. The choice of rescue medication and its dosage was left at the discretion of the investigator. However, other SGLT-2 inhibitors and metformin were not to be used as rescue medication. In case of repeated symptomatic or severe hypoglycemia, appropriate adjustment of oral antidiabetic therapy, such as a dose reduction/discontinuation of ongoing rescue medication was to be initiated.

If no further effect from the rescue medication was anticipated and the patient's hyper- or hypoglycemia could not be controlled in the investigator's clinical opinion, the study medication was to be prematurely discontinued.

Withdrawals and discontinuations

A patient was to be withdrawn from the trial if they withdrew consent or if they became pregnant. A patient could discontinue study medication after discussion between Applicant and investigator if eligibility criteria were being violated or if the patient failed to comply with the protocol.

Patients who dropped out during the screening phase prior to randomization were considered screening failures. They had to be recorded as screening failures on the eCRF and no further follow-up was required.

Patients who discontinued or withdrew from trial medication after randomization were to be followed up until the end of the study using the same visit schedule until the end of the trial.

If a patient was not able to attend a study visit, they (or someone designated by the patient, e.g. a family member or personal physician) were to be contacted to inquire about medical information pertaining to AEs, particularly primary and key secondary outcome events, and/or mortality, until the end of the study. Alternatively, data were to be collected from medical records if patients provided consent for medical record review. Additionally the investigator was to ask patients who discontinued the study medication to contact the site in case of a cardiovascular outcome event that might qualify as a primary or key secondary endpoint (non-fatal MI, non-fatal stroke, and hospitalization for unstable angina).

If a patient withdrew consent, participation in the study ended, the study medication was stopped, and for the patient's safety, the study staff was to try to arrange with the patient to conduct the EOS and follow-up tests and procedures. Patients who withdrew consent were not contacted further about the study unless allowed by local guidelines or laws. Where possible, and in accordance with local laws, information on vital status was to be obtained from public data.

Patients who withdrew or discontinued from the trial after randomization were not replaced.

If a patient had to take concomitant drugs that interfered with the investigational product, or had repeated hypoglycemic episodes, the study medication could be discontinued temporarily or, if needed, permanently. However, as soon as this situation reversed the investigator was to try to resume administration of study medication to the patient.

The Applicant could stop the study in the following circumstances:

- Failure to meet expected enrolment goals overall or at a particular trial site
- Emergence of any efficacy/safety information that could significantly affect continuation of the trial and/or invalidate the earlier positive benefit-risk-assessment
- Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial

Primary Endpoint:

The primary endpoint was the time to first occurrence of 3-point MACE (major adverse cardiovascular events; composite of any of the following: cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction).

Secondary endpoints:

The key secondary endpoint was the time to first occurrence of 4-point MACE (cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction, or hospitalization for unstable angina pectoris).

Other Endpoints:

A number of additional secondary and further endpoints related to CV safety and microvascular outcomes were analyzed in an exploratory manner, based on adjudicated events, reported adverse events, or laboratory data. These included the components of the composite CV and microvascular endpoints as individual endpoints, as well as heart failure requiring hospitalization, all-cause mortality, and new or worsening nephropathy.

Statistical analysis:

The original TSAP was dated August 24, 2012, and was revised after the interim analysis, and finalized on May 13, 2015. The trial database was locked on 22 Jun 2015. Per the applicant, it was reopened to correct PK data (11 results had not been converted to nmol/L) and because for one patient (number 57225) death had been reported in error on the trial termination page. The trial database was reopened a second time to include additional adjudication data from the hepEAC for elevated liver enzyme values of 8 patients based on local laboratory data. The final snapshot of the database used in the analyses described in this report was created on 13 Aug 2015.

The primary endpoint was the time to first occurrence of cardiovascular death, non-fatal stroke, or non-fatal MI.

The key secondary endpoint, which was part of the testing strategy, was the time to first occurrence of CV death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke or hospitalization for unstable angina pectoris.

Patients who received either 10 mg or 25 mg of empagliflozin were pooled into a common empagliflozin treatment group for the purposes of formal testing according to the prespecified hierarchical testing strategy.

The statistical model for the primary analysis was the Cox proportional hazards model. The primary objective of the trial was to establish the non-inferiority of empagliflozin (pooled doses of 10 mg once daily and 25 mg once daily) relative to placebo for time to first major adverse

cardiovascular events. A 4-step hierarchical testing strategy for the primary and key secondary endpoint was followed comparing pooled doses of empagliflozin vs. placebo.

Statistical tests as part of the hierarchical testing strategy were performed 1-sided, with a significance level of α=0.0249, and based on a non-inferiority margin of 1.3 per the FDA Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. The a priori ordered hypotheses ensured that the overall error level for the study of 2.5% was kept.

If non-inferiority for the primary endpoint (3-point MACE: CV death, non-fatal MI, non-fatal stroke) was established for the 1.3 margin, non-inferiority was tested for the key secondary endpoint (4-point MACE: CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina) based on the same margin. If non-inferiority was established for both endpoints, superiority was to be tested for the primary endpoint and then the key secondary endpoint.

These hypotheses were tested for the primary endpoint based on the treated set (TS), including all randomized patients who received at least one dose of study medication. Following the intent-to-treat principle, all events observed until trial termination were included in the analysis. Patients who did not experience a primary endpoint event were censored at the individual day of trial completion.

Table 2 Hierarchical Testing Strategy for the Trial

	Testing strategy for combined 10 mg and 25 mg empagliflozin versus placebo ($\gamma_{b/p}$ denotes the hazard ratio of pooled empagliflozin vs. placebo)
Step 1	Test the null hypothesis that $\gamma_{b/p} \geq 1.3$ for the hazard ratio of the primary endpoint. The alternate hypothesis was $\gamma_{b/p} < 1.3$. This was a one-sided test with $\alpha = 0.0249$. If the upper bound of the 95.02% CI was less than 1.3, then non-inferiority could be concluded for a margin of 1.3 for empagliflozin and proceed to step 2 Otherwise, the procedure was to stop.
Step 2	Test the null hypothesis that $\gamma_{b/p} \geq 1.3$ for the hazard ratio of the key secondary endpoint. The alternate hypothesis was $\gamma_{b/p} < 1.3$. This was a one-sided test with $\alpha = 0.0249$. If the upper bound of the 95.02% CI was less than 1.3, then non-inferiority could be concluded for a margin of 1.3 for empagliflozin and proceed to step 3. Otherwise, the procedure was to stop.
Step 3	This was a superiority test for the primary endpoint. The null hypothesis was that $\gamma_{b/p} \geq 1$. The alternate hypothesis was $\gamma_{b/p} < 1$. This was a one-sided test with $\alpha = 0.0249$. If the upper bound of the 95.02% CI was less than 1.0, then superiority could be concluded for empagliflozin and proceed to step 4. Otherwise, superiority could not be shown and the procedure was to stop.
Step 4	This was a superiority test for the key secondary endpoint. The null hypothesis was that $\gamma_{b/p} \geq 1$. The alternate hypothesis was $\gamma_{b/p} < 1$. This was a one-sided test with $\alpha = 0.0249$. If the upper bound of the 95.02% CI was less than 1.0, then superiority could be concluded for empagliflozin.

Source: Table 9.7.1.2:1 study report NDA 204629, SDN 406

The following analyses sets were defined by the Applicant:

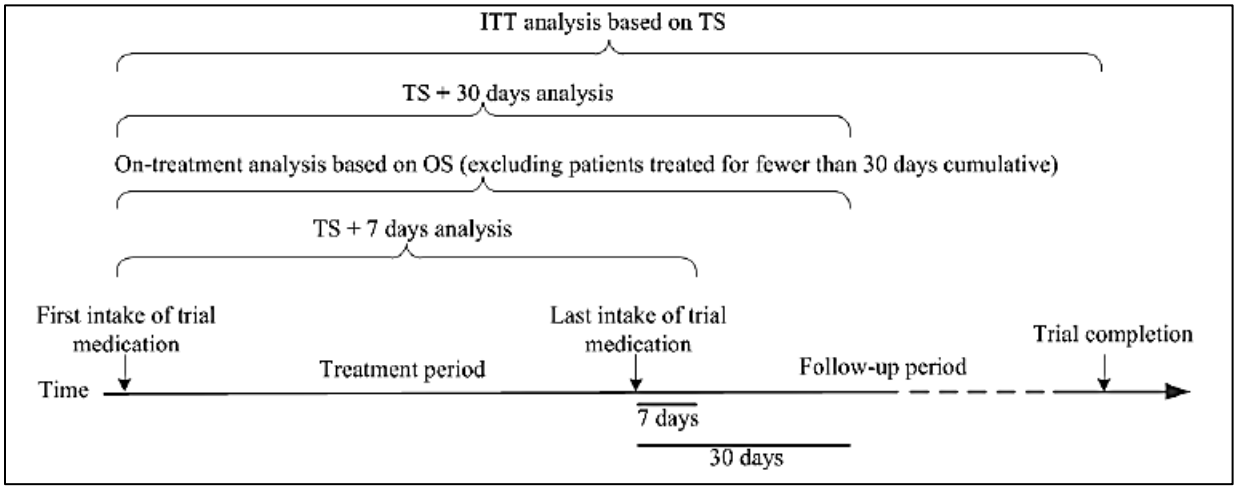
- Screened set (SCR): all patients screened for the trial, with informed consent, that completed at least one screening procedure at visit 1
- Randomized set (RS): all patients randomized to study medication, regardless of whether the medication was taken
- Treated set (TS): all randomized patients who received at least one dose of study medication
- On treatment set (OS): patients who received study medication for at least 30 days (cumulative). Events were considered that occurred not later than 30 days after last intake of study medication or until the end of the entire trial, whichever was earlier. Patients who did not experience the endpoint were censored at the earliest of end of individual observation period or at 30 days after last intake of study medication.
- Full analysis set (FAS): patients in the TS that had a baseline HbA1C value
- Treated set follow-up (TS-FU): patients in the TS for whom a follow-up visit was performed between 28 and 50 days after last intake of study medication
- Per protocol set (PPS): patients treated with at least one dose of study medication that did not have important protocol violations.

- Metformin+DPP4-inhibitor set (FAS-MDPP4): all patients in the FAS who were on metformin and DPP4-inhibitor with or without one additional oral antidiabetic medication at baseline
- Pharmacokinetic set (PK set): all patients in the TS who had a PK sample taken

The primary analysis, key secondary, secondary, and further CV endpoints were analyzed using TS. Certain sensitivity analyses of all CV endpoints were performed on the OS, considering events up to 30 days after last after last intake of study drug or up to the end of the individual observation period (whichever was earlier). In addition an analysis on the TS, considering events up to 30 days after last after last intake of study drug or up to the end of the individual observation period (whichever was earlier), was performed for certain endpoints.

For patients with an event, the time to event was calculated as date of event – start date +1. For patients without an event, the time at risk is calculated as: date of censoring – start date + 1.

Figure 2 Illustration of the analyses based on the TS and OS



Source: Figure 9.7.1.3:1 study report NDA 204629, SDN 406

In general, the time to event was to be derived from the date at randomization, with the exception of the events listed below, where the date of the first drug intake was used as start date:

- Silent MI
- New onset albuminuria (albumin/creatinine ratio$\geq$30 mg/g)
- New onset macroalbuminuria (albumin/creatinine ratio$\geq$300 mg/g)
- Doubling of serum creatinine level compared to baseline, accompanied by an eGFR based on MDRD formula $\leq$45 ml/min/1.73m^2
- Intake of rescue medication
- AE analyses

For laboratory based endpoints, the determination of baseline is related to the date of first drug intake.

For composite endpoints that include components using randomization date and other components using first drug intake date as start date, the time at risk for the composite will start with date of randomization.

For composite outcomes, such as time to 3P-MACE, or 4P-MACE, the earliest onset date of the corresponding components was used (except for CV death). For events which are included as a fatal and non-fatal component into a composite endpoint (applies only to MI and stroke), the onset of the event was considered for the derivation of time to first occurrence, not the date of death. For all other CV death types (e.g. sudden death), the date of death was used. Whenever the onset date of an event is used, the date determined by the adjudication committee was considered even if different from the investigator reported date.

For the analysis of the endpoints 'time to CV death' and 'time to all-cause mortality', the time to death rather than time to the first onset of the fatal AE was used.

Censoring: censoring date was the last date a patient was known to be free of an endpoint event.

Protocol amendments

In total, 4 global revisions of the CTP were issued (amendment 1, 22 Sep 2010; amendment 2, 22 Apr 2011; amendment 3, 29 Dec 2011; amendment 4, 15 Oct 2013). There were 9 local amendments. The amendments did result in significant changes, and details regarding protocol amendments are discussed in Section 2.4.

6 Review of Efficacy

Efficacy Summary

The EMPA-REG OUTCOME trial was a randomized, double-blind, multi-national, 3 parallel group, event-driven trial comparing two doses of empagliflozin to placebo as add-on to standard of care treatment in 7020 patients with T2DM and increased cardiovascular risk. The primary endpoint was the time to first occurrence of major adverse cardiovascular (CV) events (3-point MACE), defined as adjudicated cardiovascular (CV) death, nonfatal myocardial infarction (MI), and nonfatal stroke, (3-point MACE). The key secondary endpoint was the time to first occurrence of 4-point MACE, defined as adjudicated CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina (4-point MACE).

The trial demonstrated that empagliflozin was noninferior and superior to placebo for the primary endpoint (HR 0.86; 95% CI 0.74, 0.99; p = 0.04 for superiority). The trial also demonstrated that empagliflozin was noninferior but not superior to placebo for the key secondary endpoint (HR 0.89; 95% CI 0.78, 1.01; p = 0.08 for superiority).

The primary endpoint finding was driven almost entirely by the treatment effect on CV death. The findings on CV death are similar with both empagliflozin doses, and appear robust by withstanding various sensitivity analyses. In contrast, there was a numerical imbalance for stroke not favoring empagliflozin, and there was no clear improvement in the risk of MI with empagliflozin.

A few other issues around the primary efficacy endpoint warrant discussion.

- Non-assessable death: there were many undetermined causes of death in this trial defined as "non-assessable" and presumed to be CV deaths (124 deaths, 71 in empagliflozin, and 53 in placebo). These deaths comprise 40.1% of all CV deaths, and 26.8% of all the deaths in the trial. However, sensitivity analyses excluding the 124 deaths still demonstrated a statistically significant reduction in CV death (HR 0.59; 95% CI 0.44, 0.79) in the pooled empagliflozin doses compared to placebo and the upper bound of the 95% CI for all-cause mortality was also less than 1 (HR 0.68; 95% CI 0.57, 0.82).
- Missing data: 211 subjects prematurely discontinued the trial; hence, follow-up information for 3-P MACE data are not available for the entire trial. For 161 of these subjects, vital status is known, but for 50 of these subjects, neither vital status nor 3-P MACE are known.
- The primary endpoint excluded silent MIs and when silent MIs are included in the primary endpoint analysis, the pooled empagliflozin doses are no longer superior to placebo for the composite primary endpoint. However, the algorithm used for identifying silent MIs in this trial likely did not identify all potential events, and there was no oversight from the CEC committee for these events.
- Difference in glycemic control, blood pressure, and laboratory parameters between the treatment arms. While all treatment arms started out with a similar HbA1c at baseline, the placebo arm HbA1c at 94 weeks, and the end of the trial, did not show any significant changes compared to baseline, and both empagliflozin arms resulted in HbA1c decrease over the course of the trial. Both systolic and diastolic blood pressure were lower in the empagliflozin groups compared to placebo. Additionally hemoglobin, hematocrit, and lipid parameters were higher in the empagliflozin arms compared to placebo. It is not clear whether these differences contributed to the overall study results.

Overall, the trial does not provide substantial evidence that empagliflozin lowers the risk of strokes and MIs, but it does appear to support a reduction in the risk of CV death with empagliflozin. The mechanism by which empagliflozin lowers the risk of CV death is not clear, but it does not appear to be an ischemic atherosclerotic mechanism.

Interestingly, empagliflozin also appears to reduce the risk of hospitalization for heart failure by 35% (HR 0.65; 95% CI 0.50, 0.85). This analysis was exploratory since this endpoint was not included in the plan to control for type 1 error, and no details were collected about the population enrolled at baseline regarding heart failure (EF or New York Heart Association Functional Classification). In addition, as noted by Dr Hicks, our cardiology consultant, during the trial, the CEC made key changes to the hospitalization for heart failure definition, which resulted in what could be considered a "softer" endpoint (i.e. events that led to visits to chest pain units, initiation or uptitration of an oral diuretic would have met the criteria for hospitalization for heart failure based on the most recent event definition). Despite all these issues, I find it plausible that empagliflozin could reduce the risk for hospitalization for heart failure as it acts as a diuretic, but this hypothesis should be confirmed in a trial properly designed to capture significant heart failure events.

In conclusion, empagliflozin appears to reduce the risk of CV death in adult patients with T2DM and increased CV risk. While it is possible that the risk of hospitalization for heart failure is reduced as well, this would require further confirmation in clinical trials.

6.1 Indication

Empagliflozin is approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The Applicant proposes the following addition to the current indication:

- In adult patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the incidence of cardiovascular death.

6.1.1 Methods

For the review of efficacy, I reviewed the study report for study 1245.25, study datasets, all versions of the study protocol and TSAP, DMC, CEC, and steering committee meeting minutes.

The primary efficacy endpoint for this study was the MACE composite endpoint, which was time to first occurrence of CV death, non-fatal myocardial infarction, or non-fatal stroke (3-point MACE). All events in the primary endpoint were adjudicated by the CEC.

The Applicant performed the primary analysis based on the treated set (TS), considering all events up to individual trial completion.

6.1.2 Demographics

The Applicant reported the demographic characteristics for the treated set in Table 3 below. Overall, the treatment arms were reasonably well matched with respect to age, sex, race, ethnicity, and baseline renal function.

As seen in Table 3 below, 71.5% of patients were men, almost three quarters of patients were White (72.4%), followed by patients of Asian race (21.6%) and Black or African American patients were poorly represented in both treatment groups at 5.1%. The mean age was 63.1 years, with half of all patients (49.2%) being 50 to 64 years old at trial start and 35.3% being 65 to 74 years old; 9.3% were 75 years or older.

Before the interim analysis that accompanied the NDA submission, following FDA advice, protocol amendment 3 increased the planned sample size and duration of the trial in order to assure that EMPA-REG alone was powered to rule out both pre-marketing and post-marketing CV risk margins. In the TS, 4480 patients (63.8%) were enrolled before amendment 3 and 2540 patients (36.2%) after amendment 3. Demographics and baseline characteristics for both cohorts were largely similar; however, some differences are emphasized below. Notably, among the patients recruited after this amendment, more were from Europe (46.5% vs 38% before the amendment) and fewer from Asia (21.2% before vs 15.6% after), and North America (20.4% before vs 19% after) compared with those recruited earlier. In addition, the distribution of cardiovascular high-risk factors was somewhat different. Patients enrolled after the amendment less frequently reported coronary artery disease (77.7% of patients enrolled before the amendment vs 71.9% after the amendment), and more often reported peripheral artery disease (18.6% before the amendment vs 24.8% after) than patients enrolled before the amendment. The distribution of risk factors was balanced between the treatment arms.

For 99.2% of patients, at least one cardiovascular high-risk factor was recorded at baseline. About three quarters of all patients (75.6%) had coronary artery disease (CAD), 23.3% of patients had a history of stroke, and 20.8% of patients had peripheral artery disease. In total, 80.3% of patients had only one of these three factors reported at baseline; while 17.3% of patients had 2 of the 3 factors and 1.6% of patients had all 3 high-risk factors. All factors were reported at similar frequencies across treatment groups (Table 4).

Table 3 Demographic Data – TS

	Placebo	Empa 10 mg	Empa 25 mg	All empa	Total
Treated patients, N (%)	**2333 (100.0)**	**2345 (100.0)**	**2342 (100.0)**	**4687 (100.0)**	**7020 (100.0)**
Sex, N (%)					
Male	1680 (72.0)	1653 (70.5)	1683 (71.9)	3336 (71.2)	5016 (71.5)
Female	653 (28.0)	692 (29.5)	659 (28.1)	1351 (28.8)	2004 (28.5)
Race, N (%)					
White	1678 (71.9)	1707 (72.8)	1696 (72.4)	3403 (72.6)	5081 (72.4)
Asian	511 (21.9)	505 (21.5)	501 (21.4)	1006 (21.5)	1517 (21.6)
Black / African American	120 (5.1)	119 (5.1)	118 (5.0)	237 (5.1)	357 (5.1)
Amer. Indian / Alaska Native	20 (0.9)	11 (0.5)	23 (1.0)	34 (0.7)	54 (0.8)
Native Hawaiian or other Pacific Islander	4 (0.2)	3 (0.1)	3 (0.1)	6 (0.1)	10 (0.1)
Ethnicity, N (%)					
Not Hispanic / Latino	1912 (82.0)	1909 (81.4)	1926 (82.2)	3835 (81.8)	5747 (81.9)
Hispanic / Latino	418 (17.9)	432 (18.4)	415 (17.7)	847 (18.1)	1265 (18.0)
Region, N (%)					
Europe	959 (41.1)	966 (41.2)	960 (41.0)	1926 (41.1)	2885 (41.1)
North America	462 (19.8)	466 (19.9)	466 (19.9)	932 (19.9)	1394 (19.9)
Asia	450 (19.3)	447 (19.1)	450 (19.2)	897 (19.1)	1347 (19.2)
Latin America	360 (15.4)	359 (15.3)	362 (15.5)	721 (15.4)	1081 (15.4)
Africa	102 (4.4)	107 (4.6)	104 (4.4)	211 (4.5)	313 (4.5)
Age [years], mean (SD)	63.2 (8.8)	63.0 (8.6)	63.2 (8.6)	63.1 (8.6)	63.1 (8.6)
Age category [years], N (%)					
<50	142 (6.1)	154 (6.6)	143 (6.1)	297 (6.3)	439 (6.3)
50 to <65	1155 (49.5)	1146 (48.9)	1153 (49.2)	2299 (49.1)	3454 (49.2)
65 to <75	808 (34.6)	834 (35.6)	833 (35.6)	1667 (35.6)	2475 (35.3)
≥75	228 (9.8)	211 (9.0)	213 (9.1)	424 (9.0)	652 (9.3)

Patients with missing data are not shown
Source: Table 10.4.1:1 study report NDA 204629, SDN 406

Table 4 Patients with Cardiovascular High-Risk Factors – TS

	Placebo	Empa 10 mg	Empa 25 mg	All empa	Total
Number of patients, N (%)	**2333 (100.0)**	**2345 (100.0)**	**2342 (100.0)**	**4687 (100.0)**	**7020 (100.0)**
Any CV high-risk factor	2307 (98.9)	2333 (99.5)	2324 (99.2)	4657 (99.4)	6964 (99.2)
Coronary artery disease (CAD)[1]	1763 (75.6)	1782 (76.0)	1763 (75.3)	3545 (75.6)	5308 (75.6)
Multi-vessel CAD	1100 (47.1)	1078 (46.0)	1101 (47.0)	2179 (46.5)	3279 (46.7)
History of MI	1083 (46.4)	1107 (47.2)	1083 (46.2)	2190 (46.7)	3273 (46.6)
Coronary artery bypass graft	563 (24.1)	594 (25.3)	581 (24.8)	1175 (25.1)	1738 (24.8)
Single-vessel CAD	238 (10.2)	258 (11.0)	240 (10.2)	498 (10.6)	736 (10.5)

History of ischem./hemorrh. stroke	553 (23.7)	535 (22.8)	549 (23.4)	1084 (23.1)	1637 (23.3)
Peripheral artery disease	479 (20.5)	465 (19.8)	517 (22.1)	982 (21.0)	1461 (20.8)
CV high-risk factor categories					
Only CAD	1340 (57.4)	1398 (59.6)	1334 (57.0)	2732 (58.3)	4072 (58.0)
Only cerebrovascular disease	325 (13.9)	328 (14.0)	307 (13.1)	635 (13.5)	960 (13.7)
Only peripheral artery disease	191 (8.2)	195 (8.3)	217 (9.3)	412 (8.8)	603 (8.6)
2 of the 3 CV high-risk factors	414 (17.7)	375 (16.0)	427 (18.2)	802 (17.1)	1216 (17.3)
All 3 CV high-risk factors	37 (1.6)	37 (1.6)	39 (1.7)	76 (1.6)	113 (1.6)
No CV high-risk factor[2]	26 (1.1)	12 (0.5)	18 (0.8)	30 (0.6)	56 (0.8)

Table shows factors existing prior to signing informed consent (collected via tick boxes in the CRF).
Patients with missing information are not shown.

[1] CAD defined as any of the following: history of MI, coronary artery bypass graft, multi-vessel CAD, single-vessel CAD.

[2] These patients had no documented high CV risk. They were allowed to continue in the trial and were not excluded from the analyses because of this reason.

Source: Table 10.4.2:1 study report NDA 204629, SDN 406

Other baseline characteristics

There were no significant differences between treatment groups with regard to the duration of diabetes, baseline HbA1c, weight/BMI, , baseline blood pressure and renal parameters (eGFR and urine albumin to creatinine ratio) (Table 5). More than half of the patients (57.1%) had diabetes for 10 years or more, and the mean HbA1C at baseline was 8.07%, with half of the patients having a HbA1c value below 8% at baseline. The mean eGFR was 74.04 ml/min/1.73 $m^{2,}$ with 21.9% of patients having normal renal function; more than half of patients (52.2%) had mild renal impairment, and 25.5% had moderate renal impairment (less than 9% of patients had eGFR < 45 ml/min/1.73 m^2). The urine albumin/creatinine ratio (UACR) at baseline was normal in 59.4% of patients, while 28.7% had microalbuminuria and 11.0% macroalbuminuria.

Table 5 Other Baseline Characteristics

	Placebo	**Empa 10 mg**	**Empa 25 mg**	**All empa**	**Total**
Treated patients, N (%)	**2333 (100.0)**	**2345 (100.0)**	**2342 (100.0)**	**4687 (100.0)**	**7020 (100.0)**
Time since diagn. of T2DM, N (%)					
≤1 year	52 (2.2)	68 (2.9)	60 (2.6)	128 (2.7)	180 (2.6)
>1 to 5 years	371 (15.9)	338 (14.4)	374 (16.0)	712 (15.2)	1083 (15.4)
>5 to 10 years	571 (24.5)	585 (24.9)	590 (25.2)	1175 (25.1)	1746 (24.9)
>10 years	1339 (57.4)	1354 (57.7)	1318 (56.3)	2672 (57.0)	4011 (57.1)
HbA_{1c} [%], mean (SD)	8.08 (0.84)	8.07 (0.86)	8.06 (0.84)	8.07 (0.85)	8.07 (0.85)
HbA_{1c} category [%], N (%)					
<8.0	1156 (49.5)	1188 (50.7)	1151 (49.1)	2339 (49.9)	3495 (49.8)
8.0 to <9.0	795 (34.1)	730 (31.1)	804 (34.3)	1534 (32.7)	2329 (33.2)
≥9.0	382 (16.4)	426 (18.2)	386 (16.5)	812 (17.3)	1194 (17.0)

HbA_{1c} category [%], N (%)					
<8.5%	1607 (68.9)	1598 (68.1)	1612 (68.8)	3210 (68.5)	4817 (68.6)
≥8.5%	726 (31.1)	746 (31.8)	729 (31.1)	1475 (31.5)	2201 (31.4)
FPG [mg/dL], mean (SD)	153.5 (44.0)	153.2 (44.1)	151.9 (43.4)	152.6 (43.8)	152.9 (43.8)
Weight [kg], mean (SD)	86.62 (19.05)	85.94 (18.81)	86.46 (18.95)	86.20 (18.88)	86.34 (18.94)
BMI [kg/m^2], mean (SD)	30.66 (5.24)	30.58 (5.24)	30.62 (5.30)	30.60 (5.27)	30.62 (5.26)
Waist circumfer. [cm], mean (SD)	105.0 (14.0)	104.7 (13.7)	104.8 (13.7)	104.7 (13.7)	104.8 (13.8)
Blood pressure [mmHg], N (%)					
SBP ≥140 or DBP ≥90	934 (40.0)	877 (37.4)	903 (38.6)	1780 (38.0)	2714 (38.7)
SBP <140 and DBP <90	1399 (60.0)	1468 (62.6)	1439 (61.4)	2907 (62.0)	4306 (61.3)
eGFR (MDRD) [$mL/min/1.73m^2$], mean (SD)	73.81 (21.05)	74.28 (21.81)	74.04 (21.36)	74.16 (21.59)	74.04 (21.41)
eGFR (MDRD) category[1], N (%)					
≥90 $mL/min/1.73m^2$	488 (20.9)	519 (22.1)	531 (22.7)	1050 (22.4)	1538 (21.9)
60 to <90 $mL/min/1.73m^2$	1238 (53.1)	1221 (52.1)	1202 (51.3)	2423 (51.7)	3661 (52.2)
45 to <60 $mL/min/1.73m^2$	418 (17.9)	420 (17.9)	411 (17.5)	831 (17.7)	1249 (17.8)
30 to <45 $mL/min/1.73m^2$	183 (7.8)	178 (7.6)	182 (7.8)	360 (7.7)	543 (7.7)
<30 $mL/min/1.73m^2$	6 (0.3)	7 (0.3)	14 (0.6)	21 (0.4)	27 (0.4)
UACR [mg/g], gmean (gCV, %)	26.05 (473.09)	25.45 (451.70)	25.49 (440.38)	25.47 (445.84)	25.66 (454.67)
UACR category [mg/g], N (%)					
Normal (<30)	1382 (59.2)	1405 (59.9)	1384 (59.1)	2789 (59.5)	4171 (59.4)
Microalbuminuria (30 to 300)	675 (28.9)	645 (27.5)	693 (29.6)	1338 (28.5)	2013 (28.7)
Macroalbuminuria (>300)	260 (11.1)	261 (11.1)	248 (10.6)	509 (10.9)	769 (11.0)

gmean = geometric mean, gCV = geometric coefficient of variation
Patients with missing information are not shown.

[1] Renal function was considered normal, if eGFR ≥90 $mL/min/1.73m^2$; lower eGFR values were considered mild (60 $mL/min/1.73m^2$ to <90 $mL/min/1.73m^2$), moderate (30 $mL/min/1.73m^2$ to <60 $mL/min/1.73m^2$) or severe renal impairment/end-stage renal disease (<30 $mL/min/1.73m^2$).

Source: Table 10.4.5:1 study report NDA 204629, SDN 406

Diabetes related medical history was also similar between treatment groups (Table 6). Most patients had a history of hypertension (91.4%), and 31.3% had a history of diabetic neuropathy, 22% had a history of diabetic retinopathy, and 19.5% a history of diabetic nephropathy.

Table 6 Further Relevant Medical History at Baseline

	Placebo N (%)	**Empa 10 mg N (%)**	**Empa 25 mg N (%)**	**All empa N (%)**	**Total N (%)**
Treated patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)	7020 (100.0)
Hypertension	2153 (92.3)	2134 (91.0)	2132 (91.0)	4266 (91.0)	6419 (91.4)
Diabetic neuropathy	727 (31.2)	735 (31.3)	735 (31.4)	1470 (31.4)	2197 (31.3)
Diabetic retinopathy	523 (22.4)	521 (22.2)	502 (21.4)	1023 (21.8)	1546 (22.0)

Diabetic nephropathy	467 (20.0)	444 (18.9)	460 (19.6)	904 (19.3)	1371 (19.5)
Urinary tract infection[1]	130 (5.6)	161 (6.9)	155 (6.6)	316 (6.7)	446 (6.4)
Diabetic foot	145 (6.2)	127 (5.4)	136 (5.8)	263 (5.6)	408 (5.8)
Genital infection[1]	43 (1.8)	36 (1.5)	34 (1.5)	70 (1.5)	113 (1.6)

Table shows relevant medical history within 6 months prior to informed consent (collected via tick boxes in the CRF).

[1] Chronic or recurrent

Source: Table 10.4.3:1 study report NDA 204629, SDN 406

According to the CRF, only current conditions, and conditions for which medicinal therapy was given, as well as chronic diseases which may not manifest themselves at that time, were to be recorded as concomitant diagnoses. T2DM and the conditions from the list of cardiovascular high-risk factors, and further relevant medical history were not to be recorded again, however, this rule was not always observed. The most frequently reported concomitant diagnoses at baseline (more than 10% of all treated patients at preferred term level) were dyslipidemia (29.5%), hyperlipidemia (27.8%), obesity (15.8%), hypercholesterolemia (15.3%), cataract (12.0%), osteoarthritis (11.8%), and hypertension (10.9%). The latter was recorded on this page despite the CRF instruction. Regarding heart failure, the Applicant reported the cardiac failure diagnosis at baseline based on an Applicant created narrow SMQ, and the results are presented below. Approximately 10% of patients reported a baseline diagnosis consistent with heart failure, and there were no significant differences between the treatment groups. Ejection fraction and classification of heart failure were not collected.

Table 7 Heart Failure Diagnosis at Baseline

System organ class/ Preferred term	Placebo N (%)	Empa 10mg N (%)	Empa 25mg N (%)	All Empa N (%)	Total N (%)
Number of patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)	7020 (100.0)
Number of patients with at least one concomitant diagnosis	244 (10.5)	240 (10.2)	222 (9.5)	462 (9.9)	706 (10.1)
Cardiac disorders	239 (10.2)	237 (10.1)	220 (9.4)	457 (9.8)	696 (9.9)
Cardiac failure	99 (4.2)	87 (3.7)	93 (4.0)	180 (3.8)	279 (4.0)
Cardiac failure congestive	88 (3.8)	89 (3.8)	92 (3.9)	181 (3.9)	269 (3.8)
Cardiac failure chronic	48 (2.1)	50 (2.1)	32 (1.4)	82 (1.7)	130 (1.9)
Left ventricular failure	4 (0.2)	10 (0.4)	2 (0.1)	12 (0.3)	16 (0.2)
Cardiac asthma	0	2 (0.1)	1 (<0.1)	3 (0.1)	3 (<0.1)
Acute left ventricular failure	1 (<0.1)	0	0	0	1 (<0.1)
Cardiogenic shock	1 (<0.1)	0	0	0	1 (<0.1)
Cor pulmonale	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Cor pulmonale chronic	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Ventricular failure	0	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	9 (0.4)	4 (0.2)	7 (0.3)	11 (0.2)	20 (0.3)
Pulmonary oedema	6 (0.3)	1 (<0.1)	4 (0.2)	5 (0.1)	11 (0.2)
Acute pulmonary oedema	3 (0.1)	3 (0.1)	3 (0.1)	6 (0.1)	9 (0.1)
Investigations	3 (0.1)	2 (0.1)	1 (<0.1)	3 (0.1)	6 (0.1)
Ejection fraction decreased	3 (0.1)	2 (0.1)	1 (<0.1)	3 (0.1)	6 (0.1)

Source: Table 15.1.4.2:3 study report NDA 204629, SDN 406

Since stroke was analyzed as part of several endpoints, concomitant diagnoses of carotid artery disease were summarized, based on a list of 10 MedDRA preferred terms. Such diagnoses were reported for 3.2% of all patients (placebo: 3.0%, empagliflozin 10 mg: 3.4%, empagliflozin 25 mg: 3.1%).

Atrial fibrillation was reported for 5.5% of all patients (placebo: 6.1%, empagliflozin 10 mg: 5.6%, empagliflozin 25 mg: 4.9%).

Concomitant therapies at baseline.

Any concomitant therapies being taken at screening as well as any therapy added or stopped during the trial were to be recorded. Patients taking antidiabetic background medication at screening were to continue taking this treatment unchanged during the first 12 weeks after randomization; thereafter, changes were allowed. Antidiabetic background and rescue medications were to be recorded only on a dedicated CRF page, based on nine pre-defined categories.

Baseline intake of selected medications of interest (antihypertensives, lipid-lowering drugs, anticoagulants, and digitalis) is presented below (Table 8). Overall 95% of all patients were taking antihypertensive medications, with no significant difference between the empagliflozin and placebo arms. Even looking at the breakdown by class of antihypertensive, no major differences can be seen between the treatment groups at baseline. Slightly fewer patients in the placebo group were on diuretics (42.3% placebo vs 43.7% empagliflozin) or mineralocorticoid receptor antagonists (5.8% placebo vs 6.5% empagliflozin). With regards to lipid lowering drugs, slightly fewer patients in the placebo group were taking lipid lowering medications compared to the pooled empagliflozin group (79.9% vs 81.5% respectively), and a similar difference is observed regarding statin use at baseline (76% of placebo patients vs 77.4% of the empagliflozin patients). The overall differences are small and unlikely to impact the results of the study.

Table 8 Patients taking anticoagulants, lipid-lowering, antihypertensives or digitalis drugs at baseline - TS

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)
Treated patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)	7020 (100.0)
Antihypertensives	2221 (95.2)	2227 (95.0)	2219 (94.7)	4446 (94.9)	6667 (95.0)
ACE inhibitors/ARBs	1868 (80.1)	1896 (80.9)	1902 (81.2)	3798 (81.0)	5666 (80.7)
Beta-blockers	1498 (64.2)	1530 (65.2)	1526 (65.2)	3056 (65.2)	4554 (64.9)
Diuretics	988 (42.3)	1036 (44.2)	1011 (43.2)	2047 (43.7)	3035 (43.2)
Calcium channel blockers	788 (33.8)	781 (33.3)	748 (31.9)	1529 (32.6)	2317 (33.0)
Mineralocorticoid receptor antag.	136 (5.8)	157 (6.7)	148 (6.3)	305 (6.5)	441 (6.3)
Renin inhibitors	19 (0.8)	16 (0.7)	11 (0.5)	27 (0.6)	46 (0.7)
Other	191 (8.2)	193 (8.2)	190 (8.1)	383 (8.2)	574 (8.2)
Anticoagulants	2090 (89.6)	2098 (89.5)	2064 (88.1)	4162 (88.8)	6252 (89.1)
Platelet aggreg. inhib. excl. heparin	2003 (85.9)	2016 (86.0)	2003 (85.5)	4019 (85.7)	6022 (85.8)
Vitamin K antagonists	156 (6.7)	141 (6.0)	125 (5.3)	266 (5.7)	422 (6.0)
Heparin group	16 (0.7)	7 (0.3)	8 (0.3)	15 (0.3)	31 (0.4)
Direct thrombin inhibitors	8 (0.3)	6 (0.3)	5 (0.2)	11 (0.2)	19 (0.3)
Direct factor Xa inhibitors	5 (0.2)	0	1 (<0.1)	1 (<0.1)	6 (0.1)
Other	0	1 (<0.1)	2 (0.1)	3 (0.1)	3 (<0.1)
Lipid lowering drugs	1864 (79.9)	1926 (82.1)	1894 (80.9)	3820 (81.5)	5684 (81.0)
Statins	1773 (76.0)	1827 (77.9)	1803 (77.0)	3630 (77.4)	5403 (77.0)
Fibrates	199 (8.5)	214 (9.1)	217 (9.3)	431 (9.2)	630 (9.0)
Ezetimibe	81 (3.5)	95 (4.1)	94 (4.0)	189 (4.0)	270 (3.8)
Niacin	35 (1.5)	56 (2.4)	35 (1.5)	91 (1.9)	126 (1.8)
Other	175 (7.5)	172 (7.3)	193 (8.2)	365 (7.8)	540 (7.7)
Digitalis	72 (3.1)	62 (2.6)	66 (2.8)	128 (2.7)	200 (2.8)

Source: Table 10.4.6.1:1 study report NDA 204629, SDN 406

Antidiabetic medications at baseline are summarized in Table 9 below. 98.2% of all patients were taking at least one diabetes medication, 74% were taking metformin, 48.2% were on insulin, with no significant differences between the treatment groups. Only 29.5% of the patients were taking only one background diabetes medication, 48.5% were taking two antidiabetic medications, 17.3% were taking three medications, and 2.8% were taking four or more medications. For patients with insulin administration at baseline, the mean insulin dose was 65.2 units, similar across treatment groups. For the patients on metformin at baseline, the mean metformin dose was 1751.3 mg, with 73.5% of patients on $\geq$1500 mg metformin daily, with no significant differences between the treatment groups.

Table 9 Patients taking antidiabetic background medications at baseline (by at least 5% of patients), including the number of background medications - TS

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)
Treated patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)	7020 (100.0)
Patients with any background medication	2297 (98.5)	2299 (98.0)	2295 (98.0)	4594 (98.0)	6891 (98.2)
Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)	3459 (73.8)	5193 (74.0)
Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)	2252 (48.0)	3387 (48.2)
Sulphonylurea	992 (42.5)	985 (42.0)	1029 (43.9)	2014 (43.0)	3006 (42.8)
DPP-IV inhibitor	267 (11.4)	282 (12.0)	247 (10.5)	529 (11.3)	796 (11.3)
Patients with 1 medication	691 (29.6)	704 (30.0)	676 (28.9)	1380 (29.4)	2071 (29.5)
Insulin only	326 (14.0)	317 (13.5)	309 (13.2)	626 (13.4)	952 (13.6)
Metformin only	234 (10.0)	264 (11.3)	242 (10.3)	506 (10.8)	740 (10.5)
Patients with 2 medications	1148 (49.2)	1110 (47.3)	1149 (49.1)	2259 (48.2)	3407 (48.5)
Metformin & insulin	506 (21.7)	448 (19.1)	464 (19.8)	912 (19.5)	1418 (20.2)
Metformin & sulphonylurea	461 (19.8)	443 (18.9)	480 (20.5)	923 (19.7)	1384 (19.7)
Patients with 3 medications	387 (16.6)	419 (17.9)	411 (17.5)	830 (17.7)	1217 (17.3)
Metform. & sulphonylurea & insulin	123 (5.3)	149 (6.4)	146 (6.2)	295 (6.3)	418 (6.0)
Patients with 4 or more medications	71 (3.0)	66 (2.8)	59 (2.5)	125 (2.7)	196 (2.8)

Data were collected via tick boxes in the CRF (based on 9 pre-defined categories of antidiabetic medications).
Source: Table 10.4.6.1:2 study report NDA 204629, SDN 406

Concomitant therapies introduced after baseline:

Changes in dose for medications other than antidiabetics were not captured in the trial. The Applicant submitted the percent of patients who had a medication class of interest introduced after baseline, and this information is presented in Table 10 below. However, this does not take into consideration the baseline medications, or medications that might have been stopped after baseline. The information presented below suggests that more patients in the placebo group were started on a new antihypertensive, anticoagulant, or lipid lowering agent when compared to the pooled empagliflozin group. The same applies to classes of mediations, such as beta blockers, diuretics, and statins. It is not clear however whether changes made within a drug class (such as changes from a less potent to a more potent statin) were recorded as new medications, and the information in Table 10 does not offer an accurate picture of the medications of interest taken during the trial.

Table 10 Patients with anticoagulants, lipid-lowering or drugs introduced after baseline - TS

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)
Treated patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)
Antihypertensives	1190 (51.0)	1030 (43.9)	1058 (45.2)	2088 (44.5)
ACE inhibitors/ARBs	702 (30.1)	602 (25.7)	622 (26.6)	1224 (26.1)
Diuretics	608 (26.1)	429 (18.3)	470 (20.1)	899 (19.2)
Beta-blockers	481 (20.6)	420 (17.9)	438 (18.7)	858 (18.3)
Calcium channel blockers	481 (20.6)	311 (13.3)	361 (15.4)	672 (14.3)
Mineralocorticoid receptor antagonists	136 (5.8)	87 (3.7)	90 (3.8)	177 (3.8)
Renin inhibitors	6 (0.3)	5 (0.2)	4 (0.2)	9 (0.2)
Other	165 (7.1)	129 (5.5)	145 (6.2)	274 (5.8)
Anticoagulants	708 (30.3)	663 (28.3)	677 (28.9)	1340 (28.6)
Platelet aggregation inhibitors excl. heparin	518 (22.2)	499 (21.3)	476 (20.3)	975 (20.8)
Heparin group	265 (11.4)	267 (11.4)	281 (12.0)	548 (11.7)
Vitamin K antagonists	102 (4.4)	71 (3.0)	88 (3.8)	159 (3.4)
Direct factor Xa inhibitors	23 (1.0)	32 (1.4)	28 (1.2)	60 (1.3)
Direct thrombin inhibitors	20 (0.9)	22 (0.9)	22 (0.9)	44 (0.9)
Other	38 (1.6)	39 (1.7)	44 (1.9)	83 (1.8)
Lipid lowering drugs	719 (30.8)	673 (28.7)	693 (29.6)	1366 (29.1)
Statins	601 (25.8)	574 (24.5)	571 (24.4)	1145 (24.4)
Fibrates	128 (5.5)	89 (3.8)	122 (5.2)	211 (4.5)
Ezetimibe	49 (2.1)	43 (1.8)	51 (2.2)	94 (2.0)
Niacin	15 (0.6)	14 (0.6)	9 (0.4)	23 (0.5)
Other	71 (3.0)	53 (2.3)	56 (2.4)	109 (2.3)

Source: Table 10.4.6.2:1 study report NDA 204629, SDN 406

Antidiabetic medications introduced after baseline, including rescue medications, are presented in the efficacy section of this review.

In addition to the analyses based on the entire trial population, the most relevant parameters were summarized for the subsets of patients receiving metformin at baseline or not and for patients enrolled before or after protocol amendment 3. At baseline, 5193 patients (74.0%) received metformin. Demographics and baseline characteristics for these patients were similar to those for the overall trial population, with the following differences: the mean age of the patients who took metformin was 65.1 vs 62.5 for patients not on metformin, mean eGFR was higher in the patients taking metformin as expected since the metformin prescribing information has certain eGFR restrictions (76.95 ml/min/1.73 m^2 vs 66.14 ml/min/1.73 m^2 in patients not on metformin), and the proportion of patients from US and Canada was lower in the group taking metformin (17.8 vs 23.3% of the patients not taking metformin).

Exposure

The duration of the treatment period and of the observational period overall and for individual patients was not pre-defined in this trial, but was event-driven and dependent on the time point of randomization of a patient. The trial duration from the first enrollment of a patient to last contact was less than 5 years, more than 85% of all patients were observed for at least 2 years, and more than half of all patients observed for at least 3 years. The mean observation time was 2.91 years for the placebo group, and 2.96 years for the pooled empagliflozin group. The median observation time was minimally shorter in the placebo group (3.07 years) than in the empagliflozin groups (3.15 years).

Table 11 Observational period - TS

	Placebo	Empa 10 mg	Empa 25 mg	All empa
Treated patients, N (%)	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)
Observation time categories, N (%)				
≥12 weeks	2319 (99.4)	2337 (99.7)	2336 (99.7)	4673 (99.7)
≥26 weeks	2303 (98.7)	2327 (99.2)	2324 (99.2)	4651 (99.2)
≥52 weeks	2279 (97.7)	2304 (98.3)	2303 (98.3)	4607 (98.3)
≥78 weeks	2242 (96.1)	2273 (96.9)	2282 (97.4)	4555 (97.2)
≥104 weeks	2002 (85.8)	2047 (87.3)	2059 (87.9)	4106 (87.6)
≥156 weeks	1201 (51.5)	1229 (52.4)	1235 (52.7)	2464 (52.6)
≥208 weeks	173 (7.4)	184 (7.8)	201 (8.6)	385 (8.2)
≥260 weeks	0	3 (0.1)	0	3 (0.1)
Observation time [years]				
Mean (SD)	2.91 (0.82)	2.96 (0.98)	2.96 (0.79)	2.96 (0.89)
Median	3.07	3.15	3.16	3.15
(Q10, Q90)[1]	(1.90, 3.82)	(1.92, 3.83)	(1.92, 3.85)	(1.92, 3.83)
Total observation time [years]	6794.5	6935.6	6930.0	13865.6

The observational period was calculated as date of last observation minus date of randomisation, plus one day.
[1] Q10 and Q90 represent the 10% and 90% quantiles.

Source: Table 10.5:1 study report NDA 204629, SDN 406

The exposure to study drug (ignoring the temporary discontinuations), based on the randomized treatment, is presented below.

Table 12 Exposure to Randomized Trial Medication - TS

	Placebo	Empa 10 mg	Empa 25 mg	All empa
Treated patients, N (%)	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)
Exposure categories, N (%)				
≥12 weeks	2262 (97.0)	2263 (96.5)	2251 (96.1)	4514 (96.3)
≥26 weeks	2196 (94.1)	2220 (94.7)	2195 (93.7)	4415 (94.2)
≥52 weeks	2076 (89.0)	2121 (90.4)	2111 (90.1)	4232 (90.3)
≥78 weeks	1947 (83.5)	2023 (86.3)	2026 (86.5)	4049 (86.4)
≥104 weeks	1656 (71.0)	1750 (74.6)	1756 (75.0)	3506 (74.8)
≥156 weeks	909 (39.0)	970 (41.4)	998 (42.6)	1968 (42.0)
≥208 weeks	16 (0.7)	22 (0.9)	33 (1.4)	55 (1.2)
≥260 weeks	0	0	0	0
Exposure [years]				
Mean (SD)	2.46 (1.03)	2.55 (1.02)	2.56 (1.04)	2.56 (1.03)
Median	2.57	2.61	2.61	2.61
(Q10, Q90)[1]	(0.90, 3.68)	(1.00, 3.69)	(1.00, 3.70)	(1.00, 3.69)
Total exposure [years]	5747.0	5973.3	6006.6	11979.9

Exposure was calculated as date of last intake of trial medication minus date of first intake, plus one day. Interruptions of trial medication were ignored, i.e. considered as if patients had taken trial medication.
[1] Q10 and Q90 represent the 10% and 90% quantiles.

Source: Table 10.5:2 study report NDA 204629, SDN 406

Per Applicant report, treatment compliance was assessed at each visit based on a count of dispensed and returned medication. Overall compliance was calculated as a weighted average of the reported compliance values (disregarding the run-in phase), based on the TS. Compliance was reported by the Applicant to be similar between treatment groups, 91.2% of the placebo group patients achieved an overall compliance of 80 to 120%; 91.8% of the patients in the empagliflozin 10 mg group, and 91.8% of patients in the empagliflozin 25 mg group.

6.1.3 Subject Disposition

A total of 11,531 patients signed informed consent at 609 centers in 42 countries. The first patient was enrolled on August 26, 2010. The last on-site visit of a patient took place on April 13, 2015. The last contact date with any patient in the trial was April 21, 2015.

Of the 11531 patients screened, 7610 patients started the 2-week placebo run-in period, and 7028 patients were randomized to trial medication. Most of the 4503 patients (39.1% of screened patients) that were not randomized did not comply with inclusion or exclusion criteria (33.1% of screened patients); in most of these cases HbA1c was out of range. The proportion of randomized to screened did not show very significant differences between geographical regions, however, it is notable that North America had the lowest proportion of randomized/screened

patients. Also notable, Australia and New Zealand were analyzed as North America by the Applicant.

Table 13 Overview of Enrolled and Randomized Patients by Region - SCR

Geographical region	Countries[1]	Patients enrolled N (%)	Patients randomised N (%)
Europe	Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Greece, Hungary, Israel, Italy, Netherlands, Norway, Poland, Portugal, Romania, Russia, Spain, Ukraine, United Kingdom	4260 (100.0)	2889 (67.8)
North America	Australia, Canada, New Zealand, United States	2664 (100.0)	1395 (52.4)
Asia	Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Sri Lanka, Taiwan, Thailand	2193 (100.0)	1348 (61.5)
Latin America	Argentina, Brazil, Colombia, Mexico, Peru	1851 (100.0)	1082 (58.5)
Africa	South Africa	563 (100.0)	314 (55.8)
Total	42 countries	11531 (100.0)	7028 (60.9)

[1] Countries are listed in alphabetical order.

Source: Table 10.1:1 study report NDA 204629, SDN 406

The largest proportions of enrolled and randomized (i.e. entered) patients were from Europe, followed by North America and Asia. At country level, the United States contributed most patients, both in terms of enrolled and randomized patients (2352 and 1221 patients); the next largest contributions came from Brazil (909 and 501 patients) and South Africa (563 and 314 patients).

Of the 7028 randomized patients, 7020 patients were treated with double-blind trial medication. Eight patients were randomized but not treated because randomization had occurred in error (as per the investigators' comments). Of these 8 patients, 5 patients had uncontrolled hyperglycemia during the placebo run-in phase (in addition, one of these 5 patients had the antidiabetic background therapy changed within 12 weeks prior to randomization), 1 patient had impaired renal function (eGFR below 30 mL/min/1.73 m2), 1 patient did not have a high cardiovascular risk; for the eighth patient, no violation of an inclusion or exclusion criterion was documented in the CRF but the patient had aggravated renal failure requiring therapy during the screening period. None of these 8 patients had an adverse event qualifying for adjudication. Vital status information at the end of the trial was available for 7 of these patients (all 7 were alive).

Table 14 Number of Randomized Patients by Stratum (as per IXRS) - RS

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
Randomised patients	2337 (100.0)	2347 (100.0)	2344 (100.0)
HbA_{1c} (%)			
HbA_{1c} <8.5	1487 (63.6)	1496 (63.7)	1491 (63.6)
HbA_{1c} ≥8.5	850 (36.4)	851 (36.3)	853 (36.4)
eGFR [mL/min/1.73m^2]			
≥90	511 (21.9)	516 (22.0)	513 (21.9)
60 to <90	1222 (52.3)	1227 (52.3)	1230 (52.5)
30 to <60	604 (25.8)	604 (25.7)	601 (25.6)
BMI [kg/m^2]			
<30	1124 (48.1)	1133 (48.3)	1128 (48.1)
≥30	1213 (51.9)	1214 (51.7)	1216 (51.9)
Geographical region			
Africa	103 (4.4)	107 (4.6)	104 (4.4)
Asia	450 (19.3)	448 (19.1)	450 (19.2)
Europe	962 (41.2)	966 (41.2)	961 (41.0)
Latin America	360 (15.4)	360 (15.3)	362 (15.4)
North America	462 (19.8)	466 (19.9)	467 (19.9)

Source Table 10.1:2 study report NDA 204629, SDN 406

Of the 7020 patients treated with randomized trial medication, 211 patients (3.0%) prematurely discontinued the trial. For these patients, follow-up information for the primary endpoint 3-point MACE was not available for the entire trial period. However, vital status information at the end of the trial was available for all but 53 patients (0.8%) in the TS. There are no significant differences between the treatment groups regarding patient disposition (Table 15), except that more patients in the placebo group prematurely discontinued the trial medication (29.3%) compared to either of the empagliflozin arms (23.7%, and 23.1% in the empagliflozin 10 mg and 25 mg arms respectively). The most frequent reasons for premature discontinuation of trial medication were adverse events (other than worsening of study disease or other pre-existing disease).

Figure 3 Overview of Patient Disposition – SCR

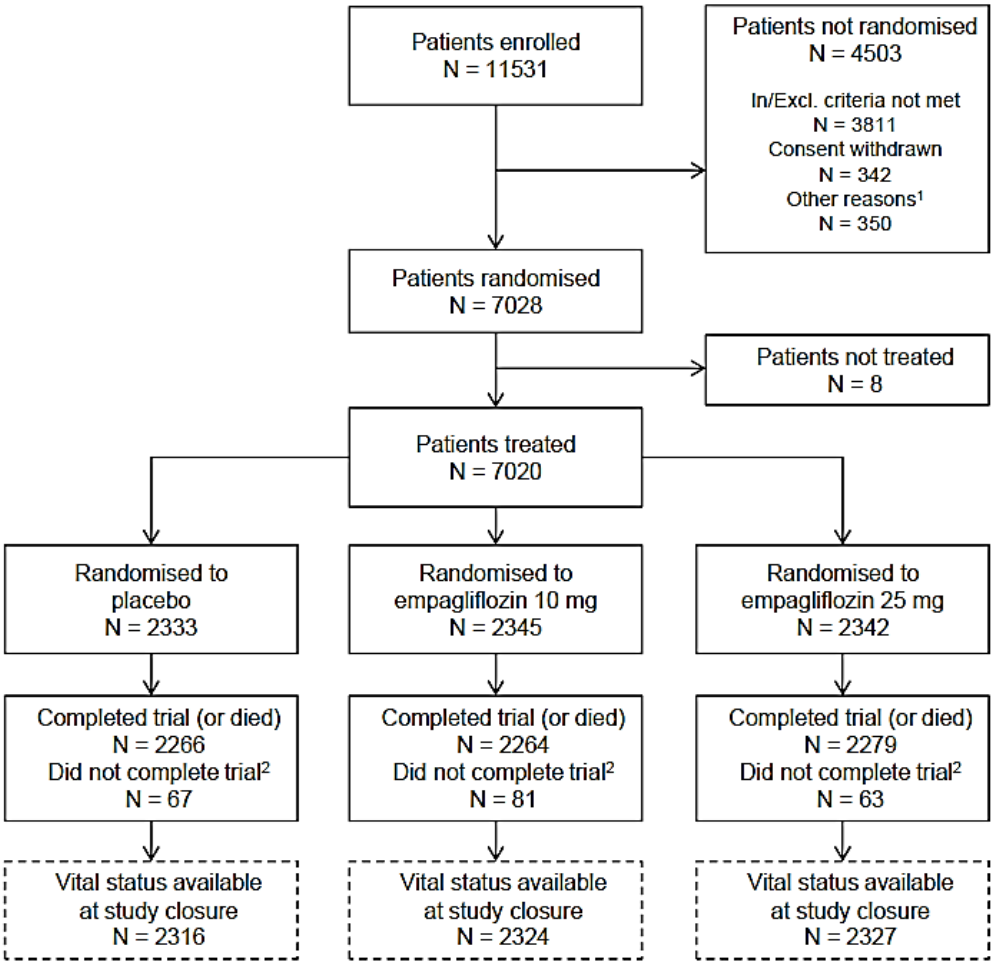


Figure 10.1: 1 Overview of patient disposition – SCR

[1] Other reasons comprise serious non-compliance at 2 sites (55 patients), adverse events (42 patients), loss to follow-up (33 patients), and 'other' (220 patients)
[2] Follow-up information for primary endpoint 3-point MACE not available for entire trial period.

Source Figure 10.1:1 study report NDA 204629, SDN 406

Table 15 Disposition of Patients - SCR

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)
Enrolled/Screened patients					11531
Patients who started placebo run-in period					7610
Entered/Randomized patients[1]	2337	2347	2344	4691	7028
Not treated patients	4	2	2	4	8
Treated patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)	7020 (100.0)
Final vital status available	2316 (99.3)	2324 (99.1)	2327 (99.4)	4651 (99.2)	6967 (99.2)
Alive	2122 (91.0)	2187 (93.3)	2195 (93.7)	4382 (93.5)	6504 (92.6)

Dead	194 (8.3)	137 (5.8)	132 (5.6)	269 (5.7)	463 (6.6)
Lost to follow-up for vital status[2]	17 (0.7)	21 (0.9)	15 (0.6)	36 (0.8)	53 (0.8)
Prematurely discontinued trial[3]	67 (2.9)	81 (3.5)	63 (2.7)	144 (3.1)	211 (3.0)
Consent withdrawn	31 (1.3)	41 (1.7)	30 (1.3)	71 (1.5)	102 (1.5)
Site closure	25 (1.1)	30 (1.3)	26 (1.1)	56 (1.2)	81 (1.2)
Lost to follow-up for 3P-MACE	11 (0.5)	10 (0.4)	7 (0.3)	17 (0.4)	28 (0.4)
Prematurely discontinued trial med.	683 (29.3)	555 (23.7)	542 (23.1)	1097 (23.4)	1780 (25.4)
Adverse event	303 (13.0)	267 (11.4)	273 (11.7)	540 (11.5)	843 (12.0)
Study disease worsening	15 (0.6)	22 (0.9)	14 (0.6)	36 (0.8)	51 (0.7)
Other pre-exist. disease worsening	65 (2.8)	38 (1.6)	48 (2.0)	86 (1.8)	151 (2.2)
Other adverse event	223 (9.6)	207 (8.8)	211 (9.0)	418 (8.9)	641 (9.1)
Lack of efficacy[4]	11 (0.5)	1 (<0.1)	0	1 (<0.1)	12 (0.2)
Non-compliance with protocol	15 (0.6)	15 (0.6)	12 (0.5)	27 (0.6)	42 (0.6)
Lost to follow-up	15 (0.6)	9 (0.4)	6 (0.3)	15 (0.3)	30 (0.4)
Refused to continue trial medication[5]	172 (7.4)	118 (5.0)	122 (5.2)	240 (5.1)	412 (5.9)
Other reason	162 (6.9)	142 (6.1)	125 (5.3)	267 (5.7)	429 (6.1)
Study drug stopped, reason missing	5 (0.2)	3 (0.1)	4 (0.2)	7 (0.1)	12 (0.2)

[1] Three patients were randomized without documented intake of run-in medication.

[2] Of these 53 patients, 3 had a non-fatal 3-point MACE event and were thereafter lost to follow-up for vital status

[3] Follow-up information for 3-point MACE endpoint not available for entire trial period because of withdrawn consent, site closure (without transfer to another site) or being lost to follow-up for 3-point MACE for other reasons. For 161 of these 211 patients, vital status information was available. Thus, for 50 patients follow-up information was available neither for 3-point MACE nor for vital status.

[4] Hyperglycemia above protocol-defined level despite rescue therapy

[5] Not due to adverse event

Source Table 10.1:3 study report NDA 204629, SDN 406

In total, 18 sites were closed globally (1 in Peru, 17 in the USA). Of these, 10 in the US were closed for administrative reasons and 8 sites (7 in the US and 1 in Peru) were closed due to serious noncompliance. The site in Peru was not re-opened; 11 sites in the US agreed to provide vital status for their patients, and submitted the vital status data via a third party. An Independent Review Committee decided which data were to be included or excluded from the database, according to the nature of the serious noncompliance. Data from 3 of the sites closed due to serious noncompliance (sites 10043, 10157, and 10053) were entirely excluded from all analyses, including the primary and key secondary analyses, due to possible serious noncompliance (following the discovery of invalid source documents, doubts over patient eligibility based on documentation of cardiovascular risk factors, or a suspicion that regulatory documentation had not been signed by the principal investigator).

Protocol violations

A summary of all important protocol violations is shown below in Table 16. There were slightly more patients with at least one important protocol violation in the empagliflozin 25 mg arm

(2.8%) vs 2.2% in the empagliflozin 10 mg arm, and 2.1% in the placebo arm. This difference is relatively small. In total, 50 treated patients were excluded from the PPS because of important protocol violations. The most frequent of these protocol violations was serious non-compliance (25 patients).

The patients from two study sites (10043, and 10157) were excluded from all analysis sets except for the screened set because of serious non-compliance. There were 55 patients screened by these two sites, 27 of whom were randomized and treated. Patients from another site (10053) were excluded from all analysis sets including the screened set because of serious non-compliance with the informed consent process (13 patients in total). Overall these numbers are small in the context of this study, and, in my opinion, unlikely to impact the final study results.

Overall, 40 patients in the TS were found to have taken trial medication from a different treatment group (placebo: 12 patients, empagliflozin 10 mg: 14 patients, empagliflozin 25 mg: 14 patients). Per Applicant report, most of these patients took the wrong medication for 'some time' in between receiving correct medication, 7 patients took the wrong trial drug as their last trial medication, and 2 patients received wrong medication as their first trial medication before switching to the correct one. Only for one patient (empagliflozin 25 mg), the exposure to wrong trial medication accounted for more than 20% of their overall treatment duration; the patient was excluded from the PPS because of this important protocol violation. Notably, the Applicant considered the randomized medication (not the actual trial medication) in all analyses.

Table 16 Protocol Violations by Treatment Arm

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)
Treated patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)
Patients with at least 1 important PV	49 (2.1)	52 (2.2)	65 (2.8)	117 (2.5)
Important PVs leading to exclusion from any analysis set	42 (1.8)	51 (2.2)	62 (2.6)	113 (2.4)
Exclusion from FAS				
No baseline HbA_{1c} value	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Exclusion from PPS				
Serious non-compliance potentially affecting primary endpoint	9 (0.4)	5 (0.2)	11 (0.5)	16 (0.3)
Participation in another trial at same time	3 (0.1)	4 (0.2)	3 (0.1)	7 (0.1)
Acute coronary syndrome, stroke or TIA within 2 months[1]	3 (0.1)	1 (<0.1)	4 (0.2)	5 (0.1)
Planned cardiac surgery / angioplasty within 3 months[1]	1 (<0.1)	2 (0.1)	1 (<0.1)	3 (0.1)
Intake of invest. drug in another trial within 30 d prior to intake of trial med.[1]	0	0	3 (0.1)	3 (0.1)
Previous participation in this trial[2]	1 (<0.1)	1 (<0.1)	0	1 (<0.1)
Incorrect trial medication taken[3]	0	0	1 (<0.1)	1 (<0.1)
Exclusion from OS				
Not on trial drug for at least 30 days[4]	25 (1.1)	38 (1.6)	41 (1.8)	79 (1.7)
Important PVs affecting rights or safety (not leading to exclusion from any analysis set)	7 (0.3)	1 (<0.1)	3 (0.1)	4 (0.1)
Indication of liver disease[1]	3 (0.1)	0	0	0
Pregnancy test not done for woman of child-bearing potential for at least one visit before last treatment discontinuation	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Informed consent too late	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Informed consent too late for substudy[5]	1 (<0.1)	0	0	0
Informed consent obtained with error	0	0	1 (<0.1)	1 (<0.1)
Pregnancy	1 (<0.1)	0	0	0

Patients could have more than 1 important protocol violation (PV).
1 Exclusion criterion
2 One patient was randomised twice at one site (both times to placebo); only data referring to the second randomisation were used for analyses because the patient was only treated after the second randomisation. One patient was randomised twice (first to empagliflozin 10 mg and then to empagliflozin 25 mg) at 2 different sites; this patient is analysed according to the first randomisation and corresponding treatment. For details about the handling of these 2 cases, see TSAP supporting document in Appendix 16.1.9.1 and Appendix 16.2.1, Listing 7
3 Wrong medication taken for more than 20% of the overall treatment duration
4 At least 30 cumulative days. In addition to the 104 patients with this important protocol violation, one further patient was excluded from the OS because information about treatment duration was not considered reliable (see TSAP supporting document in Appendix 16.1.9.1).
5 Substudy refers to the assessment of pharmacokinetic parameters

Source: Table 10.3:1 study report NDA 204629, SDN 406

Unblinding:

The interim data for this trial was analyzed as part of a cardiovascular meta-analysis for the initial global marketing authorization applications (to rule out 80% increase risk), as well as independently to rule out 30% excess risk pre-marketing. The Applicant states that this was performed by a team independent of the trial team, with an established firewall between both

teams. To maintain the integrity of this cardiovascular safety study, access to any unblinded data from this trial was controlled by a confidentiality agreement. Per Applicant report, to maintain the integrity of the study, access to the unblinded data was only provided to the independent team responsible for the interim database lock, statistical analyses, and reporting of the interim data. The Applicant provided the names of 229 people who were unblinded at the interim analysis, which included therapeutic area heads, statisticians (including the project statistician), programmers, data managers, medical writers, pharmacovigilance staff, regulatory affairs, epidemiology, Lilly representatives, etc. The interim unblinding of the trial was performed within the statistical reporting environment and not in the clinical database to ensure that ongoing data entry and data cleaning could be performed in a blinded manner. The reports and statistical outputs were not available to the trial team or to anyone with direct contact to the trial team responsible for the operational part of the ongoing trial, or to the investigators. The DMC received the randomization code and reviewed unblinded data as necessary.

During this trial, there were 4 cases of investigator unblinding via the IXRS and documented in the trial database (3 in the placebo group, 1 in the empagliflozin 10 mg group). In 3 of these 4 cases, the investigator requested the code break; in one case (placebo), the investigator was unblinded by mistake of the Applicant. This latter patient discontinued trial drug about 1 month after and because of the unblinding. The other two patients in the placebo group had died before the unblinding occurred. The patient in the empagliflozin 10 mg group discontinued trial medication on the day of unblinding because of 2 serious adverse events gastroenteritis (considered drug-related) and costochondritis (not considered drug-related), from which the patient recovered. The two living patients were followed until the end of the trial.

Reviewer comment: We were concerned regarding the pretty extensive unblinding that occurred at the level of the applicant, however, we found no evidence of unblinding impacting the results of the study. The results of the interim analysis are similar to the final analysis.

6.1.1 Analysis of Primary Endpoint

The primary efficacy endpoint for this study was the adjudicated 3-point MACE composite endpoint which was time to first occurrence of CV death, non-fatal myocardial infarction (excluding silent MI), or non-fatal stroke.

The order of the hierarchical hypothesis testing was defined as shown below, each test was only considered confirmatory if the outcome of the previous test was successful.

- Non-inferiority for the primary endpoint (3-point MACE)
- Non-inferiority for the key secondary endpoint (4-point MACE)

- Superiority for 3-point MACE

- Superiority for 4-point MACE

The Applicant performed the primary analysis based on the treated set (TS), considering all events up to individual trial completion. There were 772 patients reported with an event, with 490 patients (10.5%) reported for the all-empagliflozin treatment group (combined dose groups of 10 mg and 25 mg, 'all empagliflozin') and 282 patients (12.1%) for the placebo group. The hazard ratio (HR) based on Cox proportional hazards regression model for all empagliflozin vs. placebo was 0.86 (95.02% CI 0.74, 0.99). The Applicant therefore concluded that empagliflozin is superior to placebo, since the upper bound of the 95.02% CI was below 1.0. The 95.02% CI was based on the reduced α level of 0.0249, resulting from the interim analysis of the trial data.

Table 17 Cox Regression for Time to First 3-Point MACE Event, All Empa vs. Placebo – TS

	Placebo	**All empa**
Analyzed patients, N (100%)	**2333**	**4687**
Patients with event, N (%)	282 (12.1)	490 (10.5)
Incidence rate per 1000 years at risk	43.9	37.4
Hazard ratio vs. placebo		0.86
(95.02% CI)[1]		(0.74, 0.99)
(95% CI)		(0.74, 0.99)
p−value for HR≥1.3 (1−sided)		<0.0001
p−value for HR≥1.0 (1−sided)		0.0191
p−value for HR=1.0 (2−sided)		0.0382

[1] Based on the reduced α level of 0.0249 resulting from the interim analysis
Source: Table 11.1.1.1: 1 study report NDA 204629, SDN 406

The frequencies of patients with a 3-point MACE event by component for all empa vs placebo are presented in Table 18 below. The superiority of empagliflozin vs placebo appears to be driven by the CV death component of the 3-point MACE – 4.6% of patients in the placebo group vs 3.1% of patients in the all empagliflozin arm. Non-fatal MI was only borderline more frequent in placebo (5.1%) vs empagliflozin (4.4%), and non-fatal stroke was more frequent in the empagliflozin arm (3.0% vs 2.4% of patients in placebo).

Table 18 Patients [N (%)] with First 3-Point MACE Event by Component, All Empa vs. Placebo – TS

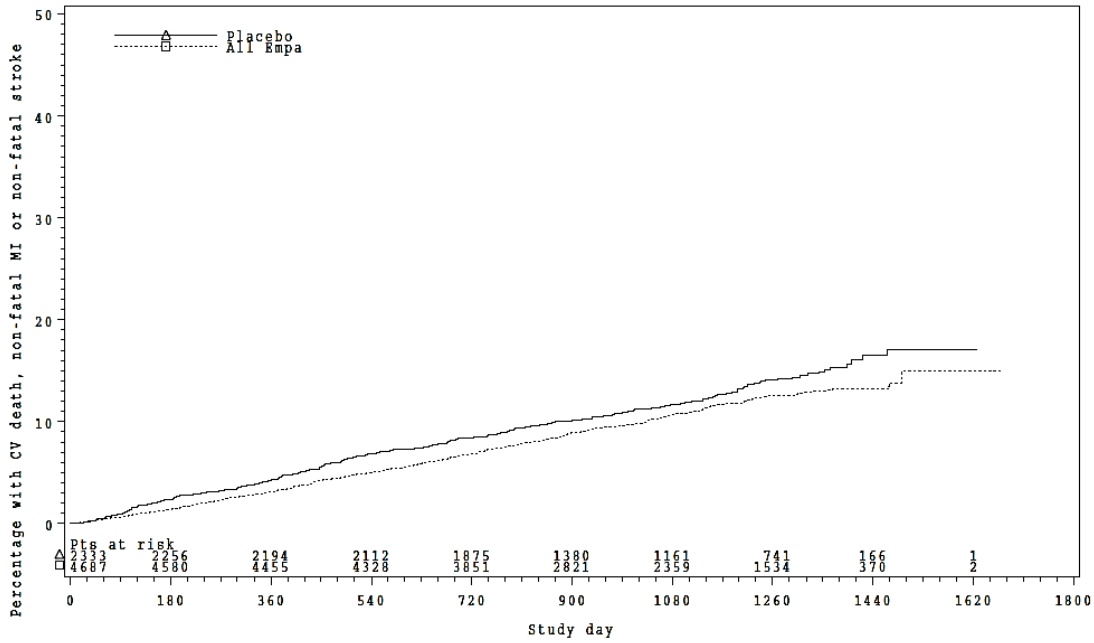
	Placebo	**All empa**
Patients, N (100%)	**2333**	**4687**
Patients with event	282 (12.1)	490 (10.5)
CV death	107 (4.6)	143 (3.1)
Non-fatal MI	120 (5.1)	208 (4.4)

Non-fatal stroke	55 (2.4)	142 (3.0)

Patients could be reported with multiple events if a non-fatal MI and a non-fatal stroke occurred on the same day.
Source: Table 11.1.1.1: 2 study report NDA 204629, SDN 406

Kaplan-Meier estimation of time to first 3-point MACE event for all empagliflozin vs. placebo is shown below in Figure 3. Interestingly, the difference between empagliflozin and placebo arms is apparent relatively early in the trial, around study day 90.

Figure 3 Kaplan-Meier Estimation of Time to First 3-Point MACE Event, All Empa vs. Placebo - TS



Source: Figure 15.2.1.1: 1 study report NDA 204629, SDN 406

To ensure that the patients who had a 3-point MACE event were treated to the same standards throughout the trial, we asked the Applicant to provide a breakdown of anti-diabetic, and significant cardiovascular medications for this population subset. The findings are presented in Table 19 below for antidiabetes medications. Of the patients with events, a slightly higher proportion of patients in the empagliflozin group were on metformin and DPP-4 inhibitors at the time of the event compared to placebo, while more patients in the placebo group were on insulin and sulfonylureas. Regarding other relevant concomitant medications, slightly fewer patients in the placebo group were on statins or aspirin compared to empagliflozin group, while more patients in the placebo group were on beta blockers compared to empagliflozin group. It is notable that the Applicant did not record dosage for the concomitant medications, and we cannot assess whether the treatments were optimized. However, these are post-randomization variables, and it is not clear whether they impacted the outcome of the study.

Table 19 Frequency [N(%)] of Patients with Antidiabetic Therapies at Baseline and Time of Event, Patients with 3-Point MACE Event − TS

	Placebo		All Empa	
	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)
Number of patients analysed	282 (100.0)		490 (100.0)	
Metformin	189 (67.0)	182 (64.5)	344 (70.2)	328 (66.9)
Sulfonylurea	109 (38.7)	119 (42.2)	195 (39.8)	188 (38.4)
Glitazone	11 (3.9)	13 (4.6)	23 (4.7)	22 (4.5)
A-glucosidase inhib	12 (4.3)	13 (4.6)	14 (2.9)	13 (2.7)
Glinide	4 (1.4)	7 (2.5)	12 (2.4)	12 (2.4)
DPP-IV inhibitor	28 (9.9)	38 (13.5)	67 (13.7)	76 (15.5)
GLP-1 agonist	10 (3.5)	11 (3.9)	15 (3.1)	15 (3.1)
Insulin	142 (50.4)	170 (60.3)	265 (54.1)	275 (56.1)
Other antidiabetics	4 (1.4)	4 (1.4)	6 (1.2)	6 (1.2)

Source: Excerpted from Table 24.1.2 Response to information request dated April 8, 2016, sequence number 128

Table 20 Frequency [N(%)] of Patients with Concomitant Therapies at Baseline and Time of Event, Patients with 3-Point MACE Event − TS

	Placebo		All Empa	
	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)
Number of patients analysed	282 (100.0)		490 (100.0)	
Antihypertensives	271 (96.1)	269 (95.4)	469 (95.7)	461 (94.1)
Beta-blockers	192 (68.1)	187 (66.3)	331 (67.6)	316 (64.5)
Beta-blockers prim. for rhythm control	1 (0.4)	1 (0.4)	1 (0.2)	0
Diuretics	144 (51.1)	156 (55.3)	262 (53.5)	258 (52.7)
ACE inhibitors/ARBs	221 (78.4)	213 (75.5)	399 (81.4)	382 (78.0)
ACE inhibitors	134 (47.5)	128 (45.4)	278 (56.7)	261 (53.3)
ARBs	95 (33.7)	94 (33.3)	142 (29.0)	137 (28.0)
Calcium channel blockers	103 (36.5)	116 (41.1)	169 (34.5)	157 (32.0)
Mineralocorticoid receptor antagonists	25 (8.9)	34 (12.1)	47 (9.6)	52 (10.6)
Renin inhibitors	4 (1.4)	1 (0.4)	4 (0.8)	4 (0.8)
Other	27 (9.6)	33 (11.7)	57 (11.6)	58 (11.8)
Lipid lowering drugs	229 (81.2)	226 (80.1)	400 (81.6)	400 (81.6)
Niacin	4 (1.4)	2 (0.7)	7 (1.4)	8 (1.6)
Fibrates	27 (9.6)	24 (8.5)	43 (8.8)	45 (9.2)
Statins	209 (74.1)	208 (73.8)	384 (78.4)	381 (77.8)
Ezetimibe	6 (2.1)	7 (2.5)	18 (3.7)	25 (5.1)
Other	34 (12.1)	31 (11.0)	42 (8.6)	44 (9.0)
Anti-coagulants	263 (93.3)	248 (87.9)	440 (89.8)	432 (88.2)
Platelet aggregation inhibitors excl. heparin	247 (87.6)	227 (80.5)	419 (85.5)	409 (83.5)
ASA	229 (81.2)	210 (74.5)	402 (82.0)	387 (79.0)
Clopidogrel	42 (14.9)	40 (14.2)	52 (10.6)	55 (11.2)
Dipyridamole	0	0	1 (0.2)	1 (0.2)
Direct factor XA inhibitors	1 (0.4)	1 (0.4)	0	2 (0.4)
Direct thrombin inhibitors	1 (0.4)	3 (1.1)	5 (1.0)	7 (1.4)
Heparin group	1 (0.4)	10 (3.5)	2 (0.4)	11 (2.2)
Vitamin K antagonists	31 (11.0)	30 (10.6)	39 (8.0)	43 (8.8)
Warfarin	9 (3.2)	10 (3.5)	18 (3.7)	18 (3.7)
Other anticoagulant agents	0	0	0	1 (0.2)
Digitalis	16 (5.7)	15 (5.3)	25 (5.1)	29 (5.9)

Source: Excerpted from Table 17.1.2 Response to information request dated April 8, 2016, sequence number 128

The Applicant also analyzed the 3-point MACE results for individual empagliflozin doses vs placebo, although this was not part of the confirmatory testing. The HR for individual empagliflozin doses is still favoring empagliflozin, however, the p value was not statistically

significant for either empagliflozin dose. The Kaplan-Meier estimate for time to event for either empagliflozin arms was similar to the all empagliflozin arm. Overall the results for individual empagliflozin arms are reassuring as we make our conclusions regarding the study results.

Table 4 Cox Regression for Time to First 3-Point MACE Event, Empagliflozin doses vs. Placebo – TS

	Placebo	**Empa 10 mg**	**Empa 25 mg**
Analyzed patients, N (100%)	**2333**	**2345**	**2342**
Patients with event, N (%)	282 (12.1)	243 (10.4)	247 (10.5)
Incidence rate per 1000 years at risk	43.9	37.1	37.7
Hazard ratio vs. placebo (95% CI)		0.85 (0.72, 1.01)	0.86 (0.73, 1.02)
p−value for HR=1.0 (2−sided)		0.0668	0.0865

Source: Table 11.1.1.1: 3 study report NDA 204629, SDN 406

Sensitivity analyses

The applicant performed 3-point MACE analyses based on the TS and the on-treatment set (OS, including only patients with at least 30 cumulative days of treatment), considering only events up to 30 days after last intake of study drug or up to the end of the individual observation period (whichever was earlier). As seen in Table 21 below, although the HR favored empagliflozin, the 95% CI did cross 1.00 for all comparisons.

The Applicant hypothesized that the p-value for the individual empagliflozin arms was not significant due to the smaller number of events in the individual group, and this is probably a reasonable assumption.

Table 21 Cox Regression for Time to First 3-Point MACE Event up to Treatment Stop + 30 Days – OS, TS

	Placebo	**Empa 10 mg**	**Empa 25 mg**	**All empa**
Analyzed patients (OS), N (100%)	2308	2306	2301	4607
Patients with event, N (%)	227 (9.8)	201 (8.7)	206 (9.0)	407 (8.8)
Incidence rate per 1000 years at risk	39.5	33.7	34.4	34.1
Hazard ratio vs. placebo (95% CI)		0.86 (0.71, 1.04)	0.87 (0.72, 1.05)	0.87 (0.74, 1.02)
Analyzed patients (TS), N (100%)	2333	2345	2342	4687
Patients with event, N (%)	229 (9.8)	202 (8.6)	210 (9.0)	412 (8.8)
Incidence rate per 1000 years at risk	39.8	33.9	35.0	34.4
Hazard ratio vs. placebo (95% CI)		0.86 (0.71, 1.04)	0.88 (0.73, 1.06)	0.87 (0.74, 1.02)

Source: Table 11.1.1.2: 1 study report NDA 204629, SDN 406

Also, analyses based on the per-protocol set (99.3% of the patients of the TS) were consistent with the primary analysis, as were other sensitivity analyses.

Please see the biometrics review by Dr Clark for details regarding the FDA analysis of the primary endpoint.

6.1.2 Analysis of Secondary Endpoints(s)

Key secondary endpoint

The key secondary endpoint was time to first occurrence of adjudicated CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina (4-point MACE), and it was analyzed as part of the hierarchical testing strategy.

There were a total of 932 patients reported with a 4-point MACE event, with 599 patients (12.8%) reported for the all-empagliflozin treatment group and 333 patients (14.3%) for the placebo group. The hazard ratio (HR) based on Cox regression for all empagliflozin vs. placebo was 0.89 (95.02% CI 0.78, 1.01). Therefore, empagliflozin was found to be non-inferior to placebo, but not superior since the upper bound of the 95.02% CI was above 1. The breakdown for adjudicated 4-point MACE events by component is presented in Table 23 below, and, again, the favorable HR is driven by the difference in CV death that favors empagliflozin, as the endpoint hospitalization for unstable angina occurred in an equal proportion of empagliflozin and placebo patients.

Table 22 Cox Regression for Time to First 4-Point MACE Event, all Empa vs. Placebo – TS

	Placebo	**All empa**
Analyzed patients, N (100%)	**2333**	**4687**
Patients with event, N (%)	333 (14.3)	599 (12.8)
Incidence rate per 1000 years at risk	52.5	46.4
Hazard ratio vs. placebo		0.89
(95.02% CI)[1]		(0.78, 1.01)
(95% CI)		(0.78, 1.01)
p−value for HR≥1.3 (1−sided)		<0.0001
p−value for HR≥1.0 (1−sided)		0.0397
p−value for HR=1.0 (2−sided)		0.0795

[1] Based on the reduced α level of 0.0249 resulting from the interim analysis
Source: Table 11.1.2.1.1: 1 study report NDA 204629, SDN 406

Table 23 Patients [N (%)] with first 4-point MACE event by component, all empa vs. placebo – TS

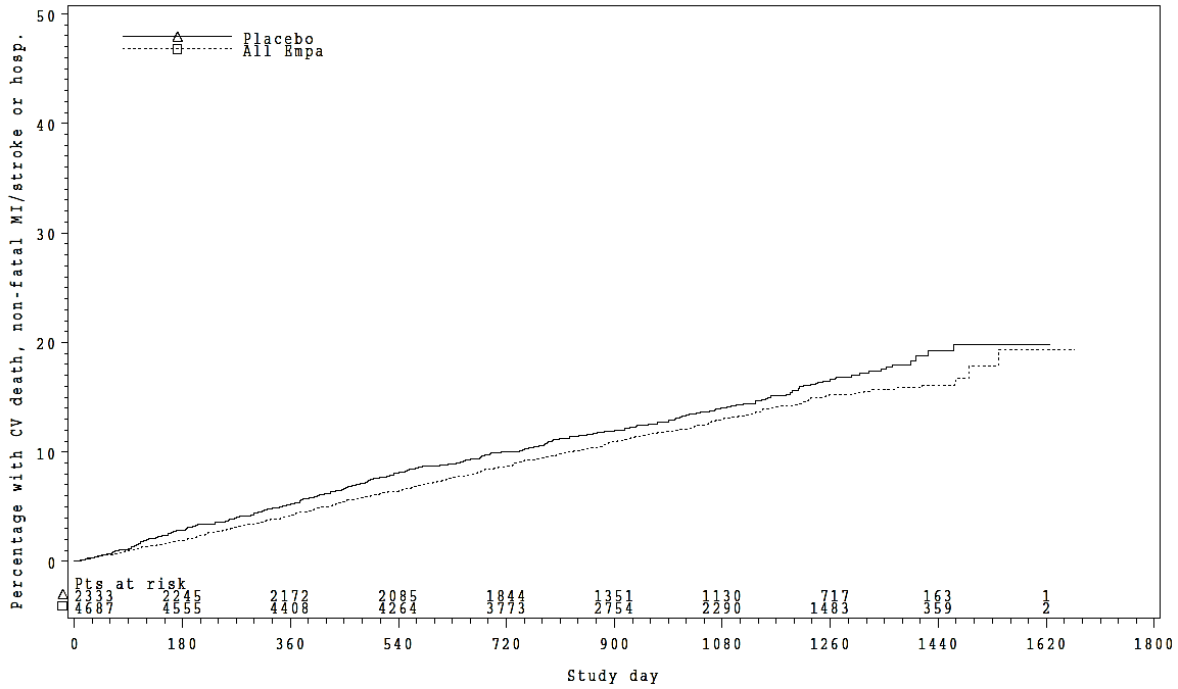
	Placebo	**All empa**
Patients, N (100%)	**2333**	**4687**
Patients with event	333 (14.3)	599 (12.8)
CV death	104 (4.5)	142 (3.0)

Non-fatal MI	116 (5.0)	200 (4.3)
Non-fatal stroke	55 (2.4)	140 (3.0)
Hospitalization for unstable angina	61 (2.6)	120 (2.6)

Source: Table 11.1.2.1.1: 2 study report NDA 204629, SDN 406

The Kaplan-Meier estimation of time to first 4-point MACE event for all empagliflozin vs. placebo is similar to the 3-point MACE.

Figure 4 Kaplan-Meier estimation of time to first 4-point MACE event, all empagliflozin vs. placebo – TS



Source: Figure11.1.2.1.1: 1 study report NDA 204629, SDN 406

The key secondary endpoint was further analyzed by the applicant by comparing the individual empagliflozin doses, and the results were similar to those for all empagliflozin, which is supportive of the primary analysis.

6.1.3 Other Endpoints/Exploratory Endpoints

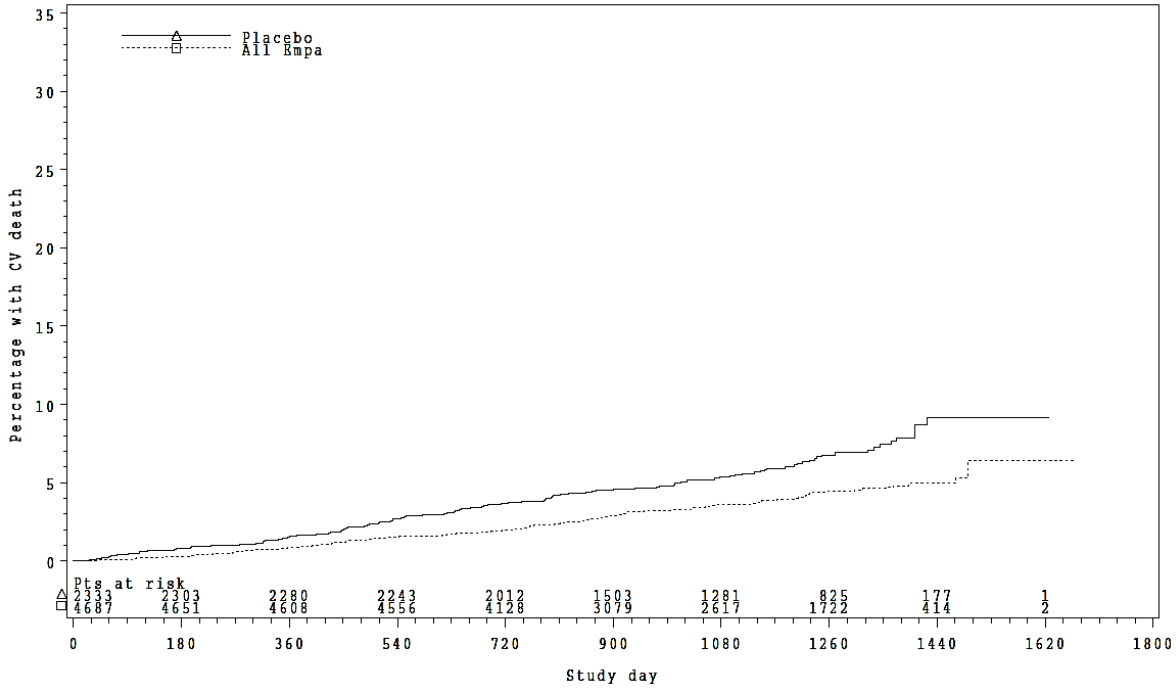
The Applicant presented further secondary endpoints not included in the statistical testing strategy. Selected exploratory endpoints relevant for the review of this application are presented below.

<u>CV death and all-cause mortality</u>

Both CV death and all-cause mortality (ACM) were significantly reduced in the pooled empagliflozin arm compared to placebo. As expected considering the patient population enrolled in EMPA-REG, the majority of deaths in this study were due to CV death (adjudicated endpoint), and this is the driver behind the ACM results, as well as the driver for superiority of the 3-point MACE primary endpoint.

The Kaplan-Meier estimation of time to CV death for all empagliflozin vs placebo for the TS is shown below, and it is notable that the separation of the event rates for empagliflozin and placebo started shortly after trial onset and was maintained throughout the trial (before study day 90). The reason for this finding is unclear, as is the mechanism behind the reduction in CV mortality with empagliflozin.

Figure 5 Kaplan-Meier estimation of time to CV death, all empagliflozin vs. placebo – TS



Source: Excerpted from Figure 11.1.2.2.1: 1study report NDA 204629, SDN 406

Notably, 40% of all CV deaths are categorized as “fatal event not assessable”. It is not clear whether these events are truly CV death, and while the Agency generally agreed that this type of event be categorized as CV death in the past, the proportion of patients with this categorization in this particular trial is very high. This brings concerns regarding trial conduct and collection of the information necessary to properly assess the cause of death. A slightly higher proportion in the placebo arm had adjudicated fatal event not assessable when compared to empagliflozin (2.3% vs 1.5%). Multiple information requests were sent to the Applicant in an attempt to

further clarify the cause of death for the deaths deemed "not assessable", and the information available was reviewed, including selected CEC adjudication packages. It was not possible to assess causality based on the information available to us. Of the patients with "not assessable" death, less than half had a death certificate or proof of death available, and none had had an autopsy.

Table 24 Patients [N(%)] with Adjudicated CV Death by Subcategory – TS

Patients, N (100%)	**Placebo 2333**	**Empa 10 mg 2345**	**Empa 25 mg 2342**	**All Empa 4687**
Patients with CV death	137 (5.9)	90 (3.8)	82 (3.5)	172 (3.7)
Acute MI	11 (0.5)	6 (0.3)	9 (0.4)	15 (0.3)
Sudden death	38 (1.6)	30 (1.3)	23 (1.0)	53 (1.1)
Worsening of heart failure	19 (0.8)	7 (0.3)	4 (0.2)	11 (0.2)
Cardiogenic shock	3 (0.1)	1 (<0.1)	2 (0.1)	3 (0.1)
Stroke	11 (0.5)	9 (0.4)	7 (0.3)	16 (0.3)
Other cardiovascular death	55 (2.4)	37 (1.6)	37 (1.6)	74 (1.6)
Fatal event not assessable	53 (2.3)	34 (1.4)	37 (1.6)	71 (1.5)

Source: Table 11.1.2.2.1: 2 study report NDA 204629, SDN 406

Preferred terms reported by the investigators in patients with "not assessable" deaths are presented in Table 25. While most are suggestive of cardiovascular cause of death, this could not be confirmed by the adjudicators.

Table 25 Preferred Terms Reported by Investigators for "Non-assessable" Deaths

	Most Common Terms	Placebo (N=53)	All Empa (N=71)
General Disorders	Death, Cardiac Death, Sudden Death	51%	51%
Cardiac Disorders	AMI, Cardiac Failure, Cardiogenic Shock, Cardiac Arrest	30%	34%
Nervous Systems Disorders	CVA, Thrombotic stroke, Ischemic stroke	6%	7%
Non-CV related Disorders	----	13%	8%

Source: Data from response to information request, sequence number 131, April 13, 2016

The Applicant was asked to provide an analysis where not assessable death was excluded from the primary endpoint of 3-point MACE, and, in this case, empagliflozin is no longer superior to placebo with an HR 0.90 (95% CI 0.77, 1.06). CV death excluding not assessable death is presented in Table 26 below, the results are still favoring empagliflozin.

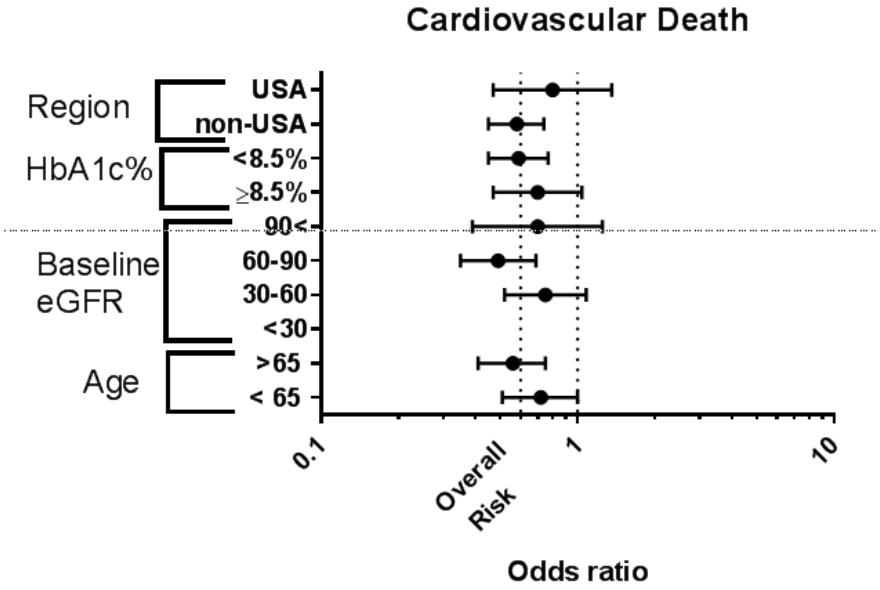
Table 26 Cox Regression for CV Death Excluding not Assessable Death, All Empa vs. Placebo – TS

	Placebo	All Empa
Number of patients in analysis set	2333	4687
Number of analysed patients	2333	4687
Number of patients with event [N(%)]	84 (3.6)	101 (2.2)
Time at risk for event [years]	6794.5	13833.8
Incidence rate [patients with events per 1000 years at risk]	12.4	7.3
95% confidence interval	(9.9,15.1)	(5.9, 8.8)
Comparison vs Placebo*		
Hazard ratio		0.59
95% confidence interval		(0.44,0.79)
p-value		0.0004

Source: Table 9.8.1.3 response to information request dated April 1, 2016, sequence number 127

While it is questionable whether all the not assessable death events belong in the CV death category, even when excluding non-assessable there remains an imbalance in CV death that favors empagliflozin. Also, the analysis of ACM is favorable to empagliflozin. The mechanism for this imbalance is not clear, as empagliflozin does not appear to decrease the risk for MI and/or stroke. In addition, both empagliflozin arms rendered similar results, and the CV death findings were consistent for various subgroups of patients. Selected subgroup analyses for CV death are presented in Figure 6 below.

Figure 6 Subgroup analyses for CV death, all empa vs placebo



Source: Table created using GraphPad and data generated by Dr Jennifer Clark, Biostatistics.

The results of the Cox regression analyses of ACM and CV death up to the earliest of 30 days after the last intake of study drug and end of the individual observation period (TS) were consistent with the analysis for TS using all events.

Table 27 Cox regression for time to CV death and time to ACM up to treatment stop + 30 days – TS

Analyzed patients, N (100%)	**Placebo 2333**	**Empa 10 2345**	**Empa 25 2342**	**All Empa 4687**
CV death				
Patients with event, N (%)	92 (3.9)	63 (2.7)	51 (2.2)	114 (2.4)
Incidence per 1000 years at risk	15.5	10.2	8.2	9.2
Hazard ratio vs placebo (95%CI)		0.66 (0.48, 0.91)	0.52 (0.37, 0.74)	0.59 (0.45, 0.78)
All-cause mortality				
Patients with event, N (%)	112 (4.8)	86 (3.7)	76 (3.2)	162 (3.5)
Incidence per 1000 years at risk	18.9	14.0	12.3	13.1
Hazard ratio vs placebo (95%CI)		0.74 (0.56, 0.98)	0.65 (0.48, 0.86)	0.69 (0.54, 0.88)

Source: Tables 11.1.2.2.1: 1 and 11.1.2.2.2: 1 study report NDA 204629, SDN 406

The Applicant reported no significant differences in the results of time to all-cause mortality across subgroups for any parameter, including baseline characteristics such as age, sex, renal function, glucose control, and baseline medication use.

In order to further clarify this issue, we asked the applicant to provide information regarding antidiabetic and concomitant relevant medications for the subsets of patients with CV death and ACM. For the patients with CV death, a higher proportion of the patients on empagliflozin were on metformin, and DPP-4 inhibitors compared to the placebo patients, while there were more placebo patients on insulin compared to empagliflozin. For the concomitant non-diabetic medications, a lower proportion of patients on placebo were on beta-blockers, and statins compared to the empagliflozin patients. While more patients in the placebo group were on diuretic medications compared to the empagliflozin group, it should be taken into consideration that all the patients in the empagliflozin group were taking a medication that would qualify as a diuretic (the study medication). It is not possible to fully assess the impact of these differences on the outcome.

Table 28 Frequency [N(%)] of Patients with Antidiabetic Therapies at Baseline and Time of Event CV Death, Patients with Event − TS

	Placebo		All Empa	
	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)
Number of patients analysed	137 (100.0)		172 (100.0)	
Metformin	84 (61.3)	77 (56.2)	118 (68.6)	109 (63.4)
Sulfonylurea	51 (37.2)	52 (38.0)	67 (39.0)	62 (36.0)
Glitazone	6 (4.4)	6 (4.4)	7 (4.1)	4 (2.3)
A-glucosidase inhib	7 (5.1)	7 (5.1)	3 (1.7)	4 (2.3)
Glinide	1 (0.7)	2 (1.5)	3 (1.7)	4 (2.3)
DPP-IV inhibitor	7 (5.1)	9 (6.6)	16 (9.3)	20 (11.6)
GLP-1 agonist	4 (2.9)	4 (2.9)	6 (3.5)	7 (4.1)
Insulin	74 (54.0)	84 (61.3)	93 (54.1)	99 (57.6)
Other antidiabetics	2 (1.5)	2 (1.5)	1 (0.6)	1 (0.6)

Source: Excerpted from Table 24.2.2 Response to information request dated April 8, 2016, sequence number 128

Table 29 Frequency [N(%)] of Patients with Concomitant Therapies at Baseline and Time of Event CV Death, Patients with Event − TS

	Placebo		All Empa	
	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)
Number of patients analysed	137 (100.0)		172 (100.0)	
Antihypertensives	132 (96.4)	128 (93.4)	162 (94.2)	162 (94.2)
Beta-blockers	88 (64.2)	86 (62.8)	111 (64.5)	116 (67.4)
Beta-blockers prim. for rhythm control	0	0	1 (0.6)	0
Diuretics	80 (58.4)	95 (69.3)	96 (55.8)	103 (59.9)
ACE inhibitors/ARBs	109 (79.6)	98 (71.5)	137 (79.7)	127 (73.8)
ACE inhibitors	63 (46.0)	58 (42.3)	98 (57.0)	93 (54.1)
ARBs	51 (37.2)	47 (34.3)	45 (26.2)	38 (22.1)
Calcium channel blockers	50 (36.5)	55 (40.1)	52 (30.2)	47 (27.3)
Mineralocorticoid receptor antagonists	17 (12.4)	24 (17.5)	27 (15.7)	28 (16.3)
Renin inhibitors	2 (1.5)	1 (0.7)	2 (1.2)	2 (1.2)
Other	10 (7.3)	13 (9.5)	20 (11.6)	18 (10.5)
Lipid lowering drugs	103 (75.2)	108 (78.8)	132 (76.7)	132 (76.7)
Niacin	1 (0.7)	0	3 (1.7)	3 (1.7)
Fibrates	11 (8.0)	11 (8.0)	13 (7.6)	12 (7.0)
Statins	92 (67.2)	96 (70.1)	131 (76.2)	131 (76.2)
Ezetimibe	3 (2.2)	4 (2.9)	7 (4.1)	6 (3.5)
Other	17 (12.4)	15 (10.9)	9 (5.2)	10 (5.8)
Anti-coagulants	125 (91.2)	117 (85.4)	149 (86.6)	147 (85.5)
Platelet aggregation inhibitors excl. heparin	116 (84.7)	103 (75.2)	137 (79.7)	135 (78.5)
ASA	106 (77.4)	95 (69.3)	132 (76.7)	127 (73.8)
Clopidogrel	16 (11.7)	21 (15.3)	18 (10.5)	20 (11.6)
Dipyridamole	0	0	0	0
Direct factor XA inhibitors	0	0	0	3 (1.7)
Direct thrombin inhibitors	0	1 (0.7)	3 (1.7)	4 (2.3)
Heparin group	1 (0.7)	15 (10.9)	0	7 (4.1)
Vitamin K antagonists	20 (14.6)	18 (13.1)	18 (10.5)	18 (10.5)
Warfarin	5 (3.6)	5 (3.6)	10 (5.8)	8 (4.7)
Other anticoagulant agents	0	0	0	2 (1.2)
Digitalis	13 (9.5)	13 (9.5)	13 (7.6)	20 (11.6)

Source: Excerpted from Table 17.2.2 Response to information request dated April 8, 2016, sequenced number 128

Silent myocardial infarction

In EMPA-REG, silent MI was not included in the non-fatal MI component of the primary endpoint. While initially the study protocol had a definition for silent MI that included ECG changes and clinical assessment, the silent MI definition that was final and used for analyses was based solely on ECG criteria, and it was not an adjudicated endpoint.

The ECG criteria were outlined as follows:

- Any Q-wave in leads V2-V3 ≥0.02 seconds or QS complex in leads V2 and V3

- Q-wave ≥0.03 seconds and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)

- R-wave ≥0.04 seconds in V1-V2 and R/S ≥1 with a concordant positive T-wave in the absence of a conduction defect

The silent MI endpoint was not adjudicated. It was also required that there had been no adjudicated and confirmed event of either acute MI, hospitalization for unstable angina, coronary revascularization procedures or stent thrombosis following randomization up to and including the date of the specified ECG measurement.

To further limit the interpretability of this endpoint, the silent MI as defined by the Applicant was only analyzed in a subset of patients - patients without silent MI or relevant cardiac conductions effects at baseline and with available post-baseline ECG measurements. As a result, only a very small number of silent MI events (53) were identified for this study, and I am concerned that missing data precludes us from drawing any meaningful conclusions. The incidence rate for Applicant-defined silent MI was higher in the all empagliflozin arm compared to placebo. Also, when silent MIs are included in the 3-point MACE analysis, the endpoint no longer statistically favorable to empagliflozin (HR 0.92 (0.79, 1.06)). While I believe that silent MIs are significant events, especially for patients with diabetes, it is difficult to ascertain the meaning of analyses that include silent MI for this study due to inaccurate definition, poor data collection for this event, and lack of adjudication.

Table 30 Cox regression for time to first Silent MI– TS

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
Silent MI				
Analyzed patients, N (100%)	1211	1174	1204	2378
Patients with event, N (%)	15 (1.2)	19 (1.6)	19 (1.6)	38 (1.6)
Incidence rate per 1000 years at risk	5.4	7.1	7.0	7.0

Hazard ratio vs. placebo (95% CI)	1.32 (0.67, 2.60)	1.24 (0.63, 2.45)	1.28 (0.70, 2.33)
p-value	0.4215	0.5282	0.4172

Source: Excerpted from Table 11.1.2.3: 1 study report NDA 204629, SDN 406

Table 31 Time to First Event of 3-point MACE Including Silent MI

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
3-point MACE including silent MI				
Analyzed patients (TS), N (100%)	1378	1327	1347	2674
Patients with event, N (%)	295 (21.4)	259 (19.5)	264 (19.6)	523 (19.6)
Incidence rate per 1000 years at risk	97.8	89.0	89.1	89.1
Hazard ratio vs. placebo (95% CI)		0.92 (0.78, 1.09)	0.91 (0.77, 1.07)	0.92 (0.79, 1.06)
p-value		0.3517	0.2558	0.2274
Analyzed patients (OS), N (100%)	1313	1281	1290	2571
Patients with event up to treatment stop + 30 days, N (%)	239 (18.2)	216 (16.9)	221 (17.1)	437 (17.0)
Incidence rate per 1000 years at risk	86.4	79.3	80.1	79.7
Hazard ratio vs. placebo (95% CI)		0.93 (0.77, 1.12)	0.92 (0.76, 1.10)	0.92 (0.79, 1.08)

Source: Excerpted from Table 11.1.2.6: 1 study report NDA 204629, SDN 406

Heart failure requiring hospitalization

This endpoint was adjudicated by the CEC, but not included in the statistical testing strategy, and not controlled for type 1 error. In addition, the CEC definition used for adjudication of the events changed significantly over the course of the trial, resulting in potential collection of events that were milder forms of heart failure, or not heart failure at all. The final definition used for adjudication also differed significantly from the current event definition

At baseline, history of heart failure was reported as balanced between the treatment groups, with 244 patients (10.46%) in the placebo group, and 462 (9.86% in the pooled empagliflozin group. However, details regarding the heart failure history, such as ejection fraction, and New York Heart Association Classification were not collected in this trial.

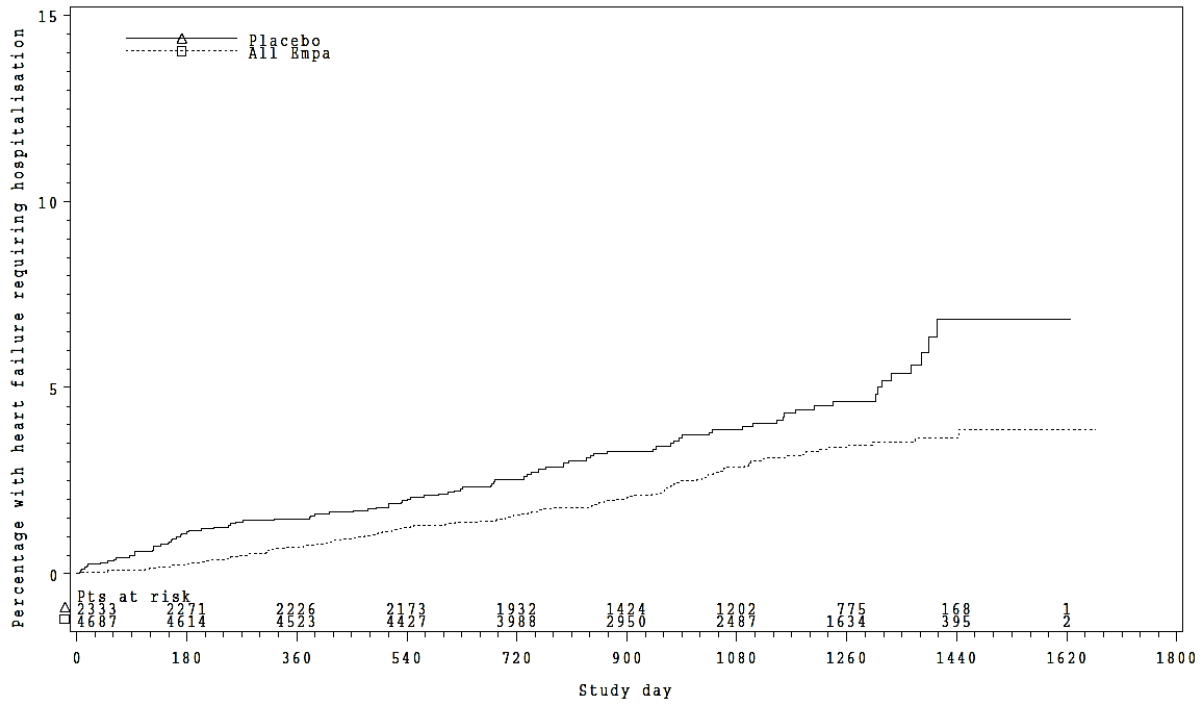
As seen in Table 32 below, there was a nominally statistically significant decrease in heart failure related events with empagliflozin compared to placebo, in both TS and OS. For the event "heart failure requiring hospitalization", the Kaplan-Meier estimates are presented below. A separation in the incidence of this type of event is observed early on in the study which is of interest as it mimics the findings for CV death.

Table 32 Cox Regression for Endpoints Related to Heart Failure Requiring Hospitalization – TS, OS

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
Heart failure requiring hospitalization				
Analyzed patients (TS), N (100%)	2333	2345	2342	4687
Patients with event, N (%)	95 (4.1)	60 (2.6)	66 (2.8)	126 (2.7)
Incidence rate per 1000 years at risk	14.5	8.9	9.8	9.4
Hazard ratio vs. placebo (95% CI)		0.62 (0.45, 0.86)	0.68 (0.50, 0.93)	0.65 (0.50, 0.85)
p-value		0.0044	0.0166	0.0017
Analyzed patients (OS), N (100%)	2308	2306	2301	4607
Patients with event up to treatment stop + 30 days, N (%)	77 (3.3)	53 (2.3)	46 (2.0)	99 (2.1)
Incidence rate per 1000 years at risk	13.2	8.7	7.5	8.1
Hazard ratio vs. placebo (95% CI)		0.66 (0.46, 0.93)	0.56 (0.39, 0.81)	0.61 (0.45, 0.82)
Heart failure requiring hospitalization or death from heart failure				
Analyzed patients (TS), N (100%)	2333	2345	2342	4687
Patients with event, N (%)	104 (4.5)	62 (2.6)	67 (2.9)	129 (2.8)
Incidence rate per 1000 years at risk	15.8	9.2	9.9	9.6
Hazard ratio vs. placebo (95% CI)		0.59 (0.43, 0.81)	0.63 (0.46, 0.86)	0.61 (0.47, 0.79)
p-value		0.0010	0.0034	0.0002
Analyzed patients (OS), N (100%)	2308	2306	2301	4607
Patients with event up to treatment stop + 30 days, N (%)	82 (3.6)	54 (2.3)	46 (2.0)	100 (2.2)
Incidence rate per 1000 years at risk	14.0	8.9	7.5	8.2
Hazard ratio vs. placebo (95% CI)		0.63 (0.45, 0.89)	0.53 (0.37, 0.76)	0.58 (0.43, 0.77)

Source: Excerpted from Table 11.1.2.5: 1 study report NDA 204629, SDN 406

Figure 7 Kaplan-Meier Estimation of Time to First Heart Failure Requiring Hospitalization, all Empagliflozin vs. Placebo- TS



Source: Excerpted from Figure 11.1.2.5.1: 1study report NDA 204629, SDN 406

The results of Cox regression analyses of heart failure requiring hospitalization up to the earliest of 30 days after last intake of study drug and end of the individual observation period (TS) were consistent with those for the TS using all events.

Table 33 Cox Regression for Time to First Heart Failure Requiring Hospitalization up to Treatment Stop + 30 Days – TS

	Placebo	**Empa 10 mg**	**Empa 25 mg**	**All Empa**
Analyzed patients, N (100%)	**2333**	**2345**	**2342**	**4687**
Patients with event, N (%)	79 (3.4)	53 (2.3)	46 (2.0)	99 (2.1)
Incidence rate per 1000 years at risk	13.5	8.7	7.5	8.1
Hazard ratio vs. placebo (95% CI)		0.64 (0.45, 0.91)	0.55 (0.38, 0.79)	0.59 (0.44, 0.80)

Source: Table 11.1.2.5.1: 1 study report NDA 204629, SDN 406

The Applicant reported that the results for time to first heart failure requiring hospitalization were generally consistent across subgroups for any parameter, including baseline characteristics such as age, sex, renal function, glucose control, and baseline medication use.

The results for heart failure and serious heart failure based on the Applicant reported narrow SMQ 'cardiac failure' were consistent with those for the adjudicated endpoints related to heart failure, with significant reduction in this endpoint for empagliflozin compared to placebo.

Table 34 Cox Regression for Time to First Heart Failure and Serious Heart Failure (SMQ) – TS

	Placebo	**Empa 10 mg**	**Empa 25 mg**	**All Empa**
Analyzed patients, N (100%)	**2333**	**2345**	**2342**	**4687**
Heart failure				
Patients with event, N (%)	143 (6.1)	106 (4.5)	98 (4.2)	204 (4.4)
Incidence rate per 1000 years at risk	22.0	15.9	14.6	15.3
Hazard ratio vs. placebo (95% CI)		0.73 (0.57, 0.94)	0.67 (0.52, 0.86)	0.70 (0.56, 0.87)
p-value		0.0144	0.0021	0.0010
Serious heart failure				
Patients with event, N (%)	136 (5.8)	99 (4.2)	93 (4.0)	192 (4.1)
Incidence rate per 1000 years at risk	20.9	14.9	13.8	14.4
Hazard ratio vs. placebo (95% CI)		0.72 (0.55, 0.93)	0.67 (0.51, 0.87)	0.69 (0.55, 0.86)
p-value		0.0117	0.0025	0.0010

Source: Table 11.1.2.5.4: 1 study report NDA 204629, SDN 406

FDA analysis using the broad MAED SMQ "cardiac failure", revealed different results, however the findings were still favorable to empagliflozin. In this analysis, 310 patients in the placebo group were reported with a heart failure event (13.3%) vs 36 patients in the pooled empagliflozin group (7.8%).

Looking at concomitant medications in the sugbgroup of patients that experienced an adjudicated heart failure event, for antidiabetic medications, a higher proportion of patients on empagliflozin were also taking DPP-4 inhibitors and GLP-1 agonists (Table 35). Regarding other relevant concomitant medications, it is notable that fewer patients in the placebo group were taking diuretics at the time of the event compared to the patients in the pooled empagliflozin group (Table 36).

Table 35 Frequency [N(%)] of patients with antidiabetic therapies at baseline and time of event Hospitalization for heart failure, patients with event − TS

	Placebo		All Empa	
	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)
Number of patients analysed	95 (100.0)		126 (100.0)	
Metformin	59 (62.1)	57 (60.0)	79 (62.7)	82 (65.1)
Sulfonylurea	30 (31.6)	31 (32.6)	40 (31.7)	42 (33.3)
Glitazone	2 (2.1)	3 (3.2)	5 (4.0)	5 (4.0)
A-glucosidase inhib	2 (2.1)	3 (3.2)	4 (3.2)	1 (0.8)
Glinide	2 (2.1)	3 (3.2)	1 (0.8)	1 (0.8)
DPP-IV inhibitor	8 (8.4)	10 (10.5)	11 (8.7)	16 (12.7)
GLP-1 agonist	3 (3.2)	3 (3.2)	5 (4.0)	9 (7.1)
Insulin	61 (64.2)	69 (72.6)	84 (66.7)	85 (67.5)
Other antidiabetics	0	1 (1.1)	0	0

Source: Table 24.14.2 response to information request sequence number 128

Table 36 Frequency [N(%)] of patients with concomitant therapies at baseline and time of event Hospitalization for heart failure, patients with event − TS

	Placebo		All Empa	
	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)
Number of patients analysed	95 (100.0)		126 (100.0)	
Antihypertensives	93 (97.9)	90 (94.7)	124 (98.4)	124 (98.4)
Beta-blockers	70 (73.7)	71 (74.7)	92 (73.0)	91 (72.2)
Beta-blockers prim. for rhythm control	0	0	0	1 (0.8)
Diuretics	59 (62.1)	64 (67.4)	95 (75.4)	99 (78.6)
ACE inhibitors/ARBs	81 (85.3)	74 (77.9)	104 (82.5)	97 (77.0)
ACE inhibitors	50 (52.6)	45 (47.4)	63 (50.0)	54 (42.9)
ARBs	35 (36.8)	34 (35.8)	47 (37.3)	46 (36.5)
Calcium channel blockers	32 (33.7)	30 (31.6)	48 (38.1)	46 (36.5)
Mineralocorticoid receptor antagonists	8 (8.4)	18 (18.9)	29 (23.0)	36 (28.6)
Renin inhibitors	2 (2.1)	0	3 (2.4)	0
Other	10 (10.5)	15 (15.8)	15 (11.9)	18 (14.3)
Lipid lowering drugs	82 (86.3)	83 (87.4)	107 (84.9)	105 (83.3)
Niacin	2 (2.1)	2 (2.1)	2 (1.6)	2 (1.6)
Fibrates	10 (10.5)	9 (9.5)	10 (7.9)	13 (10.3)
Statins	79 (83.2)	80 (84.2)	103 (81.7)	100 (79.4)
Ezetimibe	5 (5.3)	7 (7.4)	3 (2.4)	3 (2.4)
Other	8 (8.4)	7 (7.4)	14 (11.1)	12 (9.5)
Anti-coagulants	90 (94.7)	91 (95.8)	118 (93.7)	117 (92.9)
Platelet aggregation inhibitors excl. heparin	83 (87.4)	83 (87.4)	106 (84.1)	106 (84.1)
ASA	77 (81.1)	80 (84.2)	100 (79.4)	99 (78.6)
Clopidogrel	18 (18.9)	20 (21.1)	21 (16.7)	21 (16.7)
Dipyridamole	1 (1.1)	1 (1.1)	0	0
Direct factor XA inhibitors	1 (1.1)	2 (2.1)	0	3 (2.4)
Direct thrombin inhibitors	0	0	0	4 (3.2)
Heparin group	1 (1.1)	1 (1.1)	2 (1.6)	2 (1.6)
Vitamin K antagonists	15 (15.8)	18 (18.9)	19 (15.1)	25 (19.8)
Warfarin	3 (3.2)	4 (4.2)	6 (4.8)	8 (6.3)
Other anticoagulant agents	0	0	0	0
Digitalis	9 (9.5)	8 (8.4)	14 (11.1)	11 (8.7)

Source: Table 17.14.2 response to information request sequence number 128

A decrease in heart failure events is plausible in the context of the mechanism of action for empagliflozin, which has a diuretic effect. However, the definition for the endpoint was somewhat broad and may have captured events that were not heart failure, and was analyzed as exploratory per the statistical analysis plan.

Please see DCRP review by Dr Hicks for a detailed review of heart failure events.

Stroke and transient ischemic attacks (TIA) (adjudicated endpoints)

An imbalance in stroke events not favoring empagliflozin was observed in the original empagliflozin NDA review. In this study, although not statistically significant, the HR empagliflozin vs placebo for all stroke, and non-fatal stroke was above 1 which is consistent with previous findings. The analyses considering events only up to 7 days, 30 days, and 90 days after treatment stop yielded similar results, as did the analyses based on OS (Table 37). As seen in Table 37 below, the incidence rate was slightly higher for the empagliflozin 10 mg arm compared to the 25 mg arm in all analyses, however, the differences are minimal and it is unclear whether this trend is significant.

Strokes were adjudicated endpoints, and the majority of events were ischemic strokes. The adjudication of stroke in the EMPA-REG study was based on all available data. Standardized assessments for stroke events such as clinical assessment or specific imaging were not required or specified in the protocol or the CEC charter.

The CEC charter outlined 4 criteria for identification of stroke

- Rapid onset of focal/global neurological deficit
- Duration $\geq$ 24 hours (unless therapeutic intervention, imaging shows new infarct or hemorrhage, or death)
- No readily identifiable non-stroke cause for presentation
- Confirmation by specialist, imaging, or lumbar puncture

From the Kaplan-Meier time to event estimate below for non-fatal strokes, it appears that there is an initial imbalance for the first 150 days after inception of study treatment, with more strokes in the pooled empagliflozin arm. The gap closes afterwards, and the incidence of non-fatal stroke is similar between the treatment arms by 1 year (1.1% in both arms). Around study day 600, an increase in non-fatal strokes is observed with empagliflozin compared to placebo, and this is maintained for the duration of the study.

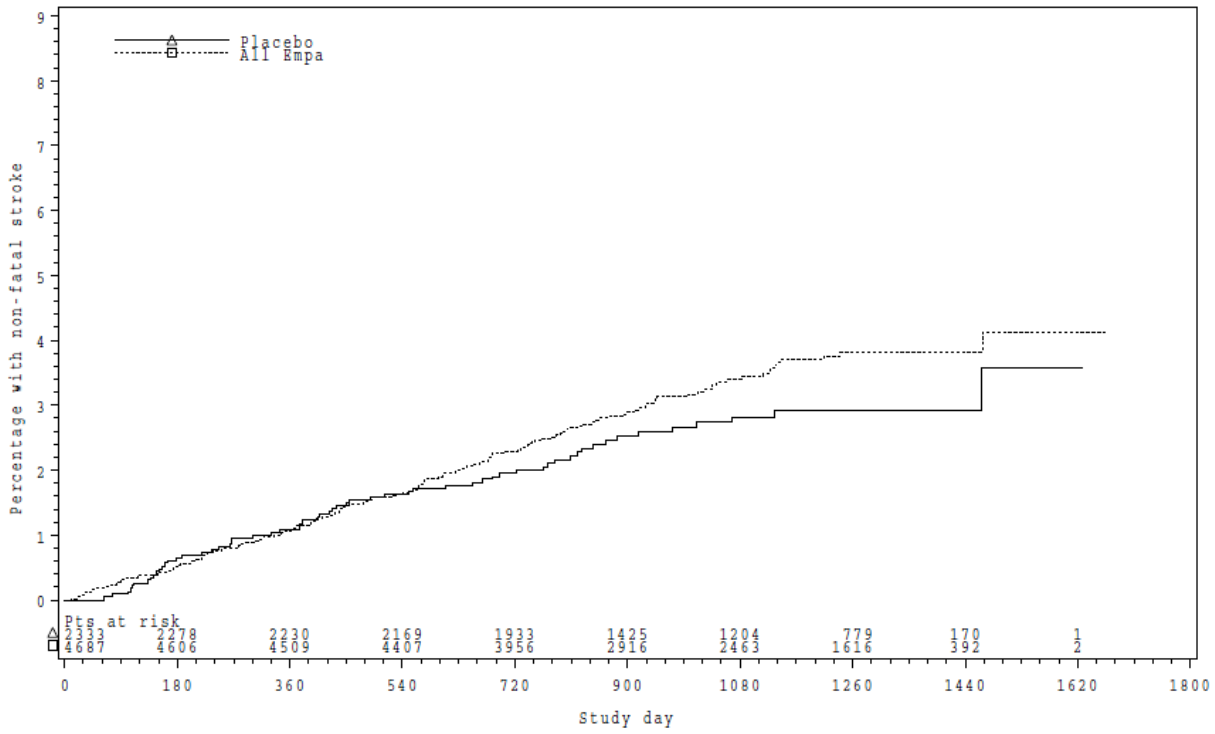
Table 37 Cox regression analyses for stroke and non-fatal stroke – TS, OS

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
Stroke (fatal/non-fatal)				
Analysed patients (TS), N (100%)	2333	2345	2342	4687
All patients with event, N (%)	69 (3.0)	85 (3.6)	79 (3.4)	164 (3.5)
Incidence rate per 1000 years at risk	10.5	12.7	11.8	12.3
Hazard ratio vs. placebo (95% CI)		1.22 (0.89, 1.68)	1.13 (0.82, 1.56)	1.18 (0.89, 1.56)
p-value		0.2119	0.4594	0.2567
Events up to treatment stop + 7 d, N (%)	62 (2.7)	72 (3.1)	67 (2.9)	139 (3.0)
Incidence rate per 1000 years at risk	10.8	12.1	11.2	11.7
Hazard ratio vs. placebo (95% CI)		1.14 (0.81, 1.60)	1.05 (0.75, 1.49)	1.09 (0.81, 1.48)
Events up to treatment stop + 30 d, N (%)	66 (2.8)	73 (3.1)	70 (3.0)	143 (3.1)
Incidence rate per 1000 years at risk	11.3	12.0	11.4	11.7
Hazard ratio vs. placebo (95% CI)		1.08 (0.78, 1.51)	1.03 (0.74, 1.44)	1.06 (0.79, 1.41)
Events up to treatment stop + 90 d, N (%)	66 (2.8)	74 (3.2)	72 (3.1)	146 (3.1)
Incidence rate per 1000 years at risk	11.1	12.0	11.6	11.8
Hazard ratio vs. placebo (95% CI)		1.10 (0.79, 1.53)	1.06 (0.76, 1.48)	1.08 (0.81, 1.45)
Analysed patients (OS), N (100%)	2308	2306	2301	4607
Events up to treatment stop + 30 d, N (%)	66 (2.9)	73 (3.2)	68 (3.0)	141 (3.1)
Incidence rate per 1000 years at risk	11.3	12.0	11.1	11.6
Hazard ratio vs. placebo (95% CI)		1.08 (0.78, 1.51)	1.00 (0.71, 1.40)	1.04 (0.78, 1.40)
Non-fatal stroke				
Analysed patients (TS), N (100%)	2333	2345	2342	4687
All patients with event, N (%)	60 (2.6)	77 (3.3)	73 (3.1)	150 (3.2)
Incidence rate per 1000 years at risk	9.1	11.5	10.9	11.2
Hazard ratio vs. placebo (95% CI)		1.27 (0.91, 1.79)	1.20 (0.85, 1.69)	1.24 (0.92, 1.67)
p-value		0.1593	0.2954	0.1638
Events up to treatment stop + 7 d, N (%)	55 (2.4)	67 (2.9)	63 (2.7)	130 (2.8)
Incidence rate per 1000 years at risk	9.6	11.3	10.5	10.9
Hazard ratio vs. placebo (95% CI)		1.19 (0.83, 1.70)	1.11 (0.78, 1.60)	1.15 (0.84, 1.58)
Events up to treatment stop + 30 d, N (%)	58 (2.5)	68 (2.9)	65 (2.8)	133 (2.8)
Incidence rate per 1000 years at risk	9.9	11.2	10.6	10.9
Hazard ratio vs. placebo (95% CI)		1.15 (0.81, 1.63)	1.09 (0.76, 1.55)	1.12 (0.82, 1.52)
Events up to treatment stop + 90 d, N (%)	58 (2.5)	69 (2.9)	66 (2.8)	135 (2.9)
Incidence rate per 1000 years at risk	9.7	11.2	10.6	10.9
Hazard ratio vs. placebo (95% CI)		1.16 (0.82,1.65)	1.11 (0.78,1.58)	1.14 (0.84, 1.55)
Analysed patients (OS), N (100%)	2308	2306	2301	4607
Events up to treatment stop + 30 d, N (%)	58 (2.5)	68 (2.9)	63 (2.7)	131 (2.8)
Incidence rate per 1000 years at risk	9.9	11.2	10.3	10.8
Hazard ratio vs. placebo (95% CI)		1.15 (0.81, 1.63)	1.06 (0.74, 1.51)	1.10 (0.81, 1.50)

Source: Table 11.1.2.4.1: 1 study report NDA 204629, SDN 406

Kaplan-Meier estimates for patients with non-fatal stroke events at 2 years were 2% for placebo and 2.3% for pooled empagliflozin, at 3 years: 2.8% for placebo and 3.4% for empagliflozin, and at 4 years: 2.9% for placebo, and 3.8% for empagliflozin.

Figure 8 Kaplan-Meier Estimate of Time to First Non-fatal Stroke, Pooled Empa vs Placebo – TS



Source: Figure 15.2.4.1.3: 1 study report NDA 204629, SDN 406

Few patients in the trial had more than one event of stroke, with similar frequencies across treatments (0.3% each for placebo and all empagliflozin). The Applicant reported that the results for time to first stroke (fatal/non-fatal) were generally consistent across subgroups with a few exceptions. Empagliflozin was nominally statistically significantly worse than placebo for patients less than 65 years of age, patients with baseline HbA1C ≥8.5%, and patients from Europe. Selected subgroup analyses are presented below in Table 38

Table 38 Subgroups Analyses for Time to First Stroke Event, Pooled Empagliflozin vs Placebo - TS

	Placebo	All Empa
Age		
<65		
Number of patients in the analysis set/number of	1297/26 (2.0)	2596/84 (3.2)

	patients with event (%)		
	HR (95%CI)		1.60 (1.03, 2.49)
	p-value		0.0359
≥65			
	Number of patients in the analysis set	1036/43 (4.2)	2091/80 (3.8)
	HR (95%CI)		0.91 (0.63, 1.32)
	p-value		0.6127
Geographical region			
Europe			
	Number of patients in the analysis set/number of patients with event (%)	959/21 (2.2)	1926/85 (4.4)
	HR (95%CI)		2.04 (1.26, 3.29)
	p-value		0.0035
North America			
	Number of patients in the analysis set/ number of patients with event (%)	462/19 (4.1)	932/32 (3.4)
	HR (95%CI)		0.82 (0.46, 1.45)
	p-value		0.4940
Latin America			
	Number of patients in the analysis set	360/10 (2.8)	721/9 (1.2)
	HR (95%CI)		0.44 (0.18, 1.07)
	p-value		0.0704
Africa			
	Number of patients in the analysis set	102/3 (2.9)	211/3 (1.4)
	HR (95%CI)		n/a
	p-value		n/a
Asia			
	Number of patients in the analysis set	450/16 (3.6)	897/35 (3.9)
	HR (95%CI)		1.08 (0.60, 1.95)
	p-value		0.7981
Baseline HbA1c			
<8.5%			
	Number of patients in the analysis set	1607/54 (3.4)	3212/100 (3.1)
	HR (95%CI)		0.91 (0.66, 1.27)
	p-value		0.5896
≥8.5%			
	Number of patients in the analysis set	726/15 (2.1)	1475/64 (4.3)
	HR (95%CI)		2.13 (1.21, 3.74)
	p-value		0.0084

Source: Table 7.4.1.24.12.3, Table 7.4.1.24.8.3, Table 7.4.1.24.6.3, Table 7.4.1.24.3.3, Table 7.4.1.24.2.3, Table 7.4.1.24.1.3 study report NDA 204629, SDN 406

Transient ischemic attack (adjudicated endpoint)

For TIA, no significant difference to placebo was observed for all empagliflozin and the individual doses for the TS (HR all empagliflozin vs placebo 0.85 [0.51, 1.42]), or OS (HR all empagliflozin vs placebo 0.81 [0.47, 1.40]).

In conclusion, a numeric imbalance is seen regarding stroke events, not favoring empagliflozin. While our Neurology consultant felt that it is possible that this is due to chance, I remain concerned regarding the possibility that empagliflozin may increase the risk for stroke as this trend was also observed with other members of the class.

Please see Neurology review by Dr Green for detailed analyses of stroke events.

Nephropathy-related endpoints

Analyses based on renal endpoints were exploratory in the EMPA-REG study. There was no plan to control for type 1 error across these analyses in any version of the protocol or statistical analysis plan. The definitions for various renal endpoints were changed significantly throughout the trial. Specifics of renal endpoints to be used in the final analyses were defined late in the trial in the final statistical analysis plan submitted after the interim analysis and after the trial had ended.

In addition, the clinical trial protocol or statistical analysis plan did not specify processes for identifying or confirming potential renal events. These endpoints were identified based on investigator reported adverse events, and laboratory findings, and were not adjudicated.

In the final clinical trial protocol, renal endpoints included occurrence and time to first occurrence of:

- New onset of albuminuria (defined as urine albumin to creatinine ratio [UACR] ≥ 30 mg/g),
- New onset of macroalbuminuria (defined as UACR ≥ 300 mg/g), and
- New or worsening nephropathy, defined as:
    - New onset of macroalbuminuria (defined as UACR > 300 mg/g),
    - Doubling of serum creatinine with an eGFR (MDRD) ≤45 mL/min/1.73 m^2,
    - Initiation of continuous renal replacement therapy, or

  - Death due to renal disease

- A composite microvascular outcome defined as:
  - Initiation of retinal photocoagulation,
  - Vitreous hemorrhage,
  - Diabetes-related blindness, or
  - New or worsening nephropathy, defined as above

The analysis for new onset albuminuria included subjects without albuminuria at baseline. Similarly, the analysis for new onset macroalbuminuria included subjects without macroalbuminuria at baseline. Measurement of UACR was performed by a central laboratory at the start of the placebo run-in period; randomization; at Weeks 4, 12, 28, and 52; then every 14 weeks until the end of study visit. It was also performed at the end of study visit; and 30 days after the end of study visit. The analyses were based on a single measurement, and the timing of urine collection (e.g., first morning void) was not specified. There was no difference between treatments for new onset of albuminuria. There was a nominally statistically significant difference between placebo and empagliflozin for the endpoint of 'new or worsening nephropathy' (HR vs. placebo 0.61, 95% CI 0.53, 0.70; Table 39). This was primarily driven by the effect of empagliflozin on albuminuria. There were too few clinical events to draw meaningful conclusions that differences between therapies truly existed.

Table 39 Results of Cox regression analyses for new onset albuminuria and 'new or worsening nephropathy' composite

	N	N	%	Rate/1000 pt-yrs	HR (95% CI)	p-value
New onset albuminuria[1]						
- Placebo	1374	703	51.2	266		
- All Empa	2779	1430	51.5	252.5	0.95 (0.87, 1.04)	0.2547
Composite of 'new or worsening nephropathy'						
- Placebo	2061	388	18.8	76		
- All Empa	4124	525	12.7	47.8	0.61 (0.53, 0.70)	< 0.0001
Components of composite						
New onset macroalbuminuria[2]						
- Placebo	2033	330	16.2	64.9		
- All Empa	4091	459	11.2	41.8	0.62 (0.54, 0.72)	< 0.0001
Doubling of serum creatinine plus eGFR ≤ 45 ml/min/1.73 m2						
- Placebo	2323	60	2.6	9.7		
- All Empa	4645	70	1.5	5.5	0.56 (0.39, 0.79)	0.0009

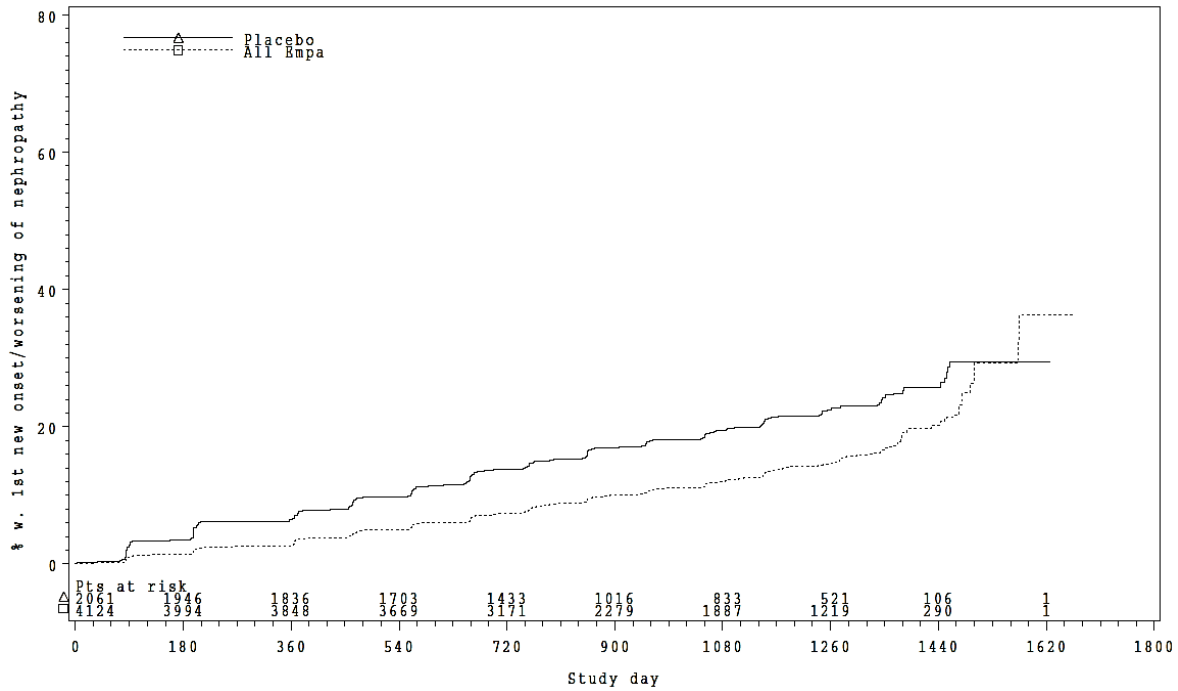
Initiation of continuous renal replacement therapy						
- Placebo	2333	14	0.6	2.1		
- All Empa	4687	13	0.3	1	0.45 (0.21, 0.97)	0.0409
Death due to renal disease						
- Placebo	2333	0	0			
- All Empa	4687	3	0.1	0.2	--	--

[1] includes only those subjects without albuminuria at baseline; [2] includes only those subjects without macroalbuminuria at baseline
N = number analyzed; n = number with event; Rate/1000 pt-yrs = events per 1000 patient years; HR = hazard ratio vs. placebo; CI = confidence interval; eGFR = estimated glomerular filtration rate
Source: Adapted from Table 11.1.2.8.1: 1 and Table 11.1.2.8.2: 1 of the study report NDA 204629, SDN 406

As seen in the Kaplan-Meier figure below, the empagliflozin and placebo curves started separating after study day 90, and remained separated for the remaining of the study duration. While this is an interesting finding, this endpoint was set up as exploratory, it is unclear whether this is the appropriate population to study for assessment of renal protective effect of the study drug. In addition, the component that most overwhelmingly contributed to the total number of events for the composite endpoint of "new or worsening nephropathy", new onset macroalbuminuria, is influenced by additional factors such as glucose control, and a repeat measurement might yield different results. In addition, the effects of empagliflozin on albuminuria appear to be hemodynamic as the decrease in albuminuria correlates with the decrease in systolic blood pressure and eGFR, and there is an increase of urine albumin to creatinine ratio after treatment discontinuation back to baseline.

The corresponding Kaplan-Meier figure for new onset macroalbuminuria is very similar to the one presented for the composite endpoint in Figure 9.

Figure 9 Kaplan-Meier estimation of time to first new or worsening nephropathy, all empagliflozin vs. placebo – TS



Source: Figure 15.2.4.2.4: 1 study report NDA 204629, SDN 406

The results for time to first new or worsening nephropathy were generally consistent across subgroups by baseline characteristics such as age, sex, renal function, glucose control, and baseline medication use.

A statistically significant difference for the composite microvascular outcome was also seen (HR vs. placebo 0.62, 95% CI 0.54, 0.70; Table 40), but this was due to the 'new or worsening nephropathy' composite component. There were too few clinical events to make meaningful conclusions on the clinical endpoints (i.e., the retinopathy related endpoints). As I already discussed, the clinical relevance of the 'new or worsening nephropathy' composite is unclear.

Table 40 Results of Cox regression analyses for 'microvascular outcome' composite

	N	n	%	Rate/1000 pt-yrs	HR (95% CI)	p-value
Composite microvascular outcome						
- Placebo	2068	424	20.5	83.6		
- All Empa	4132	577	14	52.8	0.62 (0.54, 0.70)	< 0.0001
Components of microvascular composite						
New or worsening nephropathy'						
- Placebo	2061	388	18.8	76		

- All Empa	4124	525	12.7	47.8	0.61 (0.53, 0.70)	< 0.0001
Initiation of retinal photocoagulation						
- Placebo	2333	29	1.2	4.4		
- All Empa	4687	41	0.9	3	0.69 (0.43, 1.12)	0.1337
Vitreous hemorrhage						
- Placebo	2333	16	0.7	2.4		
- All Empa	4687	30	0.6	2.2	0.93 (0.51, 1.71)	0.8147
Diabetes related blindness						
- Placebo	2333	2	0.1	0.3		
- All Empa	4687	4	0.1	0.3	--	--

N = number analyzed; n = number with event; Rate/1000 pt-yrs = events per 1000 patient years; HR = hazard ratio vs. placebo; CI = confidence interval; eGFR = estimated glomerular filtration rate
Source: Adapted from Table 11.1.2.7: 1, Table 11.1.2.8.1: 1 and Table 11.1.2.9: 1 of the study report NDA 204629, SDN 406

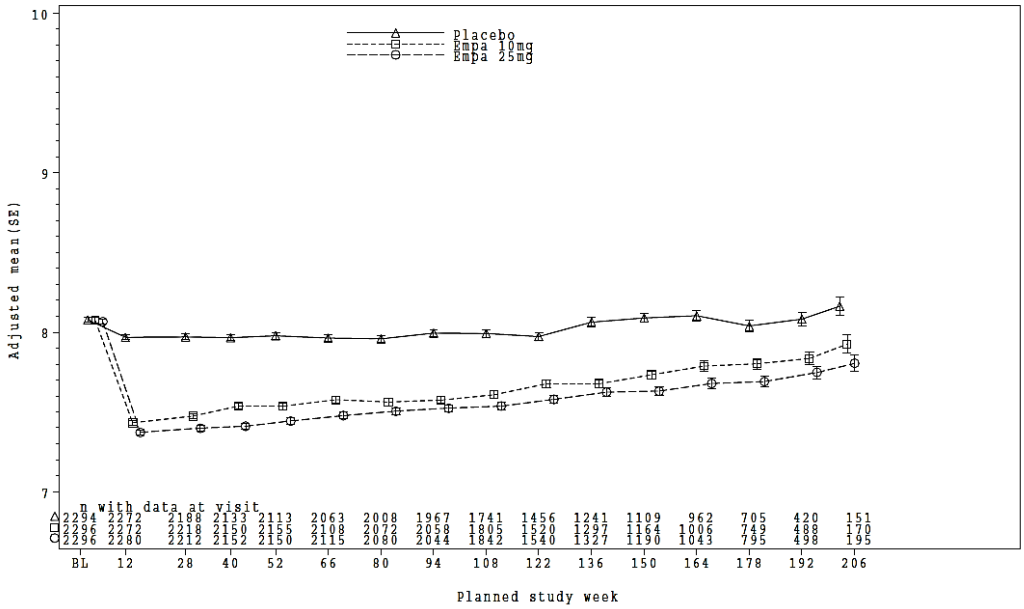
For details regarding the effect of empagliflozin on nephropathy endpoints please see Nephrology consult by Dr Kimberly Smith.

HbA1c

Notably, per the trial protocol, background antidiabetic medications were not to be adjusted up to week 12 if possible. After week 12, the background antidiabetic medication was to be changed based on the investigators' clinical judgment to achieve glycemic control in accordance to local guidelines. HbA1C was analyzed until end of treatment, but also specifically up to week 94. This period corresponds to the treatment time all patients could have reached in this trial. The period of 94 weeks was not pre-specified in the CTP but calculated after the close-out date of the trial had been determined. For HbA1c, analyses of the on-treatment period included values until 7 days after the last permanent treatment stop date.

At baseline, HbA1C was similar between the study arms. As seen in Figure 10 below, both empagliflozin arms resulted in a similar decrease in HbA1C at 12 weeks while the placebo arm remained relatively unchanged. This was expected since diabetes medications were not to be adjusted during the first weeks. However, this difference between the placebo and empagliflozin arms was sustained for the duration of the trial, with no further significant changes to either treatment arm. In the model below, all HbA1C values, including the post-rescue values were included.

Figure 10 Adjusted Mean HbA1c [%] Over Time - MMRM FAS (OC-AD)



Source: Figure 15.2.4.3.1.3: 2 study report NDA 204629, SDN 406

The placebo arm HbA1c at 94 weeks, and the end of the trial, did not show any significant changes in HbA1C compared to baseline, while the empagliflozin arms still carried the advantage obtained in the first 12 weeks of the trial. In this context, it is questionable whether the treatment arms were treated to an equal goal throughout this study, since no effort appears to have been made for optimization of diabetes treatment in the placebo arm. It does appear that more patients in the placebo arm received additional diabetes medications throughout the course of the trial when compared to the empagliflozin (Table 41).

Table 41 Frequency [N(%)] of Patients with Antidiabetic Therapies at Baseline and Time of Event / Censoring - TS

	Placebo		Empa 10mg		Empa 25mg		All Empa	
	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)
Number of patients analysed	2333 (100.0)		2345 (100.0)		2342 (100.0)		4687 (100.0)	
Metformin	1734 (74.3)	1738 (74.5)	1729 (73.7)	1747 (74.5)	1730 (73.9)	1716 (73.3)	3459 (73.8)	3463 (73.9)
Sulfonylurea	992 (42.5)	1074 (46.0)	985 (42.0)	997 (42.5)	1029 (43.9)	1004 (42.9)	2014 (43.0)	2001 (42.7)
Glitazone	101 (4.3)	134 (5.7)	96 (4.1)	99 (4.2)	102 (4.4)	104 (4.4)	198 (4.2)	203 (4.3)
A-glucosidase inhib	75 (3.2)	94 (4.0)	77 (3.3)	88 (3.8)	83 (3.5)	94 (4.0)	160 (3.4)	182 (3.9)
Glinide	38 (1.6)	58 (2.5)	58 (2.5)	68 (2.9)	54 (2.3)	62 (2.6)	112 (2.4)	130 (2.8)
DPP-IV inhibitor	267 (11.4)	425 (18.2)	282 (12.0)	392 (16.7)	247 (10.5)	339 (14.5)	529 (11.3)	731 (15.6)
GLP-1 agonist	70 (3.0)	116 (5.0)	68 (2.9)	89 (3.8)	58 (2.5)	85 (3.6)	126 (2.7)	174 (3.7)
Insulin	1135 (48.6)	1376 (59.0)	1132 (48.3)	1243 (53.0)	1120 (47.8)	1200 (51.2)	2252 (48.0)	2443 (52.1)
Other antidiabetics	29 (1.2)	48 (2.1)	25 (1.1)	38 (1.6)	26 (1.1)	47 (2.0)	51 (1.1)	85 (1.8)

Source: Table 24.1.1 Response to information request April 8, 2016, sequence number 128

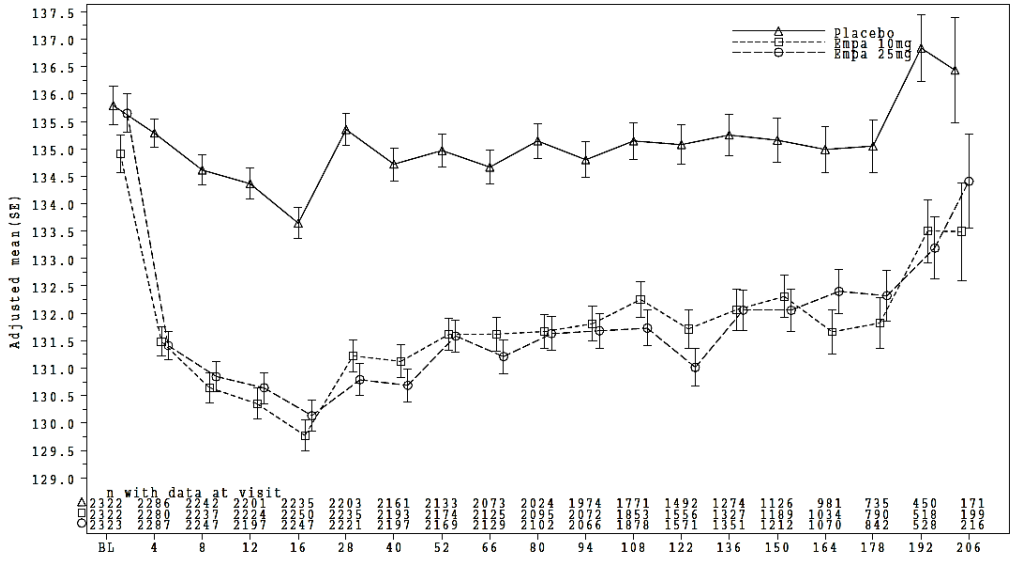
Blood pressure

Analyses of blood pressure for the on-treatment period included values until 1 day after the last permanent treatment stop date.

Systolic blood pressure

The baseline mean systolic blood pressure was similar between the treatment groups. When analyzing the entire on-treatment period with the MMRM model for the TS (OC), reductions were observed for the adjusted mean SBP in both empagliflozin groups compared to placebo. No significant changes in SBP were seen in the placebo arm. The changes in systolic blood pressure were noted starting at week 4, and were maintained for most of the rest of the study (Figure 11).

Figure 11 SBP (mmHg) MMRM Results Over Time - Treated Set (OC-AD)

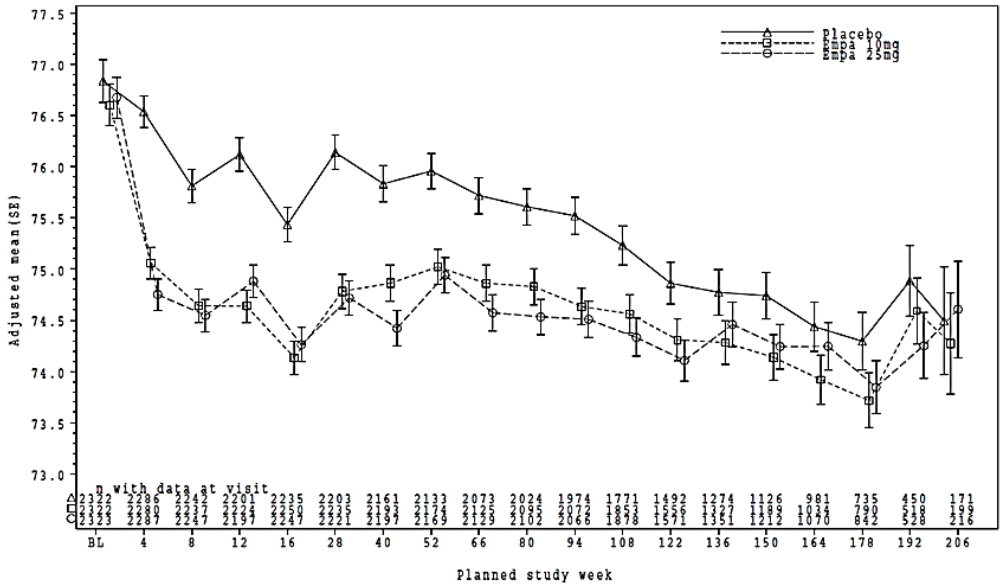


Source: Figure 15.2.4.3.5.3: 2 study report NDA 204629, SDN 406

Diastolic blood pressure

The changes in DBP were similar to what was observed for SBP, with empagliflozin arms resulting in a small reduction in DBP over time compared to placebo. However, a decrease in DBP was seen over time in the placebo arm as well. The decrease was seen early in the study, starting with week 4.

Figure 12 DBP (mmHg) MMRM results over time - treated set (OC-AD)



Source: Figure 15.2.4.3.6.3: 2 NDA 204629, SDN 406

The findings regarding changes in blood pressure with empagliflozin are consistent with the findings in the original empagliflozin NDA, and with the mechanism of action of empagliflozin which effectively acts as a diuretic. In all treatment arms, most patients were on an anti-hypertensive medication at baseline (95.2% of the placebo patients, and 94.9% of the all empa patients). This was expected considering the population enrolled in this trial. Surprisingly, only 64.2% of the placebo patients, and 65.2% of the empagliflozin patients were on beta-blockers at baseline, and the percentage did not change significantly throughout the trial for either treatment arm. The use of diuretics as increased slightly in the placebo group from 42.3% of patients at baseline to 46.3% of patients at censoring, while the use of diuretics has been relatively stable in the empagliflozin arms (from 43.7% at baseline to 43.9% of patients at censoring). This is in the context where all patients in the empagliflozin groups were taking a medication acting as a diuretic (empagliflozin).

It is not clear whether the small changes observed in blood pressure with empagliflozin compared to placebo contributed to the overall improvement in CV death seen with empagliflozin in this study.

Table 42 Frequency [N(%)] of patients with concomitant therapies at baseline and time of event / censoring - TS

	Placebo		Empa 10mg		Empa 25mg		All Empa	
	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)	At baseline N (%)	At event /censor N (%)
Number of patients analysed	2333 (100.0)		2345 (100.0)		2342 (100.0)		4687 (100.0)	
Antihypertensives	2221 (95.2)	2235 (95.8)	2227 (95.0)	2218 (94.6)	2219 (94.7)	2217 (94.7)	4446 (94.9)	4435 (94.6)
Beta-blockers	1498 (64.2)	1536 (65.8)	1530 (65.2)	1534 (65.4)	1526 (65.2)	1539 (65.7)	3056 (65.2)	3073 (65.6)
Beta-blockers prim. for rhythm control	9 (0.4)	8 (0.3)	12 (0.5)	15 (0.6)	14 (0.6)	17 (0.7)	26 (0.6)	32 (0.7)
Diuretics	988 (42.3)	1081 (46.3)	1036 (44.2)	1038 (44.3)	1011 (43.2)	1019 (43.5)	2047 (43.7)	2057 (43.9)
ACE inhibitors/ARBs	1868 (80.1)	1882 (80.7)	1896 (80.9)	1889 (80.6)	1902 (81.2)	1864 (79.6)	3798 (81.0)	3753 (80.1)
ACE inhibitors	1154 (49.5)	1090 (46.7)	1187 (50.6)	1130 (48.2)	1208 (51.6)	1158 (49.4)	2395 (51.1)	2288 (48.8)
ARBs	765 (32.8)	845 (36.2)	763 (32.5)	814 (34.7)	761 (32.5)	778 (33.2)	1524 (32.5)	1592 (34.0)
Calcium channel blockers	788 (33.8)	901 (38.6)	781 (33.3)	787 (33.6)	748 (31.9)	786 (33.6)	1529 (32.6)	1573 (33.6)
Mineralocorticoid receptor antagonists	136 (5.8)	176 (7.5)	157 (6.7)	168 (7.2)	148 (6.3)	159 (6.8)	305 (6.5)	327 (7.0)
Renin inhibitors	19 (0.8)	7 (0.3)	16 (0.7)	7 (0.3)	11 (0.5)	6 (0.3)	27 (0.6)	13 (0.3)
Other	191 (8.2)	248 (10.6)	193 (8.2)	211 (9.0)	190 (8.1)	230 (9.8)	383 (8.2)	441 (9.4)

Source: Table 17.1 Response to IR march 31, 2016, sequence number 126

6.1.4 Subpopulations

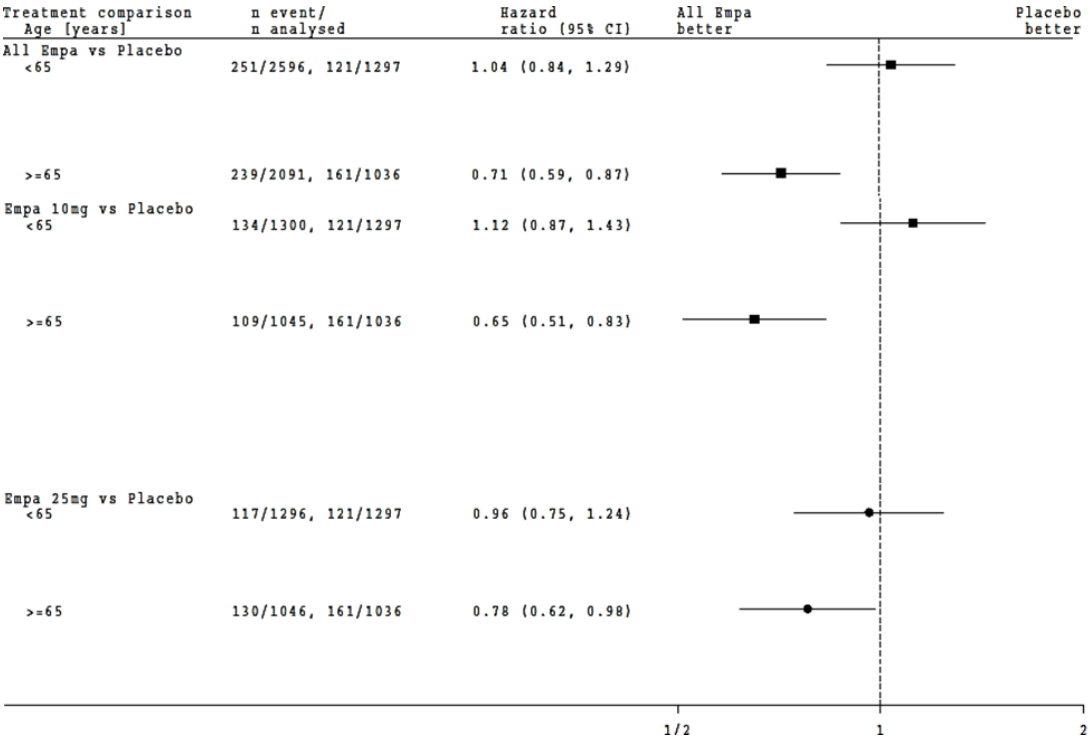
Below are subgroup analyses for the primary endpoint, and for other endpoints that are relevant for this review (although none of these were prespecified in the statistical analysis strategy).

For the 3-point MACE events, the Applicant reported that a nominal treatment-by-subgroup interaction p-value <0.05 was observed for the parameters age, weight, history of hypertension, and baseline HbA1c. However, subgroup analyses were not adjusted for multiple testing and small groups were included.

By age

As seen below, the results for 3-point MACE are only statistically significant for patients 65 years or older. In patients younger than 65, although the size of the subgroups and the number of events are comparable with patients 65 years and older, neither empagliflozin group (including pooled empa) was different from placebo. This may suggest that empagliflozin might benefit older patients with cardiovascular risk in particular, rather than the entire diabetic population with increased cardiovascular risk.

Figure 13 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by age - TS

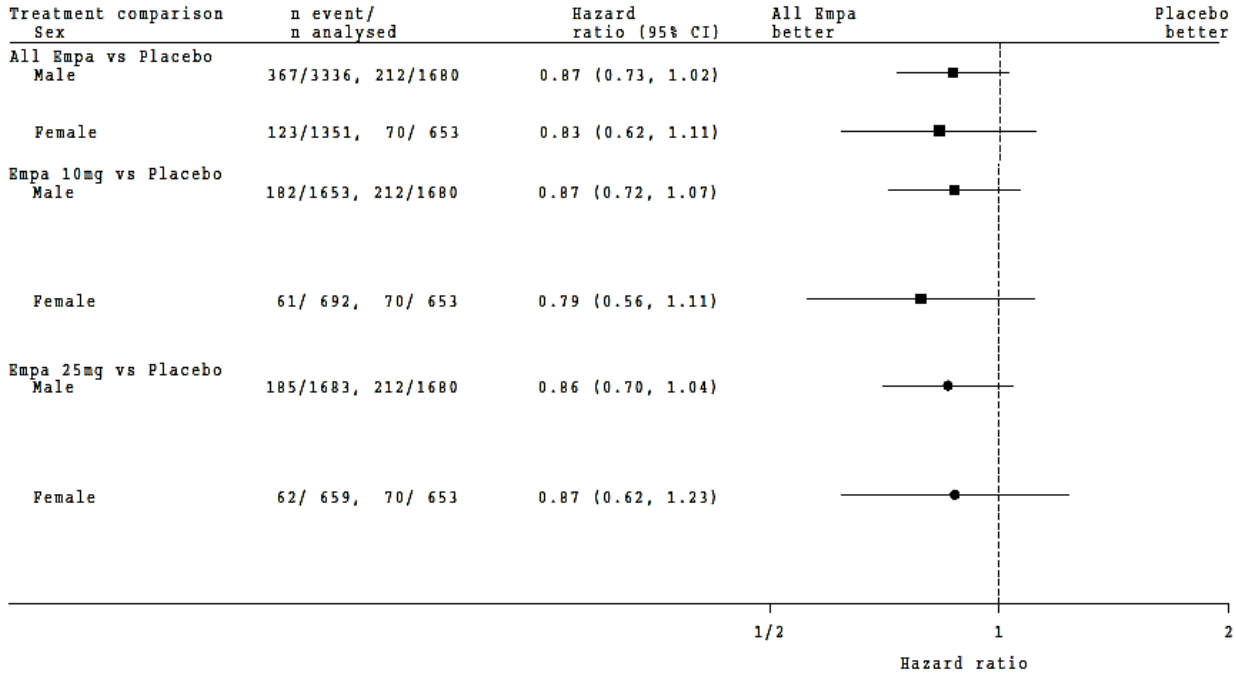


Source: Adapted from Figure 15.2.1.3.1.1:2 study report NDA 204629, SDN 406

By sex

No significant differences were observed between males and females with regard to the primary endpoint 3-point MACE. For both sexes, the HR for the primary endpoint was favorable to empagliflozin compared to placebo.

Figure 14 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by sex - TS

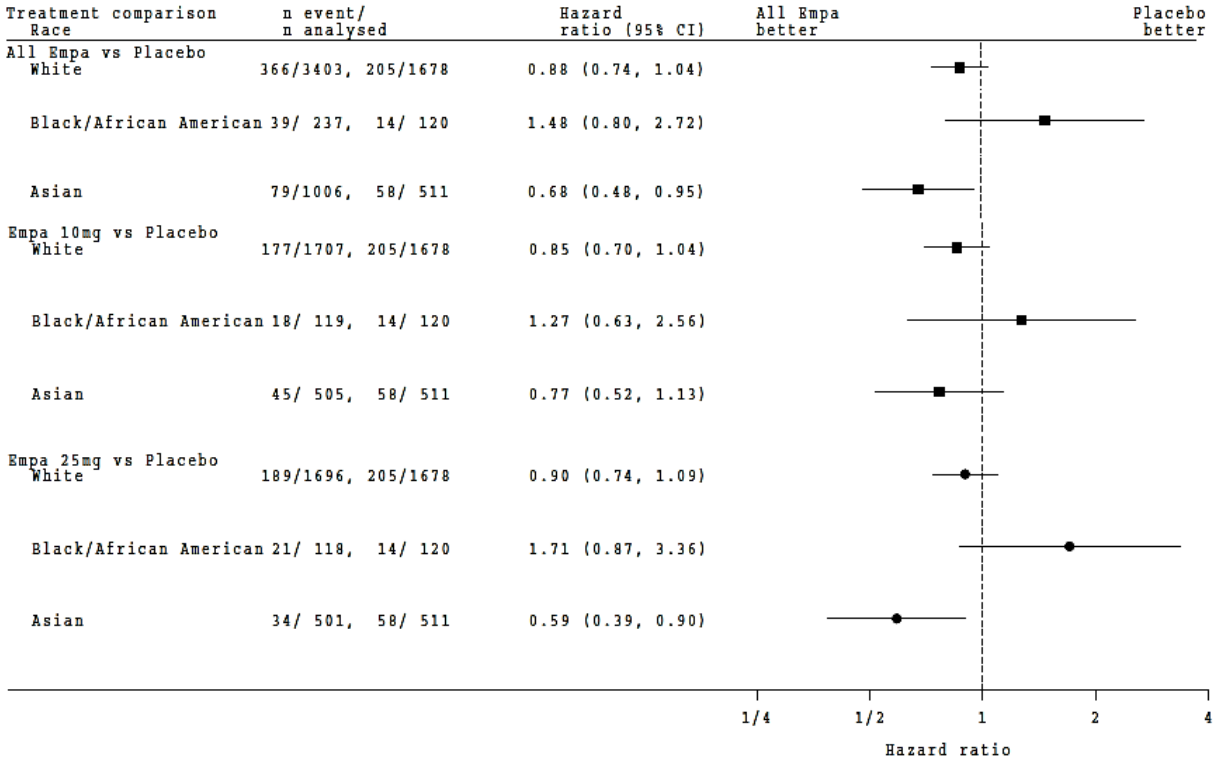


Source: Adapted from Figure 15.2.1.3.1.2: 2 study report NDA 204629, SDN 406

By race

The HR for 3-point MACE events was favorable for empagliflozin in White and Asian patients, while African American patients did not appear to benefit from empagliflozin. It is not clear whether this has any significance since the number of African American patients in this study was small.

Figure 15 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by race - TS

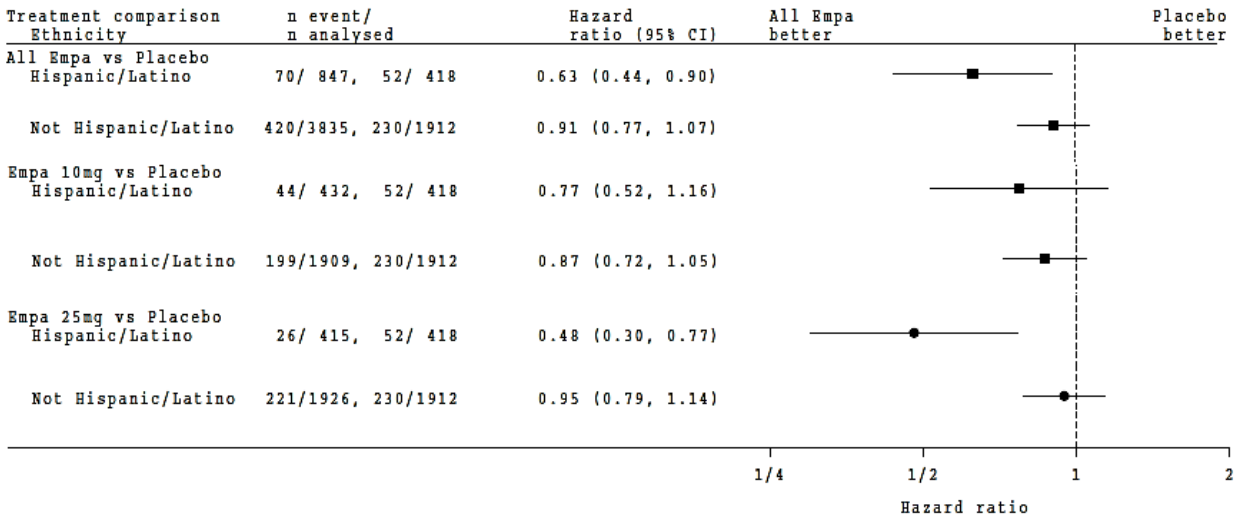


Source: Adapted from Figure 15.2.1.3.1.3: 2 study report NDA 204629, SDN 406

By ethnicity

The 3-point MACE event distribution by ethnicity and study treatment is presented below. There was overall no significant difference between Hispanic and not Hispanic patients.

Figure 16 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by ethnicity - TS



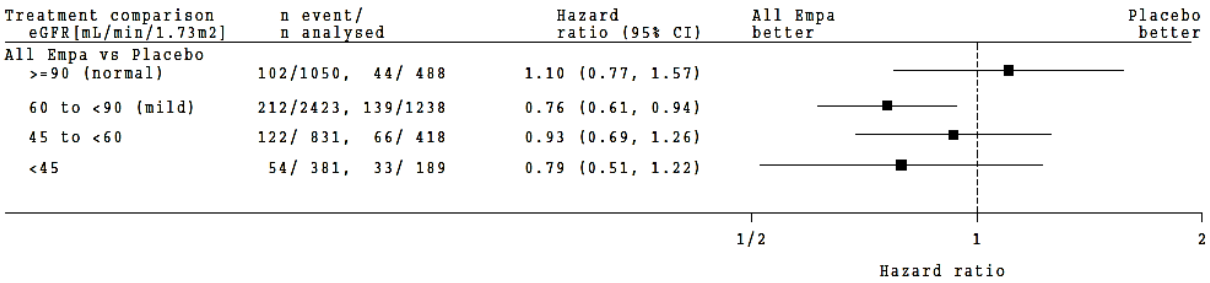
Source: Figure 15.2.1.3.1.4: 2 study report NDA 204629, SDN 406

By eGFR categories

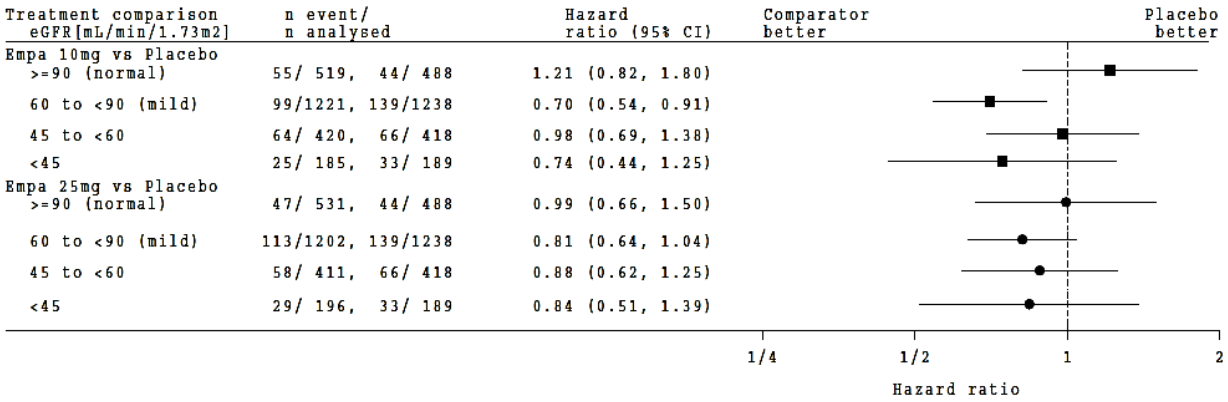
The patients with baseline normal renal function (eGFR >90 ml/min/1.73m^2) did not appear to benefit from taking empagliflozin with regard to 3-point MACE outcomes (Figure 17). The subgroup of patients that appeared to benefit the most from empagliflozin treatment were the patients with a baseline mild renal dysfunction. While it is difficult to interpret subgroup analyses, it is concerning that the findings for 3-point MACE are not reproducible across eGFR categories, and may suggest that empagliflozin may not benefit the entire T2DM population as selected in this study, but rather only certain subcategories.

Figure 17 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by eGFR categories – TS (A-all empa vs placebo, B-individual empa doses vs placebo)

A.



B.

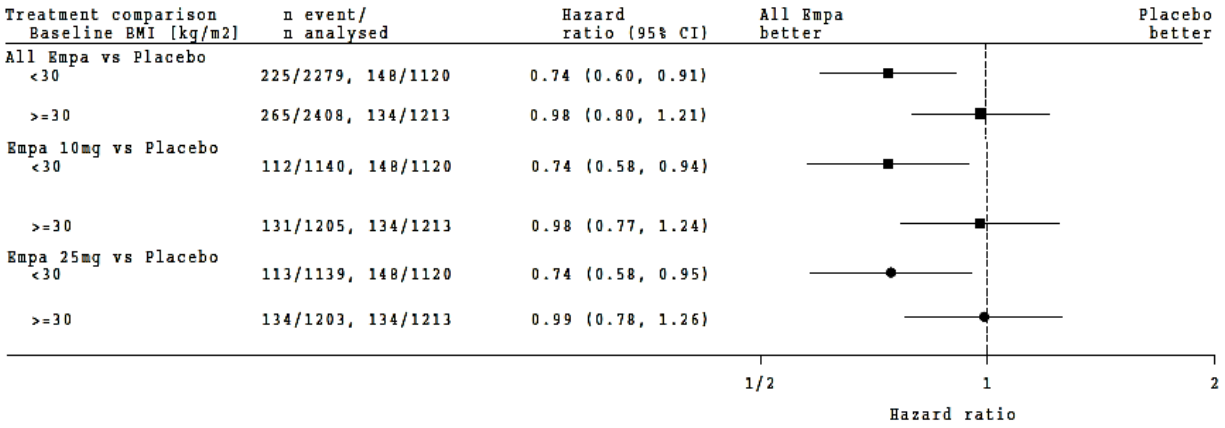


Source: Figures 15.2.1.3.7.2: 1 and 15.2.1.3.7.2: 2 study report NDA 204629, SDN 406

By BMI

It appears that patients with lower baseline BMI (<30 kg/m2) benefitted more from empagliflozin compared to the patients with higher BMI. Both BMI groups appeared to be almost equally represented in this study, however, for the US population, 72% of the patients on empagliflozin, and 73% of the patients on placebo, had a BMI ≥30 kg/m2. While this finding could still be due to chance, it is concerning because in the US, most patients with T2DM that take empagliflozin are likely to be obese. Regardless, no excess CV risk was seen with empagliflozin in obese patients.

Figure 18 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by BMI - TS

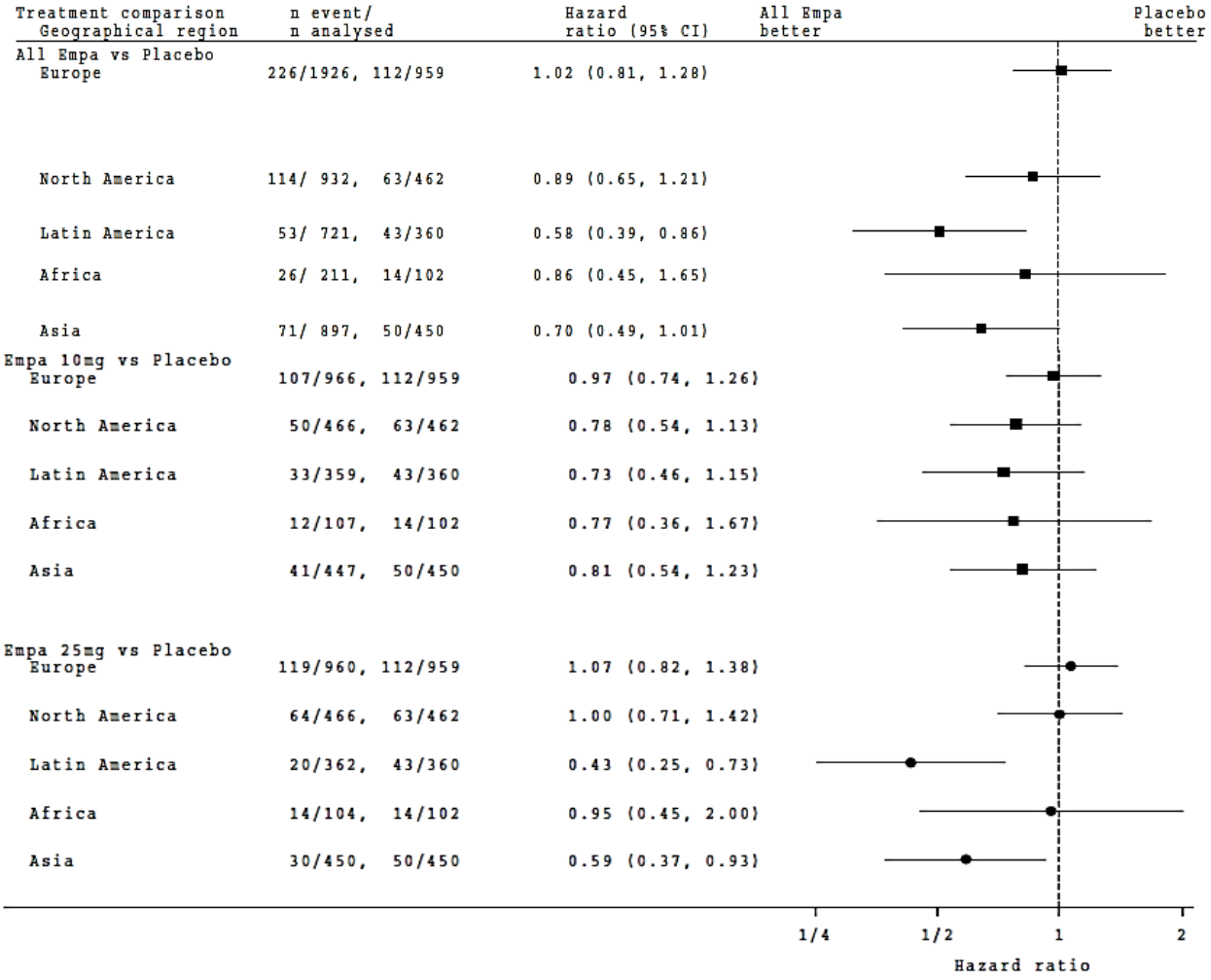


Source: Adapted from Figure 15.2.1.3.2.1: 2 study report NDA 204629, SDN 406

By geographical region

It appears that empagliflozin was neutral in terms of 3-point MACE events for patients from Europe, with almost half the patients in the study coming from Europe. The HR was less than 1 for all other geographical regions.

Figure 19 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by Geographical Region - TS

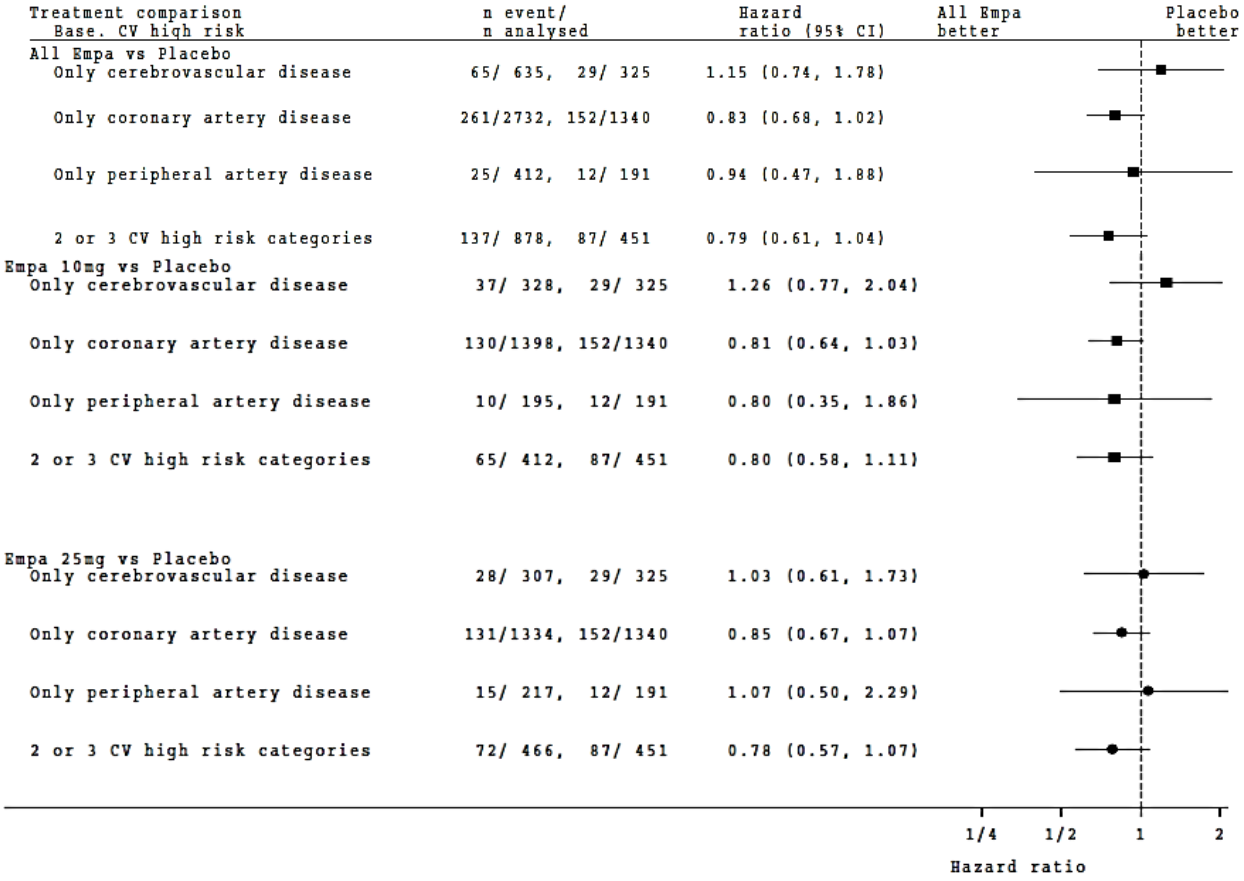


Source: Adapted from Figure 15.2.1.3.3.1: 2 study report NDA 204629, SDN 406

Baseline CV risk

In patients who had only cerebrovascular disease as a qualifying event for this study, it appears that empagliflozin did not offer an advantage over placebo for 3-point MACE events (HR >1 for pooled, and independent empagliflozin doses). The subgroups where empagliflozin was better than placebo were the patients with only coronary artery disease at baseline, and the patients with 2 or 3 high risk categories.

Figure 20 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by Baseline CV Risk - TS

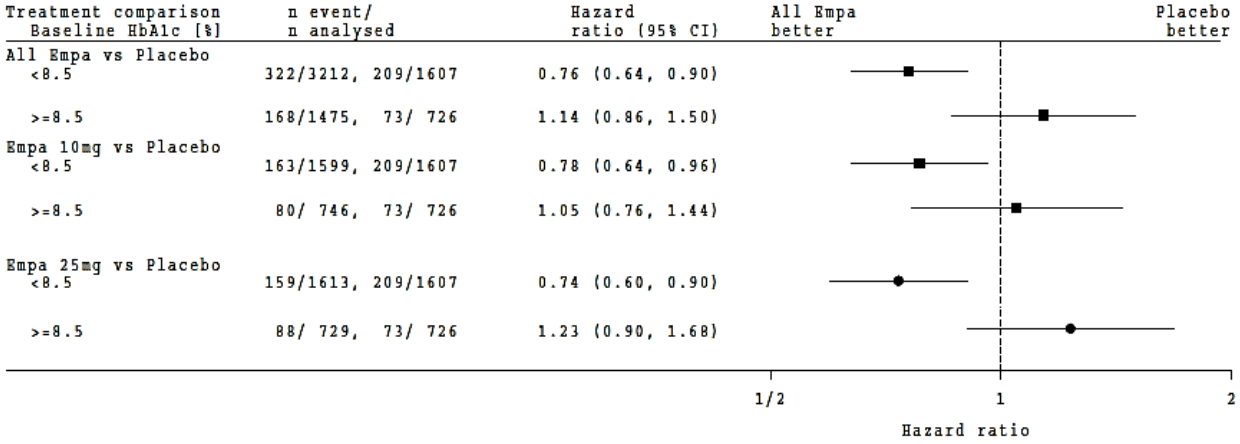


Source: Figure 15.2.1.3.4: 1, 15.2.1.3.4: 2 study report NDA 204629, SDN 406.

By baseline HbA1c

A large proportion of patients in this study had baseline HbA1C below 8.5%. As seen below in Figure 21, it appears that patients who had more uncontrolled diabetes at baseline (HbA1C >8.5%) did not see a significant difference between empagliflozin and placebo with regard to the 3-point MACE events, even more, the HR was above 1 for both empagliflozin doses, and the pooled empagliflozin arm.

Figure 21 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by Baseline HbA1c - TS

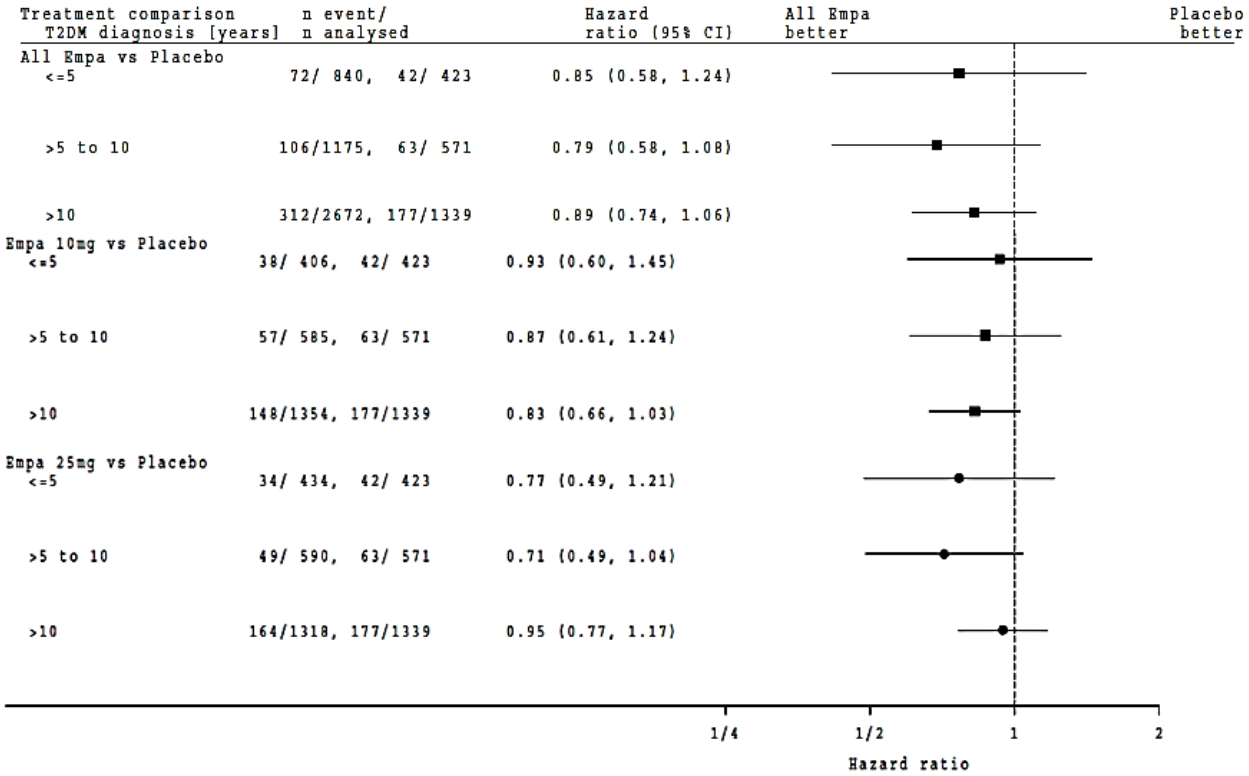


Source: Figure 15.2.1.3.5.1: 1, 15.2.1.3.5.1: 2 study report, NDA 204629, SDN 406

By time since the diagnosis of diabetes

No clear interaction can be seen between duration of diabetes and the results for 3-point MACE events (Figure 22).

Figure 22 Forrest plot of Cox regression HR (95%CI) of time to first event of 3-point MACE by Duration of Diabetes - TS



Source: Figure 15.2.1.3.5.2: 1, 15.2.1.3.5.2: 2 study report, NDA 204629, SDN 406

For further details, please see biometrics review by Dr Clark.

6.1.5 Analysis of Clinical Information Relevant to Dosing Recommendations

Empagliflozin is approved for use at 10 mg with a possibility of increasing to 25 mg daily if needed. In this efficacy supplement, the Applicant states that the relationship of drug dose or drug concentration to response was not investigated.

6.1.6 Discussion of Persistence of Efficacy and/or Tolerance Effects

No changes.

6.1.7 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The review of this efficacy supplement did not identify any new safety concerns for empagliflozin. The safety findings from EMPA-REG are overall in line with the current prescribing information for empagliflozin.

Exposure was similar in the treatment groups, and dropouts and discontinuations were balanced between the treatment groups.

There were fewer deaths in patients treated with empagliflozin compared to placebo, mostly due to a difference in cardiovascular death. Additionally, there were fewer 3-point, and 4-point adjudicated MACE events in the empagliflozin treated patients compared to placebo, also due to the favorable effect of empagliflozin on cardiovascular death.

There was no significant imbalance regarding the rate of hypoglycemia, including severe events. Overall fracture rates were also similar between treatment arms, although upper extremity fractures were more common with empaliflozin, and the Applicant noted that osteoporosis was more commonly reported in the empagliflozin arms compared to placebo. However, this was not a study that collected detailed information regarding osteoporosis, and bone density scans were not performed as part of the study.

As expected, genital infections were disproportionately represented in the patients treated with empagliflozin compared to placebo, and this is consistent with the current prescribing information. Diabetic ketoacidosis was also observed more frequently in the empagliflozin treated patients, but the total number of events is very small.

A decrease in eGFR was observed initially with empagliflozin, however, this appeared to be reversible with continued treatment. As a result, clinical renal events were more common in the empagliflozin groups for the first three months of treatment, but over the course of the trial there were slightly more events in the placebo arm compared to empagliflozin. While it is not clear whether empagliflozin has a renal protective effect in the long run, I remain concerned regarding the possibility of acute renal events early after the initiation of empagliflozin treatment.

Liver events were adjudicated for causality in this study. While there were more liver events in the placebo arm compared to the pooled empagliflozin arm, severe liver events were more common in the empagliflozin arm. In addition, events adjudicated as possibly related to the study drug (3 events) or indeterminate (2 events) were only in the empagliflozin groups. Review of the narratives revealed limited information and it made it difficult to ascertain whether these

events were truly related to the empagliflozin treatment. In addition, there were seven patients, six on empagliflozin and one on placebo, who had liver laboratories suggestive of Hy's law, and were all determined to be unlikely related to the study drug by the adjudication committee. In most of these cases there were other potential causes for the liver abnormality. One patient on empagliflozin did not have any potential alternative etiology for the liver function elevation, however, the liver laboratories normalized in two days, which may be suggestive of lab error. Overall, more events that were potentially drug related were found in the empagliflozin treated patients, however, most had potentially alternative etiology. In all cases except for one, the study drug was not discontinued because of the liver event. In the one case that led to study drug discontinuation, the patient was also taking simvastatin, and ciprofloxacin, which were both discontinued at the time of the event. I do not find that there is conclusive evidence in this study that empagliflozin causes liver injury.

Malignancy events were also adjudicated for causality, due to imbalances observed in the empagliflozin development program. While overall events were balanced between the treatment groups, bladder, pancreatic cancer, and melanoma were observed disproportionately more in the empagliflozin treated patients compared to placebo.

Small, sustained, increases in hemoglobin and hematocrit were observed with empagliflozin, which was not reflected in a difference in thromboembolic events overall. However, strokes were seen more frequently in the patients on empagliflozin compared to placebo, although the results were not statistically significant.

Also, dose-dependent small increases in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were observed with empagliflozin compared to placebo.

7.1 Methods

Issues and concerns identified from the clinical study report safety section were addressed by the in-depth review of the narratives and datasets. JReview and MAED were used to confirm the Applicant's findings, for additional analyses, and for reviewer-generated tables.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 5.1 for a description of the clinical trial (1245.25) pertinent to this review. The safety review in this section addresses data from the entire duration of the study for the purpose of estimating incidences of adverse events and focuses on serious adverse events and unusual patterns or trends.

7.1.2 Categorization of Adverse Events

Safety data were analyzed descriptively for all patients who took at least one dose of randomized trial medication (TS). The Applicant presented the safety data according to the randomized treatment group, and, while this is unusual, there were only a few patients who took study medication other than as randomized, and using randomized treatment groups is unlikely to bias the analyses. Narratives were provided for all deaths, SAEs, AEs leading to discontinuation, pregnancies, and cardiovascular outcome events. In addition, narratives were provided for some AESIs as follows: potential Hy's law cases; ALT/AST >5 x ULN, creatinine increase >2 x baseline value and >ULN; acute renal failure (based on SMQ); urosepsis; pyelonephritis; malignancies; volume depletion. For other AESIs, case narratives were prepared only if the events were serious or led to discontinuation of study medication.

Preferred terms for adverse events were finally coded using MedDRA version 18.0, although various MedDRA versions were used for collecting events throughout the trial. The analyses of AEs were based on patients with events occurring during the on-treatment period (i.e. those reported with an onset from the first dose of randomized study medication until treatment stop + 7 days). Additionally, summaries of hepatic injury AEs were presented for the period up to 30 days after last dose of study medication and bone fractures and malignancies up to individual trial termination following an ITT approach.

Cardiovascular and microvascular events were analyzed as efficacy endpoints, but they were also included in the AE analyses.

Reviewer comment: Analysis of AE coding performed by the FDA Jumpstart program team did not reveal any concerns regarding coding. However, I have identified the following issues that pertain to coding: when trying to explore a potential issue of amputations, I noted that there were no preferred terms that were suggestive of amputations, while over 100 patients were identified based search of narratives and comments. In addition, when searching for patients who experienced renal events during the trial, I noticed that a sizeable number of patients were coded to PT diabetic nephropathy, and nephrotic syndrome. Review of a few selected narratives revealed that some of these events were actually acute kidney injury events that should have been classified appropriately. However, I believe that this heterogeneity in coding could be due to MedDRA itself rather than intentional miscoding.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Safety data were analyzed descriptively for all patients who took at least one dose of randomized trial medication (TS) or open-label medication (OLS).

Total exposure was also similar across randomized treatment groups, with a mean (SD) exposure of 2.46 years (1.03) in the placebo group, and 2.56 years (1.03) in the pooled empagliflozin group. The median exposure was 2.57 years in the placebo group, and 2.61 in the pooled empagliflozin group.

Treatment compliance was assessed at each visit based on tablet count of dispensed and returned medication. The Applicant reported that in the placebo group, 91.2% of patients achieved an overall compliance of 80 to 120%; proportions in the empagliflozin treatment groups were very similar (10 mg: 91.8%, 25 mg: 91.8%).

7.2.2 Explorations for Dose Response

There was no exploration of dose response in this study as the doses of empagliflozin were pooled for the primary analysis.

7.2.3 Special Animal and/or In Vitro Testing

No additional preclinical data were submitted for the purpose of this efficacy supplement.

7.2.4 Routine Clinical Testing

Routine testing that took place as part of the clinical study included measurement of vital signs (including weight), and laboratory testing (including measures of glycemic control, renal function, serum electrolytes, hematologic parameters, and liver enzymes).

7.2.5 Metabolic, Clearance, and Interaction Workup

No new information was submitted for this efficacy supplement.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

From the previous reviews of SGLT2 inhibitors, including empagliflozin, some potential adverse events were identified. Adverse events of concern included fractures, changes in plasma lipids, volume depletion events, decreased renal function, genitourinary infections, DILI, malignancies (specifically bladder), and incidence of early cardiovascular events. In addition, diabetic ketoacidosis and urosepsis have emerged as a postmarketing concern in patients with type 2 diabetes treated with SGLT2 inhibitors and recently resulted in a safety labeling change issued on December 4, 2015.

More recently, we were made aware of a safety signal of increased risk of lower limb amputations with canagliflozin in the CANVAS trial (Drug Safety Communication dated May 18, 2016).

7.3 Major Safety Results

7.3.1 Deaths

The Applicant reported that 463 patients died during the study, 194 in the placebo arm, and 269 in the pooled empagliflozin arms (treated set, all-cause mortality). The majority of all deaths were labeled as CV deaths (137 patients in placebo, and 172 patients in the pooled empagliflozin arms). Non CV death occurred in 57 patients in the placebo arm, and 97 patients in the pooled empagliflozin arms. As seen in Table 43 below, for non-CV death, the hazard ratio of all empagliflozin vs. placebo was also below 1, indicating that the reduced risk of CV death for all empagliflozin was not accompanied by an increased risk of non-CV death. Non-CV death occurred most commonly due to events in the system organ class 'benign, malignant and unspecified neoplasms (incl. cysts and polyps)' and 'infections and infestations'.

Table 43 Overview of all-cause mortality and CV death (TS, OS)

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
CV death				
Analyzed patients (TS), N (100%)	2333	2345	2342	4687
Patients with event, N (%)	137 (5.9)	90 (3.8)	82 (3.5)	172 (3.7)
Incidence rate per 1000 years at risk	20.2	13.0	11.8	12.4
Hazard ratio vs. placebo (95% CI)		0.65 (0.50, 0.85)	0.59 (0.45, 0.77)	0.62 (0.49, 0.77)
p-value		0.0016	0.0001	<0.0001
Analyzed patients (OS), N (100%)	2308	2306	2301	4607
Patients with event up to treatment stop + 30 days, N (%)	90 (3.9)	62 (2.7)	50 (2.2)	112 (2.4)
Incidence rate per 1000 years at risk	15.2	10.1	8.1	9.1
Hazard ratio vs. placebo (95% CI)		0.67 (0.48, 0.92)	0.53 (0.37, 0.74)	0.60 (0.45, 0.79)
All-cause mortality				
Analyzed patients (TS), N (100%)	2333	2345	2342	4687
Patients with event, N (%)	194 (8.3)	137 (5.8)	132 (5.6)	269 (5.7)
Incidence rate per 1000 years at risk	28.6	19.8	19.0	19.4
Hazard ratio vs. placebo (95% CI)		0.70 (0.56, 0.87)	0.67 (0.54, 0.83)	0.68 (0.57, 0.82)
p-value		0.0013	0.0003	<0.0001
Analyzed patients (OS), N (100%)	2308	2306	2301	4607
Patients with event up to treatment stop + 30 days, N (%)	109 (4.7)	84 (3.6)	74 (3.2)	158 (3.4)

Incidence rate per 1000 years at risk	18.4	13.7	12.0	12.8
Hazard ratio vs. placebo (95% CI)		0.75 (0.56, 0.99)	0.64 (0.48, 0.87)	0.69 (0.54, 0.89)
Non-CV death (TS), N (100%)	2333	2345	2342	4687
Patients with event, N (%)	57 (2.4)	47 (2.0)	50 (2.1)	97 (2.1)
Incidence rate per 1000 years at risk	8.4	6.8	7.2	7.0
Hazard ratio vs. placebo (95% CI)		0.81 (0.55, 1.20)	0.86 (0.59, 1.26)	0.84 (0.60, 1.16)

Source: Table 11.1.2.2: 1 Study report NDA 204629, SDN 406

Reviewer comment: I reviewed selected narratives for fatal events, the review did raise a few issues regarding the cause of death. In many cases labeled as not-assessable CV death, the Applicant did not collect sufficient information to clarify the cause of death. As I have already discussed in the efficacy section, this is concerning because this study has a very large proportion of deaths labeled as not assessable and could therefore be considered missing data. Regardless, removing the non-assessable deaths does not change the results for CV death. In addition, ACM analysis also significantly favors empagliflozin vs placebo.

7.3.2 Nonfatal Serious Adverse Events

The Applicant provided a listing of SAEs by treatment, primary system organ class and preferred term for the TS, as well as case narratives. The Applicant submitted incidence rates of SAEs (which included fatal and non-fatal SAEs) were slightly lower for patients treated with empagliflozin compared to patients treated with placebo, largely due to a lower incidence rates of serious cardiac disorders in the empagliflozin groups compared with placebo. My JReview analysis of the datasets revealed data that was identical with the Applicant provided table.

Overall 988 (42.3%) of the patients in the placebo group experiences an SAE, and 1789 (38.2%) of patients in the pooled empagliflozin group. The incidence rates for all SAEs in either treatment group by SOC is presented in Table 44 below.

Table 44 Frequency of Patients with Serious Adverse Events by SOC and Treatment Arm

System Organ Class	All Empa	Placebo
Cardiac disorders	652 (13.9%)	398 (17.1%)
Infections and infestations	360 (7.7%)	213 (9.1%)
Nervous system disorders	306 (6.5%)	159 (6.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	219 (4.7%)	87 (3.7%)
Vascular disorders	191 (4.1%)	116 (5.0%)
Gastrointestinal disorders	169 (3.6%)	85 (3.6%)
General disorders and administration site conditions	154 (3.3%)	94 (4.0%)
Musculoskeletal and connective tissue disorders	135 (2.9%)	78 (3.3%)
Injury, poisoning and procedural complications	129 (2.8%)	77 (3.3%)

Renal and urinary disorders	112 (2.4%)	73 (3.1%)
Respiratory, thoracic and mediastinal disorders	101 (2.2%)	75 (3.2%)
Metabolism and nutrition disorders	79 (1.7%)	61 (2.6%)
Hepatobiliary disorders	51 (1.1%)	19 (0.8%)
Skin and subcutaneous tissue disorders	48 (1.0%)	29 (1.2%)
Eye disorders	43 (0.9%)	21 (0.9%)
Reproductive system and breast disorders	33 (0.7%)	11 (0.5%)
Investigations	33 (0.7%)	29 (1.2%)
Blood and lymphatic system disorders	29 (0.6%)	17 (0.7%)
Surgical and medical procedures	27 (0.6%)	16 (0.7%)
Psychiatric disorders	19 (0.4%)	15 (0.6%)
Ear and labyrinth disorders	16 (0.3%)	15 (0.6%)
Endocrine disorders	7 (0.1%)	2 (0.1%)
Immune system disorders	6 (0.1%)	3 (0.1%)
Congenital, familial and genetic disorders	4 (0.1%)	4 (0.2%)
Social circumstances	1 (0.0%)	0 (0.0%)
Total patients with events	**1789 (38.2%)**	**988 (42.3%)**

Source: Reviewer generated using JReview, ADAE, and ADSL datasets, NDA 204629, SDN 406

In order to offer a better perspective regarding the serious events in this trial, Table 45 below also presents the SAEs that occurred >1% in either treatment arm by HLT.

Table 45 Frequency of Patients with Serious Adverse Events by HLT and Treatment Arm

High Level Term	**All Empa**	**Placebo**
Ischemic coronary artery disorders	417 (8.9%)	215 (9.2%)
Central nervous system hemorrhages and cerebrovascular accidents	165 (3.5%)	75 (3.2%)
Heart failures NEC	140 (3.0%)	106 (4.5%)
Lower respiratory tract and lung infections	106 (2.3%)	71 (3.0%)
Peripheral vasoconstriction, necrosis and vascular insufficiency	103 (2.2%)	43 (1.8%)
Pain and discomfort NEC	83 (1.8%)	39 (1.7%)
Coronary artery disorders NEC	75 (1.6%)	59 (2.5%)
Renal failure and impairment	63 (1.3%)	48 (2.1%)
Supraventricular arrhythmias	60 (1.3%)	29 (1.2%)
Abdominal and gastrointestinal infections	57 (1.2%)	25 (1.1%)
Bacterial infections NEC	56 (1.2%)	34 (1.5%)
Transient cerebrovascular events	53 (1.1%)	23 (1.0%)
Non-site specific injuries NEC	47 (1.0%)	28 (1.2%)
Death and sudden death	39 (0.8%)	23 (1.0%)
Urinary tract infections	39 (0.8%)	25 (1.1%)
Skin and subcutaneous tissue ulcerations	37 (0.8%)	23 (1.0%)
Ventricular arrhythmias and cardiac arrest	28 (0.6%)	30 (1.3%)
Infections NEC	28 (0.6%)	24 (1.0%)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets, NDA 204629, SDN 406

Overall, a lower proportion of patients in the empagliflozin pooled group had an SAE consistent with ischemic coronary artery disorders, heart failures, coronary arterydisorders, ventricular arrhythmias and cardiac arrest compared to the placebo group. In contrast, there were more central nervous system haemorrhages and cerebrovascular accidents and transient cerebrovascular events in the empagliflozin group compared to placebo.

Surprisingly, renal failure and renal impairment events were more frequent in the placebo group (2.1%) compared to the pooled empagliflozin group (1.3%).

Although not represented in the above tables, serious events of diabetic ketoacidosis (DKA) were reported in four patients in the pooled empagliflozin group (0.09%) and none in the placebo group.

The applicant also presented data for the SAEs that led to death or were immediately life threatening and noted that the overall incidence rates for immediately life threatening SAEs (and for immediately life threatening cardiac disorders) were slightly higher in the empagliflozin groups than in the placebo group (incidence rates for cardiac disorders: empagliflozin 10 mg: 0.47/100 pt-yrs; empagliflozin 25 mg: 0.57/100 pt-yrs; placebo: 0.40/100 pt-yrs). The incidence rates for fatal and/or immediately life threatening SAEs overall (and for cardiac disorders) were lower for both empagliflozin groups than for the placebo group (incidence rates for cardiac disorders empagliflozin 10 mg: 0.88/100 pt-yrs; empagliflozin 25 mg: 0.98/100 pt-yrs; placebo: 1.16/100 pt-yrs). Details regarding cardiovascular SAE are covered in the efficacy section of this review as part of the study endpoints.

Reviewer comment: The overall safety of empaglflozin in EMPA-REG appears consistent with the information present in the prescribing information.

7.3.3 Dropouts and/or Discontinuations

The clinical trial protocol stated that, if a patient discontinued the trial medication for any reason (including due to an AE), the patient could subsequently restart the trial medication unless there was some underlying condition that discouraged its reintroduction. As a result, the summary of AEs leading to discontinuation of study medication includes patients who only temporarily discontinued the study medication. Narratives were provided for all patients with AEs leading to discontinuation. I evaluated selected narratives, and did not identify any concerning issues.

There were 453 patients in the placebo group (19.4%) who had the study medication discontinuation due to an AE, and 813 patients (17.4%) in the pooled empagliflozin group. On the PT level, the most frequently reported AEs leading to discontinuation were myocardial infarction and acute myocardial infarction. PTs and HLTs responsible for at least 0.5%

discontinuations in either treatment group are presented in Table 46 and Table 47 below. There were no marked imbalances between the empagliflozin and placebo treatment groups with regard to incidence rates for PTs, and HLTs leading to discontinuation of study medication.

Table 46 Adverse Events Leading to Discontinuation by Preferred Term, and Treatment Arm

Preferred Term	All Empa	Placebo
Myocardial infarction	35 (0.7%)	20 (0.9%)
Acute myocardial infarction	29 (0.6%)	17 (0.7%)
Urinary tract infection	28 (0.6%)	7 (0.3%)
Renal impairment	26 (0.6%)	10 (0.4%)
Angina unstable	24 (0.5%)	8 (0.3%)
Cerebrovascular accident	24 (0.5%)	6 (0.3%)
Pneumonia	17 (0.4%)	14 (0.6%)
Cardiac failure	14 (0.3%)	16 (0.7%)
Cardiac arrest	5 (0.1%)	11 (0.5%)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets, NDA 204629, SDN 406

Table 47 Adverse Events Leading to Discontinuation by High Level Term, and Treatment Arm

High Level Term	All Empa	Placebo
Ischemic coronary artery disorders	102 (2.2%)	52 (2.2%)
Central nervous system hemorrhages and cerebrovascular accidents	52 (1.1%)	23 (1.0%)
Renal failure and impairment	48 (1.0%)	27 (1.2%)
Death and sudden death	34 (0.7%)	20 (0.9%)
Urinary tract infections	33 (0.7%)	9 (0.4%)
Heart failures NEC	23 (0.5%)	25 (1.1%)
Lower respiratory tract and lung infections	18 (0.4%)	17 (0.7%)
Peripheral vasoconstriction, necrosis and vascular insufficiency	16 (0.3%)	12 (0.5%)
Ventricular arrhythmias and cardiac arrest	14 (0.3%)	19 (0.8%)
Coronary artery disorders NEC	11 (0.2%)	11 (0.5%)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets, NDA 204629, SDN 406

My analysis of the ADAE dataset submitted by the Applicant revealed that hospitalization due to AE leading to discontinuation of the drug was reported in 233 patients on placebo (10%), and 392 patients in the pooled empagliflozin group (8.4%).

7.3.4 Significant Adverse Events

The Applicant defined other significant AEs according to ICH E3 which included non-serious AEs leading to temporary or permanent discontinuation of study medication. The information submitted by the Applicant is presented in Table 48 below.

Table 48 Incidence rate of other significant AEs according to ICH E3, with a frequency of >=0.2%, sorted by frequency and system organ class - TS

MedDRA SOC	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	137 (5.9)	2.41	144 (6.1)	2.44	147 (6.3)	2.47
Gastrointestinal disorders	32 (1.4)	0.56	19 (0.8)	0.32	18 (0.8)	0.30
Diarrhoea	8 (0.3)	0.14	6 (0.3)	0.10	3 (0.1)	0.05
Vomiting	6 (0.3)	0.10	0	0	2 (0.1)	0.03
Abdominal distension	5 (0.2)	0.09	0	0	0	0
Infections and infestations	19 (0.8)	0.33	35 (1.5)	0.59	25 (1.1)	0.41
Urinary tract infection	6 (0.3)	0.10	14 (0.6)	0.23	10 (0.4)	0.17
Renal and urinary disorders	19 (0.8)	0.33	21 (0.9)	0.35	34 (1.5)	0.56
Renal impairment	6 (0.3)	0.10	3 (0.1)	0.05	11 (0.5)	0.18
Dysuria	0	0	4 (0.2)	0.07	5 (0.2)	0.08
Nervous system disorders	15 (0.6)	0.26	8 (0.3)	0.13	9 (0.4)	0.15
Dizziness	4 (0.2)	0.07	3 (0.1)	0.05	6 (0.3)	0.10
Investigations	12 (0.5)	0.21	11 (0.5)	0.18	20 (0.9)	0.33
Lipase increased	6 (0.3)	0.10	1 (<0.1)	0.02	6 (0.3)	0.10
Weight decreased	0	0	3 (0.1)	0.05	5 (0.2)	0.08
Skin and subcutaneous tissue disorders	11 (0.5)	0.19	15 (0.6)	0.25	14 (0.6)	0.23
Pruritus	1 (<0.1)	0.02	3 (0.1)	0.05	4 (0.2)	0.07
Rash	0	0	2 (0.1)	0.03	5 (0.2)	0.08
Psychiatric disorders	7 (0.3)	0.12	0	0	1 (<0.1)	0.02
Depression	4 (0.2)	0.07	0	0	0	0
Reproductive system and breast disorders	3 (0.1)	0.05	16 (0.7)	0.27	16 (0.7)	0.26
Balanoposthitis	0	0	6 (0.3)	0.10	6 (0.3)	0.10
Vulvovaginal pruritus	0	0	2 (0.1)	0.03	4 (0.2)	0.07

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

Note, other significant AEs according to ICH E3 in this study included nonserious AEs leading to temporary or permanent discontinuation of study medication (see Section 9.7.1.3.3 for further details).

Source: Table 12.2.3:1 study report NDA 204629, SDN 406

The overall incidence of significant adverse events was sligltly higher in the empagliflozizn arms compared to placebo. As expected, there were more significant genitourinary tract infections and dysuria with empagliflozin compared to placebo. Significant renal impairment events were reported more commonly with empa 25 compared to placebo and empa 10, however the overall rate of such events was small.

7.3.5 Submission Specific Primary Safety Concerns/Adverse Events of Special Interest

An AE of special interest (serious or non-serious) was an AE of scientific and medical concern specific to the Applicant's product or the clinical development program. AESIs were defined in the clinical development program and included, but were not limited to, AESIs defined in the trial protocol. Safety topics to be evaluated following requests from the health authorities were included in the analysis of AESIs.

For the safety analysis of empagliflozin in this trial, the following categories of AESIs were defined in the CTP or TSAP:

- hypoglycemic adverse events (pre-specified in the CTP)
- hepatic injury and assessment of liver enzymes (elevated AST and/or ALT ≥3 x ULN with, and ≥5 x ULN without, elevated bilirubin ≥2 x ULN)
- decreased renal function (creatinine ≥2 x fold increase from baseline and >ULN)
- urinary tract infection
- genital infection
- volume depletion
- bone fractures (note, investigators were asked to add in the comment field of the eCRF whether the cause of the fractures was traumatic or pathological, and the bone affected; coding of the AEs for traumatic fractures was based on the site of the fracture; pathological fractures were coded based on the pathology rather than the site of fracture)
- malignancies
- hypersensitivity
- venous embolic and thrombotic events
- diabetic ketoacidosis

Notably, AEs related to hepatic events and malignancies were adjudicated by the hepEAC and oncAAC, respectively (for causality only).

Each of these adverse events of special interest will be discussed below:

Hypoglycemia

Hypoglycemic events were to be recorded as adverse events if the patient displayed the typical symptoms of hypoglycemia or required external assistance, or if the patient's plasma glucose concentration was <54 mg/dL (3.0 mmol/L), or if the investigator considered the event to be an AE. A confirmed hypoglycemia adverse events was defined as a hypoglycemic adverse event that had a plasma glucose concentration ≤ 70 mg/dL or the patient required assistance. All symptomatic hypoglycemic events were to be recorded as a hypoglycemic event on the 'adverse

event' eCRF page. An asymptomatic hypoglycemic event was to be reported on a separate eCRF page, and not as an AE if the patient did not display the typical symptoms of hypoglycemia and the plasma glucose concentration was between 54 and 70 mg/dL (3.0 to 3.9 mmol/L).

For the analyses, all hypoglycemic events were classified according to the following criteria:

- asymptomatic hypoglycemia: Event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L);
- documented symptomatic hypoglycemia with glucose concentration ≥54 mg/dL and ≤70 mg/dL (≥3.0 mmol/L and ≤3.9 mmol/L): Event accompanied by typical symptoms of hypoglycemia;
- documented symptomatic hypoglycemia with glucose concentration <54 mg/L (< 3.0 mmol/L): Event accompanied by typical symptoms of hypoglycemia but no need for external assistance;
- severe hypoglycemic episode: Event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

In addition, a BIcMQ using the following PTs was used by the Applicant for further selection of hypoglycemic events: blood glucose decreased, hypoglycemia, hypoglycemia neonatal, hypoglycemia unawareness, hypoglycemic coma, hypoglycemic encephalopathy, shock hypoglycemic, hypoglycemic seizure, neuroglycopenia, hyperinsulinemia, hyperinsulinism, hypoglycemic unconsciousness. Hypoglycemic events that occurred 12 or less hours apart were collapsed into a single event by the Applicant, and I do not agree with this approach as the events occurring in a 12 hour period are likely to be separate events, and should be analyzed as such.

Table 49 Frequency of Patients with Confirmed Hypoglycemic Adverse Events by Characteristics of Hypoglycemia-TS

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
Number of patients	2333 (100.0)	2345 (100.0)	2342 (100.0)
Patients with confirmed hypoglycaemic AE [1]	650 (27.9)	656 (28.0)	647 (27.6)
Symptomatic	523 (22.4)	527 (22.5)	515 (22.0)
Asymptomatic	289 (12.4)	277 (11.8)	289 (12.3)
Severity (worst episode)			
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)
Symptomatic and plasma glucose <54 mg/dL [2]	259 (11.1)	257 (11.0)	265 (11.3)
Symptomatic and plasma glucose ≥54 and ≤70 mg/dL [2]	231 (9.9)	240 (10.2)	220 (9.4)
Asymptomatic and plasma glucose ≤70 mg/dL	124 (5.3)	126 (5.4)	132 (5.6)
Intensity (worst episode)			
Severe	43 (1.8)	38 (1.6)	33 (1.4)
Moderate	156 (6.7)	134 (5.7)	126 (5.4)
Mild	451 (19.3)	484 (20.6)	488 (20.8)
Action taken [1]			
Therapy required	329 (14.1)	304 (13.0)	326 (13.9)
Antidiabetic background medication changed [3]	70 (3.0)	82 (3.5)	69 (2.9)
Study medication discontinued [4]	2 (0.1)	4 (0.2)	1 (<0.1)
Requiring or prolonging hospitalisation	13 (0.6)	6 (0.3)	7 (0.3)
Minimum glucose level (worst episode)			
<54 mg/dL	404 (17.3)	404 (17.2)	415 (17.7)
≥54 and ≤70 mg/dL	246 (10.5)	251 (10.7)	231 (9.9)
>70 mg/dL	0	0	0
Not measured	0	1 (<0.1)	1 (<0.1)
Number of hypoglycaemic episodes per patient			
1 or 2	304 (13.0)	324 (13.8)	319 (13.6)
3 or 4	104 (4.5)	105 (4.5)	101 (4.3)
5 to 9	101 (4.3)	102 (4.3)	113 (4.8)
≥10	141 (6.0)	125 (5.3)	114 (4.9)

[1] Patients could be counted in more than 1 category
[2] No assistance required
[3] Due to the event, within 14 days
[4] Action taken with trial drug

Source: Table 12.1.3.1:1 study report NDA 204629, SDN 406

Only 37 events of severe hypoglycemia were reported as serious events by the Applicant, 17 in the placebo group (0.7%), and 20 in the pooled empagliflozin group (0.4%). The proportion of patients with hypoglycemia requiring assistance was similar between the treatment groups.

Taking into consideration all hypoglycemic events (severe and not severe), there was no significant difference between the incidence of hypoglycemia in the empagliflozin vs placebo.

Using the hypoglycemia flag (BIcMQ based) in the ADAE dataset, I identified 689 patients (29.5%) who experienced hypoglycemia during the trial in the placebo group, and 1379 (29.4%) in the empagliflozin group. A similar proportion of patients experienced investigator-defined hypoglycemia (30% in the placebo group, and 29.6% in the pooled empagliflozin group). The Applicant provided table identified slightly fewer patients with hypoglycemia in each treatment group compared to my analysis (probably due to the event collapsing by the Applicant described above). In both analyses, for both treatment groups, approximately 2/3 of patients experienced symptomatic hypoglycemia.

In conclusion, there is no indication from this trial that the addition of empagliflozin to the standard of care in the studied population leads to an increased incidence of hypoglycemia.

Cardiovascular Safety

An independent clinical event committee (CEC) was established for adjudication of potential cardiovascular endpoints. The CEC was composed of 10 members (5 cardiologists and 5 neurologists) and reviewed all reported fatal events, and any events suspected of stroke, transient ischemic attack (TIA), myocardial ischemia, hospitalization for unstable angina or heart failure, and stent thrombosis and revascularization procedures for this trial and for all phase III trials in the empagliflozin clinical development program, including, among others, empagliflozin monotherapy and empagliflozin+metformin therapy. The adjudication was performed without knowledge of the treatment assignment of any patient.

As this is a cardiovascular outcomes trial, cardiovascular safety is discussed under Review of Efficacy.

Decreased renal function

The analysis of decreased renal function included review of adverse events reports, and review of laboratory data.

The Applicant used a narrow SMQ for identifying acute renal dysfunction events, with the preferred terms listed in Section 16.2.7 of the efficacy supplement submission (page 22518). I evaluated the list of preferred terms and found it to be reasonable, however there were preferred terms not included in the search that could potentially suggest a renal event, my analysis is presented later in this review. The analysis using JReview and the ADAE and ADSL datasets, using the acute renal dysfunction flag provided by the Applicant revealed results that are identical to the ones provided by the Applicant (Table 50). A slightly greater proportion of patients in the placebo group experienced renal events (6.6%) compared to only 5.2% of patients in the pooled empagliflozin group. This finding was maintained across baseline renal function

categories. The incidence rates for SAEs of decreased renal function were also slightly lower for the empagliflozin groups than for the placebo group, and the renal events leading to treatment discontinuation occurred similarly in the placebo and empagliflozin groups. There was no major difference between the two empagliflozin arms. Since we expect that renal events will occur relatively soon after treatment start with empagliflozin, events were tallied for the first 30 days after study drug start, and first 90 days after study drug start. In both cases, the proportion of events was higher in the pooled empagliflozin group compared to placebo.

Table 50 Summary of Patients with Renal Adverse Events or Renal Laboratory Findings- TS

Preferred Term	**All Empa**	**Placebo**
Renal impairment	146 (3.1%)	77 (3.3%)
Renal failure	54 (1.2%)	42 (1.8%)
Acute kidney injury	45 (1.0%)	37 (1.6%)
Azotemia	5 (0.1%)	1 (0.0%)
Prerenal failure	1 (0.0%)	0 (0.0%)
Anuria	1 (0.0%)	1 (0.0%)
Acute prerenal failure	1 (0.0%)	2 (0.1%)
Oliguria	0 (0.0%)	1 (0.0%)
Total	**245 (5.2%)**	**155 (6.6%)**
SAE	57 (1.2%)	46 (2.0%)
Leading to discontinuation	41 (0.9%)	24 (1.0%)
Events that occurred in the first 30 days	41 (0.9%)	16 (0.7%)
Events that occurred in the first 90 days	70 (1.5%)	29 (1.2%)

Source: Reviewer generated using Jreview, ADAE, ADSL datasets, AESI renal impairment flag, NDA 204629, SDN 406

I selected my own list of preferred terms suggestive of renal impairment. While I am not sure that all the events selected belong in this category, based on my review of selected narratives, I believe that at least some of the events coded as diabetic nephropathy, nephrotic syndrome, etc, represent an acute increase in creatinine over baseline and would therefore qualify as an adverse renal event. The list that I generated is presented below in Table 51. While this analysis is significantly different compared to the one that the Applicant generated, it is important to note that the conclusion in both cases is similar, there was a higher proportion of renal events in the placebo group compared to the empagliflozin group. Again, for the first 30 days, and the first 90 days, there were more events in the empagliflozin group compared to placebo.

Table 51 Summary of Patients with Renal Adverse Events or Renal Laboratory Findings- Reviewer Selected PTs- TS

Preferred Term	**All Empa**	**Placebo**
Acute kidney injury	64 (1.4%)	48 (2.1%)
Acute prerenal failure	1 (0.0%)	2 (0.1%)

Anuria	1 (0.0%)	3 (0.1%)
Azotaemia	5 (0.1%)	1 (0.0%)
Blood creatinine	0 (0.0%)	1 (0.0%)
Blood creatinine increased	88 (1.9%)	72 (3.1%)
Blood urea increased	33 (0.7%)	17 (0.7%)
Blood urea nitrogen/creatinine ratio increased	0 (0.0%)	1 (0.0%)
Creatinine renal clearance decreased	2 (0.0%)	0 (0.0%)
Creatinine urine increased	0 (0.0%)	1 (0.0%)
Diabetic nephropathy	94 (2.0%)	61 (2.6%)
Hypercreatinaemia	0 (0.0%)	1 (0.0%)
Microalbuminuria	62 (1.3%)	29 (1.2%)
Nephritis	2 (0.0%)	0 (0.0%)
Nephropathy	26 (0.6%)	19 (0.8%)
Nephropathy toxic	2 (0.0%)	0 (0.0%)
Nephrosclerosis	0 (0.0%)	1 (0.0%)
Nephrotic syndrome	2 (0.0%)	1 (0.0%)
Oliguria	0 (0.0%)	1 (0.0%)
Prerenal failure	1 (0.0%)	0 (0.0%)
Renal disorder	2 (0.0%)	0 (0.0%)
Renal failure	72 (1.5%)	47 (2.0%)
Renal function test abnormal	6 (0.1%)	3 (0.1%)
Renal impairment	155 (3.3%)	82 (3.5%)
Renal injury	1 (0.0%)	1 (0.0%)
Renal tubular necrosis	0 (0.0%)	2 (0.1%)
Urine flow decreased	4 (0.1%)	3 (0.1%)
Patients with event	**536 (11.4%)**	**341 (14.6%)**
Total patients	4687 (100.0%)	2333 (100.0%)

Source: Reviewer generated using JReview, ADAE, ADSL datasets, NDA 204629, SDN 406

The incidence rates of decreased renal function AEs by subgroups according to age or sex were slightly higher for patients in the placebo group than for patients in the empagliflozin groups.

The incidence rates for decreased renal function AEs increased with increased renal impairment (based on eGFR at baseline) and were slightly higher in the placebo group than in the empagliflozin groups.

Renal function is also evaluated in the efficacy section under composite microvascular endpoints – nephropathy-related endpoints with the following individual components:

- New onset of macroalbuminuria

- Doubling of serum creatinine plus eGFR ≤45 mL/min/1.73m2

- Initiation of continuous renal replacement therapy

- Death due to renal disease,

Reviewer comment: While more events were observed with empagliflozin compared to placebo in the first 90 days of treatment, over the course of the study, this finding was not sustained. Although not conclusive, this finding is somewhat reassuring regarding long term effects of empagliflozin on renal function. The concern regarding acute renal events early after drug start remains.

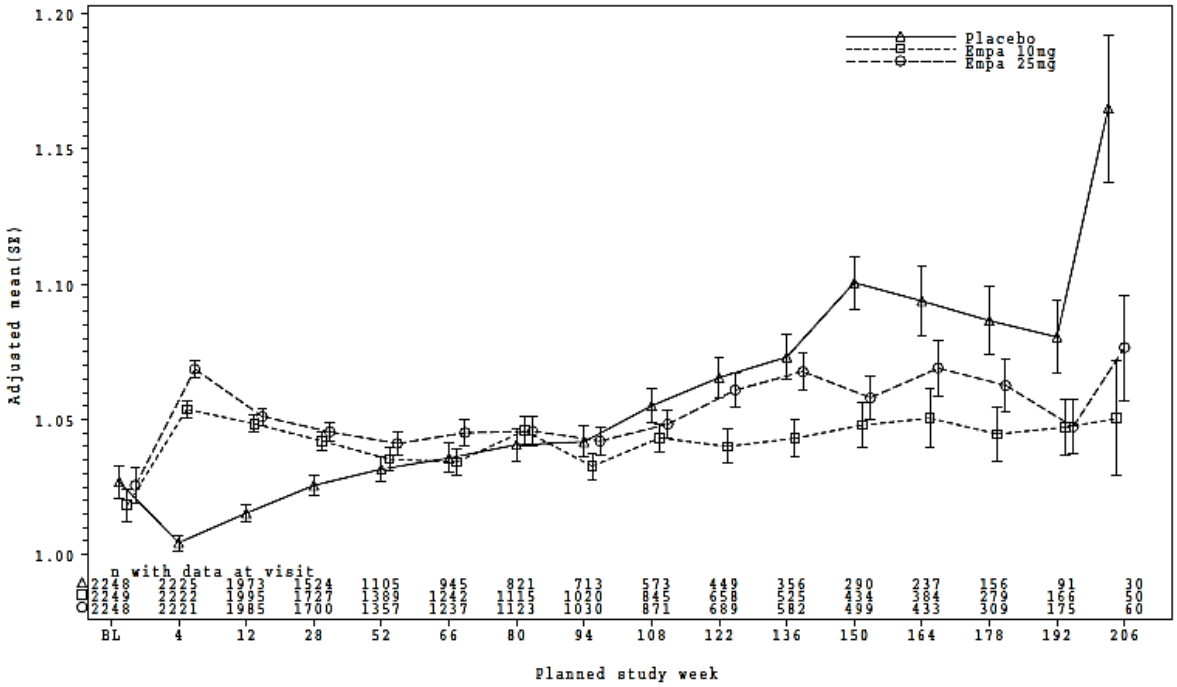
a. Renal function based on serum creatinine

Creatinine was monitored over time and the Applicant presented descriptive statistics. At baseline, the mean creatinine value was similar between the treatment groups [1.03 (0.01) for the placebo group, and 1.02 (0.01) and 1.03 (0.01) for the empagliflozin 10 mg and 25 mg groups respectively]. As observed in Figure 23 below, at week 4, there was an increase in creatinine in both empagliflozin groups, while the creatinine in the placebo group decreased slightly. However, despite the initial spike in creatinine in the empagliflozin groups, the creatinine came back to almost baseline levels in both empagliflozin groups by week 52, and it was maintained relatively stable for the duration of the study. In contrast, the placebo group experienced a slight increase over time in the mean creatinine level after week 52.

Decreased renal function (defined as increase in creatinine >2X from baseline and >ULN) was a protocol-specified AE and was to be reported by the investigators. The Applicant reported that 50 patients in the placebo group (2.1%) fit this definition, and 55 patients (1.2%) in the pooled empagliflozin group. However, our renal consultant concluded that the decrease in serum creatinine was sustained in less than half of these patients.

Please see nephrology consult by Dr Smith for details.

Figure 23 Descriptive Statistics for Creatinine (mg/dL) MMRM Results Over Time by Treatment– TS (OC)

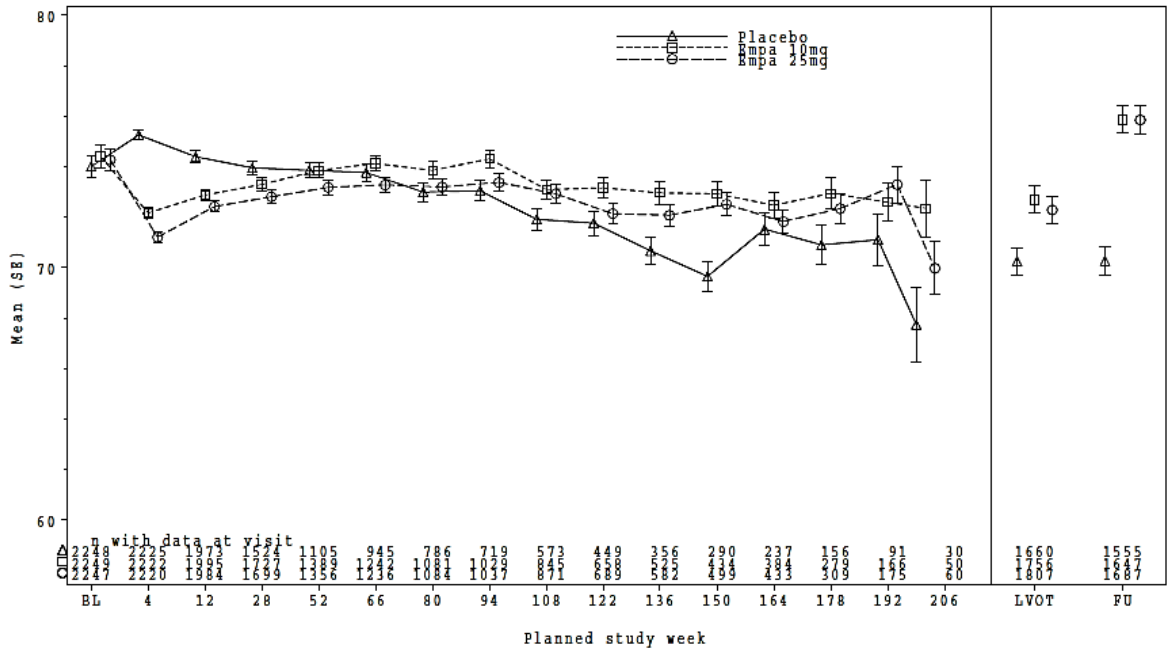


Source: Figure 15.3.2.3.1.2:2 study report NDA 204629, SDN 406

b. Renal function based on eGFR

The Applicant submitted over time changes for eGFR using MMRM. The baseline mean eGFR was similar between the treatment groups. Mirroring the creatinine changes over time, there was a decrease in eGFR at week 4 in both empagliflozin groups, after which the eGFR values were relatively stable over time. In contrast, the mean eGFR in the placebo group was observed to slowly decline over time.

Figure 24 eGFR [mL/min/1.73m2] MMRM results over time (OC), with unadjusted last value on treatment and follow-up value (OR) – TS



Source: Figure 15.2.4.2.11.2:3 study report NDA 204629, SDN 406

Approximately 75 % of patients in this study had a follow-up visit, and the Applicant analyzed the data for these patients separately, to show that even the slight decrease over time observed with empagliflozin is fully reversible at follow-up while the decline observed in the placebo group is not reversible (Table 52).

Table 52 Change in eGFR [mL/min/1.73m2] from baseline at last value on treatment and follow-up – TS-FU (OR)

Number of patients, N (%)	**Placebo 1668 (100.0)**	**Empa 10 mg 1773 (100.0)**	**Empa 25 mg 1824 (100.0)**
Baseline eGFR, median (Q1, Q3)	73.59 (60.87, 87.62)	73.79 (61.08, 88.57)	74.27 (60.15, 88.92)
Last value on treatment, median (Q1, Q3)	69.79 (55.61, 84.15)	71.83 (57.24, 85.78)	71.68 (57.33, 85.55)
Change from baseline	-3.68 (-11.64, 3.54)	-2.26 (-9.93, 5.00)	-2.56 (-10.42, 5.14)
Follow-up, median (Q1, Q3)	69.67 (55.34, 84.63)	75.24 (61.25, 89.49)	74.94 (61.26, 90.58)
Change from baseline	-3.86 (-12.40, 3.32)	0.71 (-6.74, 7.49)	0.71 (-6.98, 8.23)
Change from last value on treatment	-0.03 (-5.24, 5.03)	3.45 (-2.41, 8.64)	3.32 (-1.96, 9.13)

TS-FU = treated set-follow-up
Source: Table 11.1.2.8.3:1 study report NDA 204629, SDN 406

The Applicant reported that, based on descriptive values for the last value on-treatment change from baseline, eGFR changes on treatment in subgroups of patients with different age or baseline eGFR categories were similar to the overall study population.

Adverse shifts in renal function are presented in Table 53 below. A smaller proportions of patients in the empagliflozin groups than in the placebo group showed shifts to lower eGFR categories at last value on treatment, this pattern is less obvious when worst value on treatment was analyzed, which may have been due to the initial drop in eGFR values.

Table 53 Frequency of Patients (%) with Adverse Shifts in Renal Function Category (Based on MDRD) from Baseline by Treatment − Treated Set

Treatment Baseline renal function (eGFR [mL/min/1.73m²])	Last eGFR value on treatment				Minimum eGFR value on treatment			
	>=90	60 to <90	30 to <60	<30	>=90	60 to <90	30 to <60	<30
Placebo								
>=90	277 (57.0)	199 (40.9)	9 (1.9)	1 (0.2)	140 (28.8)	317 (65.2)	26 (5.3)	3 (0.6)
60 to <90	105 (8.6)	839 (68.5)	273 (22.3)	7 (0.6)	15 (1.2)	693 (56.6)	504 (41.2)	12 (1.0)
30 to <60	1 (0.2)	86 (14.4)	465 (77.9)	45 (7.5)	0	18 (3.0)	491 (82.2)	88 (14.7)
<30	0	0	2 (33.3)	4 (66.7)	0	0	1 (16.7)	5 (83.3)
Total	383 (16.6)	1124 (48.6)	749 (32.4)	57 (2.5)	155 (6.7)	1028 (44.4)	1022 (44.2)	108 (4.7)
All Empa								
>=90	642 (61.8)	377 (36.3)	19 (1.8)	0	320 (30.8)	670 (64.5)	48 (4.6)	0
60 to <90	247 (10.3)	1696 (70.9)	439 (18.3)	11 (0.5)	12 (0.5)	1343 (56.1)	1018 (42.5)	20 (0.8)
30 to <60	9 (0.8)	178 (15.3)	891 (76.7)	84 (7.2)	1 (0.1)	19 (1.6)	941 (81.0)	201 (17.3)
<30	0	1 (5.0)	10 (50.0)	9 (45.0)	0	0	6 (30.0)	14 (70.0)
Total	898 (19.5)	2252 (48.8)	1359 (29.5)	104 (2.3)	333 (7.2)	2032 (44.0)	2013 (43.6)	235 (5.1)

Source: Table 15.2.4.2.11.6:1 study report NDA 204629, SDN 406

Reviewer comment: While it is reassuring that, overall, patients on empagliflozin did not experience more renal adverse events in this study, and that the initial eGFR decrease with empagliflozin appears to be reversible with continued treatment, I remain concerned regarding potential for renal events with real life use of empagliflozin where the patient's fluid status is not monitored nearly as well as in a clinical trial, and where patients are likely to have poorer glycemic control. In addition, few patients in this study had moderate or severe renal impairment at baseline, so this might not be the appropriate patient population to see such events.

Hepatic injury

Adverse events related to hepatic injury were summarized based on an Applicant generated SMQ. The incidence rates for hepatic injury were also summarized for the period from baseline to 30 days after last administration of study medication. Hepatic injury events based on hepatic AEs or laboratory data triggers were adjudicated for causality by an independent committee, the hepEAC, as part of the surveillance conducted by the Applicant to investigate potential cases of DILI.

Table 54 Proportion of Patients with Liver Events by PT, and Treatment Arm

Preferred Term	All Empa	Placebo
Acute hepatic failure	1 (0.0%)	0 (0.0%)
Alanine aminotransferase increased	33 (0.7%)	22 (0.9%)
Ascites	7 (0.1%)	2 (0.1%)
Aspartate aminotransferase increased	22 (0.5%)	15 (0.6%)
Autoimmune hepatitis	1 (0.0%)	0 (0.0%)
Bilirubin conjugated increased	0 (0.0%)	1 (0.0%)
Blood bilirubin increased	6 (0.1%)	4 (0.2%)
Blood bilirubin unconjugated increased	1 (0.0%)	0 (0.0%)
Cholestasis	3 (0.1%)	0 (0.0%)
Drug-induced liver injury	2 (0.0%)	1 (0.0%)
Gamma-glutamyl transferase increased	13 (0.3%)	13 (0.6%)
Gastric varices	1 (0.0%)	0 (0.0%)
Hepatic calcification	0 (0.0%)	1 (0.0%)
Hepatic cirrhosis	5 (0.1%)	2 (0.1%)
Hepatic enzyme abnormal	1 (0.0%)	0 (0.0%)
Hepatic enzyme increased	21 (0.4%)	7 (0.3%)
Hepatic failure	0 (0.0%)	2 (0.1%)
Hepatic function abnormal	5 (0.1%)	5 (0.2%)
Hepatic lesion	1 (0.0%)	0 (0.0%)
Hepatic pain	0 (0.0%)	2 (0.1%)
Hepatic steatosis	46 (1.0%)	29 (1.2%)
Hepatitis	0 (0.0%)	2 (0.1%)
Hepatitis acute	1 (0.0%)	0 (0.0%)
Hepatitis cholestatic	1 (0.0%)	0 (0.0%)
Hepatomegaly	9 (0.2%)	2 (0.1%)
Hepatosplenomegaly	1 (0.0%)	0 (0.0%)
Hyperbilirubinemia	6 (0.1%)	3 (0.1%)
Hypertransaminasemia	0 (0.0%)	2 (0.1%)
Ischemic hepatitis	0 (0.0%)	1 (0.0%)
Jaundice	1 (0.0%)	0 (0.0%)
Jaundice cholestatic	1 (0.0%)	0 (0.0%)
Liver disorder	5 (0.1%)	0 (0.0%)
Liver function test abnormal	8 (0.2%)	5 (0.2%)
Liver injury	2 (0.0%)	0 (0.0%)
Liver palpable	0 (0.0%)	1 (0.0%)
Liver tenderness	1 (0.0%)	0 (0.0%)
Non-alcoholic steatohepatitis	3 (0.1%)	2 (0.1%)
Ocular icterus	0 (0.0%)	1 (0.0%)
Portal hypertension	3 (0.1%)	0 (0.0%)
Splenic varices	1 (0.0%)	0 (0.0%)
Steatohepatitis	1 (0.0%)	0 (0.0%)
Transaminases increased	9 (0.2%)	7 (0.3%)
Varices esophageal	2 (0.0%)	1 (0.0%)

Total	**173 (3.7%)**	**108 (4.6%)**
Leading to discontinuation	13 (0.3%)	8 (0.3%)
SAEs	20 (0.4%)	5 (0.2%)

Source: Reviewer generated using Jreview, ADAE and ADSL datasets, Applicant generated hepatic injury flag, NDA 204629, SDN 406

While overall there was a lower proportion of patients with reported liver events in the pooled empagliflozin group compared to placebo (3.7% vs 4.6%), the proportion of severe liver events was double in the empagliflozin group (0.4%) vs placebo (0.2%). The proportion of patients that had liver events leading to discontinuation of the study drug was similar between treatment groups.

All reported treatment-emergent events suspected of being DILIs or hepatic injuries were reviewed in a blinded fashion by the hepEAC. Events qualifying for adjudication were selected based on the SMQs, PTs, and by manual review. Laboratory results could also trigger hepatic adjudications. Notably, the committee adjudicated the category of potential causal relationship with the study drug in the respected cases by selecting one of four categories ('Unlikely', 'Possible', 'Probable' and 'Indeterminate').

The trigger event definitions are provided below:

1. ALT and/or AST elevation ≥ 3x ULN with concomitant or subsequent total bilirubin (TB) ≥ 2x ULN in a 30 day period after ALT and/or AST elevation (either identified via lab (central lab) or AE reporting (protocol specified AESI) for hepatic events),

2. ALT and/or AST elevation ≥ 5x ULN (either identified via lab (central lab) or AE reporting (protocol specified AESI) for hepatic events),

3. Serious adverse events programmatically identified by preferred term (PT):

   - Hepatitis fulminant

   - Acute hepatic failure

   - Hepatic failure

   - Hepatic necrosis

   - Hepatorenal failure

   - Drug induced liver injury

4. Cases including fatal hepatic events as identified by manual review of TM DS via the following SMQs

- Liver related investigations, signs and symptoms

- Cholestasis and jaundice of hepatic origin

- Hepatitis, non-infectious

- Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions

The Applicant reported the following regarding adjudicated hepatic events: 11 (0.5%) events in the placebo group, and 44 (0.9%) events in the pooled empagliflozin group (Table 55).

Table 55 Liver Events Adjudication by Treatment Arm

	Placebo N (%) 2333 (100)	**Empa 10mg N (%) 2345 (100)**	**Empa 25mg N (%) 2342 (100)**	**All Empa N (%) 4687 (100)**
Number of patients with adjudicated event	11 (0.5)	23 (1.0)	21 (0.9)	44 (0.9)
Unlikely	11 (0.5)	20 (0.9)	19 (0.8)	39 (0.8)
Possibly	0	2 (0.1)	1 (<0.1)	3 (0.1)
Probably	0	0	0	0
Indeterminate	0	1 (<0.1)	1 (<0.1)	2 (<0.1)

Source: excerpted from Table 15.3.1.3.2:1 study report NDA 204629, SDN 406

Using the JReview and ADAEADJ dataset selecting for liver events, I identified one extra event in the empagliflozin pool compared to the Applicant created table. However, the liver test elevation in that particular patient occurred before the study treatment was initiated, and it does not appear to be relevant for our assessment. Notably, the event frequency was almost double for the pooled empagliflozin arm compared to placebo (0.9% vs 0.5%), and, while all the events in the placebo arm were adjudicated as unlikely to be related to the study drug, 3 events in the pooled empagliflozin group were adjudicated as possibly related, and two as indeterminate. I reviewed the BI comments/alternative explanations for all the cases adjudicated as unlikely to be related to the study drug, and the explanations appear reasonable.

I will focus below on the five patients that were adjudicated with liver events possibly related to the study drug, or indeterminate, below:

- Patient no (b) (6): 60 year old black/African American female from South Africa started treatment with empagliflozin 10 mg on April 19, 2012. On April 16, 2013, the 363rd day since randomization, she was found to have increased liver functions (AST and ALT

greater than 5X ULN, elevated alkaline phosphatase, normal bilirubin). The investigator reported that the patient did not have a history of liver disease, or alcohol consumption. However, on 15 Apr 2013, one day before the event, a multi-stripper was used to strip the floors at her work, the ingredients of which included glycol ether solvents, ethanolamine, caustics, and dyes. In addition, the patient was taking an unknown dose of atorvastatin for hypercholesterolemia, "glitazone" 45 mg, and acetaminophen/codeine. On 14 May 2013, 29 days later, an ultrasound of liver and gall tract was performed, which revealed hypercholesterolosis on the endoluminal gallbladder wall, without any features of cholecystitis, but presence of two small stones of 4 mm and 5 mm in diameter each noted in the gallbladder neck. It also concluded that the liver was of normal size, and the common bile duct, pancreas, retroperitoneum, spleen, and both kidneys were normal and that the bladder was intact with no fluid collection in the abdomen or pelvis. Liver laboratories started trending down since the date of the event, and the liver function abnormality was reported as resolved on May 13, 2014, more than a year after the inception. No action was taken with the study drug, and she received no treatment for the liver event. The adjudication committee determined the event to be mild-moderate hepatic injury, possibly related to the study drug.

- Patient no (b) (6) 50 year old black/African American female from Brazil started treatment with empagliflozin 10 mg on October 20, 2011. The patient was taking an unknown dose of simvastatin for hyperlipidemia. On January 12, 2012, the 85th day post-randomization, the patient was found to have ALT elevation >5X ULN (baseline was only very mildly elevated). The patient was asymptomatic during this event, and no concurrent AEs were ongoing. At the time, AST was also elevated (approximately 4X ULN from a normal baseline)), bilirubin was normal, and alkaline phosphatase (AP) was elevated at 299 IU/L- however the baseline alkaline phosphatase was elevated as well (183 IU/L). GGT was elevated compared to baseline at the time, however, the patient had an elevated GGT more than 2X ULN prior to the initiation of empagliflozin. LDH was normal at the start of the treatment, and was elevated in one measurement in May 2012 (2X ULN), and normalized in subsequent measurements. No treatment was administered for the liver test abnormality, and study medication was neither discontinued nor reduced due to the elevated liver enzymes. The event was considered as resolved on October 16, 2012. The patient died on (b) (6), due to colon cancer. The adjudication committee determined the event to be mild-moderate hepatic injury, possibly related to the study drug.
- Patient no (b) (6) 64 year old white male from the US started treatment with empagliflozin 25 mg on May 17, 2011. On May 8th, 2012, AST and ALT were first noted to be elevated, and on May 11, AST and ALT were elevated >5X ULN. Repeat bloodwork on May 14, 2012, revealed continuous increase in AST, ALT, now >10X

ULN, bilirubin, GGT, AP and LDH were also elevated. The study drug was discontinued on May 16, 2012 as the patient was considered to have severe toxic/drug induced hepatitis. Simvastatin and ciprofloxacin were also discontinued at the time. Hepatitis panel was negative. An abdominal ultrasound on 21 May 2012 was reportedly normal, and computed tomography (CT) of the abdomen was scheduled to occur 2 days later because of a lipase elevation on 14 May 2012 (145 U/L; reference range 0-60 U/L), but results were not reported. Viral and autoimmune laboratory evaluation was reported negative. Simvastatin administration was restarted on 04 Jun 2012 after a gastroenterologist had reviewed the laboratory results from 25 May 2012. The toxic/drug-induced hepatitis was considered to be resolved on 13 Jun 2012 at which time all of the relevant laboratory values had returned to normal. The adjudication committee determined the event to be mild-moderate hepatic injury, possibly related to the study drug.

- Patient no (b) (6): 70 year old white female from Mexico started treatment with empagliflozin 10 mg on November 1, 2011. On January 26, 2012, the 87th day post-randomization, she was diagnosed with elevated liver enzymes >5XULN. The only ongoing event at the time was microalbuminuria. Bilirubin was normal at the time, AP was elevated (normal baseline). LDH was normal but GGT was elevated (unknown baseline). The patient was asymptomatic at the time, and physical examination was unremarkable. The event was considered resolved on July 20, 2012, and no action was taken with the study drug. The adjudication committee determined the event to be mild-moderate hepatic injury, the relationship with the study drug was indeterminate.
- Patient no (b) (6) 48 year old white male from Peru, started treatment with empagliflozin 25 mg on August 26, 2011. The patient had a history of hepatitis C, and AST and ALT were mildly elevated prior to study drug start. The patient was also taking simvastatin for treatment of hyperlipidemia. On August 29, 2012, the 370th day post-randomization, the patient was found to have elevation of ALT>5XULN and elevation of AST >3XULN, and about double the baseline values. Total bilirubin and AP were normal during the event, GGT was not reported. The event was ongoing at the time of the last available report, but the last reported results were no different from baseline. No action was taken with the study drug due to the event of increased transaminases. The adjudication committee determined the event to be mild-moderate hepatic injury, the relationship with the study drug was indeterminate.

The frequency of patients with LFT elevation based on central laboratory data in the period from baseline up to 30 days after the last dose of study medication is presented below in Table 56. ALT and/or AST elevations >5X and >10X ULN occurred more in the empagliflozin groups compared to placebo. As seen below, there were 5 patients in this study that fulfilled the

biochemical Hy's law criteria, 4 in the empagliflozin 10 mg group, and one in the placebo group. Notably, all these five cases were adjudicated as unlikely related to the study drug, and a more detailed discussion follows below:

Table 56 Proportion of Patients with LFT Elevations by Treatment Arm

Elevated liver enzymes criteria	**Placebo**	**N (%)**	**Empa 10 mg**	**N (%)**	**Empa 25 mg**	**N (%)**
Number of patients	**2333**	**(100.0)**	**2345**	**(100.0)**	**2342**	**(100.0)**
ALT and/or AST ≥3 x ULN	35	(1.5)	34	(1.4)	20	(0.9)
ALT and/or AST ≥5 x ULN	7	(0.3)	16	(0.7)	14	(0.6)
ALT and/or AST ≥10 x ULN	3	(0.1)	5	(0.2)	6	(0.3)
ALT and/or AST ≥20 x ULN	1	(<0.1)	1	(<0.1)	3	(0.1)
ALT and/or AST ≥3 x ULN with total bilirubin ≥2 x ULN	2	(0.1)	5	(0.2)	2	(0.1)
Alkaline phosphatase <2 x ULN [1]	1	(<0.1)	4	(0.2)	0	
Alkaline phosphatase ≥2 x ULN [1]	1	(<0.1)	1	(<0.1)	2	(0.1)

ULN = upper limit of normal
Note, patients were included regardless of baseline elevations.
Note, events up to 30 days after last administration of study medication are included in these incidence rates.
Note, frequencies in this table are based on central laboratory assessments.
A patient with ALT and/or AST elevation was counted in all applicable categories.
[1] Patients with ALT and/or AST ≥3 x ULN with concomitant or subsequent total bilirubin ≥2 x ULN in a 30 day period after ALT and/or AST elevation. Alkaline phosphatase was the maximum value in the 30 day period.
Source: Table 12.1.3.3.2:1 study report NDA 204629, SDN 406

The patients with LFT elevations that fit the Hy's law criteria are presented below.

- Patient no (b) (6): 49 year old male from Russia started on placebo on January 31, 2013. On November 20, 2014, the 659th day post-randomization, evaluation revealed AST 188 IU/L, and ALT at 276 IU/L. Direct bilirubin was elevated at 9 umol/L (normal 0-5 umol/L), and AP was normal at the time (at a later date it was elevated but not quite 2XULN), and the labs fulfilled the Hy's law criteria. Also, on 20 Nov 2014, the patient was diagnosed with moderate worsening of cholelithiasis and moderate extrahepatic bile duct obstruction. On March 10, 2015, the 769th day since randomization, the patient's laboratory values revealed AST at 274 IU/L, which was five times greater than ULN and ALT at 163 IU/L which was three times greater than ULN. CMV IGG antibody was positive, EBV-VCA IGG antibody positive, Varicella zoster IGG antibody positive, Parvovirus IGM antibody positive. Other laboratory abnormalities were leukocytosis, and platelet count decreased. No further information is available, and the event was adjudicated as unlikely related to the study drug.
- Patient no (b) (6): 63 year old male from India, started treatment with empagliflozin 10 mg on August 3, 2011. On (b) (6) (the (b) (6) day since randomization) the

patient was diagnosed with urosepsis which resulted in ICU hospitalization, along with ALT, bilirubin increase, and congestive heart failure. The study medication was not discontinued nor reduced because of these adverse events. The event was adjudicated as other significant hepatic injury unlikely related to the study drug.

- Patient no (b) (6): 57 year old male from Norway started treatment with empagliflozin 10 mg on September 7, 2011. The patient had a history of gallstones, and on September 5, 2012, the 365th day since randomization, the patient was found to have elevated liver enzymes (AST and ALT >5XULN). Total and direct bilirubin were also elevated at the time. At the time the patient was also experiencing diarrhea and common cold. The narrative mentions that the investigator stated that the patient was asymptomatic, hepatitis serology was negative, and the patient's alcohol consumption was minimal at 3 units per month. On 27 Sep 2012, the 387th day since randomization, the patient recovered from the event. The study drug was not discontinued because of the event. The adjudication committee determined the event to be mild-moderate hepatic injury, the relationship with the study drug was unlikely. Notably, the liver enzyme elevation was noted in one blood draw only, and normalized in two days.
- Patient no (b) (6) 66 year old male from Poland started treatment with empagliflozin 10 mg on November 4, 2011. On June 12, 2014, the 952nd day after randomization, the patient was noted to have increased bilirubin, ALT, and AST fulfilling criteria for Hy's law. AP was also elevated at the time of the event, although not to 2X ULN, and GGT was not available. At the time the patient was experiencing abdominal pain, and urinary incontinence. Per narrative hepatitis A virus (HAV) total test was positive and hepatitis B, C and anti-HAV showed negative results. The patient denied excessive alcohol use. On 26 Jun 2014, the 966th day since randomization, the patient recovered from the events increased bilirubin, AST, and ALT. On the same day he was also diagnosed with mild increased GGT. The study drug was not discontinued due to this event. The adjudication committee determined the event to be mild-moderate hepatic injury, the relationship with the study drug was unlikely.
- Patient no (b) (6): 65 year old male from the Philippines, initially started treatment with empagliflozin 10 mg on March 7, 2011. On (b) (6), the (b) (6) day after randomization, the patient was hospitalized for an MI. At the time AST was noted to be 5-6X ULN, and the narrative reports that the level declined once the concomitant medication rosuvastatin was stopped. On October 3, 2014, the patient was found to have liver laboratories consistent with Hy's law, and was diagnosed with fatty liver and cholelithiasis. On October 17, his liver labs showed only very mild increases in AST, ALT, with normal bilirubin. The study drug was not discontinued due to the adverse event. The adjudication committee determined the event to be mild-moderate hepatic injury, the relationship with the study drug was unlikely.

My analysis using JReview of the analysis and tabulations datasets provided by the Applicant revealed a two additional cases that fit Hy's law criteria.

- Patient no (b) (6): 62 year white male from US started treatment with empagliflozin 10 mg on April 6, 2011. On 11 Jul 2012, the 465th day since randomization, the patient was reported to have severe elevation of liver enzymes (ALT level was >13x ULN and AST level was >8x ULN, along with elevations in total bilirubin and direct bilirubin levels, normal AP, suspicious for Hy's law). A CT of the abdomen showed cholelithiasis, and by that time most of the liver labs returned to normal except for the ALT which was still elevated <5XULN. On 31 Aug 2012, the patient returned to the site for repeat liver enzyme tests, which had returned to normal with the exception of GGT (at <2x ULN). The study drug was temporarily discontinued for this event, and was restarted on 17 Oct 2012. The adjudication committee determined the event to be other significant hepatic injury, the relationship with the study drug was unlikely.
- Patient no (b) (6): 57 year old white male from Argentina started on empagliflozin 25mg on June 4, 2012. The patient had liver labs suggestive of Hy's law around day 180 after randomization in the context of hepatomegaly due to lymphoproliferative disorder which also lead to study medication discontinuation. The adjudication committee determined the event to be other significant hepatic injury, the relationship with the study drug was unlikely.

Reviewer comment: Although searches based on liver function parameters and preferred terms yielded a higher proportion of cases in the patients receiving empagliflozin when compared to placebo, it is difficult to conclude that empagliflozin causes liver dysfunction. In all cases, either insufficient data was available to establish causality, and/or alternative etiologies were possible. Overall the evaluation of liver events in EMPA-REG did not provide any additional knowledge compared to what was known from the original NDA review.

Urinary tract infections

The Applicant identified UTIs using a customized BIcMQ MedDRA query. The incidence rates of UTIs and the time to onset of a first UTI were comparable in both the empagliflozin and the placebo treatment groups. Using the AESI flag for UTI in the ADAE dataset provided by the Applicant, I generated a table that is identical to the one provided in the application (Table 57). The most commonly reported PT was "urinary tract infection", and the incidence was similar between treatment groups. Notably, the incidence of urosepsis was higher in the empagliflozin groups compared to placebo, and there were more patients with urinary tract infections leading to study treatment discontinuation in the empagliflozin groups compared to placebo. Most patients experiencing a UTI had only one episode (empagliflozin 10 mg: 12.3%; empagliflozin 25 mg:

11.3%; placebo: 11.9%), or two episodes (empagliflozin 10 mg: 2.6%; empagliflozin 25 mg: 3.4%; placebo: 3.7%). However, there was a higher proportion of patients in the empagliflozin groups that experienced 3 or more episodes of UTI compared to the patients in the placebo group.

Table 57 Frequency of Patients with Urinary Tract Infections by PT – TS

MedDRA SOC	**Placebo**		**Empa 10 mg**		**Empa 25 mg**	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	423 (18.1)	8.21	426 (18.2)	8.02	416 (17.8)	7.75
Infections and infestations	422 (18.1)	8.19	425 (18.1)	8.00	414 (17.7)	7.71
Urinary tract infection	352 (15.1)	6.70	347 (14.8)	6.38	347 (14.8)	6.34
Asymptomatic bacteriuria	30 (1.3)	0.52	28 (1.2)	0.47	14 (0.6)	0.23
Cystitis	23 (1.0)	0.40	35 (1.5)	0.59	34 (1.5)	0.57
Bacteriuria	14 (0.6)	0.24	11 (0.5)	0.18	5 (0.2)	0.08
Pyelonephritis chronic	10 (0.4)	0.17	4 (0.2)	0.07	6 (0.3)	0.10
Escherichia urinary tract infection	9 (0.4)	0.16	7 (0.3)	0.12	6 (0.3)	0.10
Pyelonephritis acute	6 (0.3)	0.10	7 (0.3)	0.12	1 (<0.1)	0.02
Pyelonephritis	4 (0.2)	0.07	3 (0.1)	0.05	10 (0.4)	0.17
Urinary tract infection fungal	3 (0.1)	0.05	12 (0.5)	0.20	15 (0.6)	0.25
Urosepsis	3 (0.1)	0.05	6 (0.3)	0.10	11 (0.5)	0.18
Urinary tract infection bacterial	3 (0.1)	0.05	7 (0.3)	0.12	4 (0.2)	0.07
Leading to discontinuation	10 (0.4)	0.17	22 (0.9)	0.37	19 (0.8)	0.31
Serious AEs[1]	29 (1.2)	NA	24 (1.0)	NA	34 (1.5)	NA

NA = not analyzed

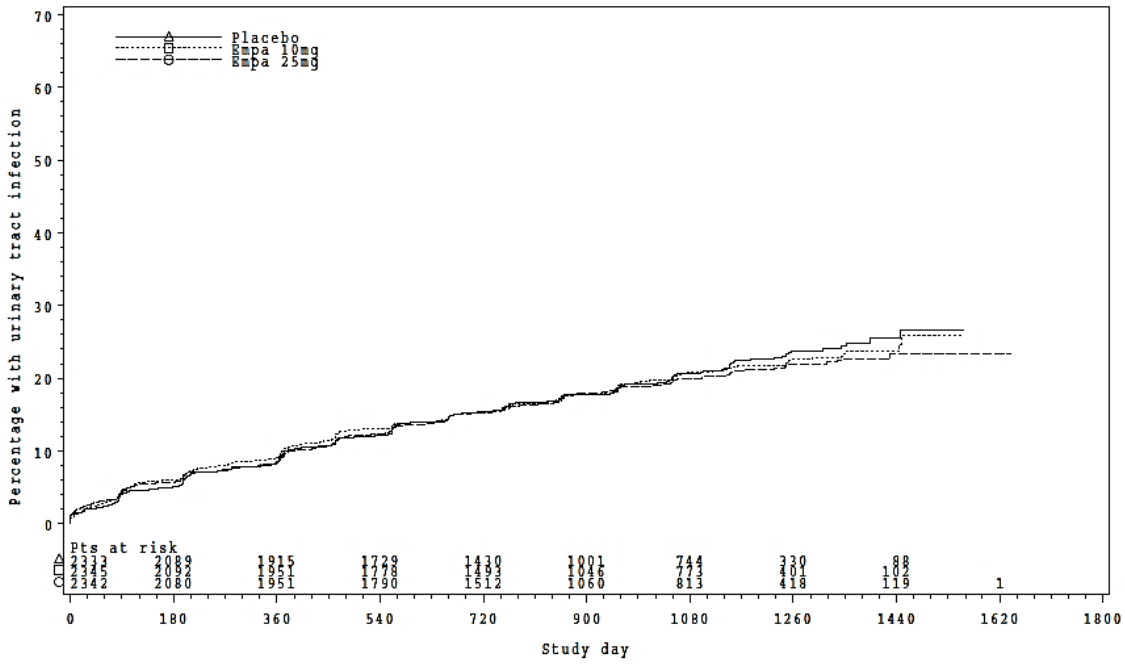
Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

[1] Required or prolonged hospitalization

Source: Table 12.1.3.4: 1 study report NDA 204629, SDN 406

In the US only, the frequency of patients with UTI events was higher in the pooled empagliflozin group compared to placebo (141 patients - 17.3% in the empagliflozin pool vs 57 patients – 14% in placebo). The same is true for the Applicant defined region of North America (which includes, US, Canada, Australia, and New Zealand) – 14.9% of patients in placebo vs 16.8% patients in the pooled empagliflozin group. In addition, there were 4 cases of urosepsis on treatment in the empagliflozin pool vs none in placebo for this population subgroup.

Figure 25 Kaplan-Meier Estimate of Time to the Onset of the First Urinary Tract Infection - TS



Source: Figure 15.3.1.6: 1 study report NDA 204629, SDN 406

Most patients experiencing a UTI had a first onset after 3 months of treatment in all treatment groups (empagliflozin 10 mg: 14.4%; empagliflozin 25 mg: 13.8%; placebo: 14.5%).

As expected, UTIs were more common in females patients compared to males, patients above the age of 65, patients with reduced eGFR at baseline, as well as in patients with a history of chronic or recurrent UTIs. The incidence rates of UTIs in subgroup analyses were similar in the empagliflozin groups and the placebo group.

Table 58 Incidence rates of urinary tract infection AEs by subgroup - TS

Sub-group variable	Subgroup category	Placebo			Empa 10 mg			Empa 25 mg		
		N	n (%)	Rate/ 100 pt-yrs	N	n (%)	Rate/ 100 pt-yrs	N	n (%)	Rate/ 100 pt-yrs
Age [years]	<50	142	26 (18.3)	8.78	154	20 (13.0)	5.39	143	24 (16.8)	6.93
	50 to <65	1155	177 (15.3)	6.60	1146	189 (16.5)	7.04	1153	167 (14.5)	6.10
	65 to <75	808	165 (20.4)	9.61	834	156 (18.7)	8.43	833	175 (21.0)	9.40
	≥75	228	55 (24.1)	12.01	211	61 (28.9)	15.05	213	50 (23.5)	11.82
Sex	Male	1680	158 (9.4)	3.96	1653	180 (10.9)	4.49	1683	170 (10.1)	4.09
	Female	653	265 (40.6)	22.81	692	246 (35.5)	18.83	659	246 (37.3)	20.38
Baseline HbA_{1c} [%]	<8.0	1156	205 (17.7)	-	1188	191 (16.1)	-	1151	196 (17.0)	-
	8.0 to <9.0	795	140 (17.6)	-	730	145 (19.9)	-	804	150 (18.7)	-
	≥9.0	382	77 (20.2)	-	426	89 (20.9)	-	386	70 (18.1)	-
Baseline eGFR [mL/min/ 1.73 m^2]	≥90	488	68 (13.9)	6.02	519	80 (15.4)	6.77	531	79 (14.9)	6.35
	60 to <90	1238	223 (18.0)	8.09	1221	198 (16.2)	6.85	1202	207 (17.2)	7.30
	45 to <60	418	83 (19.9)	9.47	420	101 (24.0)	11.22	411	85 (20.7)	9.26
	30 to <45	183	49 (26.8)	13.06	178	44 (24.7)	13.31	182	43 (23.6)	12.51
	<30	6	0	0	7	3 (42.9)	25.15	14	2 (14.3)	9.06

N = number of treated patients; n = number of patients in the subgroup with UTIs

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data tables indicated below.

Source: Table 12.1.3.4: 2 study report NDA 204629, SDN 406

a. Complicated UTIs

Adverse events related to complicated UTIs were summarized by the Applicant based on a BIcMQ; SAEs from the BIcMQ urinary tract infections, and additionally serious and non-serious AEs included in the sub-BIcMQ pyelonephritis and reported as PT urosepsis were counted as complicated UTIs. With the exception of urosepsis (which was more common in the empagliflozin groups compared to placebo), the incidence rates for the other PTs representative of complicated UTI were similar between the treatment groups. Pyelonephritis was not observed more frequently in the empagliflozin group compared to placebo.

For the PT urosepsis, there were more occurrences in the empagliflozin groups than on placebo (it was reported for 6 patients on empagliflozin 10 mg and 11 patients on empagliflozin 25 mg, compared with 3 patients on placebo). The applicant stated that these cases, and potential further cases of urosepsis were manually reviewed (AEs reported by investigators with the PTs of sepsis, Escherichia sepsis, and septic shock were assessed).

Table 59 Incidence rates for adverse events of complicated urinary tract infections, sorted by frequency and system organ class – TS

MedDRA SOC	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	41 (1.8)	0.71	34 (1.4)	0.57	48 (2.0)	0.80
Infections and infestations	41 (1.8)	0.71	33 (1.4)	0.55	47 (2.0)	0.78
Urinary tract infection	16 (0.7)	0.28	13 (0.6)	0.22	16 (0.7)	0.27
Urosepsis	3 (0.1)	0.05	6 (0.3)	0.10	11 (0.5)	0.18
Pyelonephritis	4 (0.2)	0.07	3 (0.1)	0.05	10 (0.4)	0.17
Pyelonephritis chronic	10 (0.4)	0.17	4 (0.2)	0.07	6 (0.3)	0.10
Pyelonephritis acute	6 (0.3)	0.10	7 (0.3)	0.12	1 (<0.1)	0.02
Cystitis	2 (0.1)	0.03	0	0	0	0
Kidney infection	2 (0.1)	0.03	1 (<0.1)	0.02	3 (0.1)	0.05
Urinary tract infection fungal	0	0	0	0	3 (0.1)	0.05
Cystitis bacterial	1 (<0.1)	0.02	0	0	0	0
Escherichia urinary tract infection	1 (<0.1)	0.02	0	0	0	0
Urinary tract infection pseudomonal	0	0	0	0	1 (<0.1)	0.02
Renal and urinary disorders	1 (<0.1)	0.02	1 (<0.1)	0.02	1 (<0.1)	0.02
Cystitis glandularis	0	0	0	0	1 (<0.1)	0.02
Cystitis haemorrhagic	1 (<0.1)	0.02	0	0	0	0
Nephritis	0	0	1 (<0.1)	0.02	0	0

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.
Note, complicated urinary tract infections were SAEs from the BIcMQ urinary tract infections and additionally serious and nonserious AEs included in the sub-BIcMQ pyelonephritis and the PT urosepsis

Source: Table 12.1.3.4: 3 Study report NDA 204629, SDN 406

The following cases were reviewed by the Applicant:

- PT sepsis: 3 of 20 patients with sepsis had a possible urinary tract source of sepsis; 1 of these patients also had urosepsis reported as an AE, therefore there were 2 additional potential cases of urosepsis
- PT Escherichia sepsis: 2 patients with Escherichia sepsis had events possibly originating from the urinary tract; neither patient had urosepsis reported as an AE, therefore there were 2 additional potential cases of urosepsis
- PT septic shock: 2 of 15 patients with septic shock had a possible urinary tract source; both patients also had urosepsis reported as an AE, therefore there were no additional potential cases of urosepsis

Hence, 4 additional patients not originally coded as “urosepsis” (2 on empagliflozin and 2 on placebo) likely experienced urosepsis.

Table 60 Frequency of patients with urosepsis - TS

	Placebo		Empa 10 mg		Empa 25 mg	
	N	(%)	N	(%)	N	(%)
Number of patients	2333	(100.0)	2345	(100.0)	2342	(100.0)
Patients with urosepsis	5	(0.2)	7	(0.3)	12	(0.5)
Preferred terms included:						
Urosepsis	3	(0.1)	6	(0.3)	11	(0.5)
Sepsis[1]	0		2	(0.1)	1	(<0.1)
Escherichia sepsis[2]	2	(0.1)	0		0	
Septic shock[3]	1	(<0.1)	0		1	(<0.1)
Patients:						
Male	2	(0.1)	4	(0.2)	7	(0.3)
Female	3	(0.1)	3	(0.1)	5	(0.2)
Serious AEs	5	(0.2)	7	(0.3)	12	(0.5)
Fatal adverse events	0		2	(0.1)	1	(<0.1)
Clinical signs and symptoms[4]	1	(<0.1)	2	(0.1)	5	(0.2)
Positive blood culture	3	(0.1)	1	(<0.1)	4	(0.2)

[1] Three of 20 AEs with PT sepsis possibly originated from the urinary tract. One of these patients concomitantly had an AE with the PT urosepsis.
[2] Two additional patients with PT possibly originated from the urinary tract
[3] Two of 15 AEs with PT septic shock possibly originated from the urinary tract. These 2 patients also had the PT urosepsis.
[4] Admission to intensive care; haemodynamically unstable.

Source: Table 12.1.3.4: 4 study report NDA 204629, SDN 406

A summary of each case of complicated UTI as provided by the Applicant is presented below in Table 61. It does appear that complicated UTIs occurred more in the empagliflozin 25 mg treatment group when compared to the empagliflozin 10 mg group, and more than in the placebo group regardless of the empagliflozin dose. However, this is a rare event overall and it would be difficult to draw any definitive conclusions regarding dose dependence in this context.

Table 61 Patients with Urosepsis up to Treatment Stop + 7 Days - TS

Patient number	Preferred term (outcome)	Causality per investigator	Age [years][1]/ sex	Start day	Confounding factors / BI comment
Placebo					
(b) (6)	Urosepsis	Not related	75/M	102	Placed urinary catheter and benign prostatic hyperplasia might be regarded as confounding factors for urosepsis. History of UTI was reported.
	Urosepsis	Not related	49/F	801	Ureteropelvic junction stone might be regarded as a confounding factor for urosepsis. History of recurrent UTI was reported.
	Urosepsis	Not related	67/F	78	No confounding factors were reported.
	Escherichia sepsis	Related	48/F	1201	No confounding factors were reported.
	Escherichia sepsis	Not related	63/M	535	Ureteric stone and benign prostatic hyperplasia might be regarded as confounding factors for urosepsis.
Empagliflozin 10 mg					
(b) (6)	Urosepsis (fatal)	Related	74/M	639	Community-acquired pneumonia and chronic kidney disease were comorbid conditions reflected in the death certificate and probably contributed to the fatal outcome. Benign prostatic hyperplasia might be regarded as a confounding factor.
	Urosepsis	Not related	63/M	160	No confounding factors were reported.
	Urosepsis	Not related	78/F	709	A respiratory tract infection might be regarded as a potential alternative origin of the sepsis, with UTI as concurrent disorder. No confounding factors were reported.
	Urosepsis	Related	68/F	495	Urethral stricture might be regarded as a confounding factor for urosepsis. Chronic recurrent UTI was reported.
	Urosepsis and sepsis	Not related	65/F	30	Multiple calculi ureteric might be regarded as confounding factors for urosepsis.
	Urosepsis	Not related	61/M	472	No confounding factors were reported.
	Sepsis (fatal)	Not related	79/F	99	Possibly urosepsis. The patient refused medical treatment. No confounding factors were reported.
Empagliflozin 25 mg					
(b) (6)	Urosepsis	Not related	67/M	545	Urinary retention and urinary catheter might be regarded as confounding factors for urosepsis.
	Urosepsis	Not related	69/F	634	Chronic UTI was reported. Nephrolithiasis and ureteral obstruction might be regarded as confounding factors for urosepsis.
	Urosepsis	Not related	64/M	182	No confounding factors were reported.
	Urosepsis (fatal)	Related	71/M	749	History of urinary infection and urinary incontinence of unknown cause were reported. No confounding factors were reported.
	Urosepsis	Related	70/M	706	History of urinary infection was reported. No confounding factors were reported.
	Urosepsis	Related	58/F	269	Urinary retention might be regarded as a confounding factors for urosepsis in a multimorbid patient.
	Urosepsis	Not related	75/F	500	No confounding factors were reported. History of urinary infection was reported.
	Urosepsis	Not related	72/M	666	Urinary retention and multiple urinary catheters (post-operative) might be regarded as confounding factors for urosepsis at multimorbid patient.
	Urosepsis	Not related	62/F	173	Event of asymptomatic urinary infection was reported. No confounding factors were reported.
	Urosepsis	Not related	51/M	327	Nephrolithiasis might be regarded as a confounding factor for urosepsis.
	Urosepsis	Related	66/M	278	No confounding factors were reported.
	Sepsis	Related	57/F	116	Suspected nephrolithiasis (DD calcification of parenchyma or vessels) might be regarded as a confounding factor for urosepsis.

[1] Age at randomisation

Source: Table 12.1.3.4: 5 Study report NDA 204629, SDN 406

The results of the UTI/urosepsis analyses are consistent with the prescriber information for empagliflozin and no new concerning signals are identified in the review of the current study.

Genital infections

The Applicant identified genital infections using a BIcMQ for genital infections. Notably, the BIcMQ does not contain the PT "phimosis" which is relevant in this context because this could be a consequence of genital infections and may require surgery for treatment, and phimosis was found to occur with increased frequency in patients treated with empagliflozin throughout the development program. As expected, the overall incidence rates for genital infections were higher in patients treated with empagliflozin than in patients treated with placebo. The incidence rates of genital infections leading to discontinuation of study medication were also higher in patients treated with empagliflozin than in patients treated with placebo, as were the genital infection SAEs.

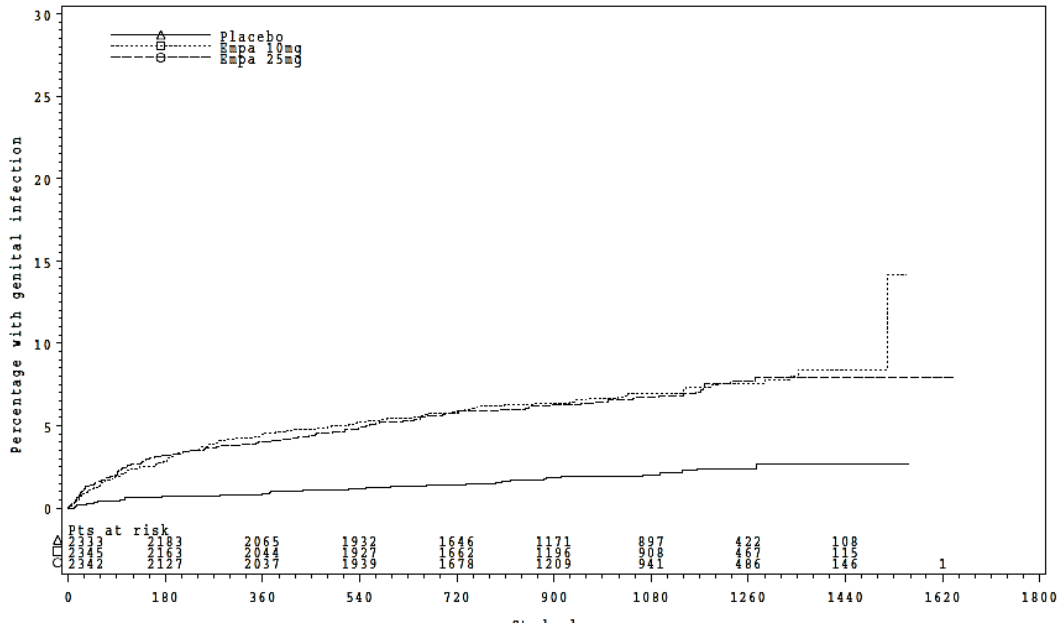
Table 62 Frequency of Patients with Genital Infections by PT – TS

Preferred Term	All Empa	Placebo
Bacterial vaginosis	1 (0.0%)	0 (0.0%)
Balanitis candida	15 (0.3%)	2 (0.1%)
Balanoposthitis	68 (1.5%)	3 (0.1%)
Balanoposthitis infective	1 (0.0%)	0 (0.0%)
Cellulitis of male external genital organ	1 (0.0%)	0 (0.0%)
Epididymitis	10 (0.2%)	1 (0.0%)
Genital candidiasis	10 (0.2%)	0 (0.0%)
Genital infection	9 (0.2%)	2 (0.1%)
Genital infection bacterial	1 (0.0%)	0 (0.0%)
Genital infection female	1 (0.0%)	0 (0.0%)
Genital infection fungal	38 (0.8%)	3 (0.1%)
Genitourinary tract infection	8 (0.2%)	2 (0.1%)
Orchitis	2 (0.0%)	1 (0.0%)
Penile infection	4 (0.1%)	1 (0.0%)
Perineal abscess	1 (0.0%)	0 (0.0%)
Phimosis	19 (0.4%)	3 (0.1%)
Prostate infection	1 (0.0%)	0 (0.0%)
Prostatic abscess	1 (0.0%)	0 (0.0%)
Prostatitis	26 (0.6%)	14 (0.6%)
Scrotal abscess	2 (0.0%)	0 (0.0%)
Urogenital infection fungal	3 (0.1%)	0 (0.0%)
Vaginal cellulitis	1 (0.0%)	0 (0.0%)
Vaginal infection	15 (0.3%)	3 (0.1%)
Vaginitis bacterial	1 (0.0%)	1 (0.0%)
Vulval abscess	1 (0.0%)	0 (0.0%)
Vulvitis	7 (0.1%)	3 (0.1%)
Vulvovaginal candidiasis	48 (1.0%)	5 (0.2%)
Vulvovaginal mycotic infection	34 (0.7%)	2 (0.1%)
Vulvovaginitis	18 (0.4%)	3 (0.1%)
Patients with event	**309 (6.6%)**	**45 (1.9%)**
Total patients	**4687 (100.0%)**	**2333 (100.0%)**

Source: Reviewer generated using JReview, ADAE, and ADSL datasets, NDA 204629, SDN 406

A Kaplan-Meier analysis of the time to first occurrence of a genital infections showed a more rapid onset of such events and a higher incidence in patients treated with empagliflozin compared with placebo that continued throughout the period of observation.

Figure 26 Kaplan-Meier estimate of time to the onset of the first genital infection - TS



Source: Figure 15.3.1.8:1 study report NDA 204629, SDN 406

Most patients experiencing a genital infection had only one episode (empagliflozin 10 mg: 4.7%; empagliflozin 25 mg: 4.9%; placebo: 1.6%), or 2 episodes (empagliflozin 10 mg: 0.9%; empagliflozin 25 mg: 0.9%; placebo: <0.1%). A small number of patients had ≥5 episodes (empagliflozin 10 mg: 0.2%; empagliflozin 25 mg: 0.2%; placebo: 0%). Most patients experiencing a genital infection had a first onset after 3 months of treatment in both the empagliflozin groups (10 mg: 4.8%; 25 mg: 4.5%), and in the placebo group (1.4%).

The incidence rates of genital infections were consistently increased in the empagliflozin groups compared with placebo in all subgroups. Applicant-provided incidence rates for genital infection AEs (excluding phimosis) by subgroups according to age, baseline HbA1c, and baseline eGFR categories are summarized in Table 63 below.

No clear dose dependence was observed. The analyses are consistent with the prescribing information for empagliflozin.

Table 63 Frequency of patients with genital infections AEs by subgroup - TS

Sub-group variable	Subgroup category	Placebo			Empa 10 mg			Empa 25 mg		
		N	n (%)	Rate/ 100 pt-yrs	N	n (%)	Rate/ 100 pt-yrs	N	n (%)	Rate/ 100 pt-yrs
Age [years]	<50	142	3 (2.1)	0.89	154	12 (7.8)	3.19	143	11 (7.7)	2.93
	50 to <65	1155	20 (1.7)	0.68	1146	86 (7.5)	3.01	1153	72 (6.2)	2.50
	65 to <75	808	17 (2.1)	0.88	834	45 (5.4)	2.21	833	52 (6.2)	2.52
	≥75	228	2 (0.9)	0.38	211	10 (4.7)	2.10	213	13 (6.1)	2.71
Sex	Male	1680	25 (1.5)	0.60	1653	89 (5.4)	2.16	1683	77 (4.6)	1.78
	Female	653	17 (2.6)	1.09	692	64 (9.2)	3.93	659	71 (10.8)	4.81
Baseline HbA_{1c} [%]	<8.0	1156	21 (1.8)	NA	1188	82 (6.9)	NA	1151	59 (5.1)	NA
	8.0 to <9.0	795	15 (1.9)	NA	730	49 (6.7)	NA	804	60 (7.5)	NA
	≥9.0	382	6 (1.6)	NA	426	22 (5.2)	NA	386	29 (7.5)	NA
Baseline eGFR [mL/min/ 1.73 m^2]	≥90	488	8 (1.6)	0.65	519	41 (7.9)	3.30	531	39 (7.3)	2.98
	60 to <90	1238	24 (1.9)	0.78	1221	89 (7.3)	2.91	1202	68 (5.7)	2.22
	45 to <60	418	8 (1.9)	0.82	420	17 (4.0)	1.62	411	31 (7.5)	3.12
	30 to <45	183	2 (1.1)	0.47	178	6 (3.4)	1.54	182	9 (4.9)	2.26
	<30	6	0	0	7	0	0	14	1 (7.1)	4.13

N = number of treated patients; n = number of patients in the subgroup with genital infections; NA = not analysed
Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data tables indicated below.

Source: Table 12.1.3.5: 2 study report NDA 204629, SDN 406

Serious genital infections

The incidence rates for serious genital infections is summarized below in Table 64. As expected, the incidence was higher in the empagliflozin treated patients compared to placebo.

Table 64 Incidence of Serious Genital Infections

Preferred Term	All Empa	Placebo
Cellulitis of male external genital organ	1 (0.0%)	0 (0.0%)
Epididymitis	0 (0.0%)	1 (0.0%)
Prostatic abscess	1 (0.0%)	0 (0.0%)
Prostatitis	4 (0.1%)	2 (0.1%)
Scrotal abscess	2 (0.0%)	0 (0.0%)
Vaginal cellulitis	1 (0.0%)	0 (0.0%)
Patients with event	**9 (0.2%)**	**3 (0.1%)**
Total patients	**4687 (100.0%)**	**2333 (100.0%)**

Source: Reviewer generated using ADAE and ADSL, Jreview, NDA 204629, SDN 406

The analysis of genital infections in EMPA-REG is in agreement with the current prescribing information for empagliflozin.

Volume depletion

The Applicant presented AEs possibly related to volume depletion identified using a BIcMQ including the following PTs: blood pressure ambulatory decreased, blood pressure decreased, blood pressure systolic decreased, dehydration, hypotension, hypovolemia, orthostatic hypotension, syncope. The results of this analysis are presented in Table 65 below.

Table 65 Patients with Volume Depletion Events Reported by the Applicant - TS

MedDRA PT	Placebo		Empa 10 mg		Empa 25 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	115 (4.9)	2.04	115 (4.9)	1.97	124 (5.3)	2.11
Hypotension	58 (2.5)	1.02	57 (2.4)	0.96	62 (2.6)	1.04
Syncope	32 (1.4)	0.56	31 (1.3)	0.52	41 (1.8)	0.68
Dehydration	16 (0.7)	0.28	18 (0.8)	0.30	18 (0.8)	0.30
Orthostatic hypotension	12 (0.5)	0.21	16 (0.7)	0.27	12 (0.5)	0.20
Blood pressure decreased	3 (0.1)	0.05	1 (<0.1)	0.02	3 (0.1)	0.05
Hypovolaemia	0	0	0	0	2 (0.1)	0.03
Leading to discontinuation	7 (0.3)	0.12	1 (<0.1)	0.02	4 (0.2)	0.07
Serious AEs	24 (1.0)	0.42	19 (0.8)	0.32	26 (1.1)	0.43

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

Source Table 12.1.3.6: 1 study report NDA 204629, SDN 406

However, the Applicant BIcMQ did not include other preferred terms that can suggest volume depletion such as dizziness, vertigo, loss of consciousness. I analyzed the datasets using JReview, and including the above mentioned preferred terms (in addition to those from the BIcMQ). The results are presented in Table 66 below. Regardless of the smq used, no significant difference can be observed between placebo and pooled empagliflozin group regarding the overall number for volume depletion events.

Table 66 Patients with Volume Depletion Events – Reviewer Generated

Preferred Term	**All Empa**	**Placebo**
Blood pressure decreased	4 (0.1%)	3 (0.1%)
Blood pressure diastolic decreased	2 (0.0%)	1 (0.0%)
Blood pressure orthostatic	1 (0.0%)	0 (0.0%)
Blood pressure orthostatic decreased	1 (0.0%)	0 (0.0%)
Dehydration	55 (1.2%)	22 (0.9%)
Dizziness	386 (8.2%)	176 (7.5%)
Dizziness exertional	1 (0.0%)	0 (0.0%)
Dizziness postural	19 (0.4%)	8 (0.3%)
Hypotension	133 (2.8%)	64 (2.7%)
Hypovolemia	2 (0.0%)	0 (0.0%)
Hypovolemic shock	4 (0.1%)	3 (0.1%)

Loss of consciousness	13 (0.3%)	6 (0.3%)
Orthostatic hypotension	30 (0.6%)	13 (0.6%)
Syncope	79 (1.7%)	35 (1.5%)
Vertigo	113 (2.4%)	70 (3.0%)
Vertigo labyrinthine	0 (0.0%)	1 (0.0%)
Vertigo positional	24 (0.5%)	15 (0.6%)
Total patients with event	**733 (15.6%)**	**351 (15.0%)**

Source: Reviewer generated using JReview, ADAE, and ADSL datasets, NDA 204629, SDN 406

As expected, the incidence rates for volume depletion increased with age, with increased renal impairment (based on eGFR at baseline), and with baseline use of diuretics or ACE inhibitors/ARBs in all treatment groups.

While volume depletion events were not significantly increased in patients receiving empagliflozin compared to placebo, I believe this is still a concerning issue for this drug based on the mechanism of action. The potential risk of volume depletion with empagliflozin is appropriately represented in the prescribing information.

Diabetic ketoacidosis

Diabetic ketoacidosis AEs were summarized based on a BIcMQ. Notably, diabetic ketoacidosis AEs were defined as AESIs after completion of the trial, prior to database lock. There were 4 patients with reported diabetic ketoacidosis (all SAEs) in the pooled empagliflozin group, and one patients reported with AE ketoacidosis (not an SAE) in the placebo group. Only 2 patients (empagliflozin 10 mg) had diabetic ketoacidosis AEs leading to discontinuation of study medication.

All treatment arms had a slight decrease in bicarbonate from baseline to last value on treatment (Table 67), and there were no differences between treatment arms.

Table 67 Median Values for Bicarbonate (normalized values) - TS

Parameter [units] Treatment group	Patients analysed	Baseline Median (Q1, Q3)	Last value on treatment Median (Q1, Q3)	Change from baseline to last value on treatment Median (Q1, Q3)
Bicarbonate [mEq/L]				
Placebo	2261	25.0 (23.0, 27.0)	24.0 (22.0, 26.0)	-1.0 (-3.0, 1.0)
Empa 10 mg	2269	25.0 (23.0, 27.0)	24.0 (22.0, 26.0)	-1.0 (-3.0, 1.0)
Empa 25 mg	2252	25.0 (23.0, 27.0)	24.0 (22.0, 25.0)	-1.0 (-3.0, 1.0)

Source: Table 12.3.2: 1 study report NDA 204629, SDN 406

Bicarbonate shifts are represented in Table 67 below. A higher proportion of patients in the empagliflozin groups had shifts from normal range at baseline to less than lower limit of normal at last value on treatment compared to placebo. In addition, there was a slightly higher proportion of patients in the empagliflozin groups with possibly clinically relevant abnormalities (PCSAs) for low bicarbonate compared to placebo, but overall the frequency of PCSAs was low in all treatment groups (Table 69). The significance of this finding is not clear, however, it might be helpful in understanding the DKA safety signal.

Table 68 Frequency of patients [N(%)] with bicarbonate shifts categorized by reference range at baseline and last value on treatment − treated set

Treatment/ Baseline RR	Last value on treatment: < LLN	[LLN, ULN]	> ULN	Total
Placebo (N= 2333)				
< LLN	63 (33.7)	122 (65.2)	2 (1.1)	187 (100.0)
[LLN, ULN]	181 (9.7)	1625 (86.9)	63 (3.4)	1869 (100.0)
> ULN	7 (3.5)	157 (78.5)	36 (18.0)	200 (100.0)
Total	251 (11.1)	1904 (84.4)	101 (4.5)	2256 (100.0)
Empa 10mg (N= 2344)				
< LLN	56 (32.6)	114 (66.3)	2 (1.2)	172 (100.0)
[LLN, ULN]	242 (12.8)	1611 (85.0)	42 (2.2)	1895 (100.0)
> ULN	8 (4.1)	153 (79.3)	32 (16.6)	193 (100.0)
Total	306 (13.5)	1878 (83.1)	76 (3.4)	2260 (100.0)
Empa 25mg (N= 2341)				
< LLN	68 (41.2)	95 (57.6)	2 (1.2)	165 (100.0)
[LLN, ULN]	221 (11.8)	1604 (85.7)	47 (2.5)	1872 (100.0)
> ULN	12 (5.7)	173 (82.4)	25 (11.9)	210 (100.0)
Total	301 (13.4)	1872 (83.3)	74 (3.3)	2247 (100.0)
All Empa (N= 4685)				
< LLN	124 (36.8)	209 (62.0)	4 (1.2)	337 (100.0)
[LLN, ULN]	463 (12.3)	3215 (85.3)	89 (2.4)	3767 (100.0)
> ULN	20 (5.0)	326 (80.9)	57 (14.1)	403 (100.0)
Total	607 (13.5)	3750 (83.2)	150 (3.3)	4507 (100.0)

Source: Table 15.3.2.1: 2 study report NDA 204629, SDN 406

Table 69 Frequency of patients with possibly clinically significant abnormal bicarbonate values TS

	Placebo n/N (%)	Empa 10 mg n/N (%)	Empa 25 mg n/N (%)
High			
Bicarbonate	53/2235 (2.4)	40/2233 (1.8)	41/2212 (1.9)
Low			
Bicarbonate	112/2235 (5.0)	136/2233 (6.1)	147/2212 (6.6)

n=number of patients with possibly clinically significant high value on treatment, N=number of patients with no possibly clinically significant abnormality at baseline and at least 1 available on-treatment value

Source: Table 12.3.2: 3 study report NDA 204629, SDN 406

Overall there were more patients with DKA in the empagliflozin groups compared to placebo, although the incidence was low. DKA is already a labeled concern with empagliflozin and the findings from EMPA-REG do not offer any new information.

Bone Fractures

The Applicant reported bone fractures and based on a BIcMQ. The incidence rates of bone fractures were comparable in both the empagliflozin and the placebo treatment groups in the period up to treatment stop + 7 days, and in the period up to trial termination. Selecting all preferred terms for bone fracture in JReview and using the Applicant-generated treatment emergent flag+7 days, I identified three patients that do not appear in the Applicant analysis (one in placebo, and two in the pooled empagliflozin group). However, because this finding does not impact the results of the study, I will present the Applicant reported findings below.

There was no imbalance observed between the treatment group regarding fracture AEs leading to study drug discontinuation, and fracture SAEs.

Table 70 Incidence rates for adverse events of bone fractures according to the BIcMQ for bone fractures, with a frequency of >=0.3% up to trial termination, sorted by frequency - TS

MedDRA PT	Placebo		Empa 10 mg		Empa 25 mg	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Up to treatment stop + 7 days						
Overall incidence of bone fracture	91 (3.9)	1.61	92 (3.9)	1.57	87 (3.7)	1.46
Leading to discontinuation	14 (0.6)	0.24	4 (0.2)	0.07	8 (0.3)	0.13
Serious AEs	35 (1.5)	0.61	24 (1.0)	0.40	33 (1.4)	0.55
Up to trial termination						
Overall incidence of bone fracture	105 (4.5)	1.61	105 (4.5)	1.58	98 (4.2)	1.47
Rib fracture	15 (0.6)	0.23	18 (0.8)	0.27	15 (0.6)	0.22
Foot fracture	13 (0.6)	0.20	12 (0.5)	0.18	15 (0.6)	0.22
Humerus fracture	4 (0.2)	0.06	11 (0.5)	0.16	5 (0.2)	0.07
Pathological fracture	10 (0.4)	0.15	8 (0.3)	0.12	7 (0.3)	0.10
Radius fracture	5 (0.2)	0.07	9 (0.4)	0.13	2 (0.1)	0.03
Upper limb fracture	4 (0.2)	0.06	7 (0.3)	0.10	9 (0.4)	0.13
Ankle fracture	7 (0.3)	0.10	8 (0.3)	0.12	4 (0.2)	0.06
Femur fracture	6 (0.3)	0.09	2 (0.1)	0.03	3 (0.1)	0.04
Hip fracture	2 (0.1)	0.03	1 (<0.1)	0.01	7 (0.3)	0.10
Tibia fracture	7 (0.3)	0.10	0	0	3 (0.1)	0.04
Tooth fracture	5 (0.2)	0.07	4 (0.2)	0.06	7 (0.3)	0.10

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

Source: Table 12.1.3.7: 1 study report NDA 204629, SDN 406

In the analysis of all AEs, it was noted that the preferred term ‘osteoporosis’ occurred with higher incidence rates on empagliflozin (25 patients - 0.53% in pooled empagliflozin vs 2 patients - 0.09% in placebo). Consequently, a post hoc analysis based on the SMQ osteoporosis was undertaken by the Applicant, and the results are presented below. A higher percentage of patients in the empagliflozin group have been reported with preferred terms suggestive of low bone density. Formal bone density testing was not part of this study. This is concerning because the study observation period was only approximately 2.5 years, and it is possible that longer exposure is needed to see a difference in bone fracture rates.

Table 71 Osteoporosis Analysis by PT and Treatment Arm

Preferred Term	**All Empa**	**Placebo**
Bone density decreased	1 (0.02%)	0 (0.00%)
Bone loss	1 (0.02%)	1 (0.04%)
Osteopenia	13 (0.28%)	7 (0.30%)
Osteoporosis	25 (0.53%)	2 (0.09%)

Osteoporosis postmenopausal	0 (0.00%)	1 (0.04%)
Osteoporotic fracture	2 (0.04%)	2 (0.09%)
Total	**41 (0.87%)**	**13 (0.56%)**

Source: Reviewer generated using Jreview, ADAE, ADSL datasets, NDA 204629, SDN 406

Laboratory safety data measured in this study that were markers for bone health included calcium, magnesium, phosphate, and alkaline phosphatase. There were no noteworthy changes in median values from baseline to the last value on treatment for patients on empagliflozin or patients on placebo for calcium, magnesium, phosphate, or alkaline phosphatase. However, more specific bone turnover markers were not evaluated in this study.

Table 72 Changes from Baseline to Last Value on Treatment for Calcium, Magnesium, and Phosphate by Treatment Arm

Parameter [units] Treatment group	Patients analysed	Baseline Median (Q1, Q3)	Last value on treatment Median (Q1, Q3)	Change from baseline to last value on treatment Median (Q1, Q3)
Calcium [mg/L]				
Placebo	2261	9.7 (9.5, 10.0)	9.7 (9.4, 10.1)	0.0 (-0.3, 0.3)
Empa 10 mg	2269	9.7 (9.5, 10.0)	9.7 (9.5, 10.0)	0.0 (-0.3, 0.3)
Empa 25 mg	2252	9.7 (9.5, 10.0)	9.7 (9.5, 10.1)	0.0 (-0.3, 0.3)
Magnesium [mEq/L]				
Placebo	2261	1.7 (1.6, 1.9)	1.7 (1.5, 1.8)	0.0 (-0.2, 0.1)
Empa 10 mg	2269	1.7 (1.6, 1.9)	1.8 (1.6, 2.0)	0.1 (0.0, 0.2)
Empa 25 mg	2252	1.7 (1.6, 1.9)	1.8 (1.7, 2.0)	0.1 (0.0, 0.2)
Phosphate [mg/L]				
Placebo	2261	3.7 (3.5, 3.8)	3.7 (3.5, 3.9)	0.0 (-0.2, 0.2)
Empa 10 mg	2269	3.7 (3.5, 3.8)	3.7 (3.5, 3.9)	0.1 (-0.1, 0.2)
Empa 25 mg	2252	3.7 (3.5, 3.8)	3.7 (3.5, 3.9)	0.1 (-0.1, 0.2)

Source: excerpted from Table 12.3.2: 1 study report NDA 204629, SDN 406

The Applicant performed a subgroup analysis of bone fractures (Table 73). In all treatment groups, fractures were seen more frequently in patients 65 and older, with no apparent differences between the treatment groups. However, upper extremity fractures were more frequent in the pooled empagliflozin group (1%) compared to placebo (0.5%). As expected, there were more bone fractures observed in females compared to males in most treatment groups. In male patients, both empagliflozin arms appeared to have a higher incidence of bone fractures compared to placebo. The results by renal dysfunction category did not clearly indicate an increase in fracture risk with empagliflozin in either category.

Table 73 Frequency of patients with bone fracture AEs by subgroup - TS

Sub-group variable	Subgroup category	Placebo			Empa 10 mg			Empa 25 mg		
		N	n (%)	Rate/ 100 pt-yrs	N	n (%)	Rate/ 100 pt-yrs	N	n (%)	Rate/ 100 pt-yrs
Age [years]	<50	142	5 (3.5)	1.50	154	4 (2.6)	1.01	143	5 (3.5)	1.29
	50 to <65	1155	40 (3.5)	1.38	1146	39 (3.4)	1.32	1153	33 (2.9)	1.11
	65 to <75	808	35 (4.3)	1.83	834	39 (4.7)	1.90	833	37 (4.4)	1.77
	≥75	228	11 (4.8)	2.16	211	10 (4.7)	2.09	213	12 (5.6)	2.49
Sex	Male	1680	49 (2.9)	1.19	1653	52 (3.1)	1.24	1683	64 (3.8)	1.47
	Female	653	42 (6.4)	2.76	692	40 (5.8)	2.40	659	23 (3.5)	1.45
Baseline eGFR [mL/min/ 1.73 m^2]	≥90	488	9 (1.8)	0.73	519	15 (2.9)	1.16	531	13 (2.4)	0.96
	60 to <90	1238	50 (4.0)	1.65	1221	46 (3.8)	1.47	1202	48 (4.0)	1.53
	45 to <60	418	25 (6.0)	2.60	420	20 (4.8)	1.92	411	19 (4.6)	1.85
	30 to <45	183	6 (3.3)	1.42	178	11 (6.2)	2.82	182	7 (3.8)	1.76
	<30	6	1 (16.7)	8.3	7	0	0	14	0	0

N = number of treated patients; n = number of patients in the subgroup with bone fracture
Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data tables indicated below.

Source: Table 12.1.3.7: 2 study report NDA 204629, SDN 406

Reviewer comment: While it is somewhat reassuring that no significant differences were seen regarding bone fractures between placebo and empagliflozin, fractures do remain a concern with the entire class of SGLT2 inhibitors. Longer exposure may be needed to see effects. Additionally, the higher frequency of upper extremity fractures was also observed with canagliflozin, another member of the class.

Malignancy events

Adverse events related to malignancies were summarized based on an SMQ. Since malignancies detected off treatment were most likely present on treatment, all malignancy AEs up to trial termination are included in the analyses, which includes events after treatment discontinuation. In addition, patients with malignancy with an onset after 6 months cumulative exposure on treatment were also evaluated due to the latency in malignancy development.

The overall frequencies for malignancy up to trial termination were slightly higher for the empagliflozin pooled group compared to placebo (4.1% vs 3.8%), and the same was true for the patients with malignancy with an onset after 6 months cumulative exposure to study medication.

Given that malignancies typically have a long latency period for development, examining the malignancy events occurring after six months of treatment in patients treated for greater than six months may give a more accurate perspective of the risk for malignancy events associated with

empagliflozin use. I focused on the malignancies identified after at least 6 months of exposure to the drug below in Table 74.

Table 74 Malignancies that occurred after at least 6 month exposure to the study drug by HLT - TS

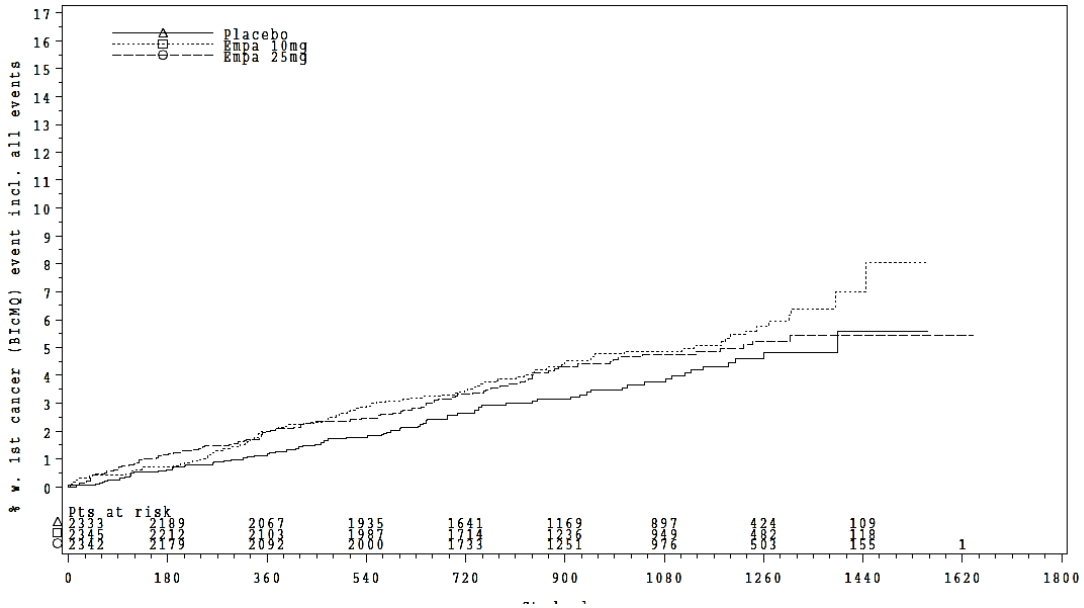
High Level Term	All Empa	Placebo
Skin neoplasms malignant and unspecified (excl melanoma)	36 (0.8%)	21 (1.0%)
Colorectal neoplasms malignant	21 (0.5%)	7 (0.3%)
Prostatic neoplasms malignant	20 (0.5%)	9 (0.4%)
Metastases to specified sites	13 (0.3%)	6 (0.3%)
Neoplasms malignant site unspecified NEC	12 (0.3%)	5 (0.2%)
Non-small cell neoplasms malignant of the respiratory tract cell type specified	11 (0.2%)	5 (0.2%)
Renal neoplasms malignant	9 (0.2%)	5 (0.2%)
Bladder neoplasms malignant	8 (0.2%)	1 (0.0%)
Pancreatic neoplasms malignant (excl islet cell and carcinoid)	8 (0.2%)	1 (0.0%)
Skin melanomas (excl ocular)	7 (0.2%)	2 (0.1%)
Breast and nipple neoplasms malignant	7 (0.2%)	3 (0.1%)
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	7 (0.2%)	6 (0.3%)
Hepatic neoplasms malignant	4 (0.1%)	2 (0.1%)
Laryngeal neoplasms malignant	3 (0.1%)	0 (0.0%)
Leukaemias chronic lymphocytic	3 (0.1%)	0 (0.0%)
Endocrine neoplasms malignant and unspecified NEC	3 (0.1%)	1 (0.0%)
Plasma cell myelomas	3 (0.1%)	1 (0.0%)
Oropharyngeal, nasopharyngeal and tonsillar neoplasms malignant and unspecified	2 (0.0%)	0 (0.0%)
Bile duct neoplasms malignant	2 (0.0%)	0 (0.0%)
Lip and oral cavity neoplasms malignant	2 (0.0%)	2 (0.1%)
Gastric neoplasms malignant	2 (0.0%)	2 (0.1%)
Urinary tract neoplasms malignant NEC	2 (0.0%)	3 (0.1%)
Esophageal neoplasms malignant	2 (0.0%)	4 (0.2%)
Gastrointestinal neoplasms malignancy unspecified NEC	1 (0.0%)	0 (0.0%)
Splenic marginal zone lymphomas	1 (0.0%)	0 (0.0%)
Fibrosarcomas malignant	1 (0.0%)	0 (0.0%)
Lymphoproliferative disorders NEC (excl leukaemias and lymphomas)	1 (0.0%)	0 (0.0%)
Nervous system neoplasms unspecified malignancy NEC	1 (0.0%)	0 (0.0%)
Leukaemias acute lymphocytic	1 (0.0%)	0 (0.0%)
Ovarian neoplasms malignant (excl germ cell)	1 (0.0%)	0 (0.0%)
Cervix neoplasms malignant	1 (0.0%)	0 (0.0%)
Penile neoplasms malignant	1 (0.0%)	0 (0.0%)
Islet cell neoplasms and APUDoma NEC	1 (0.0%)	0 (0.0%)
Metastases to unknown and unspecified sites	1 (0.0%)	0 (0.0%)
Neoplasms unspecified malignancy and site unspecified NEC	1 (0.0%)	0 (0.0%)
Soft tissue sarcomas histology unspecified	1 (0.0%)	0 (0.0%)
Respiratory tract small cell carcinomas	1 (0.0%)	0 (0.0%)
Uterine neoplasms malignant NEC	1 (0.0%)	0 (0.0%)

B-cell lymphomas NEC	1 (0.0%)	1 (0.0%)
Lymphomas unspecified NEC	1 (0.0%)	1 (0.0%)
Hepatobiliary neoplasms malignancy unspecified	1 (0.0%)	1 (0.0%)
Thyroid neoplasms malignant	1 (0.0%)	1 (0.0%)
Bone neoplasms malignant (excl sarcomas)	1 (0.0%)	1 (0.0%)
Non-Hodgkin's lymphomas NEC	1 (0.0%)	1 (0.0%)
Salivary gland neoplasms unspecified malignancy	1 (0.0%)	1 (0.0%)
Hodgkin's disease NEC	0 (0.0%)	1 (0.0%)
Skin and subcutaneous tissue ulcerations	0 (0.0%)	1 (0.0%)
Gastrointestinal neoplasms malignant NEC	0 (0.0%)	1 (0.0%)
Oncologic complications and emergencies	0 (0.0%)	2 (0.1%)
Total	**179 (4.1%)**	**83 (3.8%)**

Source: Reviewer generated using Jreview, ADAE, ADSL datasets, NDA 204629, SDN 406

The curves in the Kaplan-Meier analysis of time to the onset of the first malignancy are presented below in Figure 27. It does appear that after 180 days there is a separation of the empagliflozin curves from the placebo one, although the differences are small.

Figure 27 Kaplan-Meier Time to Event Analysis for Malignancy Events



Source: Figure 15.3.1.18: 2 study report NDA 204629, SDN 406

Malignant cases up to trial termination were manually reviewed by the Applicant and grouped by medical topic, based on HLTs, and/or PTs. Due to signals observed in the original empagliflozin NDA review, breast cancer, bladder cancer, renal cancer, lung cancer, and skin melanoma were defined as the malignancies of special interest in this trial, and their incidence is presented in Table 75 below. Lung, breast, and renal cancer occurred with similar frequency in placebo and

pooled empagliflozin groups, while pancreatic malignancies and melanoma occurred with higher frequency in the pooled empagliflozin group compared to placebo. Bladder cancer was marginally more frequent in the empagliflozin pool compared to placebo. In addition, prostate cancer occurred in a similar proportion of patients across treatment groups. While some imbalances can still be observed in this study, the overall numbers are very small and it would be difficult to hypothesize that some of these malignancies are caused by treatment with empagliflozin.

Table 75 Malignancies of Interest after 6 Months of Exposure by HLT and PT

Malignancy of interest/High Level Term	Preferred Term	All Empa	Placebo
Breast cancer	**Total**	**7 (0.16%)**	**3 (0.14%)**
Breast and nipple neoplasms malignant	Breast cancer	5 (0.11%)	2 (0.09%)
	Intraductal proliferative breast lesion	1 (0.02%)	0 (0.00%)
	Invasive ductal breast carcinoma	1 (0.02%)	1 (0.05%)
Bladder cancer	**Total**	**10 (0.23%)**	**4 (0.18%)**
Bladder neoplasms malignant	Bladder cancer	6 (0.14%)	1 (0.05%)
	Bladder transitional cell carcinoma	2 (0.05%)	0 (0.00%)
Urinary tract neoplasms malignant NEC	Transitional cell carcinoma	2 (0.05%)	3 (0.14%)
Pancreatic cancer	**Total**	**8 (0.18%)**	**1 (0.05%)**
Pancreatic neoplasms malignant (excl islet cell and carcinoid)	Adenocarcinoma pancreas	3 (0.07%)	1 (0.05%)
	Pancreatic carcinoma	4 (0.09%)	0 (0.00%)
	Pancreatic carcinoma metastatic	1 (0.02%)	0 (0.00%)
Melanoma	**Total**	**7 (0.16%)**	**2 (0.09%)**
Skin melanomas (excl ocular)	Malignant melanoma	5 (0.11%)	2 (0.09%)
	Malignant melanoma in situ	2 (0.05%)	0 (0.00%)
	Metastatic malignant melanoma	0 (0.00%)	1 (0.05%)
Lung cancer	**Total**	**19 (0.43%)**	**11 (0.50%)**
Non-small cell neoplasms malignant of the respiratory tract cell type specified	Large cell lung cancer	0 (0.00%)	1 (0.05%)
	Lung adenocarcinoma	7 (0.16%)	2 (0.09%)
	Lung adenocarcinoma metastatic	1 (0.02%)	0 (0.00%)
	Lung squamous cell carcinoma .stage III	0 (0.00%)	1 (0.05%)
	Non-small cell lung cancer stage IV	0 (0.00%)	1 (0.05%)
	Squamous cell carcinoma of lung	3 (0.07%)	0 (0.00%)
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	Bronchial carcinoma	1 (0.02%)	0 (0.00%)
	Lung cancer metastatic	1 (0.02%)	1 (0.05%)
	Lung neoplasm malignant	5 (0.11%)	5 (0.23%)
Respiratory tract small cell carcinomas	Small cell lung cancer	1 (0.02%)	0 (0.00%)
Renal cancer	**Total**	**9 (0.20%)**	**5 (0.23%)**
Renal neoplasms malignant	Clear cell renal cell carcinoma	3 (0.07%)	3 (0.14%)
	Renal cancer	2 (0.05%)	0 (0.00%)

	Renal cancer metastatic	1 (0.02%)	0 (0.00%)
	Renal cell carcinoma	2 (0.05%)	1 (0.05%)
	Renal cell carcinoma stage I	1 (0.02%)	0 (0.00%)
	Renal cell carcinoma stage II	0 (0.00%)	1 (0.05%)

Source: Reviewer generated using JReview, ADAE, ADAEADJ, and ADSL datasets, NDA 204629, SDN 406

Adjudication results for malignancies by the adjudication committee (oncAAC) could be reported as possibly related to study medication, not related to study medication, or not assessable. The WHO causality categories were to be used as a guide in assessing the relationship. According to the guidance in the oncAAC charter, cases not related to study medication included any assessable cases in which the event or laboratory test abnormality had a time relative to drug intake that made a relationship improbable (but not impossible) or in which disease or other drugs provided plausible explanations. All other assessable cases were considered to be possibly related to study medication.

Out of the 83 patients (3.78%) in the placebo group that were reported with a malignancy after at least 6 months exposure to study drug, 79 (3.6%) had the events sent for adjudication. In the empagliflozin pool, out of the 179 patients (4.05%) with malignancy events after at least 6 months of exposure to study drug, 169 (3.83%) had events sent for adjudication. Of those, 16 (0.73%) events in the placebo group were reported as positively adjudicated (meaning adjudicated as possibly related), and 31 (0.70%) events in the empagliflozin pool. The events that were not sent for adjudication were hematologic malignancies in all treatment groups.

Patients with specific cancers where an imbalance was noted are discussed below.

Pancreatic cancer

Placebo

Only one patient was identified with PT 'adenocarcinoma pancreas' in the placebo group, patient no (b) (6) This is a 59 year old white male from Austria, who was started on study treatment with placebo on March 9, 2011, and was diagnosed with adenocarcinoma of the pancreas on June 13, 2012, the 463rd day since randomization. On (b) (6), the patient had pancreatectomy, splenectomy, and cholecystectomy, and histology results showed the presence of pancreatic adenocarcinoma (Grade III) with little differentiation. Study medication was discontinued on November 1, 2012 because of this event.

Empagliflozin

Patient no (b) (6): 66 year old white male from US started on empagliflozin 25 mg on July 19, 2012. On April 16, 2014, the 637th day post randomization, he was found to have elevated liver

function tests which met the criteria for Hy's law at a later date, and weight loss of approximately 20 lbs. On (b) (6), the (b) (6) day post randomization, he was diagnosed with pancreatic papillary adenocarcinoma and underwent pancreaticoduodenectomy. Notably the patient was not on DPP-4 inhibitors or GLP-1 receptor agonist during this trial, and there is no documentation to suggest that he was ever on one of these classes of medications. The study medication was continued until February 24, 2015. The only reported background diabetes medications were metformin and SU. The SAE reported that the patient consumed 4-5 beers daily. The adjudication committee deemed the event not related to the study drug.

Patient no (b) (6): 71 year old white male from Denmark started treatment with empagliflozin 10 mg on February 15, 2011. On September 17, 2013, the 946th day after randomization, he was diagnosed with adenocarcinoma of the head of the pancreas, with metastases to the lung, which lead to death (b) (6) later. At the time of the diagnosis, he was found to have elevated glucose, elevated liver enzymes, jaundice, and ascites. According to SAE report, the patient smoked less than 10 cigarettes per day and sometimes drank more than 20 drinks per day. Background diabetes medications were metformin, DPPP-4 inhibitor, and insulin. The adjudication committee has determined that the event was not related to the study drug.

Patient no (b) (6): 65 year old white male from Canada, started empagliflozin 10 mg daily on December 6, 2012. On September 8, 2014, the 642nd day post randomization, the patient presented to the emergency room with abdominal pain, and underwent a computed tomography which lead to the diagnosis of poorly differentiated pancreatic adenocarcinoma with liver metastasis. The study drug was discontinued on December 9, 2014, due to this event, and the event was ongoing at the time of the last available report. The only background diabetes medication was metformin. It was reported that the patient was a smoker and his sister had pancreatic cancer. The adjudication committee deemed the event not related to the study drug.

Patient no (b) (6): 65 year old white male from Spain started treatment with empagliflozin 10 mg on March 16, 2011. His only previous antidiabetic treatment was metformin. On January 22, 2015, a chest/abdomen/pelvis computerized tomography (CT) was performed for an unclear reason which showed multiple cholelithiasis, calcifications in arterial walls, vertebrate degenerative signs and hypodense pancreatic lesion of 28 mm in pancreatic tail. The patient was diagnosed with neoplasm of pancreas with infiltration and metastasis to the colon. The pancreatic carcinoma remained ongoing at study completion. The narrative stated that the study medication was discontinued on December 30, 2014, due to the event of pancreatic carcinoma. The adjudication committee deemed the event non assessable.

Patient no (b) (6): 61 year old white male from Italy started on empagliflozin 25 mg daily on January 7, 2011. The only reported background antidiabetic medications were metformin and

repaglinide. In January 2015 (the 1470th day post randomization), the patient presented with abdominal, and lower back pain, and was diagnosed with pancreatic carcinoma (6 cm lesion pancreatic tail with infiltration of the splenic hilum). The patient was off treatment, the study drug had already been discontinued on January 14, 2015 when the patient completed the study according to the protocol. The adjudication committee considered the event possibly related to the study drug.

Patient no (b) (6): 67 year old white female from Italy started treatment with empagliflozin 10 mg on March 22, 2011. Insulin alone was reported as background diabetes medication. On September 10, 2014, the 1269th day since randomization, the patient was diagnosed with pancreatic carcinoma, which resulted in the patient's death on (b) (6). The adjudication committee considered the event possibly related to the study drug.

Patient no (b) (6): 65 year old white male patient from Russia, started treatment with empagliflozin 10 mg on October 29, 2012. The background diabetes medications were metformin and SU, and the patient had a history of chronic pancreatitis. The patient was a non-smoker, did not drink any alcohol, and there was no family history of cancer. On June 10, 2013, the 225th day post randomization, the patient was diagnosed with pancreatic carcinoma, which lead to discontinuation of the study medication on June 19, 2013, and to death on (b) (6) as a result of postoperative complications. The adjudication committee deemed the event not related to the study drug

Patient no (b) (6) 70 year old Asian male from Japan started on empagliflozin 25 mg on January 9, 2013. The background diabetes medications were metformin and SU. The patient was an ex-smoker, with a family history of gastric cancer (mother), and pharyngeal cancer (sister). He was diagnosed with carcinoma of the head of the pancreas with superior mesenteric artery invasion on September 9, 2013, the 244th day post randomization. The patient died (b) (6) later due to interstitial pneumonia vs lung metastasis. The study drug was permanently discontinued due to the event of pancreatic carcinoma. The adjudication committee deemed the event not related to the study drug.

Characteristics and risk factors for the patients with pancreatic cancer are summarized in Table 76 below. It is difficult to discuss the potential association between empagliflozin treatment and pancreatic cancer despite the large numerical imbalance in this particular study, since the event is rare, and it is not clear how empagliflozin could cause pancreatic cancer given what we know so far about its mechanism of action. In addition, this patient population is at increased risk of pancreatic cancer due to having T2DM.

Table 76 Characteristics and Risk Factors for Patients with Pancreatic Cancer by Treatment Arm

Treatment	Patient no	Days post randomization	DPP4i/ GLP-1	Alcohol/s moking	Fatal	FH malignancy	Adjudicated
Placebo	(b) (6)	463	no	Not available	No	Not available	Not related
Empa 10		946	DPP4	Yes both	Yes	Not available	Not related
Empa 10		642	no	Smoker	No	Sister pancreatic cancer	Not related
Empa 10		Almost 4 years	no	Not available	No	Not available	Not assessable
Empa 10		1269	no	Not available	Yes	Not available	Possibly related
Empa 10		225	no	No	Yes	No	Not related
Empa 25		637	no	4-3 beers/day	No	Not available	Not related
Empa 25		1470	no	Not available	No	Not available	Possibly related
Empa 25		244	no	Ex-smoker	Yes	gastric cancer (mother), and pharyngeal cancer (sister)	Not related

Source: Reviewer generated from narratives provided by the Applicant, NDA 204629, SDN 406

Bladder cancer:

Placebo

Patient no (b) (6): 78 year old white male from Spain started treatment on placebo on March 1, 2011. On March 12, 2013, he was diagnosed with grade papillary urothelial carcinoma which lead to discontinuation of the study drug. The SAE report indicated that a possible bladder neoplasm was suspected, and, on the same day, a transurethral resection of the bladder lesions was performed to further evaluate the ongoing hematuria. The adjudication committee deemed the event not assessable.

Patient no (b) (6): 70 year old white male from Poland started on placebo on July 5, 2011. On December 9, 2014, he was diagnosed with transitional bladder cancer for which he underwent transurethral resection of the tumor, and also received doxorubicin. On 04 Feb 2014, the 946th day since randomization, the patient took the last dose of the study drug and completed the study as per protocol on 26 Mar 2015. The external independent committee has determined the event was not assessable.

Patient no (b) (6): 71 year old white male from Italy started placebo on April 26, 2012. It was reported that the patient was non-smoker, and his mother had uterine cancer. As per SAE report the patient had no exposure to any toxic drugs, or external beam radiation. On 20 Nov 2014, the 939th day since randomization, the patient underwent trans urethral resection of high grade urothelial carcinoma. No action was taken with the study drug. The external independent committee has determined the event was not related to the study drug.

Empagliflozin

Patient no (b) (6): 72 year old white male started on empagliflozin 10 mg January 11, 2011. It was reported that the patient had no history of frequent bladder infections or cancer in the family. He also did not have exposure to any toxic drugs, chemicals or radiation. Ex-smoker since 1998. On October 31, 2014, the 1390th day since randomization, the patient experienced hematuria and was diagnosed with bladder cancer. He had bladder polyps surgically removed, followed by treatment with mitomycin. The event was ongoing at the time of the last available report. No action was taken with the study drug due to this event. The adjudication committee deemed the event possibly related to the study drug.

Patient no (b) (6) 73 year old white male from Ukraine, treated with empagliflozin 25 mg since May 26, 2011. He did not have any reported history of cancer, smoking, chemical or toxicological injury. On March 31, 2014, the 1041st day post randomization, he was diagnosed with bladder cancer and BPH. He underwent a transurethral resection of the bladder and prostate. He died due to this event on (b) (6). The histopathology report stated that the urinary bladder cancer was Grade 1 and classified as T2BN0M2 on TNM classification, as per SAE report, but according to the source documents it was characterized as Stage II, high grade moderately differentiated transitional cell carcinoma, infiltrative muscle layer of the wall with numerous emboli in vessel with T2gNxM0. The adjudication committee deemed the event possibly related to the study drug.

Patient no (b) (6): 72 year old white male from US, on empagliflozin 25 mg since July 26, 2012. He was a smoker. On May 18, 2014, the 662nd day post randomization, he presented with hematuria, and was diagnosed with bladder cancer. It was reported that on 12 May 2014, the patient underwent removal of 3 bladder tumors with placement of one stent. The event bladder cancer was ongoing at the time of the last available report. The adjudication committee has determined the event to be not related to the study drug.

Patient no (b) (6): 74 year white male from Norway started empagliflozin 25 mg on December 22, 2011. On January 16, 2014, the 757th day post randomization, he was diagnosed with bladder cancer. The study drug was permanently discontinued due to this event. The patient

underwent a radical cystectomy with cutaneous uretero-ileostomy. The adjudication committee deemed the event possibly related to the study drug.

Patient no (b) (6): 70 year old male from US on empagliflozin 25 mg since November 13, 2012. The patient had a family history of cancer (mother experienced mouth cancer), and he stopped smoking in 1982 after 27 years. On November 7, 2013, the 360th day post randomization, he was diagnosed with bladder cancer, for which he received chemotherapy with cisplatin. He presented with symptoms of difficulty in urination, erectile dysfunction; and pain in lower back, hips, and upper thighs. The study drug was permanently discontinued due to the event, and the patient refused further follow-up. He died on (b) (6). The adjudication committee determined the event to be not assessable.

Patient no: (b) (6): 67 year old white male from Brazil started on empagliflozin 25 mg on August 22, 2012. The patient was an ex-smoker who smoked 10 cigarettes per day for 44 years (22 pack/years), since 1964 until 2008. He had a family history of cancer, which included his brother who had larynx and esophageal cancer. On an unspecified day in Jun 2014, the 663th day since randomization (the exact onset date is unknown, hence calculation assuming the onset date as 15 Jun 2014), the patient was diagnosed with pyelonephritis and bladder cancer. The study drug was permanently discontinued due to both events. He underwent diagnostic transurethral resection, and upon further examination it was revealed that it was invasive urothelial carcinoma of high degree with squamous differentiation in prostate and bladder. He also underwent radiotherapy for the bladder cancer. The patient did not come to the scheduled follow up after this event. He did have a history of recurrent asymptomatic UTIs. The adjudication committee determined the event to be not assessable.

Patient no (b) (6): 70 year old white male from Austria on placebo since March 20, 2012. The study medication was discontinued at the patient's request on December 24, 2013, no AEs were ongoing at the time. He was diagnosed with bladder cancer on July 1, 2014, the 834th day post randomization, and 190th day after discontinuation of the study drug. The patient had no history of cancer, alcohol use or smoking. He had recurrent urinary tract infections which led to further evaluation and diagnosis of the bladder cancer. He underwent transurethral resection of urinary bladder and prostate and chemotherapy was planned. The event remained ongoing at study completion. However, outcome of the event was reported as recovered with sequelae on an unknown date. The adjudication committee deemed the event possibly related to the study drug.

Patient no (b) (6): 70 year old white male from Italy, started empagliflozin 25 mg on December 12, 2011. The SAE report noted that the patient smoked 20 packs per year until 1994, he had no family history of bladder cancer, no known exposures to environmental risk factors for bladder cancer, and he denied alcohol consumption. On January 22, 2013, the 408th day since

randomization, he was diagnosed with bladder cancer during evaluation for hematuria, which led to permanent discontinuation of the study medication on March 5, 2013. The patient underwent an unspecified surgery for the bladder cancer. The AE was ongoing at the time of study completion which was March 19, 2015. The adjudication committee deemed the event not related to the study drug.

Patient no (b) (6): 70 year old white female from South Africa started on empagliflozin 10 mg on October 26, 2011. She was a known smoker per the narrative, but did not have any other toxin exposure, did not consume alcohol, and there was no family history of bladder cancer. On July 31, 2012, the 280th day since randomization, she was diagnosed with bladder cancer (presented with hematuria). Cystoscopy with tumor resection was performed, and the study drug was continued until the completion of the study, on April 1, 2015. The adjudication committee deemed the event not related to the study drug.

Patient no (b) (6) 65 year old white male from France started empagliflozin 10 mg on April 18, 2011. The patient was an ex-smoker (stopped 2003), and denied any exposure to radiation therapy. On March 27, 2012, the 345th day post-randomization, he was diagnosed with bladder cancer during workup for hematuria. On May 9, 2012, the patient underwent an endoscopic resection of the urothelial papilloma. He had a relapse of the bladder cancer on May3, 2013, the 747th day since randomization. No action was taken with the study drug because of this event. The adjudication committee deemed the event not related to the study drug.

Patient no (b) (6): 69 year old Asian male from Taiwan started empagliflozin 25 mg on May 13, 2011. On January 7, 2013, the 606th day since randomization, he was diagnosed with bladder transitional cell carcinoma (presented with hematuria). The tumor course was complicated, and it appears that the right ureter was also involved. He underwent iliac artery endarterectomy, transurethral resection of bladder tumor, laparoscopic nephroureterectomy and partial cystectomy on (b) (6). The event papillary urothelial carcinoma was ongoing at the time of the last available report. No action was taken with the study drug due to the event. The adjudication committee deemed the event possibly related to the study drug.

Reviewer comments: Review of EMPA-REG did alleviate some concerns that came up at the time of the empagliflozin NDA review, as malignancies were overall balanced between the treatment groups. However, certain malignancies did occur more frequently with empagliflozin compared to placebo. As discussed above, an imbalance not favoring empagliflozin was observed for pancreatic cancer, however, most cases were adjudicated as not related to the study drug as the patients had confounding risk factors. Two cases, adjudicated as possibly related, lacked information regarding other potential risk factors. It is difficult to conclude that this represents a real signal since type 2 diabetes represents a risk

factor for pancreatic cancer, and this finding is difficult to explain given the mechanism of action for empagliflozin. In my opinion, this finding is likely to be due to chance.

An imbalance also not favoring empagliflozin was observed for melanomas, however the overall numbers were small and unlikely to be related to the study drug. Breast, renal, and bladder cancer, which were concerning at the time at the time of the NDA review, were balanced in EMPA-REG.

Embolic and thrombotic adverse events

Venous embolic and thrombotic events were analyzed as AESIs due to the increase in hemoglobin/hematocrit observed with empagliflozin throughout the development program. The applicant summarized the events based on a narrow SMQ (PTs listed in appendix 16.2.7 of the submission). Cerebrovascular events were not included in this section by the Applicant as they are discussed in the efficacy section as part of the primary endpoint.

As defined by the Applicant, the incidence rates of venous embolic and thrombotic AEs were comparable in both the empagliflozin and the placebo treatment groups.

The most frequently reported PT was deep vein thrombosis, which did occur more frequently in the empagliflozin 25 mg arm compared to placebo and empagliflozin 10 mg. However, this is likely to be due to chance as the overall occurrence is rare, and a higher proportion of patients in the placebo group had this AE compared to the patients in the empagliflozin 10 mg arm. The proportion of patients with thromboembolic SAEs was higher in the placebo group compared to either of the empagliflozin groups.

Table 77 Incidence rates for adverse events of venous embolic and thrombotic adverse events (narrow SMQ), sorted by frequency - TS

	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	20 (0.9)	0.35	9 (0.4)	0.15	21 (0.9)	0.35
Deep vein thrombosis	5 (0.2)	0.09	3 (0.1)	0.05	10 (0.4)	0.17
Pulmonary embolism	4 (0.2)	0.07	0	0	6 (0.3)	0.10
Thrombophlebitis	4 (0.2)	0.07	3 (0.1)	0.05	1 (<0.1)	0.02
Retinal vein occlusion	2 (0.1)	0.03	0	0	0	0
Thrombophlebitis superficial	2 (0.1)	0.03	2 (0.1)	0.03	1 (<0.1)	0.02
Venous occlusion	2 (0.1)	0.03	0	0	0	0
Venous thrombosis limb	2 (0.1)	0.03	0	0	1 (<0.1)	0.02
Deep vein thrombosis postoperative	0	0	0	0	1 (<0.1)	0.02
Mesenteric vein thrombosis	0	0	0	0	1 (<0.1)	0.02
Post thrombotic syndrome	1 (<0.1)	0.02	0	0	0	0
Pulmonary thrombosis	0	0	0	0	1 (<0.1)	0.02
Venous thrombosis	1 (<0.1)	0.02	1 (<0.1)	0.02	1 (<0.1)	0.02
Leading to discontinuation	2 (0.1)	0.03	0	0	2 (0.1)	0.03
Serious AEs	13 (0.6)	0.23	5 (0.2)	0.08	19 (0.8)	0.31

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

Source: Table 12.1.3.10: 1 study report NDA 204629, SDN 406

When nonfatal cerebrovascular events are included in this analysis, the results are as follows: 114 patients (4.89%) in the placebo arm, and 223 patients (4.76%) in the pooled empagliflozin arm. This analysis used Applicant provided flags for non-fatal stroke, TIA, and other embolic events.

In conclusion, thromboembolic events excluding stroke (discussed under the primary endpoint) were balanced between treatment groups.

Hypersensitivity

The Applicant summarized adverse events related to hypersensitivity based on a narrow SMQ.

While the overall incidence rates of hypersensitivity were comparable in both the empagliflozin and the placebo treatment groups, serious events such as anaphylactic shock, and anaphylactic reaction, only occurred in the empagliflozin arms (2 patients with PT anaphylactic shock – one in

each empagliflozin treatment arm and 2 patients with PT anaphylactic reaction – again, one in each empagliflozin treatment arm).

The most frequently reported PT was 'rash', which was reported at higher incidence rates in empagliflozin treatment groups compared with placebo (empagliflozin 10 mg: 0.72/100 pt-yrs; empagliflozin 25 mg: 0.89/100 pt-yrs; placebo: 0.59/100 pt-yrs).

Table 78 Incidence rates for adverse events of hypersensitivity according to the narrow SMQ for hypersensitivity, with a frequency of >=0.3%, sorted by frequency - TS

	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	197 (8.4)	3.59	158 (6.7)	2.75	181 (7.7)	3.14
Rash	34 (1.5)	0.59	43 (1.8)	0.72	53 (2.3)	0.89
Eczema	27 (1.2)	0.47	25 (1.1)	0.42	21 (0.9)	0.35
Dermatitis	18 (0.8)	0.31	15 (0.6)	0.25	20 (0.9)	0.33
Rhinitis allergic	19 (0.8)	0.33	17 (0.7)	0.28	16 (0.7)	0.27
Hypersensitivity	10 (0.4)	0.17	12 (0.5)	0.20	14 (0.6)	0.23
Urticaria	15 (0.6)	0.26	9 (0.4)	0.15	14 (0.6)	0.23
Dermatitis contact	6 (0.3)	0.10	7 (0.3)	0.12	12 (0.5)	0.20
Dermatitis allergic	10 (0.4)	0.17	9 (0.4)	0.15	6 (0.3)	0.10
Bronchospasm	8 (0.3)	0.14	1 (<0.1)	0.02	2 (0.1)	0.03
Conjunctivitis allergic	6 (0.3)	0.10	6 (0.3)	0.10	6 (0.3)	0.10
Drug hypersensitivity	6 (0.3)	0.10	8 (0.3)	0.13	4 (0.2)	0.07
Rash macular	6 (0.3)	0.10	0	0	2 (0.1)	0.03
Rash pruritic	8 (0.3)	0.14	5 (0.2)	0.08	2 (0.1)	0.03
Swelling face	6 (0.3)	0.10	1 (<0.1)	0.02	0	0
Leading to discontinuation	10 (0.4)	0.17	7 (0.3)	0.12	11 (0.5)	0.18
Serious AEs	7 (0.3)	0.12	3 (0.1)	0.05	10 (0.4)	0.17

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

Source: Table 12.1.3.9: 1 study report NDA 204629, SDN 406

Narratives of the patients who were reported with anaphylactic shock, and anaphylactic reaction, are presented below.

Patient no [redacted] (b) (6): 53 female from US, started empagliflozin 10 mg on March 31, 2011. The patient did not have a prior history of anaphylaxis, drug reaction, urticaria, angioedema, or other type of allergic diseases. The patient's antidiabetic background medication at study entry were insulin, metformin, and sulfonylurea. Concomitant therapies within 2 weeks before the anaphylactic reaction included aspirin, calcium, diltiazem, esomesoprazole, folic acid,

gabapentin, isosorbide dinitrate, levothyroxine, lisinopril, metoprolol, multivitamin, paroxetine, pravastatin, and ticlopidine. On (b) (6), the 292nd day since randomization, the patient experienced a severe anaphylactic reaction of unknown origin, which led to hospitalization on that day, and was considered resolved the next day. Treatment for the anaphylactic reaction included Benadryl (diphenhydramine), Allegra (fexofenadine), and prednisone, and she also received Zantac (ranitidine). No further details, including diagnostic or laboratory assessments were reported. The study medication was not discontinued due to this AE. Vital status follow up on December 22, 2014 revealed that she was still alive.

Patient no (b) (6): 58 year old white male from South Africa started empagliflozin 10 mg on February 15, 2012. On (b) (6), the 120th day since randomization, the patient experienced severe anaphylactic shock which led to being hospitalized; no further description of the clinical signs/symptoms were provided. No other adverse events were reported at the onset of this condition. Treatments included Adrenaline (epinephrine) and Solu-Cortef (hydrocortisone). Study medication was neither discontinued nor reduced because of the anaphylactic shock. The patient's antidiabetic background medication was 144 IU insulin and 1500 mg metformin at study entry. Concomitant therapies within 2 weeks before the event included Ecotrin (acetylsalicylic acid), felodipine, and simvastatin.

Patient no (b) (6): 64 year old white male from Spain started empagliflozin 25 mg on January 26, 2011. On (b) (6), the (b) (6) day since randomization, the patient experienced severe anaphylactic shock which was considered serious since it was immediately life-threatening, and resulted in hospitalization. The only ongoing adverse event was mild tooth pain. The patient was stung by a bee, which led to an immediate life-threatening condition and was treated with prednisone. No further details of the hospital course or discharge date were reported. The anaphylactic shock was considered resolved the next day. Study medication was neither discontinued nor reduced because of the anaphylactic shock.

Patient no (b) (6): 61 year old female from the Philippines started empagliflozin 25 mg on September 22, 2011. On (b) (6), the (b) (6) day since randomization, the patient developed severe anaphylactic reaction secondary to food intake (shrimp, as per SAE report) which led to hospitalization. As per SAE report, a few minutes after eating shrimp, the patient experienced sudden onset of discomfort along with severe difficulty breathing. She was treated with intravenous fluids, hydrocortisone, and albuterol/ipratropium. She recovered from the event the next day. On (b) (6), the (b) (6) day since randomization, the patient experienced moderate hypersensitivity reaction secondary to food intake and mild gastritis, which led to hospitalization on the same day. It was reported that the hypersensitivity reaction was secondary to food intake along with sudden onset of epigastric pain, after eating chicken and fried eggs. She received treatment with 'dudront plus' and bromazepam (according to the SAE report),

hydrocortisone nebulisation, ipratropium/salbutamol, and budesonide for the event food allergy. On the next day the patient recovered from the event food allergy and gastritis. No action was taken with the study drug.

Reviewer comment: Only two of the patients presented above had an anaphylactic event not related to food allergies, or bee sting. Since the number of such events is exceedingly small, it is difficult to ascertain whether there this imbalance is clinically relevant, or just occurred by chance.

Pancreatitis

Pancreatitis has not been identified as an AESI for the empagliflozin development program. However, we have received notification of postmarketing reports of acute pancreatitis in patients treated with empagliflozin. No imbalance in pancreatitis was observed in this study with 12 patients (0.26%) reported in the empagliflozin group, and 8 patients (0.34%) reported in placebo (MAED narrow smq analysis, events on treatment +7 days), however pancreatitis is currently a tracked safety signal for empagliflozin.

Lower extremity amputations

Amputations were not identified as an AESI in the empagliflozin development program. However, another member of the class, canagliflozin, reported to the FDA that a higher incidence of lower extremity amputations was observed with canagliflozin when compared to placebo, and proposed increased vigilance for collecting such events. While it is not clear whether this is a real safety signal with canagliflozin and/or the SGLT2 inhibitor class, we performed analyses of lower extremity amputations in the EMPA-REG study. This has been a difficult endeavor as amputations were not collected in a structured way, and no events were coded to the PT "amputations" in the entire trial. The applicant performed a manual review and found that the incidence of lower extremity amputations was similar between the treatment groups (Table 79). The applicant reports that the search was done as follows: all cases in which amputation or disarticulation was reported as concomitant therapy, or as a comment in the adverse event listings were extracted. The search included 'amput'and 'disarticul'. The retrieved cases were medically reviewed and excluded, if they were no lower limb amputation. In addition, narrative text was searched (the search included 'amput', 'disarticul', 'remov', and 'resect'), to account for potential additional cases.

Table 79 Cases of lower limb amputations (ITT) –Applicant manual review and calculation

Treatment (number of treated patients)	Number of cases	Frequency
Empagliflozin 10 mg (N = 2345)	42	1.79%

Empagliflozin 25 mg (N = 2342)	47	2.01%
Placebo (N = 2333)	44	1.89%
Overall (N = 7020)	**133**	**1.89%**

Source: Applicant Table 5:2 Response to information request April 20, 2016

We performed a similar analysis by selecting narratives that contained 'Ampu', 'Resect', 'Remov', 'Biops', 'Disarticulation', 'Necrectomy', 'Gangr', as well as ADAE search for preferred terms potentially suggestive of amputations. We have not confirmed all the cases identified by the Applicant, however the conclusions do not change. The results of the FDA analysis revealed 46 patients in the placebo arm, 44 in the empagliflozin 10 mg arm, and 49 in the empagliflozin 25 mg arm with either narrative describing an amputation procedure during the study, amputation present in the comments in the ADAE dataset, or amputation present in the CM dataset.

Reviewer comment: While our analysis revealed two patients in each treatment arm that were not identified by the applicant, the overall results are very similar, and I do not see any evidence that empagliflozin treatment lead to increased risk of amputations based on my analysis of EMPA-REG. However, amputations have not been collected systematically in this trial, and the analysis is limited for that reason.

Other significant AEs

The Applicant submitted an analysis of other significant AEs included those non-serious AEs that led to premature discontinuation of trial medication or that were marked as other significant by the investigator or by the BI clinical monitor. AEs leading to discontinuation were discussed in Section 7.3.3.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The analysis of AEs was based on patients with events occurring during the on-treatment period (i.e. those reported with an onset from the first dose of randomized study medication until treatment stop + 7 days). Additionally, summaries of hepatic injury AEs were presented for the period up to 30 days after last dose of study medication and bone fractures and malignancies up to individual trial termination following an ITT approach. The overall incidence of any adverse event was comparable between the treatment arms.

Table 80 Adverse events overall summary - TS

Category of AEs	Placebo			Empa 10 mg			Empa 25 mg		
	N	(%)	Rate/100 pt-yrs	N	(%)	Rate/100 pt-yrs	N	(%)	Rate/100 pt-yrs
Number of patients	2333	(100.0)		2345	(100.0)		2342	(100.0)	
Any AE	2139	(91.7)	178.67	2112	(90.1)	150.34	2118	(90.4)	148.36
Severe AEs [1]	592	(25.4)	NA	536	(22.9)	NA	564	(24.1)	NA
Investigator-defined drug-related AEs	549	(23.5)	11.33	666	(28.4)	14.15	643	(27.5)	13.38
AEs leading to discontinuation of study medication[2]	453	(19.4)	8.26	416	(17.7)	7.28	397	(17.0)	6.89
Serious AEs [3]	988	(42.3)	22.34	876	(37.4)	18.20	913	(39.0)	19.39
Fatal	119	(5.1)	2.06	97	(4.1)	1.61	79	(3.4)	1.31
Immediately life-threatening	44	(1.9)	0.77	53	(2.3)	0.89	60	(2.6)	1.00
Disabling/incapacitating	24	(1.0)	NA	18	(0.8)	NA	22	(0.9)	NA
Requiring hospitalisation	852	(36.5)	NA	751	(32.0)	NA	818	(34.9)	NA
Prolonging hospitalisation	74	(3.2)	NA	52	(2.2)	NA	67	(2.9)	NA
Congenital anomaly	0	(0.0)	NA	0	(0.0)	NA	0	(0.0)	NA
Other	173	(7.4)	NA	151	(6.4)	NA	147	(6.3)	NA
Other significant AEs[4] (according to ICH E3)	137	(5.9)	2.41	144	(6.1)	2.44	147	(6.3)	2.47

NA = not analysed

Exposure-adjusted incidence rates are presented where calculated, with rate per 100 patient years. For the time at risk, see source data indicated below.

1 Worst intensity recorded

2 Non-serious and serious AEs; includes AEs leading to permanent discontinuation of study medication; note, per CTP, patients could subsequently restart unless there was some underlying condition that discouraged its reintroduction

3 A patient could be counted in more than 1 seriousness category.

4 Nonserious AEs, as defined in Section 9.5.3.2.1

Source: Table 12.1.1: 1 study report body

Adverse events by HLT experienced by ≥5% of patients in either treatment group are presented in Table 81**Error! Reference source not found.** below. Specific AEs of interest are discussed separately. As seen below, hyperglycemia, and hypertensive disorders occurred more frequently in the placebo group compared to empagliflozin, as did the events in the renal failure and impairment, and renal function analyses HLT. As expected based on the mechanism of action of empagliflozin, edema events were more commonly seen in placebo patients compared to the pooled empagliflozin arm.

Table 81 Adverse Events by HLT Experienced by ≥5% of Patients

High Level Term	All Empa	Placebo
Hypoglycemic conditions NEC	1370 (29.2%)	686 (29.4%)
Upper respiratory tract infections	973 (20.8%)	492 (21.1%)
Urinary tract infections	769 (16.4%)	387 (16.6%)
Musculoskeletal and connective tissue pain and discomfort	678 (14.5%)	344 (14.7%)
Ischemic coronary artery disorders	489 (10.4%)	255 (10.9%)

Lower respiratory tract and lung infections	486 (10.4%)	286 (12.3%)
Hyperglycemic conditions NEC	425 (9.1%)	432 (18.5%)
Neurological signs and symptoms NEC	384 (8.2%)	163 (7.0%)
Pain and discomfort NEC	375 (8.0%)	181 (7.8%)
Vascular hypertensive disorders NEC	340 (7.3%)	216 (9.3%)
Gastrointestinal atonic and hypomotility disorders NEC	304 (6.5%)	155 (6.6%)
Diarrhea (excl infective)	298 (6.4%)	175 (7.5%)
Non-site specific injuries NEC	293 (6.3%)	139 (6.0%)
Influenza viral infections	287 (6.1%)	167 (7.2%)
Renal failure and impairment	287 (6.1%)	182 (7.8%)
Bladder and urethral symptoms	279 (6.0%)	96 (4.1%)
Joint related signs and symptoms	268 (5.7%)	138 (5.9%)
Coughing and associated symptoms	252 (5.4%)	162 (6.9%)
Fungal infections NEC	240 (5.1%)	71 (3.0%)
Bacterial infections NEC	236 (5.0%)	127 (5.4%)
Nausea and vomiting symptoms	236 (5.0%)	126 (5.4%)
Asthenic conditions	233 (5.0%)	134 (5.7%)
Headaches NEC	230 (4.9%)	133 (5.7%)
Infections NEC	221 (4.7%)	127 (5.4%)
Gastrointestinal and abdominal pains (excl oral and throat)	211 (4.5%)	126 (5.4%)
Supraventricular arrhythmias	210 (4.5%)	102 (4.4%)
Diabetes mellitus (incl subtypes)	199 (4.2%)	185 (7.9%)
Cataract conditions	193 (4.1%)	124 (5.3%)
Breathing abnormalities	193 (4.1%)	133 (5.7%)
Edema NEC	181 (3.9%)	188 (8.1%)
Anemias NEC	178 (3.8%)	129 (5.5%)
Renal function analyses	172 (3.7%)	119 (5.1%)

Source: Reviewer generated using JReview ADAE ADSL, NDA 204629, SDN 406

7.4.2 Laboratory Findings

The Applicant submitted descriptive statistics for electrolytes, hematology parameters, uric acid, and lipid parameters.

Laboratory evaluations of hepatic and renal functions are described under Submission Specific Primary Safety Concerns/Adverse Events of Special Interest above.

Electrolytes

For evaluation of electrolytes, changes in serum sodium, potassium, calcium, magnesium, chloride, phosphate, and bicarbonate were examined. Changes in bicarbonate are discussed above under diabetic ketoacidosis (Section 7.3.5).

Median values for electrolytes at baseline, at the last value on treatment, and the change from baseline to last value on treatment are summarized in Table 82 below. No significant change in median values from baseline was reported for any of these laboratory tests. Notably, no significant changes have been observed with electrolytes relevant for bone health such as calcium, magnesium, and phosphate for either treatment group.

Table 82 Median Values for Electrolytes (Normalized Values) - TS

Parameter [units] Treatment group	Patients analysed	Baseline Median (Q1, Q3)	Last value on treatment Median (Q1, Q3)	Change from baseline to last value on treatment Median (Q1, Q3)
Sodium [mEq/L]				
Placebo	2261	141 (140, 142)	141 (140, 142)	0 (-1, 1)
Empa 10 mg	2269	141 (140, 142)	141 (140, 142)	0 (-1, 1)
Empa 25 mg	2252	141 (140, 142)	141 (140, 142)	0 (-1, 1)
Potassium [mEq/L]				
Placebo	2260	4.3 (4.0, 4.5)	4.3 (4.1, 4.5)	0.0 (-0.2, 0.3)
Empa 10 mg	2269	4.3 (4.0, 4.5)	4.3 (4.1, 4.5)	0.0 (-0.2, 0.2)
Empa 25 mg	2253	4.3 (4.0, 4.5)	4.3 (4.0, 4.5)	0.0 (-0.2, 0.2)
Calcium [mg/L]				
Placebo	2261	9.7 (9.5, 10.0)	9.7 (9.4, 10.1)	0.0 (-0.3, 0.3)
Empa 10 mg	2269	9.7 (9.5, 10.0)	9.7 (9.5, 10.0)	0.0 (-0.3, 0.3)
Empa 25 mg	2252	9.7 (9.5, 10.0)	9.7 (9.5, 10.1)	0.0 (-0.3, 0.3)
Magnesium [mEq/L]				
Placebo	2261	1.7 (1.6, 1.9)	1.7 (1.5, 1.8)	0.0 (-0.2, 0.1)
Empa 10 mg	2269	1.7 (1.6, 1.9)	1.8 (1.6, 2.0)	0.1 (0.0, 0.2)
Empa 25 mg	2252	1.7 (1.6, 1.9)	1.8 (1.7, 2.0)	0.1 (0.0, 0.2)
Chloride [mEq/L]				
Placebo	2261	102 (101, 103)	101 (100, 102)	-1 (-2, 0)
Empa 10 mg	2269	102 (101, 103)	101 (100, 103)	-1 (-2, 0)
Empa 25 mg	2252	102 (101, 103)	101 (100, 103)	-1 (-2, 0)
Phosphate [mg/L]				
Placebo	2261	3.7 (3.5, 3.8)	3.7 (3.5, 3.9)	0.0 (-0.2, 0.2)
Empa 10 mg	2269	3.7 (3.5, 3.8)	3.7 (3.5, 3.9)	0.1 (-0.1, 0.2)
Empa 25 mg	2252	3.7 (3.5, 3.8)	3.7 (3.5, 3.9)	0.1 (-0.1, 0.2)

Source: Excerpted from Table 12.3.2: 1 study report NDA 204629, SDN 406

The frequency of patients with changes in selected electrolytes from normal range to >ULN and <LLN are presented below in Table 83. There were more patients in the empagliflozin groups that experienced a shift in sodium from normal range to >ULN compared to placebo.

Table 83 Frequency of Patients with Changes in Electrolytes from Normal Range at Baseline to >ULN or to <LLN at Last Value on Treatment - TS

	Placebo n/N (%)	Empa 10 mg n/N (%)	Empa 25 mg n/N (%)
>ULN			
Sodium	14/2229 (0.6)	24/2225 (1.1)	27/2208 (1.2)
Potassium	62/2185 (2.8)	50/2193 (2.3)	56/2174 (2.6)
Calcium	89/2118 (4.2)	95/2130 (4.5)	109/2125 (5.1)
Magnesium	2/1753 (0.1)	4/1760 (0.2)	8/1755 (0.5)
Chloride	12/2231 (0.5)	7/2237 (0.3)	10/2218 (0.5)
Phosphate	47/2204 (2.1)	44/2215 (2.0)	56/2195 (2.6)
<LLN			
Sodium	20/2229 (0.9)	15/2225 (0.7)	7/2208 (0.3)
Potassium	21/2185 (1.0)	20/2193 (0.9)	23/2174 (1.1)
Calcium	57/2118 (2.7)	59/2130 (2.8)	48/2125 (2.3)
Magnesium	288/1753 (16.4)	99/1760 (5.6)	78/1755 (4.4)
Chloride	54/2231 (2.4)	40/2237 (1.8)	37/2218 (1.7)
Phosphate	28/2204 (1.3)	17/2215 (0.8)	19/2195 (0.9)

ULN: upper limit of normal; LLN: lower limit of normal; n=number of patients with value >ULN or <LLN at last observation on treatment, N=number of patients with normal value at baseline and at least 1 available on-treatment value

Source: Excerpted from Table 12.3.2: 2 study report NDA 204629, SDN 406

The Applicant identified patients with possible clinically significant abnormalities by treatment, defined as follows : for sodium – below 130 mEq/L and above 160 mEq/L, potassium – below 3 mEq/L and above 6 mEq/L, calcium – below 7.2 mg/dl and above 12 mg/dl, for chloride – below 80 mEq/L and above 120 mEq/L, phosphate – below 2.2 mg/dl and above 5.3 mg/dl, and bicarbonate – below 18 mEq/L and above 32 mEq/L. The frequencies of patients with PCSAs for electrolytes were comparable for the empagliflozin and placebo treatment groups for most electrolytes. For phosphate, there was a higher proportion of patients with PCSAs in the high range in both empagliflozin groups compared to placebo.

Table 84 Possible Clinically Significant Abnormalities for Electrolytes by Treatment

	Placebo n/N (%)	Empa 10 mg n/N (%)	Empa 25 mg n/N (%)
High			
Sodium	0/2259 (0.0)	2/2266 (<0.1)	0/2249 (0.0)
Potassium	81/2254 (3.6)	67/2260 (3.0)	71/2245 (3.2)
Calcium	0/2261 (0.0)	3/2266 (0.1)	2/2249 (<0.1)
Chloride	0/2263 (0.0)	0/2269 (0.0)	0/2252 (0.0)
Phosphate	47/2246 (2.1)	78/2253 (3.5)	82/2238 (3.7)
Bicarbonate	53/2235 (2.4)	40/2233 (1.8)	41/2212 (1.9)
Low			
Sodium	16/2259 (0.7)	9/2266 (0.4)	6/2249 (0.3)
Potassium	9/2254 (0.4)	7/2260 (0.3)	6/2245 (0.3)
Calcium	10/2261 (0.4)	16/2266 (0.7)	12/2249 (0.5)
Chloride	2/2263 (<0.1)	0/2269 (0.0)	0/2252 (0.0)
Phosphate	56/2246 (2.5)	31/2253 (1.4)	33/2238 (1.5)
Bicarbonate	112/2235 (5.0)	136/2233 (6.1)	147/2212 (6.6)

n=number of patients with possibly clinically significant high value on treatment, N=number of patients with no possibly clinically significant abnormality at baseline and at least 1 available on-treatment value
Criteria for possibly clinically significant abnormal magnesium values were not defined.
Source: Table 12.3.2: 3 study report NDA 204629, SDN 406

Overall analyses looking at changes in electrolytes in EMPA-REG are generally reassuring.

Hematology

In the original NDA review for empagliflozin, a small increase in hematocrit was observed in the empagliflozin groups from baseline to the last value on treatment. While this increase was not observed in the placebo or comparator groups, it did not result in an increase in thromboembolic or vascular events.

Consistent with this previous finding, an increase in hemoglobin, hematocrit, and RBC was observed in the study 1245.25 in the treatment groups containing empagliflozin compared to placebo (Table 85). The Applicant also presented results for all patients when compared to patients who were exposed to the study drug for at least 52 weeks and no major differences were detected for either hemoglobin or hematocrit.

There was no noteworthy difference in median changes in WBC, or platelets between the empagliflozin and placebo treatment groups. There were no noteworthy differences in median values at baseline and last value on treatment or from baseline to the last value on treatment for

patients on empagliflozin or patients on placebo for differential count based on absolute values for basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

Table 85 Median Values for Selected Hematology Parameters (Normalized Values) - TS

Parameter [units] Treatment group	Patients analysed	Baseline Median (Q1, Q3)	Last value on treatment Median (Q1, Q3)	Change from baseline to last value on treatment Median (Q1, Q3)
RBC [x10^6/µL]				
Placebo	2263	4.6 (4.3, 4.9)	4.7 (4.3, 5.1)	0.1 (-0.1, 0.3)
Empa 10 mg	2263	4.6 (4.2, 4.8)	5.1 (4.6, 5.4)	0.4 (0.2, 0.7)
Empa 25 mg	2248	4.6 (4.3, 4.9)	5.1 (4.6, 5.4)	0.4 (0.2, 0.7)
Haemoglobin [g/dL]				
Placebo	2263	13.5 (12.6, 14.4)	13.4 (12.3, 14.4)	-0.1 (-0.7, 0.6)
Empa 10 mg	2263	13.5 (12.5, 14.4)	14.3 (13.2, 15.4)	0.8 (0.1, 1.6)
Empa 25 mg	2249	13.5 (12.6, 14.4)	14.4 (13.4, 15.5)	0.9 (0.1, 1.6)
Haematocrit [%]				
Placebo	2258	41.2 (37.4, 44.5)	42.5 (38.6, 45.9)	1.3 (-1.4, 3.9)
Empa 10 mg	2255	41.2 (37.4, 45.2)	46.5 (41.7, 50.2)	5.2 (1.4, 7.8)
Empa 25 mg	2242	41.7 (37.4, 45.2)	46.5 (42.5, 50.4)	5.2 (1.4, 8.5)

Source: Excerpted from Table 12.3.1: 1 study report NDA 204629, SDN 406

Frequencies of shifts relative to the reference range from baseline to last value on treatment for hematology parameters are summarized in Table 86 below. A higher proportion of patients in the empagliflozin groups experienced shifts in hemoglobin, hematocrit, and RBC from the normal range to >ULN over the course of the study, and, at least for the hemoglobin and hematocrit, a trend towards dose-dependency is noted. Regarding shifts in hemoglobin, hematocrit, and RBC, from the normal range to <LLN, there were more patients in the placebo group compared to either empagliflozin group.

There were no major shifts observed regarding WBC. There were more shifts in platelets from normal range to <LLN in the empagliflozin groups compared to placebo, although the difference were small, and of unclear significance.

Table 86 Frequency of patients with changes in haematology parameters from normal range at baseline to >ULN or to <LLN at last value on treatment - TS

	Placebo n/N (%)	Empa 10 mg n/N (%)	Empa 25 mg n/N (%)
>ULN			
RBC	22/2013 (1.1)	108/2008 (5.4)	102/2012 (5.1)
Haemoglobin	8/1921 (0.4)	55/1912 (2.9)	59/1906 (3.1)
Haematocrit	40/1899 (2.1)	208/1910 (10.9)	227/1914 (11.9)
WBC	53/2196 (2.4)	54/2173 (2.5)	56/2175 (2.6)
Platelets	13/2131 (0.6)	10/2110 (0.5)	7/2088 (0.3)
<LLN			
RBC	82/2013 (4.0)	30/2008 (1.5)	32/2012 (1.6)
Haemoglobin	197/1921 (10.3)	100/1912 (5.2)	82/1906 (4.3)
Haematocrit	122/1899 (6.4)	70/1910 (3.7)	41/1914 (2.1)
WBC	20/2196 (0.9)	24/2173 (1.1)	20/2175 (0.9)
Platelets	45/2131 (2.1)	60/2110 (2.8)	73/2088 (3.5)

ULN: upper limit of normal; LLN: lower limit of normal; n=number of patients with value >ULN or <LLN at last observation on treatment, N=number of patients with normal value at baseline and at least 1 available on-treatment value

Source: Table 12.3.1: 3 study report NDA 204629, SDN 406

Possibly clinically significant abnormalities (PCSAs) in the high range were overall rare, however, the frequencies of patients with PCSAs for high hemoglobin and hematocrit values were higher for the empagliflozin treatment groups than for the placebo treatment group. This is consistent with previous findings. PCSAs were not defined for differential count based on absolute values for basophils, lymphocytes, or monocytes.

Table 87 Frequency of patients with possibly clinically significant abnormal values in haematology parameters - TS

	Placebo n/N (%)	Empa 10 mg n/N (%)	Empa 25 mg n/N (%)
High			
RBC	0/2258 (0.0)	0/2264 (0.0)	0/2246 (0.0)
Haemoglobin	17/2202 (0.8)	56/2205 (2.5)	66/2197 (3.0)
Haematocrit	21/2225 (0.9)	76/2224 (3.4)	87/2211 (3.9)
WBC	3/2257 (0.1)	6/2259 (0.3)	5/2249 (0.2)
Platelets	4/2259 (0.2)	1/2262 (<0.1)	2/2243 (<0.1)
Low			
RBC	18/2258 (0.8)	5/2264 (0.2)	8/2246 (0.4)
Haemoglobin	179/2202 (8.1)	100/2205 (4.5)	89/2197 (4.1)
Haematocrit	100/2225 (4.5)	55/2224 (2.5)	54/2211 (2.4)
WBC	13/2257 (0.6)	10/2259 (0.4)	18/2249 (0.8)
Platelets	6/2259 (0.3)	9/2262 (0.4)	6/2243 (0.3)

n=number of patients with possibly clinically significant high value on treatment, N=number of patients with no possibly clinically significant abnormality at baseline and at least 1 available on-treatment value

Source: Table 12.3.1: 4 study report NDA 204629, SDN 406

As expected based on the NDA review of empagliflozin, an increase in hemoglobin and hematocrit were seen again with empagliflozin. This information is consistent with the empagliflozin prescribing information, and did not appear to result in increased incidence of thromboembolic events.

Uric acid

Serum uric acid median values decreased from baseline to last value on treatment in both treatment groups containing empagliflozin (10 mg: -0.43 mg/dL; 25 mg: -0.45 mg/dL) compared to placebo (0.00 mg/dL), which is consistent with the trend observed in the original NDA review. It was hypothesized that this may indicate uricosuria due to treatment with empagliflozin, signaling a potential for causing renal insufficiency/impairment.

The follow up median value was not significantly different when compared to the last value on treatment for either treatment arm. Few patients in any treatment group had shifts from within the normal range at baseline to <LLN at the last value on treatment for uric acid, and the frequencies were comparable in all treatment groups. The frequencies of patients with shifts from normal range at baseline to >ULN for uric acid values at the last value on treatment were slightly lower for patients on empagliflozin (10 mg: 4.7%; 25 mg: 5.0%) than for placebo (8.7%). The frequencies of uric acid PCSAs (for increased values) were lower in the empagliflozin treatment groups (10 mg: 2.0%; 25 mg: 2.2%) than for the placebo treatment group (3.9%).

Table 88 Median values for uric acid at follow-up (normalized values) - TS-FU (OR)

Parameter [units] Treatment group	Patients analysed	Baseline Median (Q1, Q3)	Last value on treatment Median (Q1, Q3)	Follow-up value Median (Q1, Q3)	Change from baseline to follow-up Median (Q1, Q3)	Change from LVOT to follow-up Median (Q1, Q3)
Uric acid [mg/dL]						
Placebo	1603	5.80 (4.81, 6.89)	5.70 (4.71, 6.89)	5.70 (4.71, 6.99)	0.00 (-0.71, 0.69)	0.00 (-0.50, 0.49)
Empa 10 mg	1711	5.70 (4.81, 6.71)	5.30 (4.40, 6.51)	5.40 (4.51, 6.51)	-0.20 (-0.99, 0.49)	0.10 (-0.50, 0.61)
Empa 25 mg	1746	5.80 (4.81, 6.89)	5.50 (4.51, 6.51)	5.50 (4.51, 6.51)	-0.30 (-0.99, 0.40)	0.00 (-0.50, 0.61)

Source: Table 12.3.5: 1 study report NDA 204629, SDN 406

Table 89 Uric Acid Categorical Shifts from Baseline to Last Value on Treatment

Treatment/ Baseline RR	Last value on treatment: < LLN	[LLN, ULN]	> ULN	Total
Placebo (N= 2333)				
< LLN	27 (58.7)	18 (39.1)	1 (2.2)	46 (100.0)
[LLN, ULN]	41 (2.2)	1693 (89.1)	166 (8.7)	1900 (100.0)
> ULN	1 (0.3)	166 (52.7)	148 (47.0)	315 (100.0)
Total	69 (3.1)	1877 (83.0)	315 (13.9)	2261 (100.0)
Empa 10mg (N= 2344)				
< LLN	26 (47.3)	28 (50.9)	1 (1.8)	55 (100.0)
[LLN, ULN]	45 (2.3)	1788 (93.0)	90 (4.7)	1923 (100.0)
> ULN	2 (0.7)	160 (55.0)	129 (44.3)	291 (100.0)
Total	73 (3.2)	1976 (87.1)	220 (9.7)	2269 (100.0)
Empa 25mg (N= 2341)				
< LLN	17 (37.8)	28 (62.2)	0	45 (100.0)
[LLN, ULN]	44 (2.3)	1796 (92.7)	97 (5.0)	1937 (100.0)
> ULN	0	163 (60.4)	107 (39.6)	270 (100.0)
Total	61 (2.7)	1987 (88.2)	204 (9.1)	2252 (100.0)
All Empa (N= 4685)				
< LLN	43 (43.0)	56 (56.0)	1 (1.0)	100 (100.0)
[LLN, ULN]	89 (2.3)	3584 (92.8)	187 (4.8)	3860 (100.0)
> ULN	2 (0.4)	323 (57.6)	236 (42.1)	561 (100.0)
Total	134 (3.0)	3963 (87.7)	424 (9.4)	4521 (100.0)

Key: [or] = include limit in category, (or) = exclude limit in category, MD = marked decrease, LLN = Lower limit of normal, ULN = Upper limit of normal, MI = marked increase
Categorisation is based on original lab values.
The selected algorithm for repeat values is WORST.
The selected algorithm for multiple values is CLOSEST.

Source: Table 15.3.2.1: 2 study report NDA 204629, SDN 406

Overall the changes in uric acid were relatively minor over the course of EMPA-REG.

Serum lipids

Dyslipidemia is often seen in conjunction with diabetes mellitus, and is a risk factor for cardiovascular disease. In the original empagliflozin NDA review, several dose-dependent changes of unknown clinical significance were noted in lipid parameters: dose-dependent increase from baseline in total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and non-HDL cholesterol with empagliflozin treatment compared to placebo at 24 and 52 weeks.

Changes in serum lipids in the current study were analyzed by the Applicant using MMRM. An MMRM analysis was performed up to Week 80 (which corresponded to the last scheduled visit when lipid values were assessed that the last randomized patient could have reached at close out of this event-driven trial), and also from baseline to the end of the trial, based on the TS (OC). The analysis was also performed from baseline to the end of the trial based on the TS (OC-AD), in which data obtained on-treatment, after discontinuation, or after rescue medication intake were included.

Table 90 Lipid Changes from Baseline to Week 80

Parameter [units] Treatment group	Patients analysed	Baseline mean (SE)	Week 80 adjusted mean change from baseline (SE)	Comparison vs. placebo at Week 80	
				Adjusted mean (SE)	95% CI
Total cholesterol [mg/dL]					
Placebo	2219	161.82 (0.91)	5.97 (1.13)		
Empa 10 mg	2222	163.59 (0.96)	8.23 (1.00)	2.26 (1.51)	-0.70, 5.21
Empa 25 mg	2213	163.29 (0.91)	10.44 (1.00)	4.47 (1.51)	1.51, 7.43
HDL cholesterol [mg/dL]					
Placebo	2219	44.02 (0.24)	0.73 (0.24)		
Empa 10 mg	2222	44.67 (0.25)	1.71 (0.21)	0.98 (0.32)	0.35, 1.61
Empa 25 mg	2213	44.51 (0.25)	2.39 (0.21)	1.66 (0.32)	1.03, 2.29
LDL cholesterol [mg/dL]					
Placebo	2219	84.85 (0.75)	3.94 (0.94)		
Empa 10 mg	2221	86.22 (0.78)	5.17 (0.82)	1.23 (1.25)	-1.22, 3.68
Empa 25 mg	2211	85.61 (0.75)	6.50 (0.82)	2.56 (1.25)	0.11, 5.01
LDL/HDL cholesterol ratio					
Placebo	2219	2.04 (0.02)	0.07 (0.02)		
Empa 10 mg	2221	2.02 (0.02)	0.04 (0.02)	-0.02 (0.03)	-0.09, 0.04
Empa 25 mg	2211	2.03 (0.02)	0.04 (0.02)	-0.02 (0.03)	-0.08, 0.04
Non-HDL cholesterol [mg/dL]					
Placebo	2219	117.79 (0.89)	5.26 (1.11)		
Empa 10 mg	2222	118.93 (0.93)	6.49 (0.97)	1.23 (1.48)	-1.66, 4.12
Empa 25 mg	2213	118.78 (0.90)	8.09 (0.97)	2.83 (1.48)	-0.07, 5.72
Triglycerides [mg/dL]					
Placebo	2219	170.28 (2.54)	5.03 (3.26)		
Empa 10 mg	2222	168.32 (2.72)	8.34 (2.84)	3.31 (4.32)	-5.16, 11.78
Empa 25 mg	2213	172.23 (2.83)	9.33 (2.84)	4.30 (4.32)	-4.17, 12.77

SE = standard error

[1] The MMRM model for Week 80 included baseline lipid value and baseline HbA_{1c}, baseline BMI category, baseline eGFR (MDRD) category, geographical region, treatment, and visit as linear covariates and visit by treatment interaction, baseline HbA_{1c} by visit interaction , and baseline lipid by visit interaction as fixed effects.

Source: Table 12.3.4: 1 study report NDA 204629, SDN 406

As seen in Table 90 above, the baseline values for lipid parameters were similar between the treatment groups. Dose-dependent small increases in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were observed with empagliflozin compared to placebo at 80 weeks. However, the LDL/HDL cholesterol ratio was only minimally affected by these changes. A similar proportion of patients were taking lipid lowering medications at baseline, and during the trial.

The changes from baseline to the last value on treatment followed a similar trend, and there was a tendency towards reversibility of the changes at the 30 day follow up.

Table 91 Lipid Changes from Baseline to Last Value on Treatment, and Follow-up

Parameter [units] Treatment group	Patients analysed	Baseline Median (Q1, Q3)	Last value on treatment Median (Q1, Q3)	Follow-up value Median (Q1, Q3)	Change from baseline to follow-up Median (Q1, Q3)	Change from LVOT to follow-up Median (Q1, Q3)
Total cholesterol [mg/dL]						
Placebo	1668	154.29 (132.25, 180.20)	155.07 (132.25, 188.32)	154.29 (131.09, 185.23)	1.16 (-17.01, 20.11)	-1.93 (-15.08, 11.99)
Empa 10 mg	1773	157.39 (132.25, 187.16)	162.41 (137.28, 197.22)	159.32 (135.34, 189.48)	3.09 (-15.85, 22.82)	-3.09 (-18.95, 10.05)
Empa 25 mg	1824	154.29 (132.25, 185.23)	163.19 (139.21, 197.22)	160.09 (135.34, 190.26)	5.03 (-13.92, 24.75)	-4.64 (-18.95, 9.28)
HDL cholesterol [mg/dL]						
Placebo	1668	42.92 (35.96, 50.27)	42.92 (35.96, 51.04)	42.15 (35.96, 50.27)	0.00 (-4.25, 5.03)	0.00 (-3.87, 2.71)
Empa 10 mg	1773	42.92 (35.96, 51.04)	45.24 (37.12, 54.14)	44.08 (37.12, 52.98)	1.16 (-3.87, 6.19)	0.00 (-4.25, 3.09)
Empa 25 mg	1824	42.92 (37.12, 51.04)	45.24 (37.90, 54.14)	44.08 (37.90, 52.98)	1.93 (-3.09, 6.96)	0.00 (-4.25, 3.09)
LDL cholesterol [mg/dL]						
Placebo	1668	76.95 (59.16, 100.15)	78.11 (59.94, 106.34)	78.11 (59.16, 104.02)	0.77 (-13.92, 16.24)	-1.16 (-11.99, 9.28)
Empa 10 mg	1773	80.05 (59.94, 105.18)	84.30 (63.03, 109.05)	79.27 (61.10, 106.34)	1.16 (-15.08, 16.24)	-1.93 (-15.08, 8.12)
Empa 25 mg	1824	78.11 (59.94, 104.02)	83.14 (63.03, 111.56)	80.05 (62.26, 106.34)	2.32 (-12.76, 17.79)	-1.93 (-13.92, 8.89)
LDL/HDL cholesterol ratio						
Placebo	1668	1.83 (1.35, 2.40)	1.84 (1.36, 2.51)	1.81 (1.35, 2.52)	0.02 (-0.34, 0.42)	0.00 (-0.26, 0.24)
Empa 10 mg	1773	1.85 (1.36, 2.47)	1.87 (1.36, 2.51)	1.81 (1.32, 2.44)	-0.02 (-0.41, 0.35)	-0.03 (-0.32, 0.20)
Empa 25 mg	1824	1.82 (1.37, 2.47)	1.85 (1.39, 2.52)	1.81 (1.33, 2.40)	-0.01 (-0.38, 0.36)	-0.02 (-0.29, 0.25)
Non-HDL cholesterol [mg/dL]						
Placebo	1668	108.28 (88.17, 137.28)	111.37 (88.17, 141.92)	109.82 (87.39, 141.14)	1.16 (-16.24, 18.95)	-1.16 (-13.92, 11.21)
Empa 10 mg	1773	112.14 (87.39, 140.37)	116.01 (91.26, 147.33)	111.37 (89.33, 143.08)	1.93 (-16.24, 20.30)	-3.09 (-16.63, 9.28)
Empa 25 mg	1824	109.05 (88.17, 138.05)	116.20 (92.81, 149.27)	112.53 (90.10, 142.30)	2.32 (-15.85, 20.88)	-3.09 (-17.01, 10.05)
Triglycerides [mg/dL]						
Placebo	1668	139.95 (104.52, 201.06)	143.49 (102.75, 204.61)	144.38 (104.52, 202.83)	1.77 (-31.00, 37.20)	0.89 (-27.46, 25.69)
Empa 10 mg	1773	139.06 (100.09, 195.75)	143.49 (102.75, 204.61)	143.49 (101.86, 205.49)	3.54 (-29.23, 42.52)	-1.77 (-30.12, 25.69)
Empa 25 mg	1824	144.38 (106.29, 195.75)	146.15 (106.29, 207.26)	141.72 (101.86, 201.95)	0.00 (-31.89, 37.20)	-4.43 (-36.32, 23.91)

Source: Table 12.3.4: 2 study report NDA 204629, SDN 406

Table 92 Selected Categorical Shifts – Cholesterol Screening to End of Treatment

	Placebo	Empa 10	Empa 25	All Empa
From WRR at baseline to above ULRR at last observation on treatment				
Total cholesterol	222 (16.2%)	238 (17.9%)	257 (19.0%)	495 (18.4%)
HDL-cholesterol	20 (1.5%)	18 (1.3%)	33 (2.4%)	51 (1.8%)
LDL-cholesterol	191 (9.6%)	198 (9.9%)	221 (11.3%)	419 (10.6%)
Triglycerides	194 (10.1%)	182 (9.5%)	201 (10.5%)	383 (10.0%)

Source: Table 15.3.2.1: 2 Study report NDA 204629, SDN 406

There were no high PCSAs for HDL and LDL-cholesterol. The proportion of PCSAs for triglycerides was similar between the treatment groups (17.3% patients in placebo, 18.1% in the empagliflozin 10 mg group, and 16.8% in the empagliflozin 25 mg group).

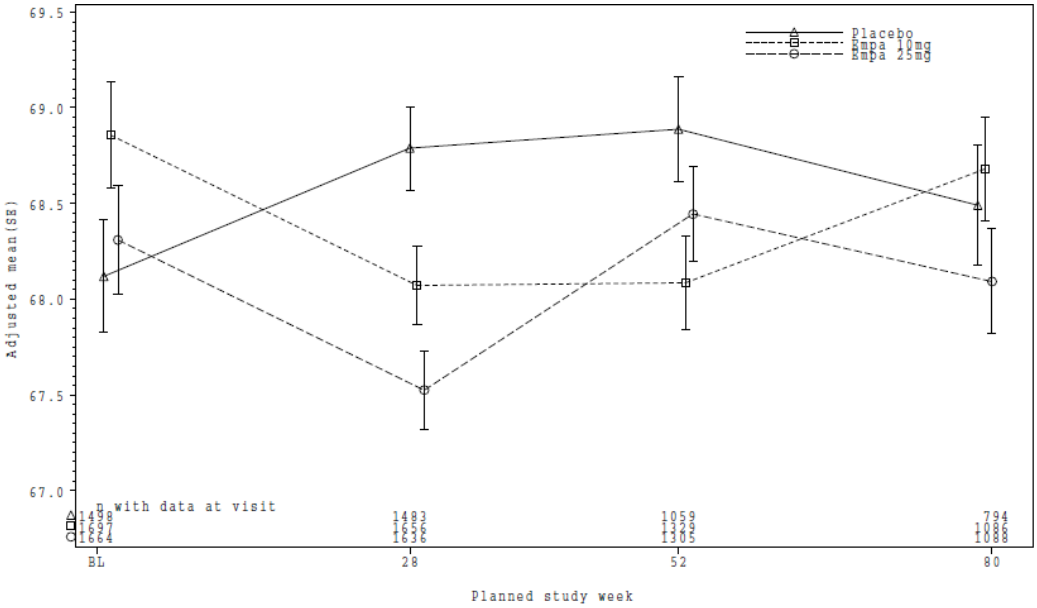
The changes in lipid parameters in EMPA-REG were similar to what was observed at the time of the NDA review, with small increased in LDL and HDL-cholesterol with empagliflozin compared to placebo. These changes did not result in an increase in lipid lowering medications in the empagliflozin arm over the course of the trial, and it is unclear whether they had any impact on the primary endpoint results.

7.4.3 Vital Signs

Vitals signs measured as part of this study included heart rate (HR), and BP. Clinically significant findings at screening or randomization visits were to be regarded as baseline conditions, and new findings were to be recorded as AEs. SPB and DBP were also evaluated as efficacy endpoints, and the findings are discussed in Section 6.1.3.

The mean pulse rate was similar between the treatment groups at baseline (empagliflozin 10 mg group 68.76 bpm, SD 11.44, the empagliflozin 25 mg group 68.39 bpm, SD 11.50, and the placebo group 68.51 bpm, SD 11.73). Adjusted mean heart rate changed only slightly from baseline to Week 80.

Figure 28 Heart rate (bpm) MMRM results over time up to week 80 – treated set (OC)



Source: Figure 15.3.3.2.1: 2 study report NDA 204629, SDN 406

Changes in heart rate from baseline to the last value on treatment and from the last value on treatment to the end of follow-up were comparable for the empagliflozin and placebo treatment groups (TS-FU, OR).

No significant differences in heart rate between treatment arms were seen over the course of the trial.

7.4.4 Electrocardiograms (ECGs)

12-lead ECG was performed at baseline, 28 weeks, 52 weeks, every 14 weeks afterwards, and at the final visit. In addition to the visits indicated, ECG was to be recorded in case of concerning cardiac symptoms (indicating rhythm disorders or cardiac ischemia). ECG was also used to define silent MI, which was an efficacy endpoint, and the results are presented in Section 6.1.3 of this review.

All ECGs were collected on standardized devices, and stored at a central digital database provided by a central ECG service.

Changes in ECG were only to be recorded as AEs if they were not associated with an already reported AE, symptom, or diagnosis, and the study medication was discontinued, reduced, or increased, or additional treatment was required.

The Applicant reported that the frequencies of patients with AEs related to ECG findings were low and comparable in the empagliflozin, and placebo treatment groups (empagliflozin 10 mg: 1.2%; empagliflozin 25 mg: 1.6%; placebo: 1.9%). Frequencies of patients with QT interval >500 ms at the end of treatment were also low, and comparable in the empagliflozin and placebo treatment groups (empagliflozin 10 mg: 0.5%; empagliflozin 25 mg: 1.0%; placebo: 0.7%).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no evident dose dependency for adverse events based on review of the data from study 1276.1. See the previously completed reviews for the individual components for additional discussion of dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

No exploration for time dependency was performed.

7.5.3 Drug-Demographic Interactions

No detailed assessment of drug-demographic interaction was performed by the Applicant. Subgroup analyses by gender for UTI events, and genital infections are discussed in 7.3.5. Overall small numbers for subpopulations limits the value of subpopulation analyses. See previously completed reviews for the individual components for additional discussion of drug-demographic interaction for adverse events.

7.5.4 Drug-Disease Interactions

No specific exploration for drug-disease interaction was performed as part of this efficacy supplement. See the previously completed reviews for the individual components for additional discussion of drug-disease interactions for adverse events.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to section 7.3.5.9 for discussion on malignancies identified during this trial.

7.6.2 Human Reproduction and Pregnancy Data

No randomized data on use in pregnant or nursing women were collected as they were excluded from the study.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. No pediatric patients were enrolled in this study.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is little concern for overdose, drug abuse, withdrawal, or rebound.

8 Postmarket Experience

Both empagliflozin and empagliflozin-metformin are FDA approved for the treatment of T2DM. Empagliflozin was approved on August 1, 2014, the fixed dose combination product empagliflozin-metformin was approved on August 28, 2015.

During the review of this application, the applicant submitted a 4 months safety update for this supplement on March 4, 2016. As agreed with the FDA (email dated October 19, 2015), this safety update was composed of:

- 6-month PBRER covering 4/18/2015-10/17/2015, submitted December 16, 2015
- Quarterly PADER covering 10/18/2015-1/17/2016, submitted February 15, 2016

In addition, another 6 month PBRER covering the time period between October 18, 2015 to April 17, 2016 was submitted on June 23, 2016.

A few safety issues have been identified postmarketing, and I will discuss them below.

Diabetic ketoacidosis

In December 2015, the FDA issued a Drug Safety Communication informing that labelling for SGLT2 inhibitors had been updated to warn about the risks of ketoacidosis. The FDA requested that BI conduct a 5-year enhanced pharmacovigilance study of ketoacidosis in patients treated with empagliflozin as a post-marketing requirement, and additionally requested an update relevant study documents (IB, study protocol, informed consent) on the topic of ketoacidosis.

Urosepsis

In December 2015, the FDA issued a Drug Safety Communication informing that labelling for SGLT2 inhibitors had been updated to warn about the risk of urosepsis.

Stroke and thromboembolic events

In correspondence dated August 20, 2015, FDA notified BI that a new DARRTS Tracked Safety Issue (TSI) had been created for SGLT-2 inhibitors regarding stroke and thromboembolic events on June 18, 2015, which includes BI marketed products JARDIANCE and GLYXAMBI (and as of August 26, 2015, SYNJARDY).

Acute kidney injury

On January 4, 2016, the FDA notified BIPI of a tracked safety issue (TSI) for sodium-glucose cotransporter-2 (SGLT-2) inhibitors regarding acute kidney injury (AKI). A decision not to include empagliflozin was made at the time because review of EMPAREG trial was pending. We remain concerned regarding the risk of AKI with empagliflozin, especially early after treatment start, and we will institute similar changes to the empagliflozin prescribing information.

9 Advisory Committee

On June 28 2015, the Endocrinologic and Metabolic Drugs Advisory Committee convened to discuss the overall findings in EMPA-REG, and to specifically address the following questions:

1. **DISCUSSION:** Discuss your interpretation of the EMPA-REG OUTCOME study conduct. Please comment on whether interim unblinding or changes made to the protocol, endpoint definitions, and analyses plan (e.g., specific exclusion of silent MI from the primary endpoint) during the course of the EMPA-REG OUTCOME study alter or do not alter your level of confidence in a conclusion that excess CV-risk was excluded and CV-benefit was established.

2. **DISCUSSION:** Discuss your interpretation of the nonfatal components in the composite endpoint (i.e., nonfatal myocardial infarction and nonfatal stroke) in relation to the overall results. Please comment on the non-fatal myocardial infarction findings in the EMPA-REG OUTCOME study and your level of concern related to potentially incomplete ascertainment of some myocardial infarction events (i.e., silent MI) in this trial. Please comment on the non-fatal stroke findings in the EMPA-REG OUTCOME study.

3. **DISCUSSION:** Discuss your interpretation of the mortality findings in the EMPA-REG OUTCOME study in relation to the overall results. Please comment on your level of

confidence in the mortality findings. In your discussion, please address any potential limitations of these data including but not limited to:

a. The divergent effect on the fatal and non-fatal components for the primary major adverse cardiovascular event (MACE) endpoint

b. The proportion of deaths that were determined "non-assessable" by adjudicators

c. The lack of granular data on potentially important information such as baseline heart failure history and dose of relevant baseline and concomitant medications

4. **DISCUSSION:** Discuss the heart failure findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on heart failure and heart-failure related outcomes.

5. **DISCUSSION:** Discuss the renal findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on kidney disease related to diabetes.

Committee discussion:

1. While the committee members were concerned regarding the various issues such as changes in the clinical trial protocol, and event definition over the course of the trial, and interim unblinding, there was general consensus that the excess cardiovascular risk with empagliflozin was ruled out. Regarding CV benefit, some committee members expressed uncertainty regarding MACE results and whether emphasis should be placed on CV death in this context, while other members were more willing to focus on the mortality findings independent of MACE. In general, the issues raised by the not assessable deaths were alleviated by the effect of empagliflozin on all-cause mortality in addition to CV mortality. The lack of a mechanistic explanation for the CV mortality benefit was an issue with some committee members, but not with others. Overall the committee expressed a high level of confidence in the mortality findings, but not in the MI and heart failure findings.
2. There was general concern expressed by committee members regarding the various sensitivity analyses for the MACE endpoint which rendered it no longer superior. However, there was a divergence of opinion regarding the mortality data in the context of a single study. Some committee members expressed concern with approving an indication based on a secondary endpoint from a single trial, especially when the mechanism for the finding is unclear.

3. Committee members weighed arguments to support the persuasiveness of the mortality data, such as the fact that 2 doses of empagliflozin were tested in this trial with similar effect on mortality which could make this the equivalent of two trials, as well as the very low p value which should withstand multiple adjustments for multiplicity. Concerns were again expressed regarding the uncertainty pertaining to the mechanism of the mortality findings, however the committee members expressed that it may not be essential to understand the mechanism as the mortality findings are persuasive, and this is the most important component of the composite MACE endpoint.
4. The consensus was that, while the hospitalization for heart failure is an important endpoint, and the applicant analysis is intriguing, it is not convincing as EMPA-REG was not designed as a heart failure study, event definition changed over the course of the trial, and, generally, better metrics are needed in the evaluation of heart failure endpoints. The committee members questioned whether the effect on heart failure was due to the diuretic properties of empagliflozin.
5. The committee consensus was that the major deficiencies in the study design provide no confidence in the data as it pertains to renal endpoints.

Voting questions posed to EMDAC and discussion:

1. **VOTE**: Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results have fulfilled the recommendations laid out in the 2008 Guidance for Industry by demonstrating that use of empagliflozin to improve glycemic control would not result in an unacceptable increase in cardiovascular risk?

a. If yes, please provide the rationale for your vote.

b. If no, please provide the rationale for your vote and comment on what additional data would be needed.

VOTE RESULTS: YES = 23 NO = 0 ABSTAIN = 0

a. Explain your rationale and recommend additional studies if you believe these are needed.

Committee Discussion: The committee members unanimously agreed that EMPA-REG ruled out an increase in cardiovascular risk with empagliflozin compared to standard of care. There was minimal discussion around this voting question as it was felt that the results are unequivocal.

2. **VOTE:** Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results provide substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied?

a. If yes, please provide the rationale for your vote.

b. If no, please provide the rationale for your vote and comment on what additional data would be needed.

VOTE RESULTS: YES = 12 NO = 11 ABSTAIN = 0

Committee Discussion: The committee members inquired whether this question refers to the evidence provided by the study vs whether this evidence should result in a labeled indication. The FDA clarified that the question addresses both the substantial evidence, and the labeled indication. The committee members who voted yes stated that they felt that, despite missing data regarding the cause of death in some patients, and the lack of a mechanistic explanation for the mortality findings, the CV mortality results are solid, and they can withstand various sensitivity analyses without changing the conclusions. They also expressed that their trust in the results of a single study are further enhanced by the fact that two doses of empagliflozin were tested with similar results on the study outcomes. The committee members who voted no expressed concerns regarding the use of the data from a single positive study for a labeled indication, as well as lack of a mechanistic explanation for the study findings.

10 Appendices

10.1 Labeling Recommendations

Labeling is not yet finalized at the time of this review.

The Applicant submitted the following changes to the prescribing information for empagliflozin and empagliflozin-metformin fixed dose combination:

10.1.1 Changes to the proposed indication:

"In adult patients with type 2 diabetes mellitus and established cardiovascular disease to reduce the incidence of cardiovascular death".

Reviewer comment: While the CV mortality data in EMPA-REG could support such an indication, it is important to keep in mind that this would be based on a single study, and the mechanism of action of action is not clear at this time but it does not appear to be ischemic. A regulatory briefing will be held on October 7, 2016, to discuss the potential change to product indication. Labeling negotiations are ongoing at the time of this review.

10.1.2 Changes to [redacted] (b) (4)

The Applicant proposes to [redacted]

Reviewer comment: The applicant has provided some data [redacted] The safety in this patient population appears consistent with the general safety of the drug product, and CV death is reduced in this patient population. However, [redacted] therefore such a change is not justified in my opinion.

10.1.3 Adverse Reactions/Warnings and Precautions:

The applicant proposes to remove the section regarding impairment in renal function, and the section on macrovascular outcomes

Reviewer comment: I do not agree that the section regarding renal function can be removed as the Applicant is basing that on over time urine albumin and eGFR trends, and they appear to be a consequence of the hemodynamic effect of empagliflozin rather than indicators of renal disease progression. In addition, the acute effects of empagliflozin in the first 3 months after drug start still suggest an increased risk of renal impairment with empagliflozin.

The applicant did demonstrate that empagliflozin does not increase the risk for 3 and 4-point MACE when compared to the local standard of care, however it is unclear whether this is due to improvement in diabetic macrovascular outcomes, as no clear effect was seen on MI and stroke. How this paragraph should be reworded will be discussed at the regulatory briefing.

10.1.4 Changes to Section 14

The Applicant proposes to add detailed data from EMPA-REG in Section 14 of the product label.

Reviewer comment: While it is appropriate to present the endpoints for which type 1 error was controlled (3 and 4-point MACE), including breakdown by component, I do not agree that any data from exploratory endpoints should be included (such as heart failure or renal endpoints, etc).

10.2 Financial Disclosures

Covered Clinical Study (Name and/or Number): 1245.25

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)

Total number of investigators identified: 3366		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
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: 2 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 2		
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) 261		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Overall, I do not feel that this information changes the validity of the study.

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/s/

ANDREEA O LUNGU
11/03/2016

WILLIAM H CHONG
11/04/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s008

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	204629 and 206111
Supplement #:	009 and 008
Drug Name:	Empagliflozin
Indication(s):	Reduced incidence of CV Death
Applicant:	Boehringer Ingelheim
Date(s):	Submitted: 4 November 2015
	Review Due: 27 July 2016
	Goal Date: 2 September 2016
Review Priority:	Standard
Biometrics Division:	DBII
Statistical Reviewer:	Jennifer Clark, PhD
Concurring Reviewers:	Mark Rothmann, PhD
	Tom Permutt, PhD
Medical Division:	DMEP
Clinical Team:	Andreea Lungu, MD
	Bill Chong, MD
Project Manager:	Michael White,

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1 EXECUTIVE SUMMARY

The applicant, Boehringer Ingelheim, submitted a supplemental new drug application (sNDA) to obtain an additional efficacy claim for the already marketed empagliflozin tablets. The current indication is for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. This submission is supported by results from the EMPA-REG OUTCOME safety trial, a cardiovascular outcomes trial (CVOT). The first patient was randomized on September 15, 2010 and the last on April 19, 2013. The trial cutoff date was December 15, 2014 with subjects seen at or after this date considered to have completed follow-up. The last patient trial stop date was April 21, 2015 with final database lock on June 22, 2015.

The single CVOT trial was initiated based on Agency guidance for industry on new diabetic treatments in order to demonstrate that the treatment with empagliflozin will not result in an unacceptable increase in cardiovascular risk. Data from the trial were used to rule out an 80% increased risk at a pre-specified interim analysis (IA). The primary objective for EMPA-REG was "to demonstrate non-inferiority of two doses of [empagliflozin] compared to placebo with respect to first occurrence of any of the adjudicated components of the primary composite Major Adverse Cardiovascular Event endpoint (cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction) in patients with type 2 diabetes mellitus and increased cardiovascular risk." These Major Adverse Cardiovascular Event (MACE) endpoints were used in a testing hierarchy which allowed for testing for superiority once the primary objective ruling out a 30% or greater increase in risk had been established. This non-inferiority hypothesis of ruling out a 30% risk was achieved for both their primary 3-point MACE (cardiovascular death, nonfatal stroke, nonfatal MI) and secondary 4-point MACE (cardiovascular death, nonfatal stroke, nonfatal MI, unstable angina) endpoints with hazard ratios (HR) and 95.02% confidence intervals (adjusted for IA) of 0.86 (0.74, 0.99) and 0.89 (0.78, 1.01), respectively. Using the same upper bound methodology, superiority was also thereby achieved for the primary 3-point MACE endpoint since the upper bound of 0.99<1, but not the secondary 4-point MACE endpoint. Currently, there is no precedent on using these types of safety trials for efficacy since this is the first of the diabetes safety trials to be considered for an efficacy claim.

An advisory committee was held for this submission on June 28, 2016. The panel unanimously voted in favor of the EMPA-REG trial having adequately achieved its original safety objective demonstrating there was not an unacceptable increase in CV risk. The vote was split 12 in favor and 11 not in favor on whether the trial offered "substantial evidence to establish that the drug reduced cardiovascular mortality in the population studied."

1.1 Statistical Issues and Findings

Findings and issues from the empa-reg trial that will be discussed include:

- **This study was designed as a cardiovascular safety study.**

Most efficacy claims typically require two phase 3 confirmatory trials. Having replication of a treatment effect with a second trial greatly diminishes the possibility of having a false positive or random high. This single CVOT trial was sized to show non-inferiority using a non-inferiority margin of 1.3. The 95.02% confidence intervals used to establish non-inferiority with upper bounds also showed a reduction in 3-point MACE. The study results for CV death may seem larger since this outcome was singled out based on trial results. See section **Error! Reference source not found.** for more details.

The safety objective may be why certain aspects of the trial are different from a trial that is directly targeting efficacy, such as the non-inclusion of silent MI in the non-fatal MI endpoint. Only approximately half the patients were screened for silent MI. When including this in the primary analysis the primary MACE endpoint still demonstrates non-inferiority but no longer shows superiority. See section 3.3.3 for more details.

- **A pre-specified interim analysis (IA) was conducted in conjunction with a meta-analysis.**
  The Agency guidance for industry on new diabetic treatments requests that the applicant be able to demonstrate the upper bound of a two-sided 95% confidence interval for the estimated risk ratio is less than 1.8 for cardiovascular safety. Interim results from this trial were used in a meta-analysis to meet this requirement. IA does not appear to be an issue as analyses looking at patients enrolled before IA and after IA yielded similar results. See section 3.3.4 for further details.

- **Significant differences in the primary MACE endpoint were chiefly due to differences in cardiovascular death between treatment arms.**
  Results for stroke and myocardial infarction (MI), two of the MACE components, did not demonstrate superiority for empagliflozin when compared with placebo. Hazard ratio (HR) estimates for cardiovascular death and all-cause death show results favoring the pooled empagliflozin arm compared to the placebo arm (Figure 5 and Figure 7). Results were similar when looking at the individual doses with both the 10mg and the 25mg arm when compared to the placebo arm (Table 3).

Overall, the study showed a benefit for 3-point MACE due to a large disparity in the number of CV deaths between the treatment arms (Figure 4). Although it was initiated and sized to rule out an adverse effect in CV risk, the pre-specified analysis plan did accommodate for the possibility of finding a beneficial effect. While any broad claims regarding the efficacy of 3-point MACE could be questionable due to the nature of the results for MI and stroke (Figure 5), results from this study do appear adequate to support claims for CV death.

2 Introduction

2.1 Overview of the EMPA-REG OUTCOME Trial

This CVOT was an event-driven, multinational, randomized, double-blind, parallel group, placebo-controlled trial. A total of 7000 patients were planned for the full trial expected to go between 6 to 8 years, until 691 patients experienced an adjudicated MACE. The applicant estimated this would provide 90% power to rule out the 1.3 post-marketing risk margin. A total of 7028 patients with type 2 diabetes and increased cardiovascular risk were randomized 1:1:1 to placebo, empagliflozin 10 mg, or empagliflozin 25 mg once daily; however, 8 randomized patients were not treated with study medication and were therefore not included in the treated set for analysis. Randomization was stratified by HbA1c, BMI, geographical region, and renal function (based on eGFR MDRD). Trial cutoff was December 15, 2014 with patients considered completed if assessed at or after this date.

There was a 2-week open-label placebo run-in. Patients were treated with both study medication in addition to background medication until the required number of adjudicated events were reached. Study visits occurred at Weeks 4, 8, 12, 16, 28, 40, 52, and every 14 weeks thereafter. Patients were to be followed up for 30 days after the last intake of study medication.
There were 2345 patients treated with 10 mg empagliflozin, 2342 with 25 mg empagliflozin, and 2333 with placebo. The final protocol specified that the primary analysis would be based on this treated set of patients after 691 3-point MACE events had occurred. The two empagliflozin treatment arms were pooled together in the treatment variable to test against placebo. The primary analysis used a Cox proportional hazards model which included factors for treatment, age, sex, baseline BMI≥30, Baseline HbA1c≥8.5%, baseline eGFR, and geographic region. The testing hierarchy was specified to first establish non-inferiority for the primary 3-point MACE and then the secondary 4-point MACE endpoints against a non-inferiority margin of 1.3. If both upper bounds for 95.02% confidence intervals were below 1.3, then superiority could also be established first for 3-point and then 4-point MACE if these bounds were below 1.

2.2 Results at the time of Interim Analysis

An interim analysis was also pre-specified and projected to occur after 80 confirmed primary events were observed. The Haybittle-Peto boundary was specified to maintain the type I error with 0.0001 of the alpha spent leading to a final one-sided alpha of 0.0249. A data monitoring committee was specified to meet three to four times per year monitoring unblinded data, supported by an independent statistician.

The first planned data cut-off for the interim analysis occurred on June 22, 2012 with 4559 patients already randomized: 1521 to 10mg empa, 1525 to 25 mg empa, 1513 to placebo. The original plan was to have the interim analysis after 80 confirmed primary MACE events had been adjudicated or based on the cut-off date of July 15, 2012, whichever was first. At the interim there were 85/3046 (2.8%) of patients in empagliflozin, and 57/1513 (3.8%) in placebo with a MACE. This led to an estimated HR of 0.74 with a corresponding 99.98% CI of (0.39, 1.39).

2.3 Advisory Committee Synopsis

The advisory committee for the EMPA-REG trial occurred on June 28, 2016. The meeting ended with five discussion questions and two voting questions for the 23 member panel. The first question for the panel was related to the trial's original safety objective and whether "results have fulfilled the recommendations laid out in the 2008 Guidance for Industry by demonstrating that use of empagliflozin to improve glycemic control would not result in an unacceptable increase in cardiovascular risk." The vote was unanimous in affirming that the study had sufficiently demonstrated this.

The second voting question concerned whether the "study results provide substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied." This question was much more litigious with virtually a tie vote of 12 in favor and 11 opposed. Many members on both sides asserted that their vote was quite borderline in favor or opposed during the discussion. Issues with study population and aspects on how the study was conducted and the "wandering road" that it took were cited by almost all members. The lack of knowledge on the clinical mechanism behind the superiority results was a key concern for those both in favor and opposed.

Those who voted in favor gave varying reasons for why they voted "yes". Almost all agreed that the trial conduct was not well done with concern expressed about the aggregate of changes that occurred throughout the trial. Sensitivity analyses done for MACE along with the robustness of the death results were cited as supporting evidence in favor of the trial. Many voting yes had reservations but chose to vote in favor since superiority results were due to the CV death component; had it been any of the other components many claimed they would not have voted favorably. There was also discussion on whether there was merit in labeling all-cause death since the reduction in CV mortality translated to all-cause death. Some panel members found this all-cause death result reassuring enough to overcome any reservations concerning the "undetermined cause of death" issues raised earlier in the day. One panel member voted yes citing that the two doses could be looked upon as two trials compared against placebo. There was, however, no discussion on this topic which is complicated since the two doses are sharing a single control and have HR upper bounds above 1. Another panel member who voted in favor gave the caveat that the only patients who are like the study population should receive this treatment for this indication.

Those who were opposed also gave a number of reasons behind their choice. Many had the same reservations that those in favor had, but didn't think the evidence in favor strong enough to overcome them. The fact that there was no adjustment made for CV death or any of the other components of the MACE endpoints was cited by members of the panel. A large proportion of the CV deaths in the study were classified as "non-assessable deaths", this was one of the issues that was discussed earlier in the day and was a contributing factor to many of the "no" votes. Concerns on the generalizability of the results, especially in the USA were expressed during the discussion period. Some reasoned that a better understanding of the mechanism behind the results and who would benefit is needed before approving the new indication. It was hypothesized that such an indication could lead to overuse in low CV risk populations that may be better treated with other medications. Many felt the bar for a first compound to receive this indication should be set higher. Ultimately, those who voted no found the results to be impressive, but not compelling enough for labeling without a second trial.

Two statisticians were on the panel, both voting in favor for the second voting question. The sensitivity analyses addressing missing data for both MACE and death outcomes were viewed as factors in this decision. One of the statisticians voted yes in spite of the fact that he believes that the results are likely overstated. His reasoning for voting yes in spite of this belief was that even if the CV death results seen in the trial were inflated to be almost double what the true treatment effect was, it would still be an impressive enough finding to include in labeling.

2.4 Data Sources

Materials for this review were submitted electronically archived under the network path location <\\CDSESUB1\EVSPROD\NDA204629\204629.enx>. Information necessary for this review was contained in Module 1, Module 2, and Module 5. Multiple information requests for information included in this review with responses filed with the submission. Independent coding for the data analysis and plots were run for this review.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Study datasets were provided by the sponsor in SAS XPORT transport files. Define files were submitted as .xml files, and later as .pdf from an information request. Data, programs, and methods were not well documented. A data walk through at the start of the submission along with multiple information requests helped clarify these issues.

Quality of datasets is questionable, some variables used to create time-to-event analysis were found to have erroneous dates. In an information request sent to the applicant on February 4, 2016 they confirmed that at least 3 subjects, all in the empagliflozin 10mg arm, had a data entry error for 3 related variables. The response to the IR indicated that results would not be changed as the time-till-event was calculated as a minimum of dates, including the date of database lock on 22 June 2015. A consequence of such errors is that time until censoring could be unreliable. Data entry errors could only be confirmed in 3 subjects. The sponsor noted in their response that they were "further investigating the data entry errors to consider possible improvement to [their] internal procedures." Randomization and blinding should minimize potential bias of analysis results from data entry errors. It is, however, troubling that the only subjects that could be confirmed to have errors are in the empagliflozin arm.

A pre-specified interim analysis allowed approximately 230 people to have access to unblinded data after approximately 65% of subjects had enrolled. While it is likely that at least high level results could have been disclosed to study personnel, it does not seem to have numerically affected results in terms of subjects entering before or after the interim analysis (section 3.3.4).

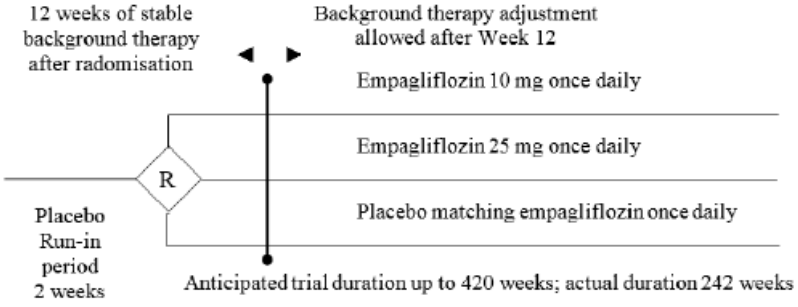
3.2 Study Design and Endpoints

EMPA-REG is a, multinational, randomized, double-blind, parallel group, placebo-controlled trial. A total of 7065 patients were randomized in the dataset 1:1:1 to placebo, empagliflozin 10 mg, or empagliflozin 25 mg once daily. Randomization was stratified by HbA1c, BMI, geographical region, and renal function (based on eGFR MDRD). There were 37 subjects who started treatment but were not included due to site non-compliance or other issues. The treated set was pre-specified as the analysis population; 8 subjects who were randomized but did not start treatment were excluded based on this criterion.

The applicant reports the trial as starting on August 26, 2010. First randomization occurred on September 15, 2010 and the last study visit for the last subject occurred on April 21, 2015. Those subjects with a study visit on or after December 15, 2014 were considered to be complete. Final database lock occurred on June 22, 2015.

After a 2-week open label placebo run-in, study visits occurred at Weeks 4, 8, 12, 16, 28, 40, 52, and every 14 weeks. Patients were to be followed up for 30 days after the last intake of study medication. The trial was specified to run until a minimum of 691 3-point MACE events had occurred. End of study visits were specified to occur when the required number of outcome events was anticipated to have been reached for those remaining in the trial at close out, or ±7 days after permanent discontinuation from study medication. Figure 1 shows an applicant created schematic of this study design.

Figure 1: Applicant Created Schematic of the Study



Subjects were treated with both study medication in addition to background medication until the required number of adjudicated events were reached. Concomitant medications could also be added or changed at the discretion of the investigator. The study medication could be temporarily stopped and re-started at the investigator's discretion. The protocol dictated that background antidiabetic medication be kept stable for the first 12 weeks, but thereafter could be changed to achieve standard of care according to the investigators discretion.

3.2.1 Endpoints and Testing Hierarchy

The primary endpoint for this trial is time to first occurrence of 3-point MACE (major adverse cardiovascular events), which is a composite of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction. The key secondary endpoint was time to first occurrence of 4-point MACE, cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction, or hospitalization for unstable angina pectoris.

A testing hierarchy, shown below, was used to control for multiplicity. Non-inferiority refers to the non-inferiority hypothesis to rule out a 30% or greater increased risk for those on treatment. Superiority refers to the superiority hypothesis showing a decreased risk for MACE.

Pre-specified testing hierarchy

1. Non-inferiority: 3-Point MACE
2. Non-inferiority: 4-Point MACE
3. Superiority: 3-Point MACE
4. Superiority: 4-Point MACE

3.2.2 Statistical Methodologies

The treatment arms for empagliflozin 10 mg and 25 mg were pre-specified to be combined into a single group for the primary analysis. A Cox proportional hazards regression was specified to test first for non-inferiority of the primary and secondary endpoints against a NIM of 1.3 using a 1-sided alpha of 0.0249 (corresponding 95.02% CI). This alpha was adjusted for an interim analysis using the Haybittle-Peto adjustment of 0.0001 to preserve the overall level of 0.025. If non-inferiority was established for both 3-point and 4-point MACE, then testing for superiority was to be conducted for first MACE and then MACE+. Analyses using different population sets were run by the applicant.

For this review, I ran sensitivity analyses imputing time until event for those who were missing follow-up time in the study. Hazard rates for the imputations with the main sensitivity analysis were based on event rates calculated during the off treatment period for those who stopped study drug but continued to be followed in the study.

I also ran an additional analysis incorporating all-cause death into the 3-point MACE endpoint. This was run to check any possible bias that may occur from censoring non-CV deaths in the primary endpoint.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 7028 patients were randomized with 7020 in the treated set used for the analysis. Of those within the treated set, 211 patients prematurely discontinued follow-up for MACE during the study without having a MACE. Within the placebo arm there were 67 (2.87%), 81 (3.45%) in the empagliflozin 10 mg arm, and 63 (2.69%) in the empagliflozin 25 mg arm. When pooling the empagliflozin arms, this translates to 3.07% of patients treated with empagliflozin versus

2.87% with placebo. Vital status was available for all but 53 patients, 17 (0.73%) in placebo and 36 (0.77%) in empagliflozin.

Baseline demographics by treatment arm are shown in Table 1. These were generally balanced between arms.

Table 1: Baseline Demographics

Characteristic	Category	Placebo (N=2333)	Empagliflozin 10mg (N=2345)	Empagliflozin 25mg (N=2342)
Sex	Male	1680 (72.0%)	1653 (70.5%)	1683 (71.9%)
	Female	653 (28.0%)	692 (29.5%)	659 (28.1%)
Race	Missing	0 (0.0%)	0 (0.0%)	1 (0.0%)
	American Indian or Alaska Native	20 (0.9%)	11 (0.5%)	23 (1.0%)
	Asian	511 (21.9%)	505 (21.5%)	501 (21.4%)
	Black or African American	120 (5.1%)	119 (5.1%)	118 (5.0%)
	Native Hawaiian/Pacific Islander	4 (0.2%)	3 (0.1%)	3 (0.1%)
	White	1678 (71.9%)	1707 (72.8%)	1696 (72.4%)
Ethnicity	Missing	3 (0.1%)	4 (0.2%)	1 (0.0%)
	Not Hispanic or Latino	1912 (82.0%)	1909 (81.4%)	1926 (82.2%)
	Hispanic or Latino	418 (17.9%)	432 (18.4%)	415 (17.7%)
Binary Age	Under 65	1297 (55.6%)	1300 (55.4%)	1296 (55.3%)
	At Least 65	1036 (44.4%)	1045 (44.6%)	1046 (44.7%)
Country	Argentina	93 (4.0%)	93 (4.0%)	98 (4.2%)
	Australia	10 (0.4%)	14 (0.6%)	8 (0.3%)
	Austria	50 (2.1%)	43 (1.8%)	53 (2.3%)
	Belgium	63 (2.7%)	58 (2.5%)	57 (2.4%)
	Brazil	164 (7.0%)	175 (7.5%)	162 (6.9%)
	Canada	44 (1.9%)	38 (1.6%)	45 (1.9%)
	Colombia	36 (1.5%)	24 (1.0%)	33 (1.4%)
	Croatia	40 (1.7%)	52 (2.2%)	43 (1.8%)
	Czech Republic	5 (0.2%)	8 (0.3%)	6 (0.3%)
	Denmark	42 (1.8%)	28 (1.2%)	36 (1.5%)
	Estonia	7 (0.3%)	9 (0.4%)	11 (0.5%)
	France	40 (1.7%)	39 (1.7%)	28 (1.2%)
	Georgia	56 (2.4%)	41 (1.7%)	46 (2.0%)
	Greece	31 (1.3%)	27 (1.2%)	35 (1.5%)

	Hong Kong	21 (0.9%)	22 (0.9%)	14 (0.6%)
	Hungary	84 (3.6%)	73 (3.1%)	92 (3.9%)
	India	53 (2.3%)	53 (2.3%)	57 (2.4%)
	Indonesia	8 (0.3%)	9 (0.4%)	9 (0.4%)
	Israel	28 (1.2%)	33 (1.4%)	38 (1.6%)
	Italy	58 (2.5%)	42 (1.8%)	57 (2.4%)
	Japan	21 (0.9%)	31 (1.3%)	31 (1.3%)
	Korea	100 (4.3%)	104 (4.4%)	98 (4.2%)
	Malaysia	74 (3.2%)	74 (3.2%)	74 (3.2%)
	Mexico	30 (1.3%)	18 (0.8%)	27 (1.2%)
	Netherlands	39 (1.7%)	44 (1.9%)	37 (1.6%)
	New Zealand	2 (0.1%)	6 (0.3%)	7 (0.3%)
	Norway	24 (1.0%)	36 (1.5%)	31 (1.3%)
	Peru	37 (1.6%)	49 (2.1%)	42 (1.8%)
	Philippines	67 (2.9%)	66 (2.8%)	55 (2.3%)
	Poland	67 (2.9%)	68 (2.9%)	62 (2.6%)
	Portugal	58 (2.5%)	53 (2.3%)	43 (1.8%)
	Romania	55 (2.4%)	42 (1.8%)	44 (1.9%)
	Russia	92 (3.9%)	102 (4.3%)	92 (3.9%)
	Singapore	7 (0.3%)	8 (0.3%)	9 (0.4%)
	South Africa	102 (4.4%)	107 (4.6%)	104 (4.4%)
	Spain	59 (2.5%)	85 (3.6%)	75 (3.2%)
	Sri Lanka	26 (1.1%)	16 (0.7%)	21 (0.9%)
	Taiwan	47 (2.0%)	42 (1.8%)	55 (2.3%)
	Thailand	26 (1.1%)	22 (0.9%)	27 (1.2%)
	Ukraine	36 (1.5%)	47 (2.0%)	41 (1.8%)
	United Kingdom	25 (1.1%)	36 (1.5%)	33 (1.4%)
	United States	406 (17.4%)	408 (17.4%)	406 (17.3%)
Region	Europe	959 (41.1%)	966 (41.2%)	960 (41.0%)
	North America	462 (19.8%)	466 (19.9%)	466 (19.9%)
	Latin America	360 (15.4%)	359 (15.3%)	362 (15.5%)
	Africa/Middle East	102 (4.4%)	107 (4.6%)	104 (4.4%)
	Asia	450 (19.3%)	447 (19.1%)	450 (19.2%)
Age	N	2333	2345	2342
	Mean (SD)	63.2 (8.8)	63.0 (8.6)	63.2 (8.6)
	Median (Min, Max)	63.0 (33.0, 88.0)	63.0 (31.0, 88.0)	63.0 (30.0, 90.0)

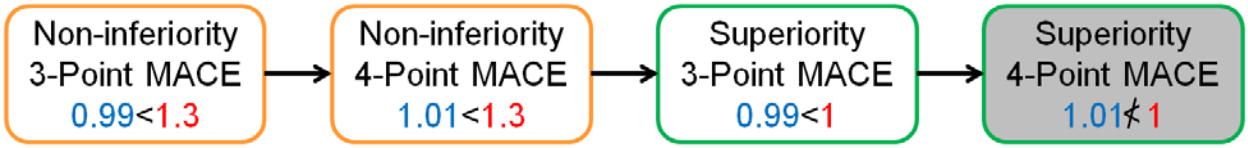
3.3 Results and Conclusions

Table 2 shows results for both 3-point and 4-point MACE endpoints. In order to understand how to interpret these results, Figure 2 shows results within the testing hierarchy. When testing the non-inferiority hypothesis to rule out a 30% increased risk, a non-inferiority margin of 1.3 (in red) is used to verify that the upper bound of the 95.02% CI (in blue) is below the margin. The superiority hypothesis for efficacy has a similar setup where the upper bound must now be below 1. We see that an increased risk of at least 30% was ruled out for both endpoints. The superiority hypothesis was only confirmed for the primary 3-point MACE. Since the 4-point MACE composite failed in the last step of the hierarchy, all remaining alpha is considered used at this point. Had there been any remaining hypotheses to be tested in the hierarchy they would principally be considered as exploratory or hypothesis generating.

Table 2: 3 and 4-Point MACE Cox Model Results

	Pooled Empa vs. Placebo	
	HR (95.02% CI)	**P**
3-Point MACE	0.86 (0.74, 0.99)	0.0382
4-Point MACE	0.89 (0.78, 1.01)	0.0795

Figure 2: Hypothesis Testing Hierarchy Results



While non-fatal MI made up a majority of first events in all treatment arms, the biggest difference between the two was in the CV death component (Table 3). Analysis of the total number of subjects experiencing an event for each of these components indicate that differences in MACE between empagliflozin and placebo treatment arms were primarily driven by differences in CV death. This is reflected when looking at all-cause death. Further details for all-cause death will be provided in Table 4 of section 3.3.1.

Table 3: Breakdown of First events contributing to the Composite 3-Point MACE

MACE First Event	**Placebo N=2333**	**Empa 10* N=2345**	**Empa 25** N=2342**
CV Death	107 (4.59%)	78 (3.33%)	65 (2.78%)
Non-fatal MI	120 (5.14%)	92 (3.92%)	116 (4.95%)
Non-fatal Stroke	55 (2.36%)	75 (3.20%)	67 (2.86%)
Total number of patients with a MACE	**282 (12.09%)**	**243 (10.36%)**	**247 (10.55%)**

*Two patients had non-fatal MI and non-fatal stroke as first events

**One patient had non-fatal MI and CV death as first events

CV death and all-cause mortality were not pre-specified in the testing hierarchy, but CV death was included as a component of the primary MACE endpoint. One of the largest differences between empagliflozin and placebo is seen in a reduction in heart failure deaths and

hospitalizations. However, heart failure was not pre-specified as part of either composite MACE endpoints or the testing hierarchy which controlled the type I error, so this would be better viewed as exploratory or hypothesis generating rather than confirmatory.

3.3.1 Analysis of Cardiovascular Outcomes

A Cox proportional hazards model with factors for treatment, age, sex, baseline BMI≥30, Baseline HbA1c≥8.5%, baseline eGFR, and geographic region was pre-specified for the primary analysis of non-inferiority and superiority for 3 and 4-point MACE. Kaplan-Meier curves for 3-point MACE (Figure 3) show a separation of survival curves starting after several months of treatment.

Figure 3: Kaplan-Meier Plot for 3-Point MACE

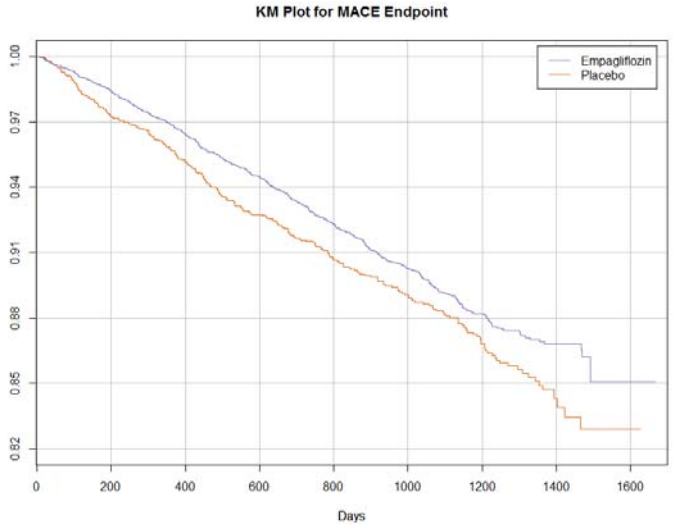


Figure 4 shows the percentage of subjects experiencing each of the 3-point MACE components within the treatment arms. There is a small imbalance favoring placebo for non-fatal strokes, but it is clear that the biggest difference is in CV death which favors empagliflozin. This difference in the number of subjects experiencing an event is seen in the hazard ratios run using the same methodology as was used for the primary analysis. In figure XXX superiority results for 3-point MACE are predominantly due to the differences seen in CV death.

Figure 4: Percentage of Subjects Experiencing 3-Point MACE Components

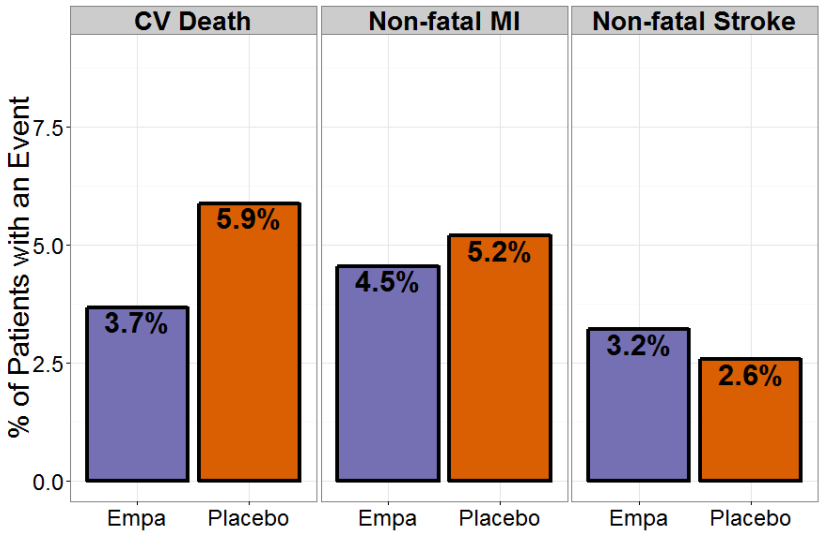
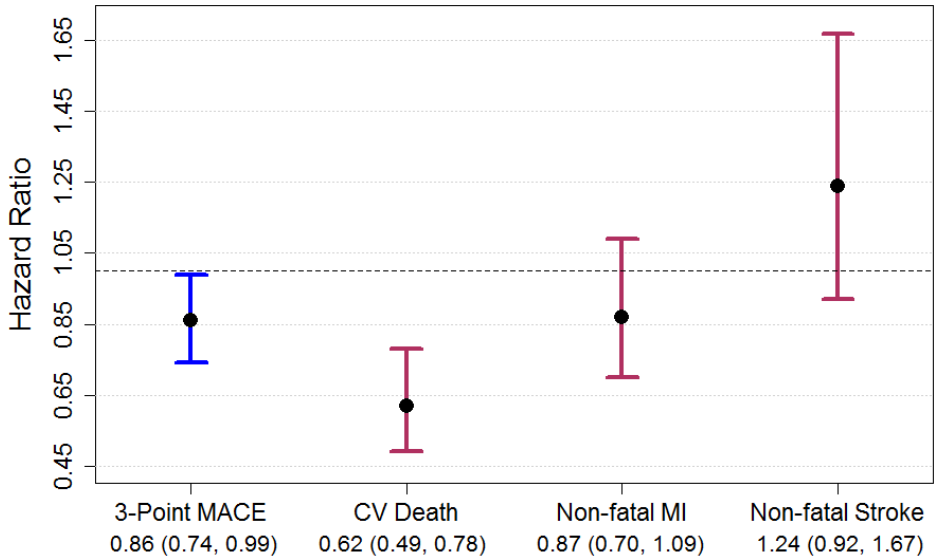


Figure 5: Cox Model Results for 3-Point MACE and Components Outcomes



While the breakdown of 3-point MACE leads us to look at CV death, non-fatal MI, and non-fatal stroke, these are not necessarily the most meaningful outcomes to interpret. These should be coupled with the related outcomes of all-cause death, fatal and non-fatal MIs, and fatal and non-fatal strokes. Figure 6 shows the percentage of subjects with each of these events, along with the percentage experiencing the related component which is a subset of each outcome. Proportionally, results are almost identical to what was seen for the MACE components with all-cause death showing the biggest difference favoring empagliflozin, and all strokes showing a small imbalance favoring placebo. These results translate to the hazard ratio results seen in Figure 7 which are quite similar to what was seen in Figure 5. The number and percentage of all the outcomes from these figures, further separated by dose treatment arms, can also be seen in

Table 4. There is no clear difference in the number of cardiovascular events when comparing the two doses of empagliflozin.

Figure 6: Percentage of Subjects experiencing a MACE Related Outcome

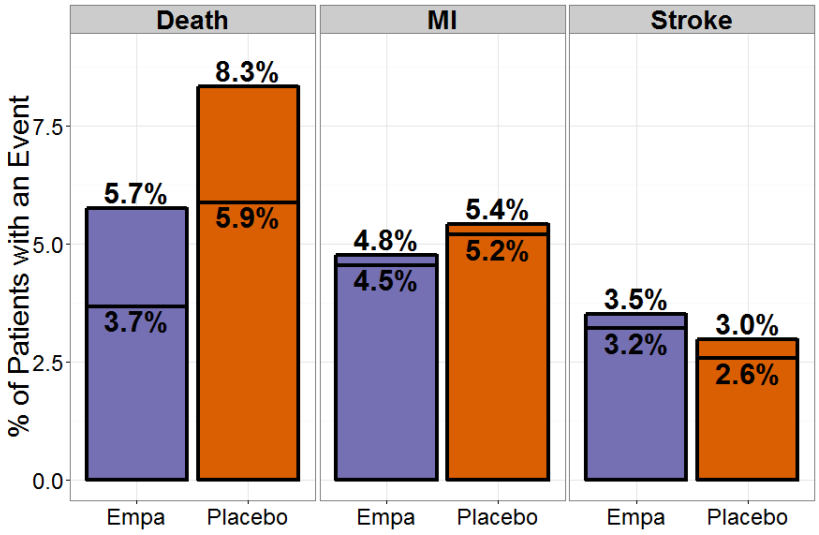


Figure 7: Cox Model Results for MACE Related Outcomes

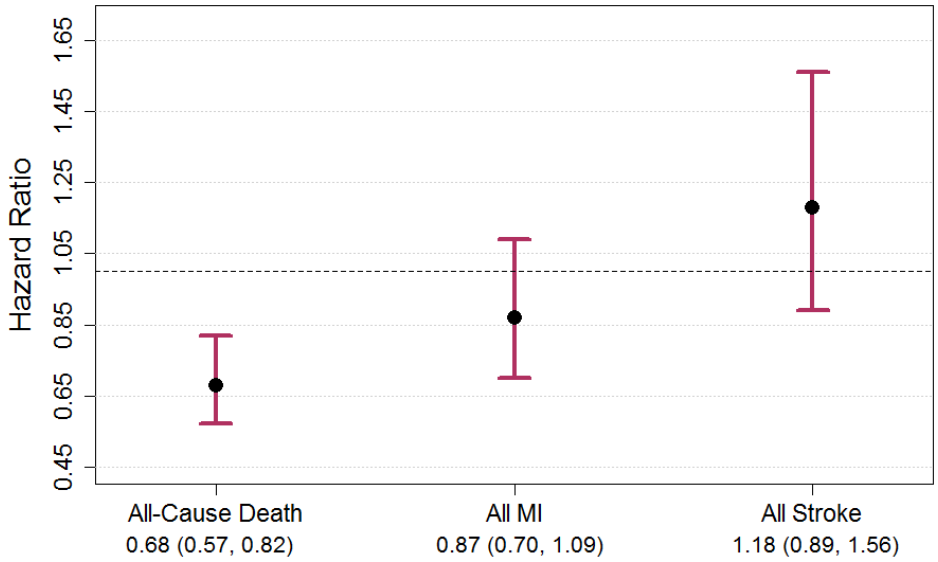


Table 4: Number of Subjects Experiencing Outcomes

	Placebo N=2333	Empa 10 mg N=2345	Empa 25 mg N=2342
3-Point MACE	282 (12.09%)	243 (10.36%)	247 (10.55%)
4-Point MACE	333 (14.27%)	300 (12.79%)	299 (12.77%)
CV Death	137 (5.87%)	90 (3.84%)	82 (3.50%)
Non-fatal Stroke	60 (2.57%)	77 (3.28%)	73 (3.12%)
Non-fatal MI	121 (5.19%)	96 (4.09%)	117 (5.00%)
UA	66 (2.83%)	69 (2.94%)	64 (2.73%)
Stroke	69 (2.96%)	85 (3.62%)	79 (3.37%)
MI	126 (5.40%)	101 (4.31%)	122 (5.21%)
All-Cause Death	194 (8.32%)	137 (5.84%)	132 (5.64%)

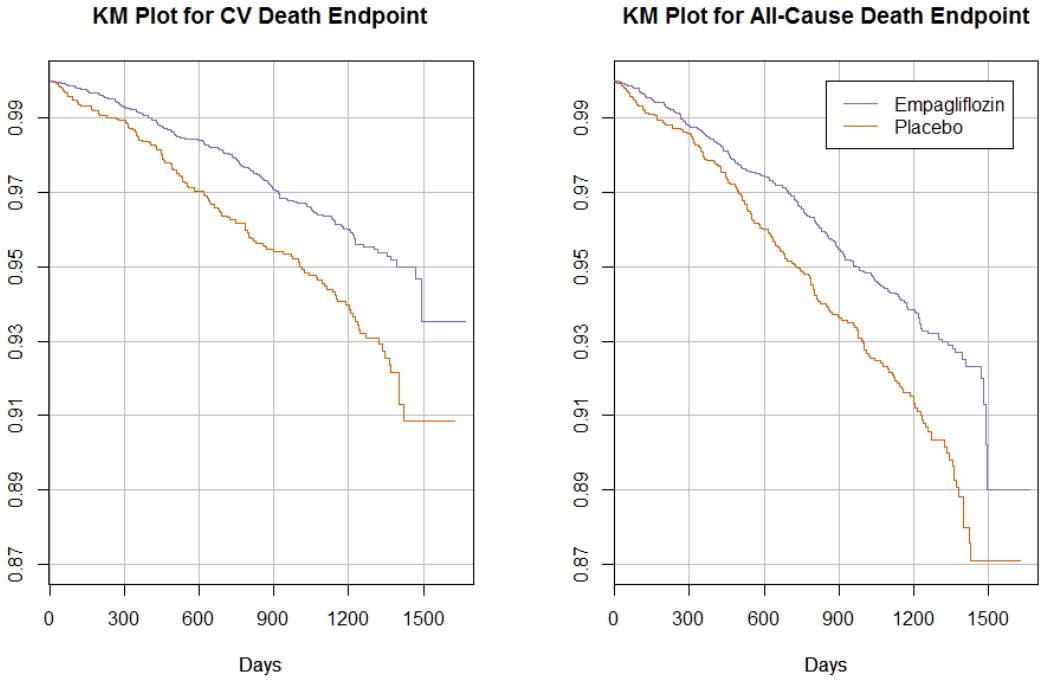
The total number of years of follow-up until censoring or MACE was approximately 6430 years for placebo and 13103 years for the pooled empagliflozin arms. Estimated incidence based on this follow-up and the total number of MACE events is shown in Table 5. Incidence was also estimated for each of the MACE components and their related outcomes. Total follow-up time until censoring or death was approximately 6795 years for placebo and 13834 years for the pooled empagliflozin arms, incidence for death and CV death are based on this follow-up time.

Table 5: Estimated Raw Incidence per 100 patient years

	Placebo N=2333	Pooled Empa N=4687
3-Point MACE	4.39	3.74
CV Death	2.02	1.24
Non-fatal MI	1.85	1.6
Non-fatal Stroke	0.91	1.12
All-Cause Death	2.86	1.94
MI	1.93	1.68
Stroke	1.05	1.23

Since primary endpoint efficacy results were mainly due to what was seen in the CV death component, it is not surprising that results seen in Figure 3 for 3-point MACE would also be more strongly seen in Figure 8 which shows KM results for both CV death and all-cause death.

Figure 8: Kaplan-Meier Plots for CV Death and All-Cause Death



It is clear from the endpoint components breakdown that CV death is the main component driving the differences seen in the 3 and 4-point MACE results. The difference between treatment arms is also reflected in the related all-cause death endpoint. The results for MI and stroke do not show as strong of an effect.

3.3.2 CV Death Outcome

Given that CV death was identified because of the primary analysis results and it was one of the most extreme results in the trial showing the largest reduction in relative risk, the treatment effect seen for this outcome could be inflated from the true value. Given the magnitude of the CV death findings, there is likely an effect, but it would be difficult to accurately quantify this treatment effect from these trial results alone. It was, however, pointed out during the advisory committee that even if the 38% hazard reduction were only 20% it would still be an impressive finding.

3.3.3 Inclusion of Silent MI

Silent MI was not included in the primary analyses. This is an event that is difficult to detect with only 3589/7020 (51.1%) of the patients, 1211 (51.9%) in placebo and 2378 (50.7%) in empagliflozin, screened for it. Of the 3589, 53 experienced a silent MI, 15 (1.2%) in placebo and 38 (1.6%) in empagliflozin. This led to a HR (95% CI) for silent MIs of 1.28 (0.7, 2.33). Additional analyses were performed which incorporated silent MIs, in a very limited capacity, to

the composite 3-point MACE. The first analysis only used the 3589 patients who were screened for silent MI. The second analysis used the same group with an additional 463 patients who were not screened but did experience a MACE during the study. Both analyses use post-randomization variables as part of the inclusion criteria, screening for silent MI and/or having experienced a MACE, which imposes strong assumptions that could lead to erroneous results.

Results only using the screened 3589 patients had a HR (95% CI) of 0.91 (0.73, 1.13). Including additional MACE events from the unscreened population had similar results of 0.92 (0.79, 1.06). While both still achieve the original non-inferiority goal against a threshold of 1.3, there is no longer demonstration of superiority. These results should be viewed with caution given the assumptions associated with them. The analyses that we were able to run indicated that the original objective on non-inferiority was still attained, but superiority is questionable. The issue of silent MIs, however, only affects the non-fatal MI component of MACE and does not affect the CV death component which is driving the difference between the two arms.

3.3.4 Interim Analysis

An interim analysis (IA) was pre-specified in the protocol with interim data used in a cardiovascular meta-analysis to rule out an 80% or greater increased risk using an upper bound threshold of 1.8. A Haybittle-Peto boundary was used to maintain the type I error with 0.0001 of alpha spent at the interim. The IA was planned to occur after 80 confirmed primary MACEs had been adjudicated or the planned cutoff day of July 15, 2012, whichever came first.

The actual data cutoff was June 22, 2012 with a data lock on August 31, 2012. At the time of the interim analysis there were 85/3046 (2.8%) of patients in empagliflozin, and 57/1513 (3.8%) in placebo with a MACE. This led to an estimated HR of 0.74 with a corresponding 95% CI of (0.53, 1.03). It should be noted that at this point in the trial there did seem to be a differential treatment effect between doses with empagliflozin 10 mg, 0.64 (0.42, 0.97), showing a larger effect than empagliflozin 25 mg, 0.83 (0.52, 1.22).

Table 6 shows results for the primary MACE endpoint using the dataset at the end of the study and subgrouping by whether or not the patient entered before data cutoff of June 22, 2012 and was included in the IA. Those included in the IA would generally have a longer follow-up with more time to experience a MACE, hence the higher proportion of events, than those who entered after the IA. The hazard ratios based on the primary Cox model yield similar results for before and after the IA. It should be noted that 33 patients were included in the original interim analysis, but not included in the results based on final analysis data due to site non-compliance or other issues.

Table 6: Results before and after Interim Analysis

	Pooled Empa Events / N	Placebo Events / N	HR (95% CI)
Included in Interim Analysis	358 / 3027 (11.8%)	207 / 1499 (13.8%)	0.85 (0.72, 1.01)
After Interim Analysis	132 / 1660 (8%)	75 / 834 (9%)	0.86 (0.65, 1.15)

3.3.5 3-Point MACE + All-cause Death

I ran an analysis which incorporated all-cause death into the 3-point MACE endpoint in order to assess how much censoring non-CV deaths under the assumption that they would have the same time to MACE event after death as those who were censored alive would affect the primary analysis results. There were 154 non-CV deaths in the trial, and of those, there were 19 subjects who had a non-fatal MACE event. When incorporating all-cause death into 3-point MACE there were an additional 135 events, 51 on placebo and 84 on empagliflozin. The bias from this assumption is minimal and seems to be in the direction favoring placebo. Table 7 shows results for this analysis along with the primary and death outcomes.

Table 7: Results for 3-Point MACE + Death

	Placebo	Pooled Empa	Hazard Ratio (95%)
3-Point Death MACE	333 (14.27%)	574 (12.25%)	0.85 (0.74, 0.97)
3-Point MACE	282 (12.09%)	490 (10.45%)	0.86 (0.74, 0.99)
CV Death	137 (5.87%)	172 (3.67%)	0.62 (0.49, 0.78)
All-Cause Death	194 (8.32%)	269 (5.74%)	0.68 (0.57, 0.82)

3.3.6 Sensitivity Analyses

Sensitivity analyses were run for both the 3-point MACE and death outcomes. Missing follow-up was imputed for the 211 subjects considered to be prematurely discontinued for 3-point MACE and combined with the observed data. Results shown in Table 8 are based on 2,000 imputations.

Estimated incidence based on the time spent off treatment for each of the treatment arms was calculated as 8.3 per 100 patient years for placebo, and 8 per 100 patient years for empagliflozin. Those who discontinued study treatment but continued follow-up in the study are referred to as retrieved dropouts. When the retrieved dropouts were pooled together the off-treatment estimated incidence is 8.1 per 100 patient years. These were used for hazard rates to impute missing follow-up. It should be noted that the results are relatively unchanged for all the hazards used in these sensitivity analyses.

Table 8: Sensitivity Analyses for 3-Point MACE

Estimated Incidence Used for Imputation	Hazard / 100 Patient Years		Average Number of Imputed Events		P-value based on observed + imputed data	HR (95% CI) based on observed + imputed data
	Placebo	Empa	Placebo	Empa		
Retrieved Dropouts - Pooled	8.08	8.08	9	20	0.046	0.86 (0.745, 0.998)
Retrieved Dropouts by Arm	8.28	7.95	10	20	0.044	0.86 (0.744, 0.996)

4 Subgroup Analysis

Subgroup analyses were run for a number of different groups. Since CV death was the only component showing superiority within the primary composite, results for that and the related all-cause death outcome are also shown for the subgroups. Table 9 shows subgroup results for 3-point MACE, CV death, and all-cause death. CV death and death could not be run for certain subgroups due to a scarcity of events. Subgroups for age, race, sex, and geographic region are shown below along with some groups which had more disparate effects for the primary endpoint. Larger differences in the primary 3-point MACE endpoint where the HR was above 1 were seen in subgroups for Black or African American, under 65, higher HbA1c, and those between 70 and 80 kg, or at least 90 kg. These differences, however, did not translate to the CV death component. There was some difference still in the African American subgroup for all-cause death. This was one of the smallest subgroups with only 357 subjects, so results should be viewed with caution until more data can be collected on this population.

Table 9: Subgroup Analyses HR (95% CI)

Group	Category	N	MACE	CV Death	Death
Age	Under 65	3893	1.04 (0.84, 1.29)	0.72 (0.51, 1.00)	0.71 (0.53, 0.95)
	65 and Over	3127	0.72 (0.59, 0.88)	0.56 (0.41, 0.75)	0.67 (0.53, 0.86)
Sex	Female	2004	0.83 (0.62, 1.11)	0.74 (0.47, 1.17)	0.91 (0.63, 1.32)
	Male	5016	0.86 (0.73, 1.02)	0.58 (0.45, 0.75)	0.62 (0.50, 0.77)
Race	White	5081	0.87 (0.73, 1.03)	0.64 (0.50, 0.83)	0.66 (0.54, 0.82)
	Black or African American	357	1.51 (0.82, 2.80)	0.81 (0.34, 1.90)	1.32 (0.60, 2.87)
	Asian	1517	0.68 (0.48, 0.96)	0.44 (0.25, 0.78)	0.63 (0.40, 1.00)
	Other	64	0.53 (0.15, 1.89)	.	.
HbA1c	At or above 8.5	2201	1.14 (0.87, 1.50)	0.70 (0.47, 1.04)	0.82 (0.59, 1.13)
	Under 8.5	4819	0.76 (0.64, 0.90)	0.59 (0.45, 0.77)	0.63 (0.50, 0.79)
Geographic Region	Outside of USA	5800	0.84 (0.71, 0.98)	0.58 (0.45, 0.74)	0.64 (0.52, 0.79)
	USA	1220	0.91 (0.66, 1.27)	0.80 (0.47, 1.36)	0.86 (0.57, 1.31)
Weight in kg	70 or less	1438	0.63 (0.46, 0.87)	0.45 (0.28, 0.72)	0.67 (0.46, 0.98)
	>70 to ≤80	1402	1.26 (0.88, 1.81)	0.94 (0.53, 1.68)	0.93 (0.59, 1.47)
	>80 to ≤90	1415	0.56 (0.41, 0.76)	0.42 (0.26, 0.68)	0.48 (0.32, 0.71)
	≥90	2765	1.06 (0.83, 1.34)	0.77 (0.54, 1.11)	0.74 (0.54, 0.99)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The EMPA-REG CVOT was initially designed as a safety study to demonstrate non-inferiority of empagliflozin against placebo for an increased risk in cardiovascular outcomes. While some aspects of the study design and components are specified differently when initially targeting efficacy, this study did show a benefit in the empagliflozin treated arms for CV death, which is also reflected in the all-cause death endpoint.

Issues that affected conclusions that can be drawn from the statistical assessment included:

- Since the mechanism which is driving the efficacy results is unknown and this is a single study where CV death was picked because it showed the strongest results within the components of the primary endpoint, the treatment effect seen for CV death could be inflated. It was, however, pointed out during the advisory committee that even if the true treatment effect is half of what was measured in the study then it is still a striking effect.

- Numerous changes in event definitions and the trial protocol could have affected how data were collected and the primary analysis results (inclusion of silent MI, etc.). While these changes could have affected results in some of the CV components, they would not have affected the all-cause death results which show strong results favoring empagliflozin.

- A large number of people were unblinded at the interim analysis. Having that many individuals with access to unblinded data makes it more likely that investigators could have been unblinded to at least high level results. I did not find any potential changes in entry criteria or how subjects were treated in the trial based on whether they entered before or after IA.

5.2 Collective Evidence

The original objective of this study was to show non-inferiority of empagliflozin when compared to placebo in the number of cardiovascular outcomes as measured by the primary 3-point MACE (CV death, non-fatal MI, and non-fatal stroke) and secondary 4-point MACE (CV death, non-fatal MI, non-fatal stroke, and unstable angina). This was achieved for both endpoints when the 95.02% upper bounds (adjusted for an interim analysis) were below 1.3. The pre-specified testing hierarchy allowed room for superiority for first the 3-point MACE and then the 4-point MACE endpoints if the same 95.02% upper bounds were below 1. This was seen with the primary, but not the secondary composite endpoint (Figure 2). The differences between the treatment arms for the primary MACE endpoint are largely due to differences in the CV death

component (Figure 4). When looking at the related endpoint of all-cause death, we see this difference reflected there as well (Figure 6).

5.3 Conclusions and Recommendations

Although the EMPA-REG study was initiated and sized to rule out an adverse effect on CV risk, it showed a favorable effect in the primary composite cardiovascular endpoint. The applicant's pre-specified analysis plan did contain provisions that would allow for claims if such an effect was found in the primary composite CV endpoint. The result for 3-point MACE is due primarily to a large difference seen in CV death and not the other two components of MI and stroke. Consequently, this study is only adequate to support an assertion for a reduced risk in CV death. Any claims beyond death or the CV death in this population are not supported by these study results alone.

5.4 Labeling Recommendations

Trial results for outcomes such as heart failure and new or worsening nephropathy and its components are included in section 14 of the applicant's label. Given that these were not a part of the primary or secondary endpoints, nor were they adjusted for in the testing hierarchy, these should not be included in the label. If subgroup analyses are included, then interaction p-values for all subgroups should also not be included in the label. Since 3-point MACE was the primary endpoint of interest, descriptive figures and subgroup analyses should be included for MACE first or as side-by-side results with CV death.

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/s/

JENNIFER J CLARK
10/18/2016

MARK D ROTHMANN
10/19/2016
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review

CLINICAL STUDIES

NDA Number:	204629
Product Name:	Empagliflozin (Jardiance)
Sponsor:	Boehringer Ingelheim
Indications:	Type-2 Diabetes
Project manager:	Michael G. White
Clinical review division:	Division of Metabolism and Endocrinology Products
Clinical reviewer:	Andreea (Ondina) Lungu
Dates:	Consult received on April 22nd, 2016
Statistical reviewer:	Changming (Sherman) Xia, Ph.D.
Concurring reviewers:	Eugenio Andraca-Carrera, Ph.D.
	Mat Soukup, Ph.D.

Keywords: Amputation, type 2 diabetes, safety

Table of Contents

1 INTRODUCTION AND BACKGROUND

This document presents a statistical review to examine the risk of lower-limb amputations associated with empagliflozin based on a retrospective evaluation of fracture data collected in the EMPA-REG trial (1245.25).

The retrospective evaluation of lower-limb amputations in the EMPA-REG trial was prompted by a potential signal observed in another product in the SGLT2 inhibitor class, canagliflozin. On March 17, 2016, Janssen Research & Development informed the Agency of an observed increase in the risk of lower-limb amputations in subjects treated with canagliflozin relative to placebo in the ongoing cardiovascular outcomes trial CANVAS. As a result of this finding, evaluation for the risk of amputations was requested to be conducted in the other currently approved products in the same class of SGLT2 inhibitors.

To evaluate the risk of amputations associated with empagliflozin, a retrospective analysis was conducted using data collected in the EMPA-REG trial, a trial designed to rule out an unacceptable increase in major adverse cardiovascular events associated with empagliflozin relative to placebo. The EMPA-REG trial randomized 7028 subjects, 7020 subjects of which were included in the safety analysis set (8 randomized subjects did not receive trial medications): empagliflozin 10 mg (N=2345), empagliflozin 25 mg (N=2342) or placebo (N=2333). The trial was completed in 2015 and had a median follow-up time of 3.1 years.

2 OBJECTIVE

Evaluate whether empagliflozin is associated with an increased risk of lower-limb amputations relative to placebo in the completed cardiovascular outcome trial EMPA-REG.

3 DATA SOURCES

Data on amputations were extracted from three datasets from the EMPA-REG trial.

- **ADAE_0095.xpt** – Adverse Events Analysis Data submitted as part of the final report of the EMPA-REG trial. This dataset contains information on adverse events collected during the conduct of the trial.
- **ADNRT.sas7bdat** – Narratives dataset submitted on May 18, 2016 as a response to an information request sent to the sponsor. Narratives of 3428 unique subjects were provided in this data set.
- **CM.xpt** (1245-0025-tabulation-sdtm-cm (0095)) – Concomitant therapy tabulation (SDTM) dataset submitted as part of the final report to the EMPA-REG trial. The data set used to search for additional potential amputations (in the CMTRT variable).

4 OUTCOME

The primary outcome of interest is lower-limb amputations that occurred after at least one dose of randomized treatment in the EMPA-REG trial.

Potential amputations were identified from three sources of data:

1. Subject-level adverse event narratives (NRT, dataset ADNRT.sas7bdat);
2. MedDRA adverse events (AE) reported as part of comments, AE terms, Preferred Terms (PT) or High Level Terms (HLT) (dataset ADAE.xpt); and
3. Concomitant therapy (dataset CM.xpt).

Events identified as potential amputations from these three sources were reviewed and adjudicated by the clinical review team. Those events that were adjudicated as lower-limb amputations by the clinical team were subsequently used in the statistical analyses (Section 5). Further details on the identification of potential amputations from the various data sources are provided in subsequent sections.

4.1 Search Strategy for Amputations Captured in the Narratives Dataset

On May 12, 2016 the FDA requested the following:

"To allow for text string searches of the narratives provided in the EMPA-REG OUTCOME trial, please provide an electronic data set with two variables: one variable to identify the unique subject ID and the other variable in text format that contains the full narrative information."

The sponsor submitted the electronic data set, ADNRT.sas7bdat, in response to this information request on May 18, 2016. In consultations with the clinical review team, the following terms were searched from the narratives in this dataset to identify subjects with potential amputations:

- 'Ampu'
- 'Resect'
- 'Remov'
- 'Biops'
- 'Disarticulation'
- 'Necrectomy'
- 'Gangr'

A total of **602** unique subjects were identified by the narratives search.

4.2 Search Strategy for Amputations in ADAE Dataset

To identify subjects with potential amputations, several variables in the ADAE data set were used; each is described below.

4.2.1 Adverse Event Comments

The ADAE data set contained a variable AECOM which was a character variable that contained a short description of the reported adverse event. The same terms used in the narrative search (see Section 4.1) were also used to identify subjects with potential amputations using the AECOM variable.

181 unique subjects were identified through the AE comment search. **59** of these unique subjects were not previously identified by the narratives search.

Reviewer Comment*: Note that the AECOM variable was not consistently used for all adverse events reported nor is it clear if this was used consistently across investigators. However, for*

those subjects that had information captured in the AECOM variable, this provides additional information on the reported adverse event beyond the preferred or verbatim terms included in the ADAE data set.

4.2.2 MedDRA Preferred Terms

The Division of Pharmacovigilance I and the clinical review team provided a list of MedDRA preferred terms (PT's) to be used to identify potential amputations and related events. The following terms were provided and searched in the variable MPT from the ADAE dataset.

- Diabetic foot
- Diabetic foot infection
- Diabetic ulcer
- Infected skin ulcer
- Skin ulcer
- Cellulitis gangrenous
- Biopsy bone
- Biopsy bone abnormal
- Bone scan
- Bone scan abnormal
- X-ray limb
- X-ray limb abnormal
- Osteolysis
- Gangrene
- Diabetic gangrene

295 unique subjects were identified through the PT search. **168** of these unique subjects were not previously identified by the narratives search or the AE comment search.

4.2.3 MedDRA High Level Term

Similar to the PT search, the Division of Pharmacovigilance I and the clinical review team provided a list of MedDRA High Level terms (HLT's) to be used to identify potential amputations and related events. The following terms were provided and searched in the variable MHLT from the ADAE dataset.

- Limb therapeutic procedures
- Diabetic complications dermal
- Skin ischaemic conditions
- Non-site specific necrosis and vascular insufficiency NEC
- Bone and joint infections
- Bone and joint infections (excl arthritis)
- Bone disorders NEC
- Bone related signs and symptoms
- Musculoskeletal necrosis and vascular insufficiency
- Peripheral vasoconstriction, necrosis and vascular insufficiency.

452 unique subjects were identified by the HLT search. **294** of these unique subjects were not previously identified by narratives search, AE comment search or PT search.

4.2.4 Reported Adverse Event Term

The reported term for the adverse event was captured in the variable AETERM in the ADAE data set. The variable AETERM was searched to identify any instance of the following term:

- "Amput"

16 unique subjects were identified by the AETERM search. **1** of these unique subjects was not previously identified by narratives search, AE comment search, PT search or HLT search.

4.3 Search Strategy for Amputations in Concomitant Medication Dataset

The concomitant medication data set (CM.xpt) also provided information on potential amputations. To identify potential events, the variable CMTRT (Reported Name of Drug, Med, or Therapy) was searched for the following term[1]:

- 'Amput'

83 subjects were identified by the concomitant medication search. **2** of these unique subjects were not previously identified by narratives search, AE comment search, PT search, HLT search, or AETERM search.

4.4 Summary of Search Results

Table 1 summarizes the number of subjects identified for each of the search strategies. The first row depicts the number of unique subjects for each search strategy, whereas the second row depicts the number of subjects for each search strategy conditional on the number of subjects identified by previous search strategies (e.g. 168 unique subjects were identified by a PT hit that were not identified by an NRT or COM hit). Overall, the search strategy described above identified a total of **1126** unique subjects, of which **963** subjects have narratives available in the ADNRT.sas7bdat dataset[2]. A listing of these 1126 subjects was sent to the clinical review team for adjudication.

Table 1 Number of Subjects Identified by Each Search Strategy

Search	NRT hits	COM hits	PT hits	HLT hits	AETERM hits	CM hits	Combined
No. of Subjects	602	181	295	452	16	83	**1629**
No. of Unique Subject	602	59	168	294	1	2	**1126**

Note: Some subjects had hits from multiple searches.

[1] The term 'Disarticul' was also searched; however, all subjects found through this search were previously identified through other search criteria. A similar search was also conducted using the variable CMDECOD (Standardized Medication Name). This search found 5 additional unique subjects; however, these 5 subjects were identified by other search criteria.

[2] Some subjects (963-602=361) have narratives available, but their narratives did not result in a "NRT hit". 963 was derived by checking whether the subject ID was included in the submitted SAS narratives dataset.

4.5 Event Adjudication

The sponsor submitted all available (3428) individual subject narratives in the EMPA-REG trial. These narratives, along with other available information including the comment field in the **AE** dataset and concomitant therapy information in the **CM** dataset, were reviewed by an endocrinologist from the Division of Metabolism and Endocrinology Products to adjudicate possible amputation cases. Out of the 1126 unique subjects identified through the above defined search strategy, a total of 139 were adjudicated as having experienced a lower-limb amputation. Note that the adjudication process was conducted unblinded to treatment allocation; blinded adjudication was not performed because the narratives used in the adjudication could contain information on randomized treatment and it was not feasible to assemble blinded adjudication information.

5 STATISTICAL ANALYSIS

5.1 Comparison of Interest

The primary analysis of interest compared subjects randomized to placebo to subjects randomized to the two approved doses of empagliflozin, 10mg and 25mg.

5.2 Multiplicity

No adjustments for multiplicity were made. All confidence intervals were estimated and reported at a nominal $\alpha = 0.05$ level (two-sided).

5.3 Sponsor's Adjudicated Amputation Summary

In a response to the European Medical Agency (EMA) dated May 2, 2016, the sponsor identified **42/47/44** subjects with lower-limb amputations in empagliflozin 10 mg, 25 mg and placebo groups, respectively (Table 2 below)[3] from the EMPA-REG trial. The sponsor stated in this communication that current data did not indicate a risk of lower-limb amputation in subjects treated with empagliflozin compared to placebo.

Table 2 Sponsor Summary of Lower Limb Amputations from EMPA-REG

Treatment (No. of treated subjects)	Number of cases	Frequency
Empagliflozin 10 mg (N=2345)	42	1.79%
Empagliflozin 25 mg (N=2345)	47	2.01%
Placebo (N=2333)	44	1.89%
Overall (N=7020)	133	1.89%

Source: Sponsor's calculation based on manual review

[3] See Appendix 1 for a description of the sponsor's search and adjudication procedure.

5.4 FDA's Adjudicated Amputation Summary

Based on the search strategy described in Section 4, the FDA review team identified 6 additional subjects who were not included in the sponsor's original list of 133 subjects with lower-limb amputation events submitted to the Agency on July 22, 2016[4]. Of these six subjects, two subjects were identified as having lower limb amputations for each of the three treatment groups.

The FDA adjudication process identified a total of 139 subjects as having experienced lower-limb amputation events. The breakdown of these subjects by treatment group is listed in Table 3.

Table 3 FDA Adjudicated Summary of Subjects with Confirmed Lower-limb Amputations by Treatment

Treatment	Number of Cases	Frequency
Empagliflozin 10 mg (N=2345)	44	1.88%
Empagliflozin 25 mg (N=2342)	49	2.09%
Placebo (N=2333)	46	1.97%
Total (N=7020)	139	1.98%

Table 4 depicts the number of subjects who had positive lower limb amputation adjudication and the source of information used to determine event status. The vast majority of positive cases were based on narrative (NRT) hits, which is not unexpected as this source of information provides the most documentation on subject experience in the EMPA-REG trial. In addition, if a subject was determined to have a lower limb amputation from the NRT hit, it was not evaluated for other search hits.

Table 4 Source of 139 Subjects with Confirmed Lower-limb Amputations

Search	NRT hit(s)	COM hit(s)	PT hit(s)	HLT hit(s)	AETERM hit(s)	CM hit(s)	**Total**
No. of Unique Subjects	119[5]	3	9	6	1	1	139

Note: Table 4 represents the source of text search, but not the source of clinical adjudication (e.g. a case identified by an NRT hit could have been clinically adjudicated via reviewing the CM information).

[4] Subject ID's for the six subjects identified by the FDA and not identified by the sponsor are: (b) (6) (b) (6).

[5] The original narratives PDF file was used for Subject (b) (6) because of missing text in its SAS narratives dataset, as described in Appendix 2.

5.5 Statistical Analysis

There were 93 events observed in 4687 subjects randomized to empagliflozin (10 mg and 25 mg combined) and 46 events among 2333 subjects randomized to placebo that were adjudicated as lower-limb amputations. The estimated odds ratio for this risk associated with empagliflozin was **1.01** with 95% confidence interval **(0.70, 1.44)** which does not show evidence that the risk of lower-limb amputation is different among subjects randomized to empagliflozin than subjects randomized to placebo (Table 5).

Table 5 Primary Analysis of Adjudicated Lower-Limb Amputations

	Empagliflozin	**Placebo**
Events / Total Subjects (%)	93 / 4687 (1.98%)	46 / 2333 (1.97%)
Odds Ratio (95%)	**1.01 (0.70, 1.44)**	

6 LIMITATIONS

Some limitations of this analysis are described below. These limitations should be considered when interpreting the strength of the findings.

(1) Initial identification (search) of potential amputations and adequate clinical adjudication depend on the detailed descriptions of the adverse events, such as narratives, comments, concomitant medication, and reported terms of AE events. Such descriptions are not available for all subjects, and it is possible some events were not captured.
(2) The date of amputation is not available for all the adjudicated events. As a result, a time-to-event analysis is not feasible. It is not possible to evaluate the association between length of exposure to empagliflozin and the risk of amputations.
(3) The SAS narratives dataset submitted by the sponsor was found to include incomplete narratives for one subject when compared to the original narratives PDFs (see Appendix 2). The missing text in the SAS narratives dataset initially prevented us from identifying a lower-limb amputation event associated with this subject. It is uncertain whether this dataset may also include incomplete narratives for other subjects.

7 CONCLUSIONS

The FDA review team conducted a retrospective analysis comparing the lower-limb amputation event rates of subjects randomized to empagliflozin and placebo in the EMPA-REG trial. The current data do not suggest a difference in risk between empagliflozin and placebo. The estimated odds ratio is **1.01** (empagliflozin to placebo) with a 95% confidence interval of **(0.70, 1.44)**.

Our analysis has some limitations and therefore should be interpreted with caution. As the trial did not actively collect amputation related events with a designed case report form, the retrospective nature of this analysis relied upon identification of potential events through a

search of narratives, adverse event comments, preferred terms, high level terms, reported adverse events terms and concomitant medication. Of those identified potential events, some of these fields were not available for some subjects in the trial and information regarding amputations may be limited to thoroughly ascertain if an identified potential event was actually an amputation. Therefore, there is a potential underreporting of the number of amputations due to (1) the ability of the search strategy to identify events and (2) the ability to ascertain event status with limited information. In addition, as it is difficult to identify a date associated with all adjudicated events, it is not possible to assess temporal relationships of the amputations with treatment exposure, for example using time-to-event analyses.

APPENDIX

Appendix 1: Sponsor's Search Strategy Described in Response to FDA on August 22, 2016

The Sponsor identified 133 subjects with lower-limb amputations.
Details of Search Strategy for Amputations:
Taking into consideration that the amputations were not routinely reported as adverse events, the following search strategy was established to identify lower limb amputations:

1. The adverse events were reviewed for any PT of amputation.

2. The concomitant treatments were searched for any amputation based on the coded entries.

3. A search for any mentioning of "amput" (to account for "amputation", "amputed", "amputing" etc.) and "disarticul" (to account for "disarticulation", "disarticulating", "disarticulated" etc.) in the concomitant therapy, adverse event comments, investigators comments or change of antidiabetic background therapy was done.

4. The narratives (in case of serious adverse event) or the trial line-listings of the adverse events and concomitant therapies of the patients included in these outputs were medically reviewed to confirm / reject the occurrence of the lower limb amputation (e.g., in case of rectum amputation).

5. To account for potential cases of amputation not reported as a comment of an event or as concomitant therapy, a medical review of all the narratives from the clinical trial report which included "amput" or "disarticul" was done. To increase the sensitivity, a search for "resect" (to account for "resection", "resected", "resecting" etc.) or "remov" (to account for "removed", "removal", "removed", "removing" etc.) was also done. Note, all the narratives were considered, including for the patients who permanently stopped the study drug but remained in the trial.

The identification of the confirmed cases of lower limb amputation was based on the medical review. Cases included were any amputation / disarticulation of the lower limb, independent of the cause. Excluded were the cases of:

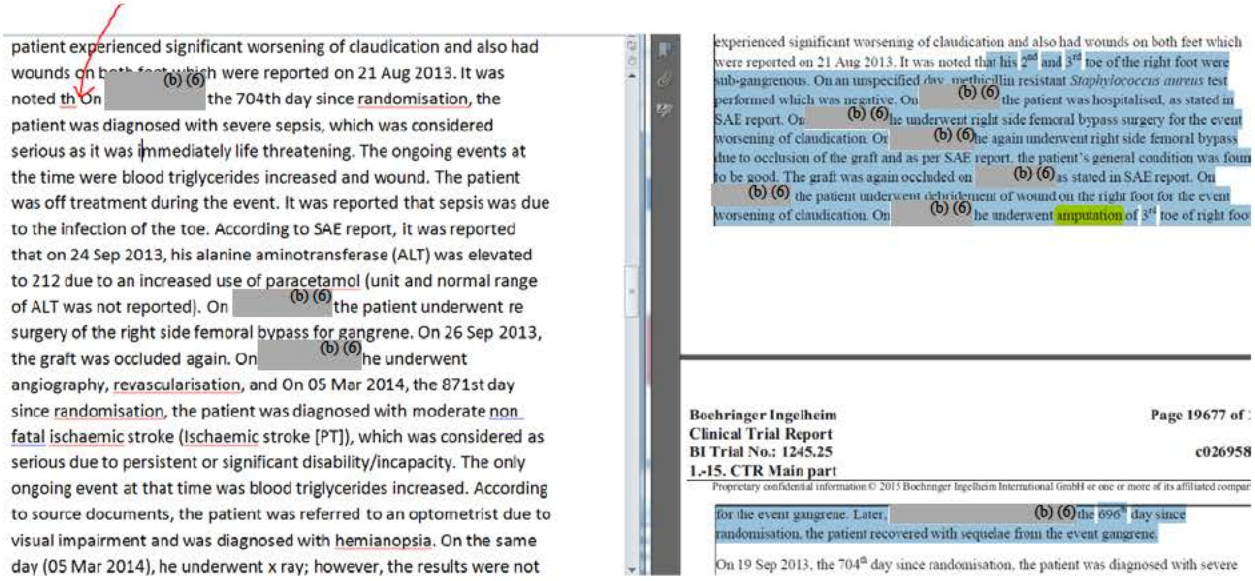
- Amputation / resection / removal of other part of the body than limb (e.g., rectum amputation).
- Amputation of the (part of) upper limb. This is in line with the common medical knowledge that the diabetes mellitus is a risk factor of lower limb amputations, not for upper limb.
- Debridement without mentioning of concomitant amputation. It does not include loss of the lower limb segment.
- Necrosectomy without mentioning of concomitant amputation. It does not include loss of the lower limb segment.
- Amputation stump revision without mentioning of an extension of the amputation.
- Amputation as a preexisting condition at study start.
- Nail removal or resection without mentioning of concomitant amputation. It does not include loss of the lower limb segment.

Appendix 2: Issues in SAS Narratives Dataset for Subject (b) (6)

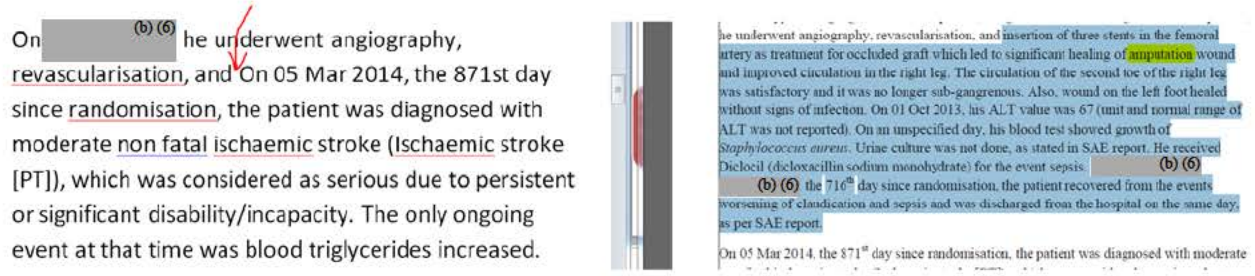
During the review process, we noticed that some parts of the text in the SAS narratives dataset for Subject (b) (6) were missing. The keyword "Amputation" was mentioned twice in the original narratives PDF file. However, both parts of the texts containing the keyword "amputation" were missing from the SAS narratives dataset. As a result, the search strategy of the narratives did not initially find this subject. After reviewing the original narratives PDF file, it was confirmed that Subject (b) (6) experienced lower-limb amputation event(s).

The pictures below show the missing texts in these two instances. The pictures on the left show narratives from the SAS dataset in which we conducted the search, and the pictures on the right show the original narratives PDFs. The highlighted texts on the right (PDF file) are missing from the SAS narratives file (on the left).

Missing text containing keyword "amputation", Instance #1:



Missing text containing keyword "amputation", Instance #2:



It is difficult to evaluate the scope and the potential impact of this type of missingness on our search and analysis results.

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/s/

CHANGMING N XIA
10/19/2016

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10/19/2016

MATTHEW J SOUKUP
10/19/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204629Orig1s008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	204629 / SEQ 0072
Link to EDR	**\\Cdsesub1\evsprod\NDA204629\0072**
Submission Date(s)	November 4, 2015
Submission Type	Required Postmarketing Final Report under 505(O)
Brand Name	JARDIANCE®
Generic Name	Empagliflozin
Dosage Form and Strength	Tablets; 10 mg, 20 mg
Route of Administration	Oral
Proposed Indication	Proposed: Reduction of the incidence of cardiovascular death for adult Type 2 Diabetes Mellitus with established cardiovascular disease AP: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with empagliflozin is appropriate
Applicant	Boehringer Ingelheim
Associated INDs	102,145
OCP Reviewer Team	Sang M. Chung, Ph.D., Manoj Khurana, Ph.D.

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1 Executive Summary

The applicant has submitted the supplement (SEQ 0072) to NDA 204629 (JARDIANCE®) for the required postmarketing final report under 505(O). The sponsor conducted a cardiovascular outcome study (CVOT, Study 1245.25 and named as EMPA-REG OUTCOME) to fulfill PMR 2755-4. The original NDA was approved on August 1, 2014 for the indication of an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) when treatment with empagliflozin is appropriate.

The latest proposed indication based on EMPA-REG results is as follows:

> *"In adult patients with type 2 diabetes mellitus and established cardiovascular disease, JARDIANCE is indicated to reduce the incidence of cardiovascular death"*

In addition, the sponsor is seeking labeling change (b) (4) (b) (4) .

Advisory Committee meeting was held on June 28, 2016 and the committee had split vote (12 for Yes and 11 for No) for the following question:

"*Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results provide substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied?*

a. *If yes, please provide the rationale for your vote.*
b. *If no, please provide the rationale for your vote and comment on what additional data would be needed.*"

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the supplemental NDA 204629/SEQ 0072 for Empagliflozin (JARDIANCE®). The clinical pharmacology data under this supplemental NDA is acceptable. OCP defers the decision on acceptability of the cardiovascular safety data and associated indication to the assessment by Clinical and Statistical Review Disciplines.

1.2 Post-Market Requirements and Commitments

None

2 Summary of Clinical Pharmacology Assessment

2.1 Highlights on Trial design and Primary results

EMPA-REG OUTCOME was a randomized, double-blind, placebo-controlled, parallel-group, event-driven trial designed to compare the safety and efficacy of 10 or 25 mg empagliflozin once daily versus placebo as add-on to standard of care treatment for diabetes and other cardiovascular risks in patients with T2DM (Figure 1). A total 7,028 patients were randomized 1:1:1 to placebo, 10 mg or 25 mg once daily. Randomization to empagliflozin added to standard of care therapies was shown to reduce the risk of a first MACE, a composite of CV death, nonfatal MI, and nonfatal stroke , by 14% (HR 0.86, 95% CI [0.74, 0.99], p-value for superiority = 0.04) compared to randomization to placebo. The median observation times were approximately 3 years for treatments. Refer for details of study design, primary endpoints and results to reviews by Drs. Andreea Lungu and Jennifer Clark related to clinical and statistical perspectives, respectively.

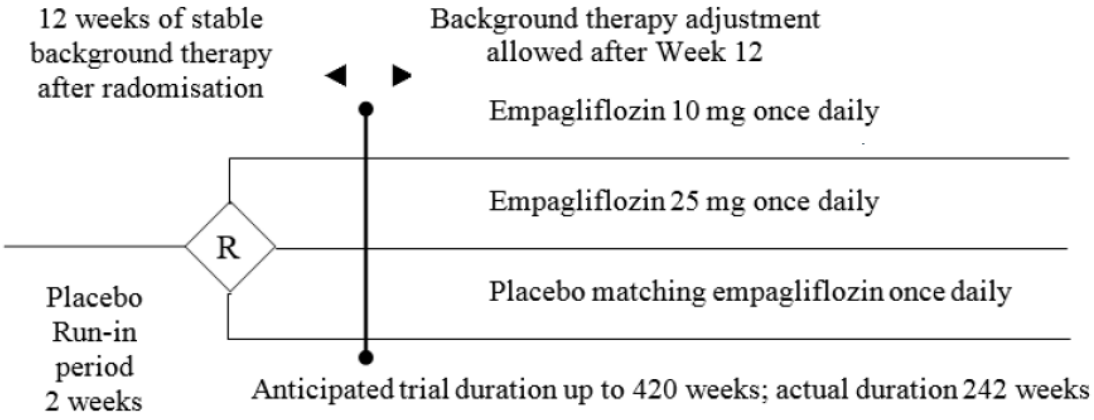

Figure 1 Schematic summary of trial design

2.2 Highlights on Clinical Pharmacology Information

Although the trial was primarily designed for safety, the trend in the dose-dependent glycemic control in the EMPA-REG OUTCOME trial, as assessed using HbA1c or fasting plasma glucose (Figure 2) was consistent with the observations in the Phase 3 trials of the original NDA.

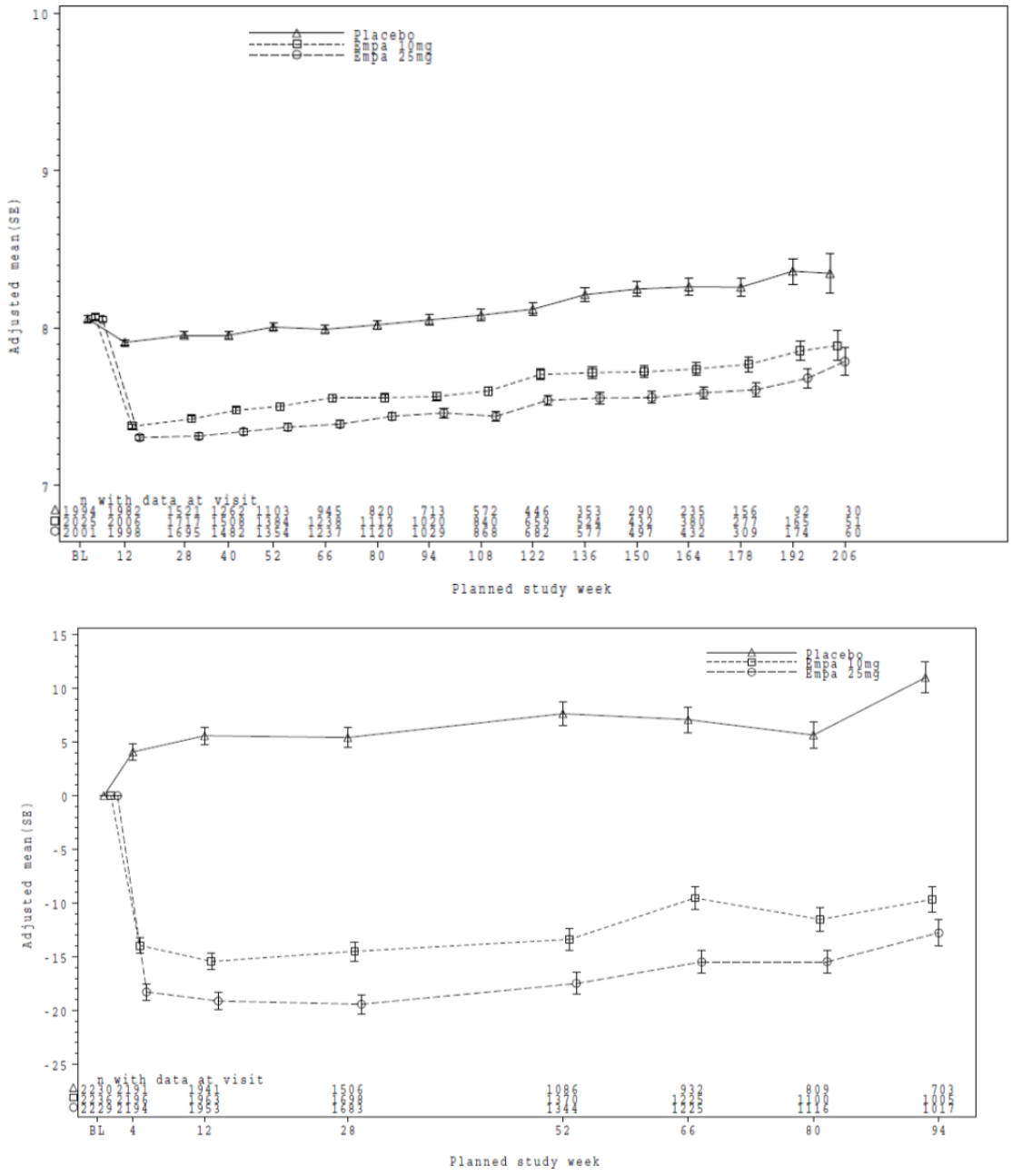

Figure 2 Adjusted mean HbA1c (upper) or FPG (lower) -time profiles (Source: Figure 11.1.2.1:1 for HbA1c and Figure 15.2.4.3.2.1:2 for FPG, CSR)

Steady-state trough concentrations of empagliflozin (C_{trough}) were analyzed at 12 weeks (Visit 6, Day 84) and 52 weeks (Visit 10, Day 364). Overall, 2835 patients (40.3% of randomized patients, Table 1) were included in the pharmacokinetic set, i.e., they had a blood sample taken for assessment of pharmacokinetics, at least 200 patients per region.

Table 1 Summary of patient analysis sets (Source: Table 10.2:1, CSR)

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)
Randomised set (RS)	2337	2347	2344	4691	7028
Treated set (TS), (% of RS)	2333 (99.8)	2345 (99.9)	2342 (99.9)	4687 (99.9)	7020 (99.9)
Full analysis set (FAS), (% of TS)	2333 (100.0)	2344 (100.0)	2341 (100.0)	4685 (100.0)	7018 (100.0)
Per-protocol set (PPS), (% of TS)	2316 (99.3)	2332 (99.4)	2322 (99.1)	4654 (99.3)	6970 (99.3)
On-treatment set (OS), (% of TS)	2308 (98.9)	2306 (98.3)	2301 (98.2)	4607 (98.3)	6915 (98.5)
Treated set follow-up (TS FU), (% of TS)	1668 (71.5)	1773 (75.6)	1824 (77.9)	3597 (76.7)	5265 (75.0)
Pharmacokinetic set, (% of RS)	928 (39.7)	953 (40.6)	954 (40.7)	1907 (40.7)	2835 (40.3)

Source data: Table 15.1.2: 1

Pharmacokinetic observations from EMPA-REG were similar to those of the original NDA information. Means of C_{trough} were apparently proportional to doses though individual concentrations were largely overlapped between 10 and 25 mg (Figure 3). There were no new intrinsic (e.g., apparent exposure increase with a decrease in renal function, Figure 4) or extrinsic factors for pharmacokinetics other than known covariates from the original NDA data.

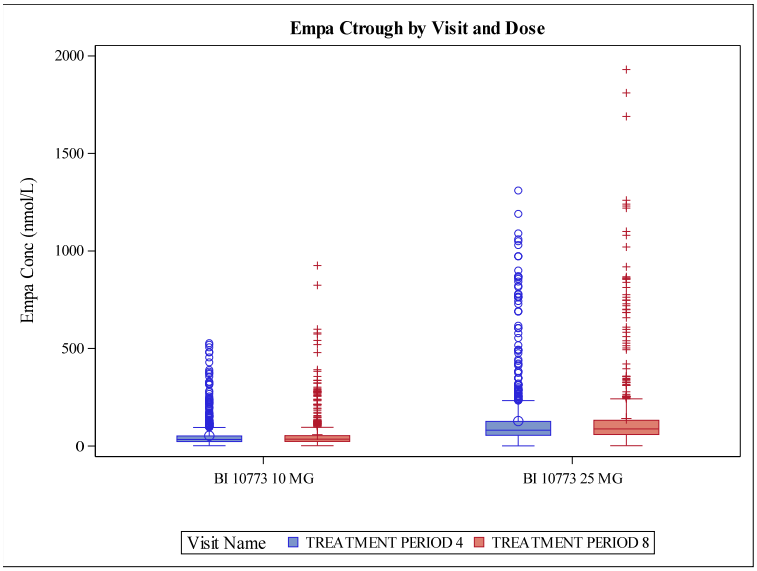

Figure 3 Box plots for C_{trough} vs. Dose (10 or 25 mg) and Visit (Treatment Period 4= Day 84, Treatment Period 8= Day 364).

There was significant initial decrease in eGFR following empagliflozin administration and values of eGFR were apparently steady-state while those of placebo group decreased (Figure 5). Clinical relevance of eGFR changes following empagliflozin is currently not well understood.

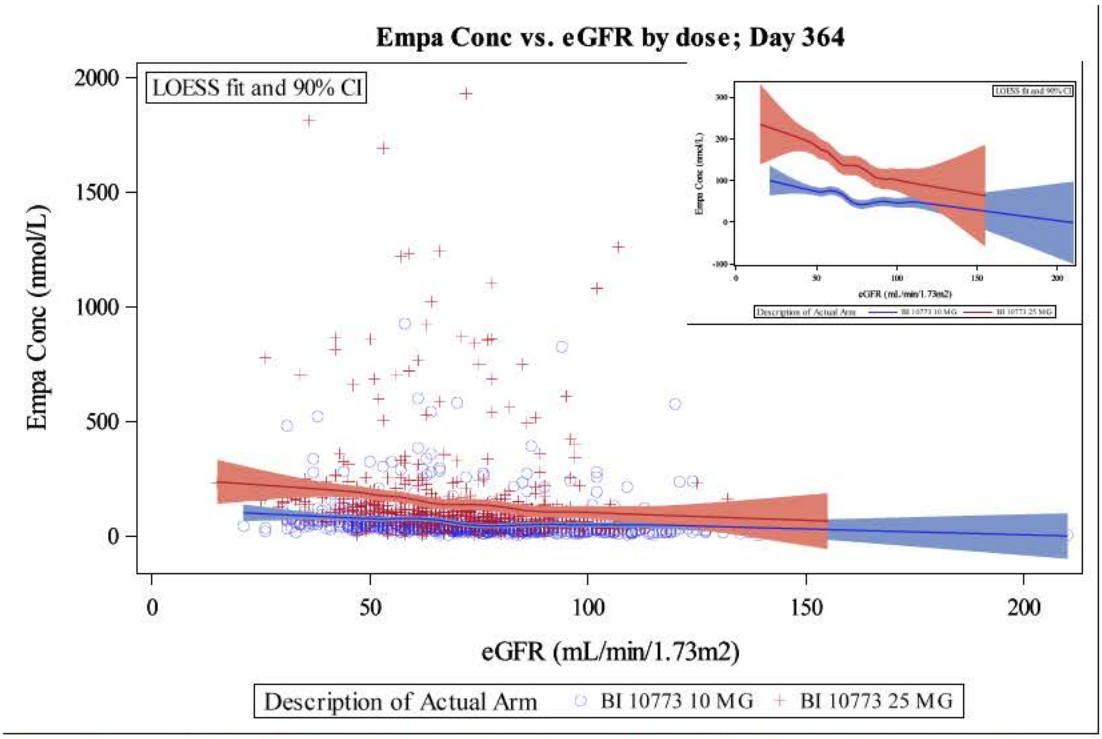

Figure 4 Ctrough vs. eGFR by dose at Day 364 (fit line: Loess fit and 90% CI, inlet: Loess fit only)

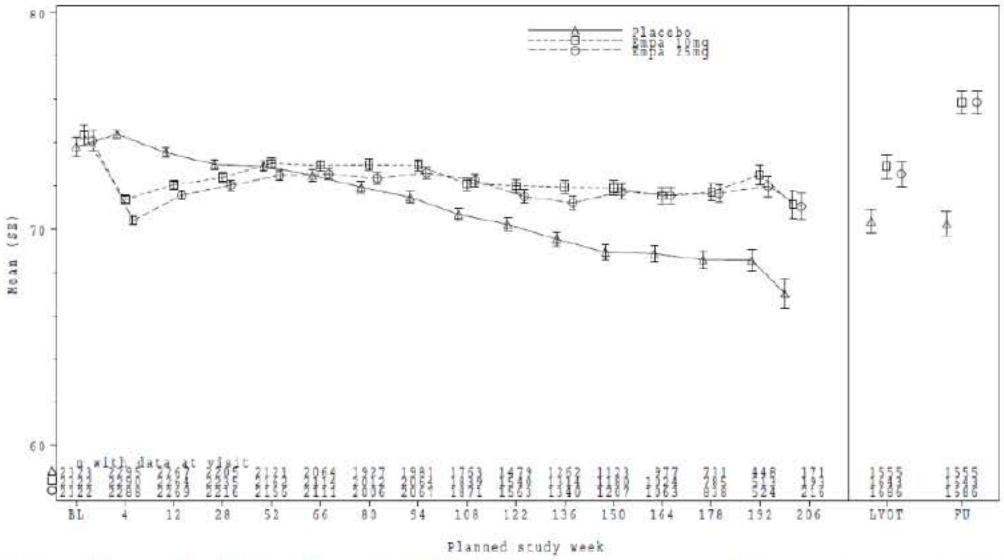

Figure 5 Mean (SE) of eGFR – time profiles by treatment groups (Source: Figure 4.3.2.3:1, Clinical Overview)

2. 3 Commentary on the proposed (b) (4)

(b) (4)

(b) (4)

Therefore, from a benefit:risk perspective HbA1c reduction *per se* does not appear to be a major contributor (b) (4) Hence, the proposed labeling change (b) (4) is not recommended from the clinical pharmacology perspective. However, we defer to the assessment by Clinical and Statistical Review disciplines whether the subgroup analysis on CV safety/mortality (b) (4) satisfies the benefit:risk assessment to favor this labeling change for empagliflozin.

Table 2 Adjusted mean change in HbA1c (%) at Week 12 (Source: \\CDSESUB1\evsprod\NDA204629\0163)

Renal impairment			Change from baseline		Difference from placebo	
Treatment group	**N**	Baseline HbA1c mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
Patients with eGFR 45 to <60 mL/min/1.73m^2						
Placebo	336	7.99 (0.05)	−0.12 (0.04)			
Empa 10 mg	364	8.07 (0.05)	−0.52 (0.04)	−0.39 (0.05)	(−0.50,−0.29)	<0.0001
Empa 25 mg	351	8.04 (0.04)	−0.53 (0.04)	−0.41 (0.05)	(−0.51,−0.31)	<0.0001
Patients with eGFR <45 mL/min/1.73m^2						
Placebo	158	8.07 (0.07)	−0.19 (0.06)			
Empa 10 mg	141	8.06 (0.07)	−0.34 (0.06)	−0.16 (0.08)	(−0.31, 0.00)	0.0492
Empa 25 mg	146	8.10 (0.07)	−0.38 (0.06)	−0.20 (0.08)	(−0.35,−0.04)	0.0136

ANCOVA model includes baseline HbA1c, baseline BMI, region, baseline eGFR, treatment, and treatment-by-baseline eGFR interaction (p<0.0001).
OC: observed cases; values off treatment or after the use of anti-diabetic rescue medication were excluded to assess the on-treatment effect.

Although patients with severe renal impairment were supposed to be excluded in EMPA-REG by protocol design, those patients participated in the study. However, those patients were excluded in reviewer's reanalysis due to small sample size (Table 3).

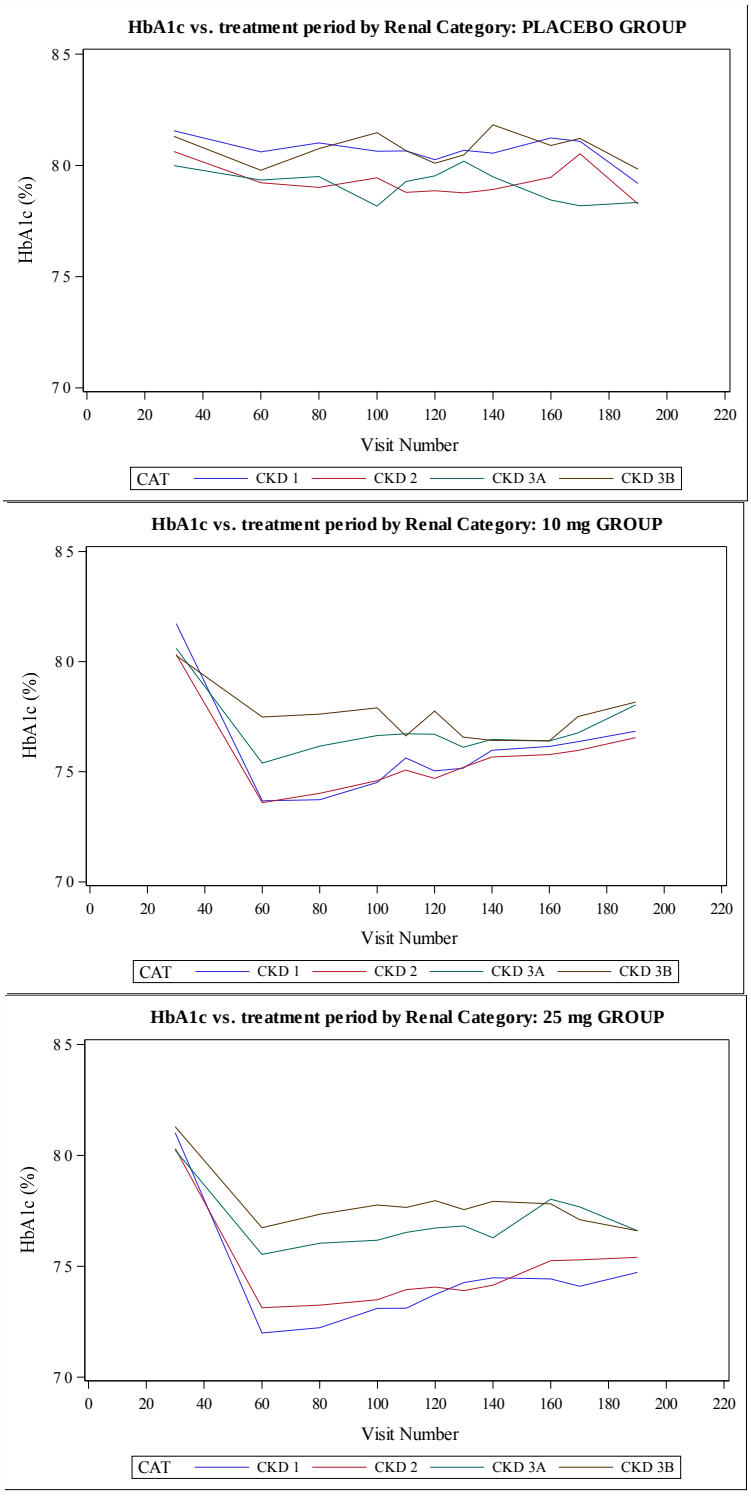

Figure 6 Mean HbA1c-time profiles during the treatment period by renal function categories following placebo (upper), 10 mg (middle) or 25 mg (lower) administration (subject with normal (CKD1), mild (CKD2) or moderate renal impairment (eGFR=45-60 mL/min/1.73m^2; CKD3A, 30-45 mL/min/1.73m^2; CKD3B)

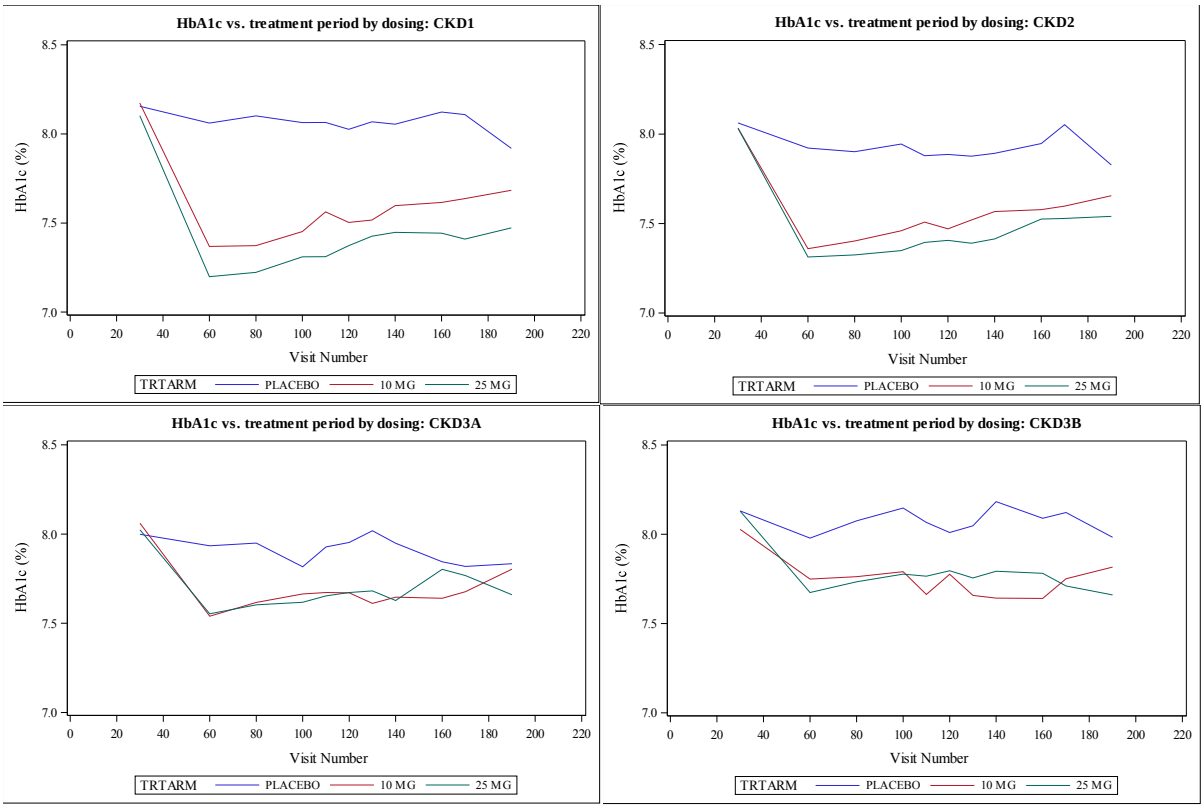

Figure 7 Dose-HbA1c by renal function categories (subject with normal (CKD1), mild (CKD2) or moderate renal impairment (eGFR=45-60 mL/min/1.73m^2; CKD3A, 30-45 mL/min/1.73m^2; CKD3B)

Table 3 Summary of baseline characteristics (Source: Table 10.4.5:1, CSR)

	Placebo	Empa 10 mg	Empa 25 mg	All empa	Total
Treated patients, N (%)	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)	7020 (100.0)
Time since diagn. of T2DM, N (%)					
≤1 year	52 (2.2)	68 (2.9)	60 (2.6)	128 (2.7)	180 (2.6)
>1 to 5 years	371 (15.9)	338 (14.4)	374 (16.0)	712 (15.2)	1083 (15.4)
>5 to 10 years	571 (24.5)	585 (24.9)	590 (25.2)	1175 (25.1)	1746 (24.9)
>10 years	1339 (57.4)	1354 (57.7)	1318 (56.3)	2672 (57.0)	4011 (57.1)
HbA_{1c} [%], mean (SD)	8.08 (0.84)	8.07 (0.86)	8.06 (0.84)	8.07 (0.85)	8.07 (0.85)
HbA_{1c} category [%], N (%)					
<8.0	1156 (49.5)	1188 (50.7)	1151 (49.1)	2339 (49.9)	3495 (49.8)
8.0 to <9.0	795 (34.1)	730 (31.1)	804 (34.3)	1534 (32.7)	2329 (33.2)
≥9.0	382 (16.4)	426 (18.2)	386 (16.5)	812 (17.3)	1194 (17.0)
HbA_{1c} category [%], N (%)					
<8.5%	1607 (68.9)	1598 (68.1)	1612 (68.8)	3210 (68.5)	4817 (68.6)
≥8.5%	726 (31.1)	746 (31.8)	729 (31.1)	1475 (31.5)	2201 (31.4)
FPG [mg/dL], mean (SD)	153.5 (44.0)	153.2 (44.1)	151.9 (43.4)	152.6 (43.8)	152.9 (43.8)
Weight [kg], mean (SD)	86.62 (19.05)	85.94 (18.81)	86.46 (18.95)	86.20 (18.88)	86.34 (18.94)
BMI [kg/m^2], mean (SD)	30.66 (5.24)	30.58 (5.24)	30.62 (5.30)	30.60 (5.27)	30.62 (5.26)
Waist circumfer. [cm], mean (SD)	105.0 (14.0)	104.7 (13.7)	104.8 (13.7)	104.7 (13.7)	104.8 (13.8)
Blood pressure [mmHg], N (%)					
SBP ≥140 or DBP ≥90	934 (40.0)	877 (37.4)	903 (38.6)	1780 (38.0)	2714 (38.7)
SBP <140 and DBP <90	1399 (60.0)	1468 (62.6)	1439 (61.4)	2907 (62.0)	4306 (61.3)
eGFR (MDRD) [$mL/min/1.73m^2$], mean (SD)	73.81 (21.05)	74.28 (21.81)	74.04 (21.36)	74.16 (21.59)	74.04 (21.41)
eGFR (MDRD) category[1], N (%)					
≥90 $mL/min/1.73m^2$	488 (20.9)	519 (22.1)	531 (22.7)	1050 (22.4)	1538 (21.9)
60 to <90 $mL/min/1.73m^2$	1238 (53.1)	1221 (52.1)	1202 (51.3)	2423 (51.7)	3661 (52.2)
45 to <60 $mL/min/1.73m^2$	418 (17.9)	420 (17.9)	411 (17.5)	831 (17.7)	1249 (17.8)
30 to <45 $mL/min/1.73m^2$	183 (7.8)	178 (7.6)	182 (7.8)	360 (7.7)	543 (7.7)
<30 $mL/min/1.73m^2$	6 (0.3)	7 (0.3)	14 (0.6)	21 (0.4)	27 (0.4)
UACR [mg/g], gmean (gCV, %)	26.05 (473.09)	25.45 (451.70)	25.49 (440.38)	25.47 (445.84)	25.66 (454.67)
UACR category [mg/g], N (%)					
Normal (<30)	1382 (59.2)	1405 (59.9)	1384 (59.1)	2789 (59.5)	4171 (59.4)
Microalbuminuria (30 to 300)	675 (28.9)	645 (27.5)	693 (29.6)	1338 (28.5)	2013 (28.7)
Macroalbuminuria (>300)	260 (11.1)	261 (11.1)	248 (10.6)	509 (10.9)	769 (11.0)

gmean = geometric mean, gCV = geometric coefficient of variation
Patients with missing information are not shown.
[1] Renal function was considered normal, if eGFR ≥90 $mL/min/1.73m^2$; lower eGFR values were considered mild (60 $mL/min/1.73m^2$ to <90 $mL/min/1.73m^2$), moderate (30 $mL/min/1.73m^2$ to <60 $mL/min/1.73m^2$) or severe renal impairment/end-stage renal disease (<30 $mL/min/1.73m^2$).

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/s/

SANG M CHUNG
10/24/2016

MANOJ KHURANA
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