FDA Briefing Document

Endocrine and Metabolic Drug Advisory Committee Meeting

June 28, 2016

The committee will discuss supplemental new drug application (sNDA) 204629, empagliflozin (JARDIANCE) tablets, and sNDA 206111, empagliflozin and metformin hydrochloride (SYNJARDY) tablets. Both sNDAs are sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., for the proposed additional indication 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 and to reduce the risk of cardiovascular death or hospitalization for heart failure.

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the EMPA-REG OUTCOMES study to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

Draft Points to Consider

The EMPA-REG OUTCOME study was designed as a safety trial to exclude an increased risk for major adverse cardiovascular events (MACE). Considering data in the briefing documents and presentations at the Advisory Committee meeting, the Agency will be seeking the opinions of the Committee members on the following:

1. Discuss your interpretation of the nonfatal components of the composite (i.e., nonfatal myocardial infarction and nonfatal stroke). Specifically comment on whether issues related to 'silent myocardial infarction' from the EMPA-REG OUTCOME study alter or do not alter your interpretation of the primary results. Please also comment on your level of concern, if any, related to the stroke findings in the EMPA-REG OUTCOME study in light of the BP differences observed in the trial.

2. Discuss the heart failure findings (including but not limited to potential limitations, if any, and expected generalizability of the findings) and comment on whether the design of the study allows you to draw meaningful conclusions with respect to the effect of empagliflozin on heart failure outcomes.

3. Discuss the mortality findings (including but not limited to potential limitations, if any, and expected generalizability of the findings). Comment on differences observed between the non-fatal (i.e., neutral) and fatal components (i.e., favorable) of the primary MACE endpoint. Comment on whether the design of the study allows you to draw meaningful conclusions with respect to the effect of empagliflozin on survival.

4. Discuss the results for the primary analysis based on a composite endpoint of 3-point MACE (consisting of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke). Specifically comment on your level of confidence for the conclusion of 'no increased risk' for 3-point MACE and for the conclusion of 'reduced risk' for 3-point MACE.

5. Discuss the benefit(s), if any, demonstrated by the EMPA-REG OUTCOME study. Comment on your level of confidence that this single trial provides substantial evidence necessary to establish a new benefit(s) for this product in the population studied such that independent substantiation of the findings would not be necessary.

EXECUTIVE SUMMARY

This document provides the briefing materials for the June 28, 2016 meeting of the Endocrinology and Metabolic Drug Advisory Committee to discuss the findings of the EMPA-REG OUTCOME trial.

At the time of approval, the FDA required that the applicant continue to characterize the cardiovascular risk attributed to the use of empagliflozin in patients with type 2 diabetes mellitus using the ongoing EMPA-REG OUTCOME trial[1] [Post Marketing Requirement (PMR) # 2755-4]. In addition to assessing major adverse cardiovascular events (MACE), the PMR also required that the EMPA-REG OUTCOME trial be used to further characterize the effect of empagliflozin on several safety issues identified in the review of the new drug application including; 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. Estimated glomerular filtration rate (eGFR) was also to be followed to assess for worsening renal function with longer term product use.

The EMPA-REG OUTCOME study was a randomized, double-blind, event-driven trial comparing two doses of empagliflozin to placebo, both added to standard of care antidiabetic treatments, in patients with T2DM at increased risk for atherosclerotic cardiovascular disease (ASCVD). The primary objective of the trial was to exclude the possibility that use of empagliflozin to control glycemia increased cardiovascular risk (predominantly ASCVD risk) by 30% or more compared to use of alternate, standard of care, glycemic lowering therapies. In contrast to the SAVOR[2] or TECOS[3] trials, the EMPA-REG OUTCOME trial was not prospectively designed (i.e., sized) with the expressed intent of demonstrating a cardiovascular benefit of the new antidiabetic therapy. CV-safety trials conducted to meet the FDA guidance generally specify that non-inferiority and superiority hypotheses will be tested in a sequential manner in their analysis plans (i.e., regardless of what the trial is initially powered to show).

The pre-specified primary endpoint in the EMPA-REG OUTCOME study was the time to first occurrence of an adjudicated major adverse cardiovascular event (MACE) defined as an incident event of either: cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke (i.e., 3-point MACE). The trial was to stop after 691 participants had experienced an adjudicated MACE event. The pre-specified secondary endpoint was the time to first occurrence of adjudicated CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina (i.e., MACE+ or 4-point MACE). Four analyses comparing the pooled empagliflozin doses to placebo were to be carried out sequentially with appropriate control of type-1 error across the four analyses. These were intended to

[1]Adjudicated MACE (n=142) from EMPA-REG OUTCOMES available up 22 June 2012 were used in a CV meta-analysis designed to exclude the pre-approval CV-risk margin.
[2] N Engl J Med 2013; 369:1317-1326
[3] N Engl J Med 2015; 373:232-242

test non-inferiority on MACE, non-inferiority on MACE+, superiority on MACE and superiority on MACE+.

Empagliflozin was found to be both noninferior and superior to placebo on the primary MACE endpoint (HR 0.86; 95% CI 0.74, 0.99; p = 0.04 for superiority). Empaglifozin was also found to be noninferior but not superior to placebo on MACE+ (HR 0.89; 95% CI 0.78, 1.01; p = 0.08 for superiority).

Issues to consider when interpreting the robustness of the primary endpoint results include:

- The trial was designed to address both a pre-approval and post-approval a safety question. The primary intent of the trial was not to establish a benefit on a specific outcome. Some unblinding occurred as the trial was ongoing to support pre-approval analyses and worldwide regulatory submissions[4]. All unblinded individuals were to keep results confidential and signed agreements to that effect.

- The risk of MACE appeared to diverge early and was almost exclusively accounted for by an effect on the CV death component (HR 0.62; 95% CI 0.49, 0.77). Empagliflozin did not reduce nonfatal stroke (HR 1.24; 95% CI 0.92, 1.67) or non-fatal MI (HR 0.87; 95% CI 0.70, 1.09).

- Many deaths (n=124) were categorized as "non-assessable" and adjudicated as presumed CV deaths (71 versus 53 for empagliflozin versus placebo). Deaths that were "non-assessable" but presumed to be CV-deaths comprised 40% of CV deaths, and 27% of overall deaths in the trial. In a sensitivity analysis that removes all "non-assessable" deaths from the primary endpoint, empagliflozin was no longer demonstrated to be superior to placebo (HR 0.90, 95% CI 0.77, 1.06).

[4] Interim information from the trial was used in the initial submission of the new drug application to support the pre-approval CV-risk assessment and pre-approval safety analyses. A trial team in charge of day to day study conduct activities which included 3 trial statisticians, 2 trial data managers, 4 clinical monitors/clinical research associates and the medical lead for the study remain blinded for the entire trial duration until database lock. Approximately 230 individuals (mostly applicant personnel but also some outside the company) had access to either adjudicated cardiovascular outcome data from the trial alone or to the cardiovascular (CV) meta-analysis report, or to the database with unblinded data from the trial. All individuals who had access to these data signed confidentiality agreements. The main reason for unblinding was involvement in preparations for global or local submissions to health authorities, or preparatory activities for a potential FDA Advisory Committee meeting. Functional areas unblinded included therapeutic area leads, statistics, programming, data management, medical writing, pharmacovigilance, regulatory affairs, project management, epidemiology, document submission, and external advisors for preparation of a potential advisory committee. Although results for the meta-analysis used to support US approval were redacted from FDA documents at the time of approval; results of a meta-analysis used for European approval have been posted publically since March 2014.

- Sensitivity analyses on the single component of CV-death excluding the 124 deaths categorized as "non-assessable" still suggested reduction in CV death (HR 0.59; 95% CI 0.44, 0.79). A reduction in all-cause mortality was also observed (HR 0.68; 95% CI 0.57, 0.82)

- Per protocol, ECG based silent MIs that were not determined to be an adverse event by investigators and entered in the advese event case report form were not sent for adjudication. The applicant conducted secondary analyses defining events of "silent MIs" based solely on ECG paramaters and other criteria (i.e., these events did not require investigator intervention or adjudication). While there are important limitations with regard to analyses that include these data, when these events are included in exploratory analyses, empagliflozin is no longer superior to placebo for MACE. How the issue should be considered in interpretation of the overall results is unclear.

- There were 211 subjects who prematurely discontinued the trial. For 161 of these subjects, vital status was determined but information on nonfatal major adverse cardiovascular events is not known. For the remaining 50 of these subjects, neither vital status nor 3-point MACE is known. Sensitivity analyses to evaluate the impact of this missing data have been carried out.

- To specifically assess the drug-related ASCVD risk, the trial design intended to minimize differences in glycemic and CV-risk factors susceptible to confounding interpretability of the results. This was to be achieved by recommending that background therapies for diabetes and cardiovascular disease be adjusted to achieve therapeutic goals consistent with local professional guideline recommendations. However this was not achieved since differences in glycemic control, blood pressure, and use of certain concomitant medications were observed in the trial.

- In an exploratory analysis, empagliflozin appears to reduce the risk of hospitalization for heart failure (HR 0.65; 95% CI 0.50, 0.85). This endpoint was not included in the plan to control for type 1 error. The trial was not designed to assess heart failure outcomes and data that may be important to the interpretation of this finding are missing or if present may not be as reliable as in a dedicated trial (e.g., New York Heart Association Functional Classification or ejection fraction, baseline therapies for the treatment of heart failure to assess adequacy of treatment at baseline). It is unclear whether the patient population was appropriate for assessing this or whether patients were receiving optimal therapy for heart failure.

The review of the non-cardiovascular safety data from the EMPA-REG OUTCOME trial did not raise any new safety concerns.

There was no significant imbalance in the rate of hypoglycemia, including severe events.

While genital infections were disproportionately represented in patients treated with empagliflozin compared to placebo, this finding is consistent with the current prescribing information.

A decrease in eGFR was observed following initiation of treatment with empagliflozin. This change in eGFR appeared to return to baseline with continued treatment in patients who continued to be assessed for this endpoint. Adverse renal events were more common in the empagliflozin groups for the first three months of treatment, but overall no increased risk for adverse renal events. This early effect on renal function and adverse renal events is consistent with the current prescribing information.

Ketoacidosis was observed to occur more frequently in empagliflozin treated patients, but the total number of events was overall very small. This is a labeled safety concern.

Overall fracture rates were similar between treatment arms. Upper extremity fractures (i.e., humerus, wrist, upper limb, forearm etc.) appeared to be numerically higher on empagliflozin. This could be consistent with events of fall in a drug expected to cause orthostatic hypotension in some susceptible individuals. Although the Applicant noted that osteoporosis was more commonly reported in the empagliflozin arms compared to placebo, the study was not designed to methodically collect detailed information regarding osteoporosis, and bone density scans were not part of the study procedures.

Liver events were adjudicated to determine the probability of a causal relationship between empagliflozin and the event. 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. Events adjudicated as possibly related to the study drug (3 events) or indeterminate (2 events) occurred only in the empagliflozin groups. Based on review of the narratives it is 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 [5]. All were adjudicated as unlikely to be related to the study drug. In most of these cases other more likely causes for the liver abnormality were identified. The findings from this study do not present evidence that empagliflozin causes liver injury.

Malignancy events were also adjudicated to determine the probability of a causal relationship between empagliflozin and the event. Overall the incidence of 'malignancy' events was balanced between treatment groups. Some specific cancer types (i.e., bladder, pancreatic, and melanoma) were observed more commonly in empagliflozin treated patients. Imbalances were driven by small numbers and it is difficult to assess whether the imbalance denotes a risk attributable to empagliflozin or is the result of chance.

Adverse reactions denoting volume depletion events were observed with similar frequency between the treatment arms over the course of the study.

[5] Elevation in AST, ALT greater than 3X ULN, and total bilirubin greater than 2X ULN without initial evidence of cholestasis, which may suggest drug-induced liver disease

Regarding hypersensitivity reactions, the overall frequency was similar between the treatment arms. Anaphylactic reactions not related to food allergies or bee sting occurred in two patients in the empagliflozin 10 mg arm.

Increases in hemoglobin and hematocrit were observed with empagliflozin in the study, a labeled finding for this drug. The impact of these changes on cardiovascular outcomes in the EMPA-REG OUTCOME is unclear. Thromboembolic events overall appeared to have been balanced. However, non-fatal strokes were seemed numerically higher in patients on empagliflozin compared to placebo.

Dose-dependent increases in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were observed with empagliflozin compared to placebo in the study, a labeled finding for this drug. The impact of these changes on cardiovascular outcomes in the EMPA-REG OUTCOME is unclear.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia due to defective insulin secretion, resistance to insulin action, or a combination of both. Type 2 diabetes mellitus (T2DM) is generally characterized by progressive insulin resistance and β-cell failure.

The goal of treatment for patients with diabetes mellitus is to alleviate suffering and prevent complications of the disease. Complications include loss of vision, chronic kidney disease, loss of small sensory peripheral nerve function (i.e., referred to as microvascular disease complications) and an increased propensity for atherosclerotic cardiovascular disease (i.e., referred to as macrovascular disease complications). In patients with T1DM, glucose control with insulin has been shown to reduce the onset and progression of microvascular complications. Long-term follow-up from this trial also suggested a potential delayed benefit of glycemic control on macrovascular disease outcomes [6]. In patients with T2DM, data have suggested that improving glycemic control with insulin, sulfonylurea and metformin can reduce microvascular complications[7]. Based largely on these studies, improvement in glycemic control captured using changes in hemoglobin A1c (HbA1c) has been used as a surrogate of clinical benefit to establish the efficacy of new antidiabetic therapies.

Patients with diabetes mellitus are at increased risk for cardiovascular disease (i.e., predominantly atherosclerotic cardiovascular disease). In 2008, the Food and Drug Administration (FDA) issued the "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" [8]. Prior to publications of the guidance document, controversy related to residual uncertainty surrounding the cardiovascular safety of several antidiabetic products used for the treatment of type 2 diabetes mellitus existed. Since 2009, all new antidiabetic therapies are tested to more precisely define drug-related ischemic cardiovascular risk and to demonstrate that use of new antidiabetic therapies in patients with type 2 DM do not result in an unacceptable increase in ischemic cardiovascular risk. To demonstrate that a new antidiabetic therapy is not associated with an increased risk for major adverse cardiovascular events (MACE), applicants are expected, in part, to show that the new antidiabetic therapy does not increase CV-risk by 80% or more relative to comparators. Post-approval, applicants are expected, in part, to show that the new antidiabetic therapy does not increase CV-risk by 30% or more relative to comparators.

The new drug application (NDA; NDA 204629) for empagliflozin was approved on August 1, 2014 with the indication *"as an adjunct to diet and exercise to improve glycemic control in adults with T2DM"*.

---

[6] Based on the Diabetes Control and Complications Trial, and Epidemiology of Diabetes Interventions and Complications study

[7] Based on the United Kingdom Prospective Diabetes Study

[8] Available at http://www.fda.gov/downloads/drugs/.../guidances/ucm071627.pdf

BACKGROUND

Drug Product Information

Drug Class

Empagliflozin belongs to the SGLT2 inhibitors class of antidiabetic drugs. There are three SGLT2 inhibitors currently approved by the FDA: empagliflozin (approved August 1, 2014), dapagliflozin (approved January 8, 2014), and canagliflozin (approved March 29, 2013). This class of drugs inhibits SGLT2, a transporter found in the proximal renal tubule responsible for renal glucose reabsorption, leading to increased glucosuria, which in turn results in improved glycemic control.

Empagliflozin

Empagliflozin is marketed as a tablet for oral administration in two dosage strengths: 10 mg, and 25 mg. The recommended dose of empagliflozin is 10 mg once daily, taken in the morning. The dose may be increased to 25 mg daily in patients tolerating empagliflozin who need additional glucose lowering. Glycemic lowering is dependent on renal function and several adverse reactions are also dependent on renal function. Renal function should be assessed before starting empagliflozin, and the drug should not be started if eGFR is less than 45 mL/min/1.73 m^2 because the glucose lowering benefits of the drug may not outweigh the risks.

Safety Issues with Empagliflozin

Empagliflozin is contraindicated in subjects with history of serious hypersensitivity reaction to empagliflozin, and subjects with severe renal impairment, end-stage renal disease, or dialysis.

The current empagliflozin label warns against the following serious empagliflozin-related adverse reactions:

- ***Hypotension***
- ***Ketoacidosis***
- ***Impairment in renal function***
- ***Urosepsis and Pyelonephritis***
- ***Hypoglycemia***
- ***Genital mycotic infections***
- ***Increased LDL-C***

Common adverse reactions associated with empagliflozin include urinary tract infections, and genital mycotic infections.

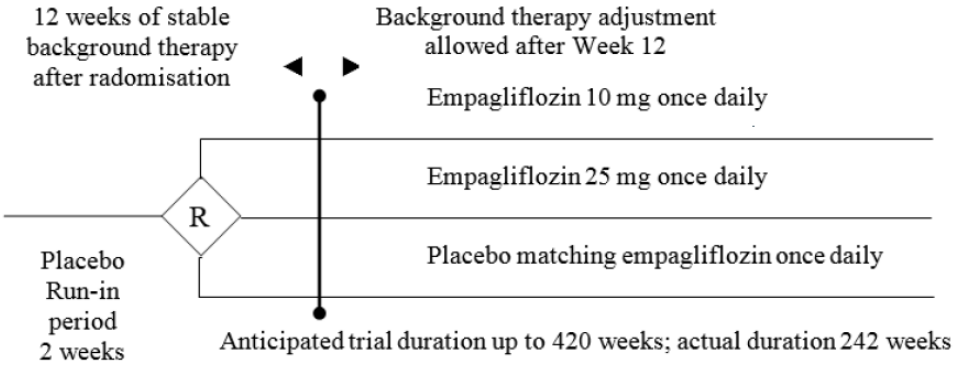
EMPA-REG OUTCOME Design

EMPA-REG was a randomized, double-blind, placebo-controlled, parallel-group, event-driven trial designed to compare the safety and efficacy of 10 mg empagliflozin once

daily and 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.

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 study report for study 1245.25

Subjects were to be followed until the study end (i.e., until the required number of events was reached), or until a fatal event occurred.

An independent external Clinical Event Committee (CEC) was 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 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 baseline characteristics of the study subjects were balanced (Table 1).

Table 1: Baseline demographics

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342	All Empa N=4687
Sex				
Male, N (%)	1680 (72.0)	1653 (70.5)	1683 (71.9)	3336 (71.2)
Female, N (%)	653 (28.0)	692 (29.5)	659 (28.1)	1351 (28.8)
Race				
White, N (%)	1678 (71.9)	1707 (72.8)	1696 (72.4)	3403 (72.6)
Asian, N (%)	511 (21.9)	505 (21.5)	501 (21.4)	1006 (21.5)
Black / African American, N (%)	120 (5.1)	119 (5.1)	118 (5.0)	237 (5.1)
Ethnicity				
Not Hispanic / Latino, N (%)	1912 (82.0)	1909 (81.4)	1926 (82.2)	3835 (81.8)
Hispanic / Latino, N (%)	418 (17.9)	432 (18.4)	415 (17.7)	847 (18.1)
Region				
Europe, N (%)	959 (41.1)	966 (41.2)	960 (41.0)	1926 (41.1)
North America, N (%)	462 (19.8)	466 (19.9)	466 (19.9)	932 (19.9)
Asia, N (%)	450 (19.3)	447 (19.1)	450 (19.2)	897 (19.1)
Latin America, N (%)	360 (15.4)	359 (15.3)	362 (15.5)	721 (15.4)
Africa, N (%)	102 (4.4)	107 (4.6)	104 (4.4)	211 (4.5)
Mean age in years (SD)	63.2 (8.8)	63.0 (8.6)	63.2 (8.6)	63.1 (8.6)
Time since diagnosis of T2DM				
>1 to 5 years, N (%)	371 (15.9)	338 (14.4)	374 (16.0)	712 (15.2)
>5 to 10 years, N (%)	571 (24.5)	585 (24.9)	590 (25.2)	1175 (25.1)
>10 years, N (%)	1339 (57.4)	1354 (57.7)	1318 (56.3)	2672 (57.0)
HbA1c [%], mean (SD)	8.08 (0.84)	8.07 (0.86)	8.06 (0.84)	8.07 (0.85)
Hypertension, N (%)	2153 (92.3)	2134 (91.0)	2132 (91.0)	4266 (91.4)
Diabetic complications				
Diabetic neuropathy, N (%)	727 (31.2)	735 (31.3)	735 (31.4)	1470 (31.4)
Diabetic retinopathy, N (%)	523 (22.4)	521 (22.2)	502 (21.4)	1023 (21.8)
Diabetic nephropathy, N (%)	467 (20.0)	444 (18.9)	460 (19.6)	904 (19.3)
Diabetic foot, N (%)	145 (6.2)	127 (5.4)	136 (5.8)	263 (5.6)

Empa = empagliflozin; SD = standard deviation; T2DM = type 2 diabetes mellitus
Source: Modified from Tables 10.4.1:1, 10.4.5:1, and 10.4.3:1 Study report

Cardiovascular risk factors were also balanced between the treatment groups (Table 2).

Table 2: Baseline cardiovascular risk factors

	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

Regulatory History

Premarketing Cardiovascular Risk Assessment for Empagliflozin

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. 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. A key secondary endpoint of the premarketing meta-analysis was 3-point MACE, which stands for major adverse cardiovascular events, and which includes cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The hazard ratio for 4-point MACE from the overall meta-analysis was estimated as 0.74 (95% CI 0.57, 0.96).

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

STATISTICAL SUMMARY

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 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 at a pre-specified interim analysis (IA) to show non-inferiority against a 1.8 non-inferiority margin (NIM) prior to approval. 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 of non-inferiority with a NIM of 1.3 had been established. Non-inferiority 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.

Findings and issues that will be discussed include:

- **This study was designed as a cardiovascular safety study.**
  Efficacy claims usually require 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. 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 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.

- **Silent MI was not included in the primary composite 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 3.1 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 5 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 (Table 5). Results were similar when looking at the individual doses with both the 10mg and the 25mg arm when compared to the placebo arm (Table 4).

2 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 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.

2.1 EMPA-REG Trial Results

Table shows results for both of these composite endpoints. We see that non-inferiority was established for both endpoints and superiority for the primary 3-point MACE. The 4-point MACE composite did not attain superiority, so 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 1: 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

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 2). 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 which is also reflected when looking at all-cause death. Further details for all-cause death will be provided in Table 5 of section 3.

Table 2: 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.

The EMPGA-REG trial had positive results for the primary 3-point MACE endpoint for both non-inferiority and superiority. On April 19, 2016, the applicant issued a press release with plans for a new trial evaluating the effect of empagliflozin for the treatment of chronic heart failure. Plans for this trial are to include patients with chronic heart failure with and without type 2 diabetes, building on the results from the EMPA-REG trial.

2.2 Results at the time of Interim Analysis

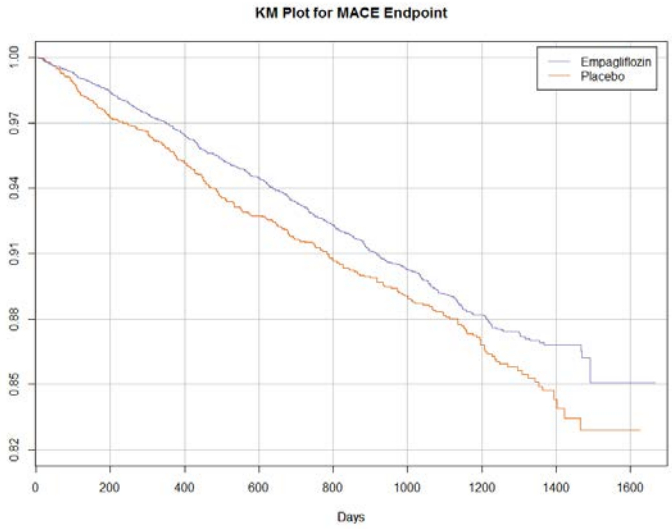
An interim analysis was also pre-specified and projected to occur after 80 confirmed primary events were observed. The Haybittle-Peto boundary was specified to maintain the type I error with 0.0001 of the alpha spent leading to a final one-sided alpha of 0.0249. A data monitoring committee was specified 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).

3 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 1) show a separation of survival curves starting after several months of treatment. 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 given in Table 4 is shown in Table 3.

Figure 1: Kaplan Meier Plot for 3-Point MACE

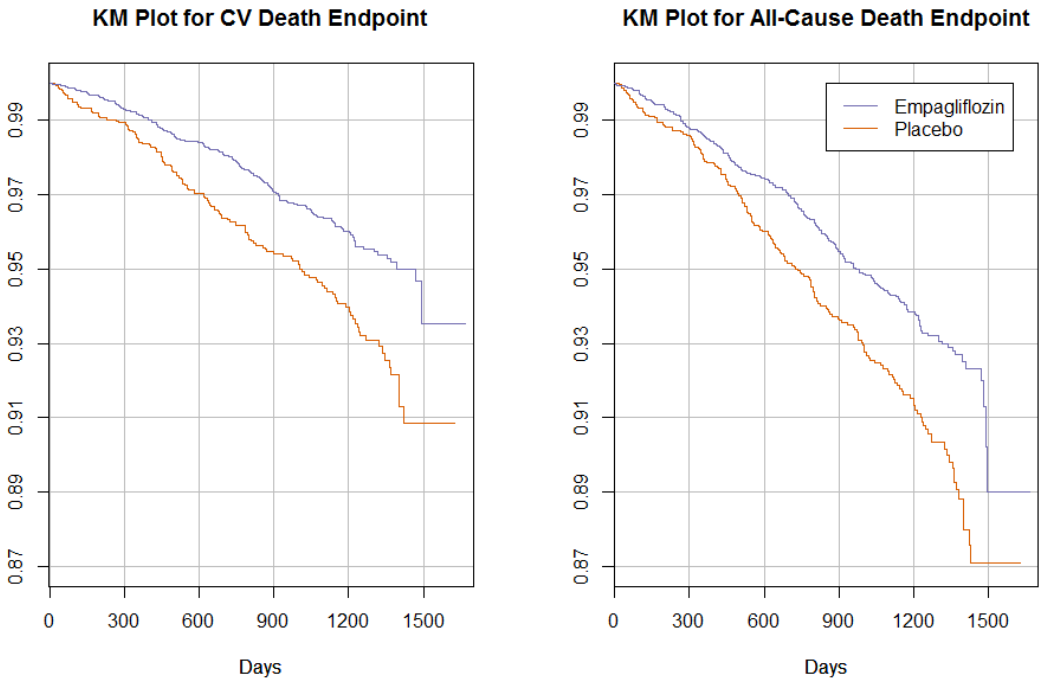


Similar results are seen when looking at the CV death component and the related all-cause death endpoint. Total follow-up time until censoring or death was approximately 6795 years for placebo and 13834 years for the pooled empagliflozin arms.

Table 3: Estimated Raw Incidence per 100 patient years

	Incidence/100 patient years	
	Placebo	**Pooled Empa**
3-Point MACE	4.39	3.74
CV Death	2.02	1.24
Death	2.86	1.94

Figure 2: Kaplan-Meier Plots for CV Death and All-Cause Death



These results are reflected in Cox proportional hazard models seen in Table 5. These results are based on the total number of first events for each of the components of the composite endpoints as well as the related endpoints. The number of patients experiencing an event in each of the endpoints is shown in Table 4. The events are separated by treatment arm with individual doses of empagliflozin and placebo. There is no clear difference in the number of cardiovascular events when comparing the two doses of empagliflozin.

Table 4: Number and % of Patients with Endpoint 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%)

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.

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

3.1 Inclusion of Silent MI

Silent MI was not included in the primary analysis for MACE. 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 event during the study. Both of these 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). Adding in 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 NIM 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 what is driving the differences between the two arms.

4 Follow-up for MACE and Death

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. A highly unlikely scenario was run as a sensitivity analysis for CV death and all-cause death wherein those prematurely censored in the empagliflozin arms were considered to be events at the time they were last known to be alive. Results for both CV and all-cause death still showed superiority in the Cox regression model when comparing the pooled empagliflozin arms to placebo. Given that these scenarios still remained superior for empagliflozin compared to placebo, all other reasonable imputations for these mortality endpoints would also show superiority.

5 Interim Analysis

An interim analysis (IA) was pre-specified in the protocol with interim data used in a cardiovascular meta-analysis to show non-inferiority using a non-inferiority margin 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 99.98% CI of (0.39, 1.39).

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)

6 Subgroup Analysis

Subgroup analyses were run for a number of different groups. Table 7 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 within the USA are shown below along with some groups which had more disparate effects for the primary endpoint.

Table 7: 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)
USA	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)

7 Summary and Concluding Remarks

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.

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 (Table). The differences between the treatment arms for the primary MACE endpoint are largely driven by differences in the CV death component (Table 4). When looking at the related endpoint of all-cause death, we see this difference reflected there as well. It does remain an issue on whether the results from a single study initially designed for safety will be sufficient to obtain efficacy claims.

CLINICAL SUMMARY

Individual Components of 3-Point MACE and Heart Failure

a. Mortality

Both cardiovascular death (CV death) and all-cause mortality were statistically significantly reduced in the pooled empagliflozin arm compared to placebo (HR vs. placebo for CV death 0.62, 95% CI 0.49, 0.77; HR vs. placebo for all-cause mortality 0.68, 95% CI 0.57, 0.82; Table 1). The majority of deaths in this study were reported as due to CV death and CV-death also appeared to account for the reduction in all-cause mortality.

Table 1: Overview of death

	Placebo N=2333	**Empa 10 N-2345**	**Empa 25 N=2342**	**All Empa N=4687**
All-cause mortality				
N (%)	194 (8.3)	137 (5.8)	132 (5.6)	269 (5.7)
Rate per 1000 pt-yrs	28.6	19.8	19	19.4
HR (95% CI)		0.7 (0.56, 0.87)	0.67 (0.54, 0.83)	0.68 (0.57, 0.82)
CV death				
N (%)	137 (5.9)	90 (3.8)	82 (3.5)	172 (3.7)
Rate per 1000 pt-yrs	20.2	13	11.8	12.4
HR (95% CI)		0.65 (0.5, 0.85)	0.59 (0.45, 0.77)	0.62 (0.49, 0.77)
Non-CV death				
N (%)	57 (2.4)	47 (2)	50 (2.1)	97 (2.1)
Rate per 1000 pt-yrs	8.4	6.8	7.2	7
HR (95% CI)		0.81 (0.55, 1.2)	0.86 (0.59, 1.26)	0.84 (0.6, 1.16)

1000 pt-yrs = 1000 patient-years; HR = hazard ratio vs. placebo; 95% CI = 95% confidence interval
Source: Adapted from Table 11.1.2.2: 1 of the study report for study 1245.25

Events adjudicated to CV death were also further subcategorized as to the type of CV death (Table 2). More than one third (40.1%) of all CV deaths are labeled as 'fatal event not assessable' which was defined as all deaths not attributed to the specified categories above and not attributed to a non-cardiovascular cause. It is not clear whether these events are truly CV deaths. If these 124 cases are excluded from the CV death analysis, there is still a statistically significant reduction in the risk of CV death (HR 0.59; 95% CI 0.44, 0.79) in the pooled empagliflozin doses compared to placebo

Table 2: Adjudicated CV Death by Subcategory

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342	All Empa N=4687
	N (%)	N (%)	N (%)	N (%)
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)
o Fatal event not assessable	53 (2.3)	34 (1.4)	37 (1.6)	71 (1.5)

Source: Adapted from Table 11.1.2.2: 2 of the study report for study 1245.25

Overall, the data support a conclusion that the use of empagliflozin in this study reduced the risk of all-cause mortality and CV death. The mechanism by which empagliflozin reduces CV-death is not clear.

b. Myocardial Infarction (including silent MI)

The analysis of nonfatal myocardial infarction suggested neither a risk nor a benefit from treatment with empagliflozin (Table 3).

Table 3: Results for Cox regression for time to first nonfatal MI related event

	Placebo N=2333	Empa 10 N-2345	Empa 25 N=2342	All Empa N=4687
N (%)	121 (5.2)	96 (4.1)	117 (5)	213 (4.5)
Rate per 1000 pt-yrs	18.5	14.4	17.6	16
HR (95% CI)		0.79 (0.6, 1.03)	0.95 (0.74.1.23)	0.87 (0.7,1.09)

1000 pt-yrs = 1000 patient-years; HR = hazard ratio vs. placebo; 95% CI = 95% confidence interval
Source: Adapted from Table 11.1.2.3: 1 of the study report for study 1245.25

Procedures in Place to Ascertain for Silent MI

Electrocardiograms (ECGs) performed as part of trial procedures were reviewed for changes consistent with a silent MI by a central ECG vendor. Investigators were instructed to agree or disagree with the ECG assessment made by the central ECG vendor, based on their knowledge of the patient and the clinical history. Agreement or non-agreement with the ECG vendor determination was to be documented in source documents.

If the ECG changes were determined by the investigator to represent a new MI event and no adjudicated and confirmed event of either acute MI, hospitalization for unstable angina, coronary revascularization procedures or stent thrombosis had occurred between randomization and the date of the ECG measurement, the event was to be entered in the case report form. Only events reported by investigators in the case report form and matching the list of pre-specified trigger event terms were sent for adjudication.

The applicant also conducted secondary analyses that included events of "silent MI" that were based on ECG paramaters and other criteria but did not require investigator intervention or adjudication. These events were not included as endpoints in the primary analysis. A total of 53 of these events were identified in the study

ECG criteria for these events were:

- 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

While the findings of an analysis based on these events suggest an increased risk with empagliflozin (Table 4), it is important to note that this endpoint was only analyzed in a subset of patients (i.e., patients without silent MI or relevant cardiac conductions effects at baseline, and with available post-baseline ECG measurements).

Table 4: Results for Cox regression for time to first applicant defined "silent MI"

	Placebo	**Empa 10**	**Empa 25**	**All Empa**
Analyzed patients	1211	1174	1204	2378
N (%)	15 (1.2)	19 (1.6)	19 (1.6)	38 (1.6)
Rate per 1000 pt-yrs	5.4	7.1	7.0	7.0
HR (95% CI)		1.32 (0.67, 2.60)	1.24 (0.63, 2.45)	1.28 (0.70, 2.33)

1000 pt-yrs = 1000 patient-years; HR = hazard ratio vs. placebo; 95% CI = 95% confidence interval
Source: Adapted from Table 11.1.2.3: 1 of the study report for study 1245.25

Inclusion of these events in the assessment of 3-point MACE continues to exclude the 1.3 margin, though it no longer suggests a reduction in the risk for 3-point MACE compared to placebo (Table 5).

Table 5: Time to first event of 3-point MACE including "silent MI"

	Placebo	**Empa 10**	**Empa 25**	**All Empa**
Analyzed patients	1378	1327	1347	2674
N (%)	295 (21.4)	259 (19.5)	264 (19.6)	523 (19.6)
Rate per 1000 pt-yrs	97.8	89	89.1	89.1
HR (95% CI)		0.92 (0.78, 1.09)	0.91 (0.77, 1.07)	0.92 (0.79, 1.06)

1000 pt-yrs = 1000 patient-years; HR = hazard ratio vs. placebo; 95% CI = 95% confidence interval
Source: Adapted from Table 11.1.2.6: 1 of the study report for study 1245.25

While occurrence of a true incident silent myocardial infarction event represents a clinically significant event, analyses using silent MI events as defined above are limited due to lack complete event ascertainment and adjudication. The Division is therefore uncertain about the meaningfulness of retrospective analyses results which include this

event in the 3-point MACE endpoint. Whether and how these events should be considered in the overall interpretation of the trial results is a point for discussion.

c. Stroke

All stroke and TIA events were adjudicated by the clinical event committee (CEC.)

The HR for non-fatal stroke was 1.24, and the HR for fatal and non-fatal stroke was 1.18 (Table 6). Sensitivity analyses using TS, and OS and events up to treatment stop +7 days, +30 days, and +90 days were generally consistent with the primary analysis (not shown). No dose dependence was observed for stroke events.

Table 6: Cox regression analyses for stroke – TS

	Placebo N=2333	**Empa 10 N-2345**	**Empa 25 N=2342**	**All Empa N=4687**
All stroke				
N (%)	69 (3)	85 (3.6)	79 (3.4)	164 (3.5)
Rate per 1000 pt-yrs	10.5	12.7	11.8	12.3
HR (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)
Rate per 1000 pt-yrs	9.1	11.5	10.9	11.2
HR (95% CI)		1.27 (0.91, 1.79)	1.2 (0.85, 1.69)	1.24 (0.92, 1.67)

1000 pt-yrs = 1000 patient-years; HR = hazard ratio vs. placebo; 95% CI = 95% confidence interval
Source: Adapted from Table 11.1.2.4: 1 of the study report for study 1245.25

There appears to be an imbalance in strokes early after initiation of treatment with empagliflozin (Figure 1 and Figure 2). By day 150, differences between arms disappear and the incidence is similar between the treatment arms by 1 year. A separation is again observed starting at approximately day 600 which persists for the remainder of the observation period.

While overall the risk of stroke was not statistically significant, there were some sub-groups where the risk reached nominal statistical significance. These included:

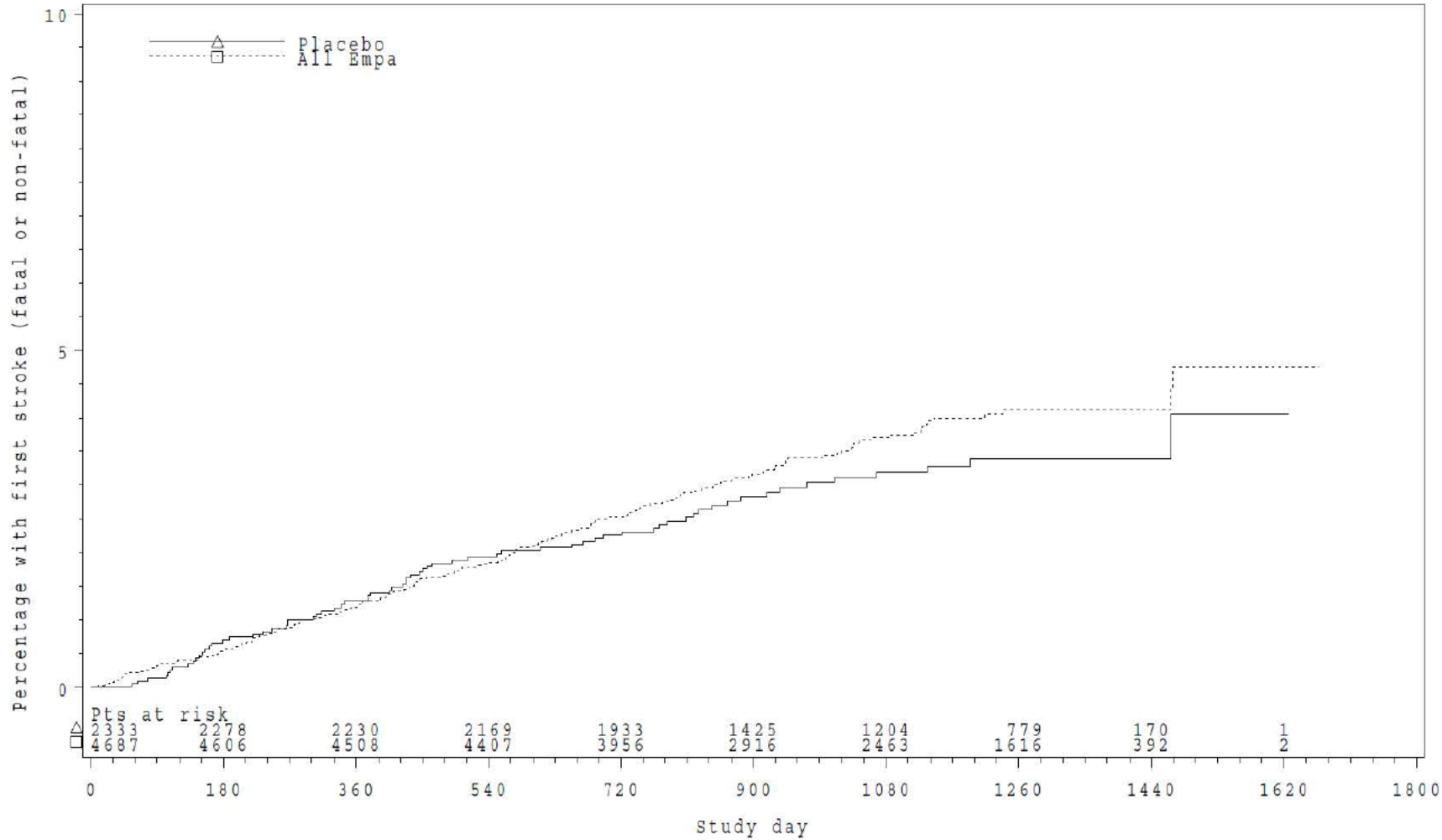
- subjects <65 years of age (HR 1.6; 95% CI 1.03, 2.49),
- subjects from Europe (HR 2.04; 95% CI 1.26, 3.29),
- subjects with a baseline HbA1c ≥8.5% (HR 2.13; 95% CI 1.21, 3.74), and
- subjects treated with insulin (HR 1.57; 95% CI 1.03, 2.41).

No dose dependence for stroke events in these subgroups was observed.

The clinical relevance of this numerical imbalance is unclear. While the finding is not statistically significant, it remains of concern for this product and drug class. As the study was not designed for the purpose of solely exploring stroke events, the event definition required documentation of clinical presentation and diagnostic work-up. Standard of care for stroke work-up may have varied across regions. Additionally, the applicant collected no information on disability related to stroke. Thus it is not clear if

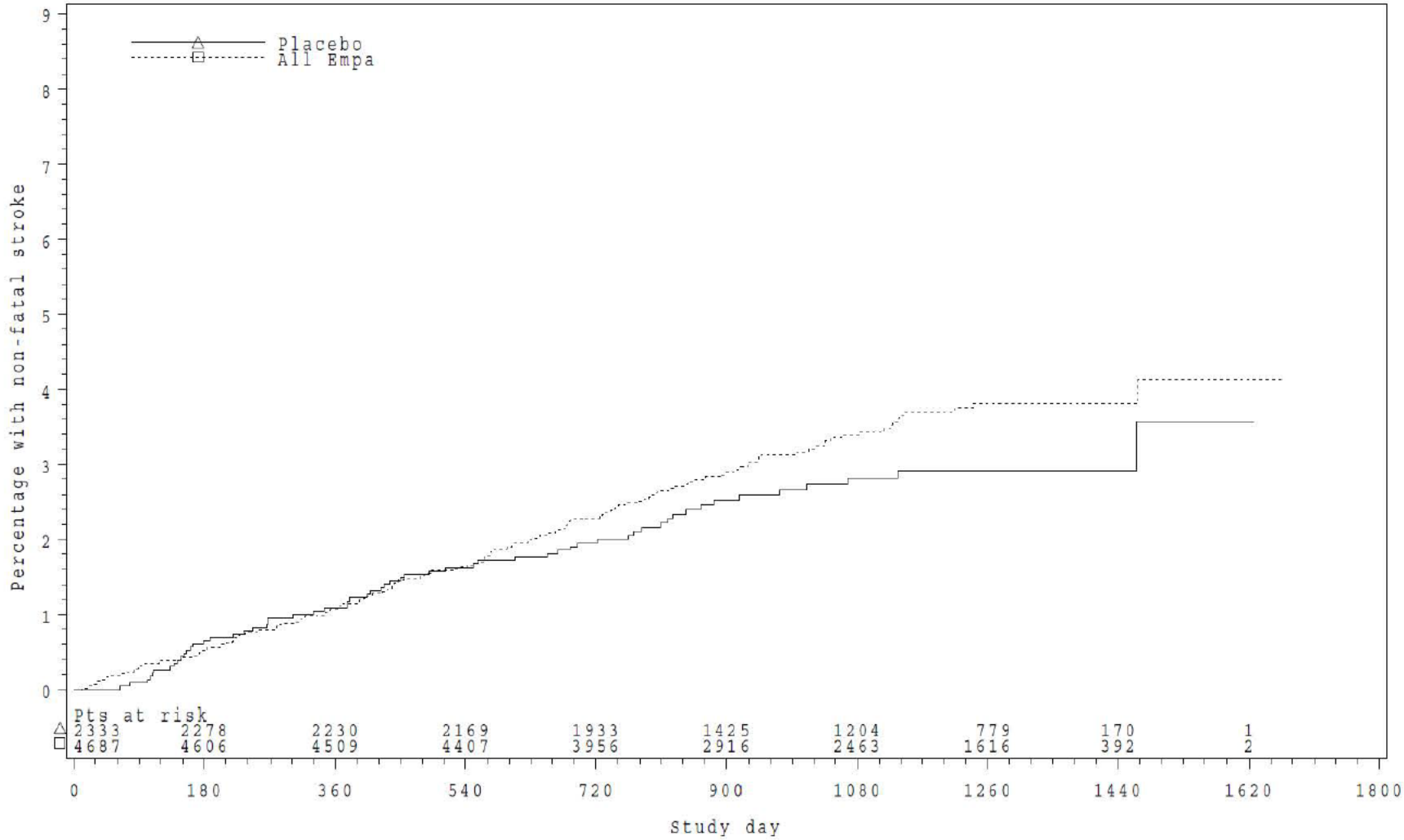
treatment with empagliflozin, while perhaps reducing the risk of death, leads to more stroke related disability.

Figure 1: Kaplan-Meier estimate of time to stroke (fatal and non-fatal) for pooled empagliflozin vs. placebo



Source: Excerpted from Figure 15.2.4.1.9: 1 of the study report for study 1245.25

Figure 2: Kaplan-Meier estimate of time to first non-fatal stroke for pooled empagliflozin vs. placebo



Source: Excerpted from Figure 15.2.4.1.3: 1 of the study report for study 1245.25

d. Heart Failure

Heart failure was an exploratory endpoint in this study. This endpoint was collected prospectively and adjudicated according to definition(s) in the CEC charter. There were not expectations that the drug would have a heart failure benefit at trial inception and there were no requirements that only patients receiving US standard of care treatment for this disease be enrolled. The findings from EMPA-REG OUTCOME suggest that treatment with empagliflozin reduces the risk of hospitalization for heart failure (Table 7).

Table 7: Results from Cox regression for heart failure related endpoints

	Placebo N=2333	**Empa 10 N-2345**	**Empa 25 N=2342**	**All Empa N=4687**
HF req hosp				
N (%)	95 (4.1)	60 (2.6)	66 (2.8)	126 (2.7)
Rate per 1000 pt-yrs	14.5	8.9	9.8	9.4
HR (95% CI)		0.62 (0.45, 0.86)	0.68 (0.5, 0.93)	0.65 (0.5, 0.85)
HF req hosp or HF death				
N (%)	104 (4.5)	62 (2.6)	67 (2.9)	129 (2.8)
Rate per 1000 pt-yrs	15.8	9.2	9.9	9.6
HR (95% CI)		0.59 (0.43, 0.81)	0.63 (0.46, 0.86)	0.61 (0.47, 0.79)

HF req hosp = heart failure requiring hospitalization; HF death = death from heart failure; 1000 pt-yrs = 1000 patient-years; HR = hazard ratio vs. placebo; 95% CI = 95% confidence interval
Source: Adapted from Table 11.1.2.5: 1 of the study report for study 1245.25

While this may be plausible based on the mechanism of action of empagliflozin (diuretic), there are limitations to the applicability of these findings to patients with heart failure and T2DM.

At baseline, the history of heart failure was relatively balanced between the treatment groups, with 244 patients (10.46%) in the placebo group, and 462 (9.86%) in the pooled empagliflozin group reporting a history of heart failure. However, neither ejection fraction nor New York Heart Association (NYHA) classification were required to be collected as part of the study. In addition, granularity of data collected on concomitant medications was not sufficiently detailed to assess the adequacy of baseline treatment for heart failure. This is in contrast to the design of studies whose primary objective is to demonstrated a reduction in heart failure morbidity and mortality. The PARADIGM-HF study for example, enrolled patients with symptomatic heart failure (NYHA class II-IV) and systolic dysfunction (ejection fraction $\leq 40\%$) treated with an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) and maximally tolerated dose of β-blocker.

Because this endpoint was an exploratory endpoint no control for type 1 error for heart failure related analyses was implemented in the statistical analysis plan.

These factors limit the conclusions that can be drawn from the heart failure finding in this study and will be a point of discussion at the AC.

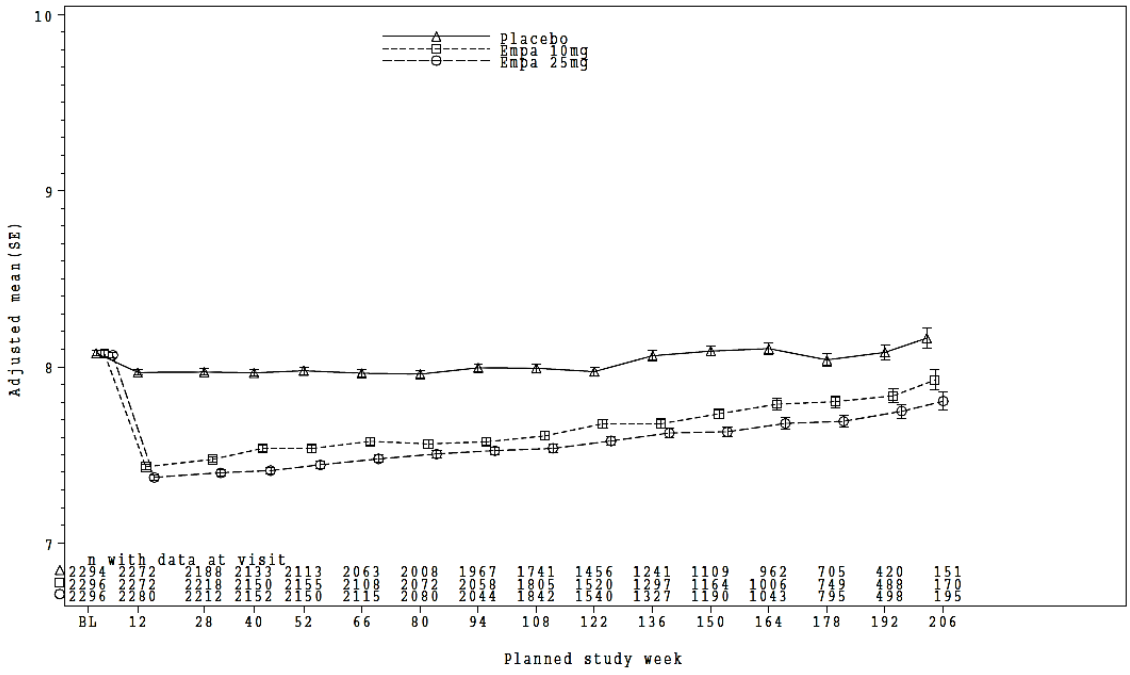
Observed differences between treatment arms

a. Glycemic control

HbA1c was an exploratory endpoint in the EMPA-REG OUTCOME study. Per the trial protocol, background antidiabetic medications were not to be adjusted up to week 12 (for safety) 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. This strategy was intended to safely introduce a new glucose lowering agent in this population and to minimize glycemic control differences across study arms for most of the study.

At baseline, HbA1c was similar between the study arms. As seen in Figure 3 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, a difference in glycemic control between the placebo and empagliflozin arms was sustained for the entire duration of the trial. In the model below, all HbA1c values, including the post-rescue values were included.

Figure 3: Adjusted mean HbA1c over time



Source: Excerpted from Figure 15.2.4.3.1.3: 2 of the study report for study 1245.25

Though glycemic control goal in in all subjects randomized were supposed to target local standard of care targets and were expected to have been similar between arms this did clearly was not achieved. The difference in HbA1c between placebo arm and comparator demonstrates that glycemic control was different between treatment arms. Whether these

differences in glycemic control could have contributed directly or indirectly to differences in observed outcomes is unknown.

b. Blood pressure

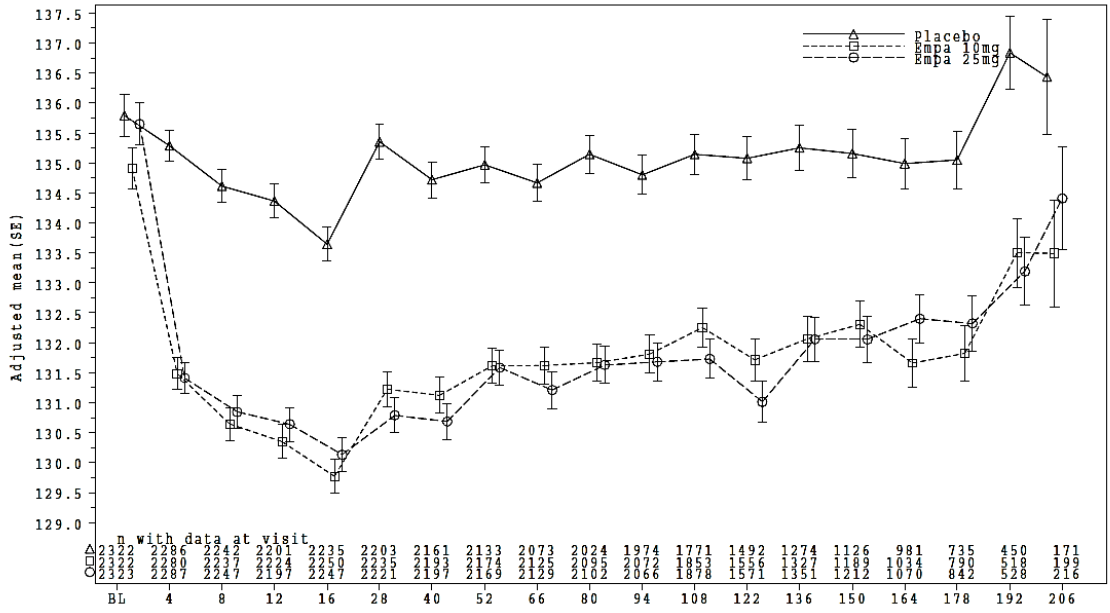
Analyses of blood pressure for the on-treatment period included values until 1 day after the last permanent treatment stop date. Small decreases in both systolic and diastolic pressure with empagliflozin were seen. These findings are consistent with previous and labeled findings. Again, the trial recommended that BP targets follow recommendations from local professional guidelines to expressly minimize differences in risk factors between groups.

The changes in blood pressure are outlined below.

Systolic blood pressure

The baseline mean systolic blood pressure (SBP) was similar between the treatment groups. When analyzing the entire on-treatment period with the Mixed Model Repeated Measures model on the Treated Set Population, 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 the difference between arms was maintained for the rest of the study.

Figure 4: SBP (mmHg) MMRM Results over Time - Treated Set (OC-AD)

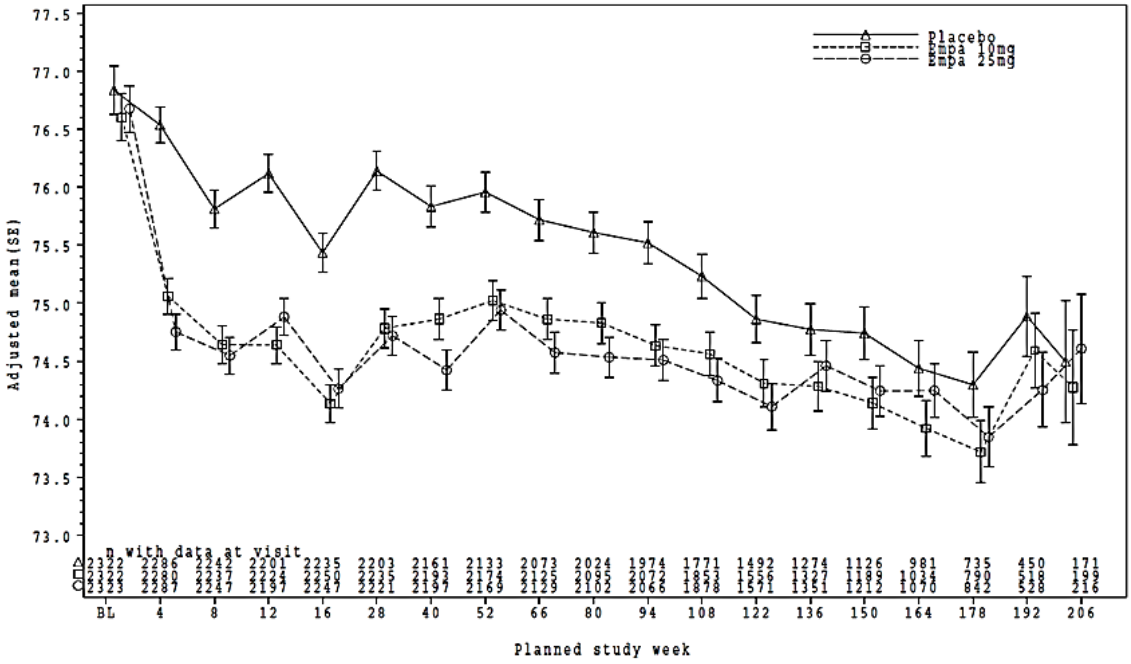


Source: Excerpted from Figure 15.2.4.3.5.3: 2 of the study report for study 1245.25

Diastolic blood pressure

The changes in diastolic blood pressure (DBP) were similar to what was observed for SBP. The empagliflozin arms had 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, and the difference between treatment arms diminished over time.

Figure 5: DBP (mmHg) MMRM Results over Time - Treated Set (OC-AD)



Source: Excerpted from Figure 15.2.4.3.6.3: 2 of the study report for study 1245.25

Reductions in BP would be expected to reduce the risk of cardiovascular events and specifically the risk of stroke. It is unknown whether or how these differences contributed to the observed outcomes.

c. Medication Changes

Concomitant medications were generally balanced between treatment groups at baseline (Table 8).

Table 8: Baseline concomitant medications

	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

More patients in the placebo group than in the empagliflozin groups required an increase in the dose of background antidiabetic medication or addition of a new antidiabetic medication (Table 9). The most frequently introduced medication was insulin, followed by DPP-4 inhibitors, sulfonylurea, and metformin. All of these were more likely to be added to the placebo group.

Table 9: Changes in antidiabetic medications during the study

	Placebo N=2333	**Empa 10 N=2345**	**Empa 25 N=2342**	**All Empa N=4687**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Number of patients with increase in dose of background medication	931 (39.9)	555 (23.7)	537 (22.9)	1092 (23.3)
Number of patients with additional antidiabetic medication	631 (27)	364 (15.5)	328 (14)	692 (14.8)
- Insulin	221 (9.5)	110 (4.7)	87 (3.7)	197 (4.2)
- DPP-4 inhibitor	151 (6.5)	106 (4.5)	88 (3.8)	194 (4.1)
- Sulphonylurea	147 (6.3)	79 (3.4)	61 (2.6)	140 (3)
- Metformin	96 (4.1)	69 (2.9)	60 (2.6)	129 (2.8)
- GLP-1 receptor agonist	51 (2.2)	22 (0.9)	31 (1.3)	53 (1.1)
- Thiazolidinedione	60 (2.6)	17 (0.7)	29 (1.2)	46 (1)
- α-glucosidase inhibitor	29 (1.2)	28 (1.2)	20 (0.9)	48 (1)
- Glinide	26 (1.1)	11 (0.5)	14 (0.6)	25 (0.5)
- Other antidiabetic medication	11 (0.5)	1 (<0.1)	4 (0.2)	5 (0.1)

DPP-IV = dipeptidyl peptidase-4; GLP-1 = glucagon like peptide-1
Source: Adapted from Table 11.1.3.7: 1 of the study report for study 1245.25

Similar to antidiabetic medications, placebo subjects were more likely to have addition of antihypertensive agents (Table 10). This was true across the different classes of antihypertensives. There was a small difference in lipid lowering agents between the treatment groups.

Table 10: Addition of medications during the study

	Placebo N=2333	**Empa 10 N=2345**	**Empa 25 N=2342**	**All Empa N=4687**
	N (%)	**N (%)**	**N (%)**	**N (%)**
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)
Anticoagulants	708 (30.3)	663 (28.3)	677 (28.9)	1340 (28.6)
- Platelet aggregation inhibitors excluding 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)
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)

DPP-4 = dipeptidyl peptidase 4; ACE inhibitor = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker
Source: Adapted from Table 10.4.6.2: 1 of the study report for study 1245.25

While these were small differences between treatment arms, it is unclear if this could have impacted the observed outcome

Non-Cardiovascular Safety

The safety outcomes in the EMPA-REG OUTCOME study were fairly balanced between treatment arms (Table 11). The incidence of adverse events was similar between treatment arms, though the event-rate was slightly lower in the empagliflozin arms.

Table 11: Adverse events overall summary – TS

	Placebo N=2333		**Empa 10 mg N=2345**		**Empa 25 mg N=2342**	
	N (%)	**Rate/100 pt-yrs**	**N (%)**	**Rate/100 pt-yrs**	**N (%)**	**Rate/100 pt-yrs**
Any AE	2139 (91.7)	178.67	2112 (90.1)	150.34	2118 (90.4)	148.36
Fatal AE	119 (5.1)	2.06	97 (4.1)	1.61	79 (3.4)	1.31
Serious AEs	988 (42.3)	22.34	876 (37.4)	18.2	913 (39.0)	19.39
- Immediately life-threatening	44 (1.9)	0.77	53 (2.3)	0.89	60 (2.6)	1
- Disabling or incapacitating	24 (1.0)	NA	18 (0.8)	NA	22 (0.9)	NA
- Requiring hospitalization	852 (36.5)	NA	751 (32.0)	NA	818 (34.9)	NA
- Prolonging hospitalization	74 (3.2)	NA	52 (2.2)	NA	67 (2.9)	NA
- Congenital anomaly	0	NA	0	NA	0	NA
- Other	173 (7.4)	NA	151 (6.4)	NA	147 (6.3)	NA
AE leading to d/c of study medication	453 (19.4)	8.26	416 (17.7)	7.28	397 (17.0)	6.89

Rate/100 pt-yrs = events per 100 patient yearsAE = adverse event; NA = not analyzed; d/c = discontinuation

Source: Adapted from Table 12.1.1: 1 of the study report for study 1245.25

a. Non-fatal Serious Adverse Events

Overall 988 (42.3%) of the patients in the placebo group and 1,789 (38.2%) of patients in the pooled empagliflozin group experienced a serious adverse event (SAE). The incidence rates for all SAEs in either treatment group by System Organ Class (SOC) are presented below.

Table 12 Frequency of Patients with Serious Adverse Events by SOC and Treatment Arm

	Placebo N=2333	**All Empa N=4687**
	N (%)	**N (%)**
Any nonfatal serious adverse event	**988 (42.3%)**	**1789 (38.2%)**
System Organ Class		
• Cardiac disorders	398 (17.1%)	652 (13.9%)
• Infections and infestations	213 (9.1%)	360 (7.7%)
• Nervous system disorders	159 (6.8%)	306 (6.5%)
• Neoplasms benign, malignant and unspecified (incl cysts and polyps)	87 (3.7%)	219 (4.7%)
• Vascular disorders	116 (5.0%)	191 (4.1%)
• Gastrointestinal disorders	85 (3.6%)	169 (3.6%)
• General disorders and administration site conditions	94 (4.0%)	154 (3.3%)
• Musculoskeletal and connective tissue disorders	78 (3.3%)	135 (2.9%)
• Injury, poisoning and procedural complications	77 (3.3%)	129 (2.8%)
• Renal and urinary disorders	73 (3.1%)	112 (2.4%)
• Respiratory, thoracic and mediastinal disorders	75 (3.2%)	101 (2.2%)
• Metabolism and nutrition disorders	61 (2.6%)	79 (1.7%)
• Hepatobiliary disorders	19 (0.8%)	51 (1.1%)
• Skin and subcutaneous tissue disorders	29 (1.2%)	48 (1.0%)
• Eye disorders	21 (0.9%)	43 (0.9%)
• Reproductive system and breast disorders	11 (0.5%)	33 (0.7%)
• Investigations	29 (1.2%)	33 (0.7%)
• Blood and lymphatic system disorders	17 (0.7%)	29 (0.6%)
• Surgical and medical procedures	16 (0.7%)	27 (0.6%)
• Psychiatric disorders	15 (0.6%)	19 (0.4%)
• Ear and labyrinth disorders	15 (0.6%)	16 (0.3%)
• Endocrine disorders	2 (0.1%)	7 (0.1%)
• Immune system disorders	3 (0.1%)	6 (0.1%)
• Congenital, familial and genetic disorders	4 (0.2%)	4 (0.1%)
• Social circumstances	0 (0.0%)	1 (0.0%)

Source: Adapted from Table 15.3.1.1: 7 of the study report for study 1245.25

No marked difference between treatment arms was noted, though empagliflozin treated subjects appeared to have a lower incidence of serious adverse events reported as 'Heart failure' compared to the subjects treated with placebo (Table 13).

Table 13: Serious adverse events reported in > 2% of subjects by high level term in any treatment arm

System organ class • **High level term** o **Preferred term**	**Placebo** **N=2333** **N (%)**	**All Empa** **N=4687** **N (%)**
Cardiac disorders	369 (15.8)	621 (13.2)
• Ischemic coronary artery disorders	205 (8.8)	398 (8.5)
o Angina unstable	86 (3.7)	152 (3.2)
o Myocardial infarction	41 (1.8)	82 (1.7)
o Angina pectoris	32 (1.4)	78 (1.7)
o Acute myocardial infarction	38 (1.6)	75 (1.6)
o Acute coronary syndrome	10 (0.4)	21 (0.4)
o Myocardial ischemia	15 (0.6)	12 (0.3)
o Silent myocardial infarction	1 (< 0.1)	6 (0.1)
o Microvascular coronary artery disease	0	1 (< 0.1)
o Postinfarction angina	1 (< 0.1)	1 (< 0.1)
• Heart failures NEC	98 (4.2)	129 (2.8)
o Cardiac failure congestive	44 (1.9)	62 (1.3)
o Cardiac failure	49 (2.1)	58 (1.2)
o Cardiac failure acute	8 (0.3)	5 (0.1)
o Cardiac failure chronic	0	5 (0.1)
o Cardiogenic shock	1 (< 0.1)	4 (0.1)
o Cardiac failure high output	0	1 (< 0.1)
o Cardiopulmonary failure	2 (0.1)	1 (< 0.1)
o Cardiorenal syndrome	0	1 (< 0.1)
• Coronary artery disorders NEC	56 (2.4)	74 (1.6)
o Coronary artery disease	43 (1.8)	49 (1.0)
o Coronary artery occlusion	6 (0.3)	10 (0.2)
o Arteriosclerosis coronary artery	1 (< 0.1)	7 (0.1)
o Coronary artery insufficiency	1 (< 0.1)	1 (< 0.1)
o Coronary artery stenosis	5 (0.2)	10 (0.2)
Infections and infestations	197 (8.4)	349 (7.4)
• Lower respiratory tract and lung infections	63 (2.7)	99 (2.1)
o Pneumonia	46 (2.0)	73 (1.6)
o Bronchitis	9 (0.4)	10 (0.2)
o Lower respiratory tract infection	4 (0.2)	9 (0.2)
o Bronchopneumonia	3 (0.1)	4 (0.1)
o Lung infection	0	2 (< 0.1)
o Atypical pneumonia	0	1 (< 0.1)
o Infectious pleural effusion	0	1 (< 0.1)
o Lobar pneumonia	3 (0.1)	1 (< 0.1)
Nervous system disorders	152 (6.5)	293 (6.3)
• Central nervous system hemorrhages and cerebrovascular accidents	71 (3.0)	151 (3.2)
o Cerebrovascular accident	31 (1.3)	75 (1.6)
o Ischemic stroke	20 (0.9)	35 (0.7)
o Cerebral infarction	7 (0.3)	17 (0.4)
o Carotid artery occlusion	0	4 (0.1)
o Cerebellar infarction	1 (< 0.1)	4 (0.1)

System organ class • High level term o Preferred term	Placebo N=2333 N (%)	All Empa N=4687 N (%)
o Subarachnoid hemorrhage	2 (0.1)	4 (0.1)
o Brain stem infarction	0	3 (0.1)
o Cerebral ischemia	1 (< 0.1)	3 (0.1)
o Cerebral artery occlusion	1 (< 0.1)	2 (< 0.1)
o Lacunar infarction	2 (0.1)	2 (< 0.1)
o Brain stem hemorrhage	0	1 (< 0.1)
o Brain stem stroke	0	1 (< 0.1)
o Carotid artery thrombosis	0	1 (< 0.1)
o Embolic cerebral infarction	0	1 (< 0.1)
o Embolic stroke	3 (0.1)	1 (< 0.1)
o Ischemic cerebral infarction	1 (< 0.1)	1 (< 0.1)
o Spinal epidural hematoma	0	1 (< 0.1)
o Thalamic infarction	0	1 (< 0.1)
o Thrombotic cerebral infarction	1 (< 0.1)	1 (< 0.1)
o Brain stem ischemia	1 (< 0.1)	0
o Hemorrhage intracranial	2 (0.1)	0
o Hemorrhagic cerebral infarction	1 (< 0.1)	0
o Hemorrhagic stroke	3 (0.1)	0
Vascular disorders	113 (4.8)	182 (3.9)
• Peripheral vasoconstriction, necrosis and vascular insufficiency	41 (1.8)	99 (2.1)
o Peripheral arterial occlusive disease	23 (1.0)	57 (1.2)
o Peripheral ischemia	7 (0.3)	15 (0.3)
o Peripheral artery stenosis	6 (0.3)	12 (0.3)
o Extremity necrosis	4 (0.2)	9 (0.2)
o Intermittent claudication	2 (0.1)	9 (0.2)
o Femoral artery occlusion	1 (< 0.1)	7 (0.1)
o Iliac artery occlusion	1 (< 0.1)	2 (< 0.1)
o Subclavian artery stenosis	0	2 (< 0.1)
o Diabetic microangiopathy	1 (< 0.1)	0

NEC = not elsewhere classified
Source: Reviewer generated based on review of ADAE.xpt

b. 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 an underlying condition prohibited reintroduction of the drug. As a result, the summary of AEs leading to discontinuation of study medication also includes some patients who temporarily discontinued the study medication.

There were 453 patients in the placebo group (19.4%) who discontinued study medication due to an AE, and 813 patients (17.4%) in the pooled empagliflozin group. The adverse events leading to discontinuation were generally balanced between placebo and empagliflozin treated subjects (Table 14). On the Preferred Term (PT) level, the most frequently reported AEs leading to discontinuation were myocardial infarction and acute myocardial infarction. PTs responsible for at least 0.5% of discontinuations are presented in Table 15.

Table 14: High level terms leading to discontinuation of study drug in > 0.2% of subjects from any arm

System Organ Class • **High Level Term**	**Placebo N=2333** **N (%)**	**All Empa N=4687** **N (%)**
Cardiac disorders	90 (3.9)	135 (2.9)
• Ischemic coronary artery disorders	44 (1.9)	87 (1.9)
• Heart failures NEC	19 (0.8)	20 (0.4)
• Ventricular arrhythmias and cardiac arrest	12 (0.5)	13 (0.3)
• Coronary artery disorders NEC	9 (0.4)	11 (0.2)
Infections and infestations	65 (2.8)	125 (2.7)
• Urinary tract infections	9 (0.4)	29 (0.6)
• Lower respiratory tract and lung infections	13 (0.6)	16 (0.3)
• Sepsis, bacteremia, viremia and fungemia NEC	2 (0.1)	14 (0.3)
• Abdominal and gastrointestinal infections	4 (0.2)	12 (0.3)
• Infections NEC	6 (0.3)	8 (0.2)
• Bacterial infections NEC	9 (0.4)	6 (0.1)
• Skin structures and soft tissue infections	8 (0.3)	5 (0.1)
Renal and urinary disorders	35 (1.5)	80 (1.7)
• Renal failure and impairment	25 (1.1)	43 (0.9)
• Bladder and urethral symptoms	3 (0.1)	17 (0.4)
Nervous system disorders	40 (1.7)	79 (1.7)
• Central nervous system hemorrhages and cerebrovascular accidents	18 (0.8)	42 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	29 (1.2)	81 (1.7)
• Colorectal neoplasms malignant	3 (0.1)	13 (0.3)
• Metastases to specified sites	4 (0.2)	11 (0.2)
• Non-small cell neoplasms malignant of the respiratory tract cell type specified	4 (0.2)	7 (0.1)
Gastrointestinal disorders	49 (2.1)	57 (1.2)
• Diarrhea (excl infective)	9 (0.4)	9 (0.2)
• Gastrointestinal and abdominal pains (excl oral and throat)	5 (0.2)	9 (0.2)
• Nausea and vomiting symptoms	7 (0.3)	5 (0.1)
• Dyspeptic signs and symptoms	6 (0.3)	1 (< 0.1)
General disorders and administration site conditions	26 (1.1)	44 (0.9)
• Death and sudden death	15 (0.6)	24 (0.5)
Skin and subcutaneous tissue disorders	19 (0.8)	41 (0.9)
• Skin and subcutaneous tissue ulcerations	8 (0.3)	14 (0.3)
Investigations	21 (0.9)	40 (0.9)
• Renal function analyses	7 (0.3)	9 (0.2)
• Digestive enzymes	8 (0.3)	7 (0.1)
Reproductive system and breast disorders	3 (0.1)	36 (0.8)
• Penile and scrotal infections and inflammations	0	12 (0.3)
Vascular disorders	27 (1.2)	27 (0.6)
• Peripheral vasoconstriction, necrosis and vascular insufficiency	11 (0.5)	16 (0.3)
Injury, poisoning and procedural complications	24 (1.0)	25 (0.5)
• Non-site specific injuries NEC	7 (0.3)	8 (0.2)
• Limb fractures and dislocations	9 (0.4)	7 (0.1)
Hepatobiliary disorders	6 (0.3)	17 (0.4)
• Cholecystitis and cholelithiasis	2 (0.1)	9 (0.2)

NEC = not elsewhere classified
Source: Reviewer generated based on review of ADAE.xpt

Table 15: Most frequently reported preferred terms (PT) leading to discontinuation of study drug

	Placebo N=2333	All Empa N=4687
	N (%)	N (%)
Preferred Term		
- Myocardial infarction	20 (0.9%)	35 (0.7%)
- Acute myocardial infarction	17 (0.7%)	29 (0.6%)
- Urinary tract infection	7 (0.3%)	28 (0.6%)
- Renal impairment	10 (0.4%)	26 (0.6%)
- Angina unstable	8 (0.3%)	24 (0.5%)
- Cerebrovascular accident	6 (0.3%)	24 (0.5%)
- Pneumonia	14 (0.6%)	17 (0.4%)
- Cardiac failure	16 (0.7%)	14 (0.3%)
- Cardiac arrest	11 (0.5%)	5 (0.1%)

Source: Reviewer generated using JReview

Adverse Events of Special Interest

c. 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 sponsor's product or the clinical development program.

For the safety analysis of empagliflozin in this trial, the following categories of AESIs were defined in the clinical trial protocol (CTP) or trial statistical analysis plan (TSAP):

- decreased renal function (based on narrow SMQ for 'acute renal failure' and creatinine ≥2–fold increase from baseline and >ULN)
- hepatic injury/elevated liver enzymes (based on SMQ for 'drug related hepatic disorders', 'liver related investigations, signs and symptoms', cholestasis and jaundice of hepatic origin', 'hepatitis, non-infectious', and 'hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions', and elevated ≥3x ULN with elevated bilirubin ≥2x ULN, and AST and/or ALT ≥5x ULN without elevated bilirubin)
- bone fractures[9]
- malignancies
- venous embolic and thrombotic events
- diabetic ketoacidosis
- hypersensitivity
- urinary tract infection

[9] Investigators were asked to add in the comment field of the eCRF whether the cause of the fractures was traumatic or pathologic, 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.

- genital infection
- volume depletion
- hypoglycemic adverse events

Findings for each of these will be discussed further below.

Renal Safety:

Renal adverse events were assessed using reported adverse events as well as using laboratory test data. In addition to the specified AESI of 'decreased renal function', the applicant has considered several additional renal-related endpoints.

The discussion of renal safety will first focus on the 'decreased renal function' AESI and changes in renal laboratory tests, then discussion the additional analyses.

'Decreased renal function' AESI

A standardized MedDRA query was used to identify events suggestive of acute renal failure/acute kidney injury. The overall incidence of these events was slightly higher in the placebo group compared to the empagliflozin group (Table 16). Serious 'decreased renal function' events were also slightly more common in the placebo group. While the incidence of events increased with increasing age and with decreasing eGFR, there was slightly higher in placebo subjects in each of the subgroups.

Using the predefined laboratory criteria (i.e., serum creatinine ≥2x baseline and > ULN), a similar relationship was seen. There were slightly more placebo subjects with laboratory tests meeting this criteria compared to empagliflozin subjects

Table 16: Incidence of adverse event rates of 'decreased renal function'

	Placebo N=2333	**All Empa N=4687**
	N (%)	**N (%)**
Total	**155 (6.6%)**	**245 (5.2%)**
Serious 'decreased renal function' events	**46 (2.0%)**	**57 (1.2%)**
'Decreased renal function' events leading to discontinuation	**24 (1.0%)**	**41 (0.9%)**
Preferred Term		
- Renal impairment	77 (3.3%)	146 (3.1%)
- Renal failure	42 (1.8%)	54 (1.2%)
- Acute kidney injury	37 (1.6%)	45 (1.0%)
- Azotemia	1 (< 0.1%)	5 (0.1%)
- Prerenal failure	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
Laboratory test criteria[1]	50 (2.1)	55 (1.2)

[1] serum creatinine > 2x baseline and >ULN

Source: Adapted from Table 12.1.3.2: 1 and Table 15.3.2.3.1.5: 1 of the study report for study 1245.25

Due to the diuretic activity of empagliflozin, an early hemodynamic effect on renal function was expected and a review of adverse events following randomization to treatment was performed (Table 17). The observed incidence in the early period suggested a slightly increased risk of acute kidney injury with empagliflozin compared to placebo. In the first 30 days, there were slightly more events in the empagliflozin treated group (0.9% with empagliflozin vs. 0.7% with placebo). Similarly, in the first 90 days there were slightly more events in the empagliflozin treated group (1.5% with empagliflozin vs. 1.2% with placebo).

Table 17: Incidence of early renal adverse events

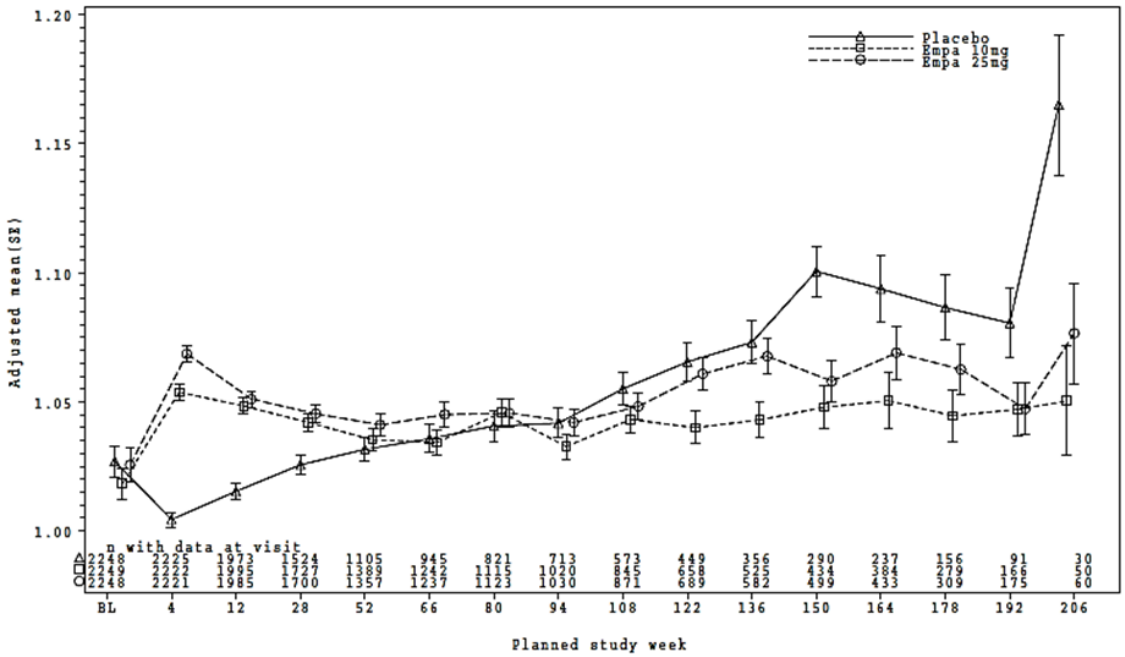
	First 30 days		**First 90 days**	
	Placebo N=2333	**All Empa N=4687**	**Placebo N=2333**	**All Empa N=4687**
Total	**16 (0.7%)**	**41 (0.9%)**	**29 (1.2%)**	**70 (1.5%)**
Preferred Term				
- Renal impairment	6 (0.3%)	24 (0.5%)	16 (0.7%)	49 (1.0%)
- Renal failure	5 (0.2%)	11 (0.2%)	7 (0.3%)	13 (0.3%)
- Acute kidney injury	3 (0.1%)	5 (0.1%)	4 (0.2%)	6 (0.1%)
- Azotemia	1 (0.0%)	1 (0.0%)	1 (0.0%)	2 (0.0%)
- Acute prerenal failure	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)

Source: Reviewer generated using JReview

Changes in renal function over time

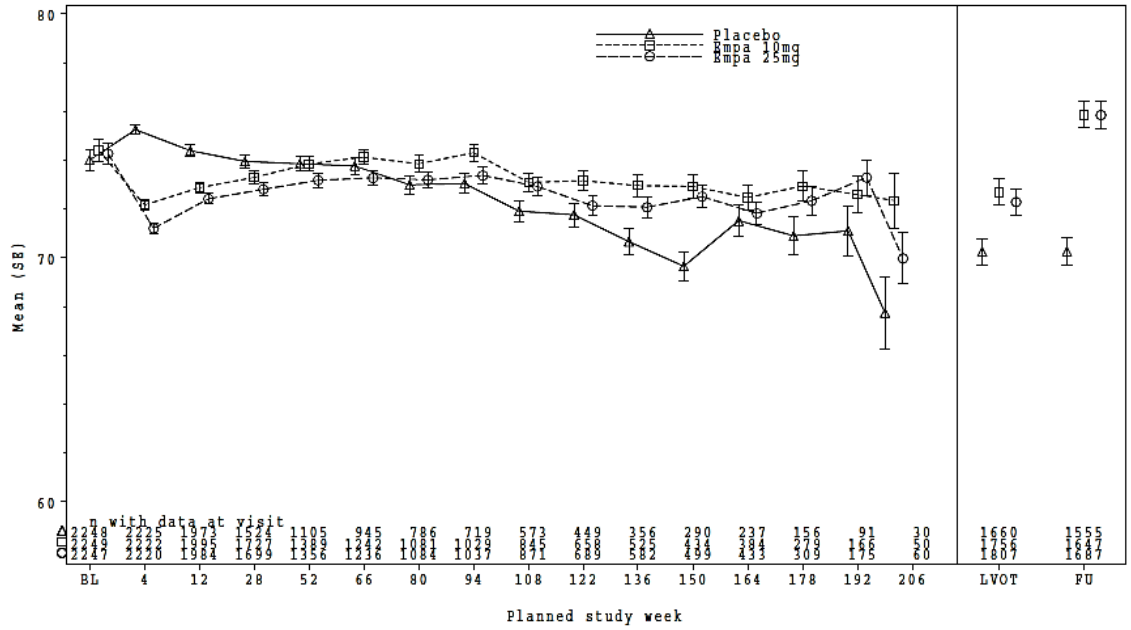
Following initiation of empagliflozin, there is an increase in serum creatinine and a decrease in eGFR. In looking at the longer term data, these acute changes appear to recover (Figure 6 and Figure 7).

Figure 6: Change in serum creatinine (mg/dL) over time



Source: Figure 15.3.2.3.1.2:2 Study report

Figure 7: Change in eGFR (mL/min/1.73 m2) over time



Source: Figure 15.2.4.2.11.2:3 Study report

Other renal endpoints

Multiple changes to the renal endpoints definitions in the protocol and used for the purpose of exploratory analyses occurred over the course of the trial. 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

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 timing of urine collection (e.g., first morning void) was not specified.

Renal endpoints were not adjudicated, and also were not prespecified. There was no control for type 1 error.

There was no difference between treatments for new onset of albuminuria (Table 18). 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 18). This was primarily driven by the laboratory test components. There were too few clinical events to draw meaningful conclusions that differences between therapies truly existed. Additionally, not all of the renal replacement therapy events reflected 'end-stage' disease as some of the events included temporary dialysis for acute kidney injury.

The clinical relevance of the findings for this composite endpoint is unclear. The findings are primarily driven by laboratory test findings. The effects of treatment on albuminuria may not reflect clinical outcomes in diabetic nephropathy, and therapies may have acute and reversible pharmacologic effects on albuminuria that may differ from the long-term effects on renal function and disease progression. Additionally, the component of doubling of serum creatinine did not require a confirmed doubling of serum creatinine to document permanent loss of renal function. As such, captured events could reflect

acute reversible changes rather than chronic irreversible changes. To date, endpoints used in studies of drugs intended to treat diabetic nephropathy have generally used a composite of confirmed doubling of serum creatinine (or confirmed 40% decline in eGFR), progression to end-stage disease (defined as need for chronic dialysis, renal transplant, or sustained eGFR < 15 ml/min/1.73 m^2).

Table 18: 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 for study 1245.25

A statistically significant difference for the composite microvascular outcome was also seen (HR vs. placebo 0.62, 95% CI 0.54, 0.70; Table 19), 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 discussed, the clinical relevance of the 'new or worsening nephropathy' composite is unclear.

Table 19: 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 for study 1245.25

Liver Safety:

Adverse events related to hepatic injury were summarized based on an Applicant generated SMQ. The incidence rates for hepatic injury were summarized for the period from baseline to 30 days after last administration of study medication.

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%), there were more serious adverse liver events with empagliflozin than placebo (0.4% with empagliflozin vs 0.2% with placebo). The proportion of patients that had liver events leading to discontinuation of the study drug was similar between treatment groups.

Table 20: Liver adverse events reported in ≥ 0.2% of the placebo or all empagliflozin group

	Placebo N=2333	All Empa N-4687
	N (%)	N (%)
Total	**108 (4.6%)**	**173 (3.7%)**
Leading to discontinuation	**8 (0.3%)**	**13 (0.3%)**
SAEs	**5 (0.2%)**	**20 (0.4%)**
Preferred Term		
- Hepatic steatosis	29 (1.2%)	46 (1.0%)
- Alanine aminotransferase increased	22 (0.9%)	33 (0.7%)
- Aspartate aminotransferase increased	15 (0.6%)	22 (0.5%)
- Hepatic enzyme increased	7 (0.3%)	21 (0.4%)
- Gamma-glutamyltransferase increased	13 (0.6%)	13 (0.3%)
- Hepatomegaly	2 (0.1%)	9 (0.2%)
- Transaminases increased	7 (0.3%)	9 (0.2%)
- Liver function test abnormal	5 (0.2%)	8 (0.2%)
- Blood bilirubin increased	4 (0.2%)	6 (0.1%)
- Hepatic function abnormal	5 (0.2%)	5 (0.1%)

Source: Reviewer generated using JReview, ADAE and ADSL datasets, Applicant generated hepatic injury flag

All reported treatment-emergent events suspected of being drug-induced liver injury (DILI) or hepatic injuries were reviewed in a blinded fashion by a hepatic events external adjudication committee (hepEAC). Events qualifying for adjudication were selected based on the SMQs, PTs, and by manual review. Laboratory results could also trigger adjudication. The committee adjudicated the category of potential causal relationship with the study drug by selecting one of four categories ('Unlikely', 'Possible', 'Probable' and 'Indeterminate').

The Applicant reported 11 adjudicated liver events in the placebo group, and 44 adjudicated events in the pooled empagliflozin group. Nearly all events were adjudicated as 'unlikely' to be related to study drug. There were three events in the empagliflozin group adjudicated as 'possibly related' to study drug and none in the placebo group. Neither group had an event adjudicated as 'probably related'. The definition of trigger events for hepEAC adjudication can be found in 'Appendix 2: Trigger event definition for liver events'.

.

Table 21: Liver events adjudication results

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342	All Empa N=4687
	N (%)	N (%)	N (%)	N (%)
Number with adjudicated events	11 (0.5)	23 (1)	21 (0.9)	44 (0.9)
- Probably related	0	0	0	0
- Possibly related	0	2 (0.1)	1 (< 0.1)	3 (0.1)
- Unlikely related	11 (0.5)	20 (0.9)	19 (0.8)	39 (0.8)
- Indeterminate	0	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)

Source: Adapted from Table 15.3.1.3.2: 1 of the study report for study 1245.25

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.

Table 22: Proportion of Patients with LFT Elevations by Treatment Arm

	Placebo N=2333	Empa 10 N=2345	Empa 25 N=2342
	N (%)	N (%)	N (%)
Elevated liver enzymes criteria			
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)
With Alkaline phosphatase <2 x ULN[1]	1 (<0.1)	4 (0.2)	0
With Alkaline phosphatase ≥2 x ULN[1]	1 (<0.1)	1 (<0.1)	2 (0.1)

Includes patients regardless of baseline elevations and includes events up to 30 days after last dose of study drug. Events were identified based on centrally measured laboratory values

[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: Adapted from Table 12.1.3.3.2: 1 of the study report for study 1245.25

The applicant reported that there were 5 patients in this study that fulfilled the biochemical Hy's law criteria, 4 treated with empagliflozin, and 1 treated with placebo. Review of the submitted data identified two additional cases that fit the biochemical criteria for Hy's law. All of these cases were reviewed the adjudication committee, and both were adjudicated as unlikely to be related to study drug (Table 23).

Table 23: Summary of possible cases of biochemical Hy's law

	Treatment	Likely alternative etiology	hepEAC adjudication of relatedness
Subject 67508	Placebo	Cholelithiasis	Unlikely related
Subject 53852	Empa	Sepsis	Unlikely related
Subject 57200	Empa	Unexplained[1]	Unlikely related
Subject 58299	Empa	Hepatitis A	Unlikely related
Subject 54242	Empa	Statin therapy	Unlikely related
Subject 56393	Empa	Cholelithiasis	Unlikely related
Subject 63028	Empa	Lymphoproliferative disorder	Unlikely related

[1] while unexplained, the liver enzyme elevation was elevated in only a single blood draw and laboratory values normalized within two days and without discontinuation of study drug.
Source: Adapted from Table 12.1.3.3.2: 3 of the study report of study 1245.25 and based on reviewer analysis using JReview and review of submitted narratives

Malignancy:

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 (See Appendix 3 for details). 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 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.

Due to signals observed in the original empagliflozin NDA review and with other SGLT2 inhibitors, breast cancer, bladder cancer, renal cancer, lung cancer, and skin melanoma were defined as the malignancies of special interest in this trial, and are presented in Table 24.

Table 24: 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)
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: Reviewer generated using JReview, ADAE, ADAEADJ, and ADSL datasets

Lung, breast, and renal cancer occurred with a similar frequency in placebo and pooled empagliflozin groups. There were disproportionately more pancreatic malignancies and

melanomas in the pooled empagliflozin group compared to placebo. Bladder cancer was marginally more frequent in the empagliflozin pool compared to placebo.

Of these, the most notable difference between treatment arms is for pancreatic cancer. Most of these were adjudicated as 'not related' by the oncAAC (Table 25). Many of these cases also had other confounding factors. Overall, the number of events is small making it difficult to draw meaningful conclusions.

Table 25: 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	55452	463	No	Not available	No	Not available	Not related
Empa 10	50901	946	DPP4	Yes both	Yes	Not available	Not related
Empa 10	66587	642	No	Smoker	No	Pancreatic cancer (sister)	Not related
Empa 10	51141	~4 yrs.	No	Not available	No	Not available	Not assessable
Empa 10	51625	1269	No	Not available	Yes	Not available	Possibly related
Empa 10	63440	225	No	No	Yes	No	Not related
Empa 25	50831	637	No	4-3 beers/day	No	Not available	Not related
Empa 25	51622	1470	No	Not available	No	Not available	Possibly related
Empa 25	68502	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: Reviewer generated based on review of narratives

Other Thromboembolic 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. Cerebrovascular thromboembolic events were not included in this section by the Applicant as they are discussed above.

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.

Table 26 Incidence rates for adverse events of venous embolic and thrombotic adverse events (narrow SMQ), sorted by frequency

	Placebo N=2333		Empa 10 N=2345		Empa 25 N=2342	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Overall incidence	20 (0.9)	0.35	9 (0.4)	0.15	21 (0.9)	0.35
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
Preferred Term						
- 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)	0.1
- 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

Rate/100 pt-yrs = events per 100 patient years; AEs = adverse events
Source: Adapted from Table 12.1.3.10: 1 of the study report for study 1245.25

Ketoacidosis:

Diabetic ketoacidosis AEs were summarized based on a custom MedDRA query. Notably, diabetic ketoacidosis AEs were defined as AESIs after completion of the trial but prior to database lock. There were four patients in the empagliflozin group with reported ketoacidosis, and only one patient in the placebo group with reported ketoacidosis. Only 2 patients (empagliflozin 10 mg) had diabetic ketoacidosis AEs leading to discontinuation of study medication.

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 the PT 'anaphylactic shock' and 2 patients with the PT 'anaphylactic reaction').

A summary of these four cases is can be found in Table 27.

Table 27: Summary of patients with severe allergic reactions

Treatment Arm	Subject ID	Study Day	Event	Alternative etiology	Study drug discontinued
Empagliflozin 10 mg	50647	292	Anaphylactic reaction	None	Yes
Empagliflozin 10 mg	54873	120	Anaphylactic shock	None	No
Empagliflozin 25 mg	51081	892	Anaphylactic shock	Bee sting	No
Empagliflozin 25 mg	60536	413, 927	Anaphylactic reaction	Food allergy	No

Source: Reviewer generated based on review of narratives

The number of events is too small to draw meaningful conclusions.

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).

In addition, a custom MedDRA query (BIcMQ) using the following preferred terms 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, and
- hypoglycemic unconsciousness.

Hypoglycemic events that occurred 12 or less hours apart were collapsed into a single event by the Applicant. We believe that hypoglycemic events that occur less than 12 hours apart are likely to represent individual events, and, for this reason, I will focus on the reviewer-generated analysis below.

Using the hypoglycemia flag (BIcMQ based) in the ADAE dataset, we 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 analysis identified 27.9% of the patients in the placebo group, and 27.8% of patients in the empagliflozin group. Only 37 events of severe hypoglycemia were reported as serious events, 17 in the placebo group (0.7%), and 20 in the pooled empagliflozin group (0.4%).

Fractures:

Fracture events were analyzed using a BIcMQ. The incidence of fractures was comparable in the empagliflozin and the placebo treatment groups (Table 28). 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 28: 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)
- Fractured coccyx	2 (0.1)	1 (< 0.1)
- Lower limb fracture	3 (0.1)	1 (< 0.1)
- Lumbar vertebral fracture	3 (0.1)	2 (< 0.1)
- Open fracture	2 (0.1)	1 (< 0.1)
- Osteoporotic fracture	2 (0.1)	2 (< 0.1)
- Patella fracture	0	2 (< 0.1)
- Pubis fracture	3 (0.1)	1 (< 0.1)
- Avulsion fracture	0	1 (< 0.1)
- Cervical vertebral fracture	0	1 (< 0.1)
- Clavicle fracture	1 (< 0.1)	2 (< 0.1)
- Forearm fracture	0	2 (< 0.1)
- Jaw fracture	0	2 (< 0.1)
- Multiple fractures	1 (< 0.1)	0
- Periprosthetic fracture	1 (< 0.1)	1 (< 0.1)
- Scapula fracture	1 (< 0.1)	1 (< 0.1)
- Skull fractured base	1 (< 0.1)	1 (< 0.1)

	Placebo N=2333	All Empa N=4687
	N (%)	N (%)
- Spinal fracture	0	1 (< 0.1)
- Thoracic vertebral fracture	1 (< 0.1)	0
- Traumatic fracture	1 (< 0.1)	0
- Ulna fracture	1 (< 0.1)	2 (< 0.1)

[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 was reported at a higher incidence in the empagliflozin group compared to the placebo group (Table 29). 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 29 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: Reviewer generated using JReview, ADAE, ADSL datasets

Urinary Tract Infections/Urosepsis:

While the overall incidence of urinary tract infections was similar for the empagliflozin group compared to the placebo group, the incidence of 'urosepsis' was higher in the empagliflozin groups compared to placebo (Table 30). Patients with urinary tract infections in the empagliflozin group were also more likely to discontinue study drug as a result of that event. These findings are generally consistent with the current labeling.

Table 30: Urinary tract infection events occurring in ≥ 0.3% of subjects in the placebo or pooled empagliflozin group

	Placebo N=2333		All Empa N=4687	
	N (%)	**Rate/100 pt-yrs**	**N (%)**	**Rate/100 pt-yrs**
Overall	**423 (18.1)**	**8.21**	**842 (18)**	**7.88**
Leading to discontinuation	**10 (0.4)**	**0.17**	**41 (0.9)**	**0.34**
Serious AE[1]	**29 (1.2)**	**NA**	**58 (1.2)**	**NA**
Preferred Term				
- Urinary tract infection	352 (15.1)	6.7	694 (14.8)	6.36
- Cystitis	23 (1.0)	0.4	69 (1.5)	0.58
- Asymptomatic bacteriuria	30 (1.3)	0.52	42 (0.9)	0.35
- Urosepsis	3 (0.1)	0.05	17 (0.4)	0.14
- Bacteriuria	14 (0.6)	0.24	16 (0.3)	0.13
- Escherichia urinary tract infection	9 (0.4)	0.16	13 (0.3)	0.11
- Pyelonephritis	4 (0.2)	0.07	13 (0.3)	0.11
- Pyelonephritis chronic	10 (0.4)	0.17	10 (0.2)	0.08
- Pyelonephritis acute	6 (0.3)	0.1	8 (0.2)	0.07

[1] event requiring or prolonging hospitalization

Rate/100 pt-yrs = rate per 100 patient years; NA = not analyzed

Source: Adapted from Table 15.3.1.6: 1, Table 15.3.1.6: 2, and Table 15.3.1.6: 5 of the study report for study 1245.25

Genital Infections:

The Applicant identified genital infections using a BIcMQ for genital infections. The BIcMQ does not contain the preferred term 'phimosis' which was observed to occur with increased frequency in patients treated with empagliflozin in prior reviews, and may be a relevant term as it could be a consequence of genital infections and may require surgery for treatment. Regardless of whether this term is included or not, the overall incidence for genital infections is higher with empagliflozin compared to placebo (Table 31).

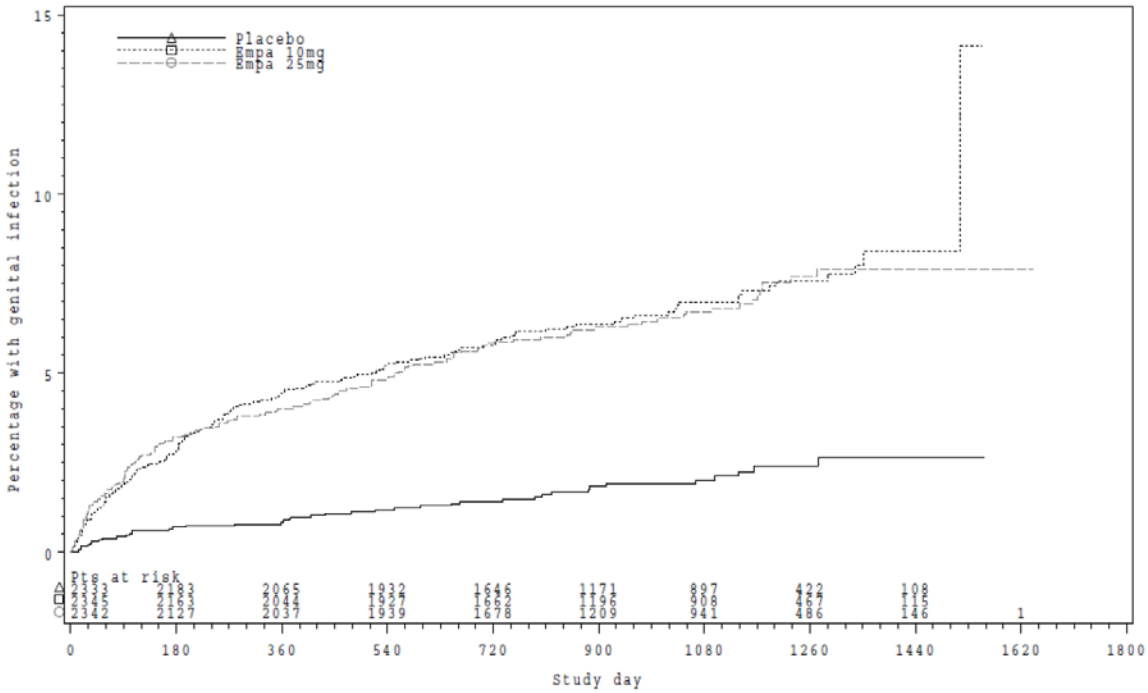
Table 31: Genital infection events occurring in ≥ 0.3% of subjects in the placebo or pooled empagliflozin group

	Placebo N=2333	**All Empa N=4687**
	N (%)	**N (%)**
Total (incl phimosis)	**45 (1.9)**	**309 (6.6)**
Total (excl phimosis)	**42 (1.8)**	**290 (6.2)**
Preferred Term		
- Balanoposthitis	3 (0.1)	68 (1.5)
- Vulvovaginal candidiasis	5 (0.2)	48 (1.0)
- Genital infection fungal	3 (0.1)	38 (0.8)
- Vulvovaginal mycotic infection	2 (0.1)	34 (0.7)
- Prostatitis	14 (0.6)	26 (0.6)
- Phimosis	3 (0.1)	19 (0.4)
- Vulvovaginitis	3 (0.1)	18 (0.4)
- Balanitis candida	2 (0.1)	15 (0.3)
- Vaginal infection	3 (0.1)	15 (0.3)

Source: Reviewer generated using JReview, ADAE, and ADSL datasets

A time to event analysis for genital infections showed an almost immediate separation of the empagliflozin curves from the placebo curve (Figure 8)

Figure 8: Kaplan-Meier curve for time of onset of first genital infection



Source: Excerpted from Figure 12.1.3.5: 1 of the study report for study 1245.25

This is generally consistent with the current labeling.

<u>Volume Depletion:</u>

Volume depletion events were assessed using a BIcMQ. Overall, these events occurred with a slightly higher incidence in the empagliflozin treated subjects compared to the placebo subjects (Table 32). In review of the terms included in the BIcMQ, it was noted that some terms which may suggest volume depletion (e.g., dizziness) were not included. Inclusion of these terms does not change the overall conclusion.

Table 32: Volume depletion events

	Placebo N=2333	**Empa 10 N=2345**	**Empa 25 N=2342**	**All Empa N=4687**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Overall incidence	**115 (4.9)**	**115 (4.9)**	**124 (5.3)**	**239 (5.1)**
Leading to discontinuation	**7 (0.3)**	**1 (<0.1)**	**4 (0.2)**	**5 (0.1)**
Serious AEs	**24 (1.0)**	**19 (0.8)**	**26 (1.1)**	**45 (1)**
Preferred Terms				
- Hypotension	58 (2.5)	57 (2.4)	62 (2.6)	119 (2.5)
- Syncope	32 (1.4)	31 (1.3)	41 (1.8)	72 (1.5)
- Dehydration	16 (0.7)	18 (0.8)	18 (0.8)	36 (0.8)
- Orthostatic hypotension	12 (0.5)	16 (0.7)	12 (0.5)	28 (0.6)
- Blood pressure decreased	3 (0.1)	1 (<0.1)	3 (0.1)	4 (0.1)
- Hypovolemia	0	0	2 (0.1)	2 (< 0.1)

Source: Adapted from Table 15.3.1.16: 1, Table 15.3.1.16: 2, and Table 15.3.1.16: 3 of the study report for study 1245.25

The incidence of volume depletion events increased with age, with degree of renal impairment (based on eGFR at baseline), and with baseline use of diuretics or ACE inhibitors/ARBs in all treatment groups. From these subgroups, the risk appeared increased in subjects > 75 years old (5.7% with placebo, 7.1% with empagliflozin 10 mg, 6.6% with empagliflozin 25 mg, and 6.8% for the all empagliflozin group) and in subjects using concurrent loop diuretics (8.2% with placebo, 10.8% with empagliflozin 10 mg, 9.9% with empagliflozin 25 mg, and 10.3% for the all empagliflozin group).

d. 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). The overall incidence of any adverse event was comparable between the treatment arms.

Adverse events by HLT experienced by ≥5% of patients in either treatment group are presented in 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 33: Adverse Events by HLT Experienced by ≥5% of Patients

	Placebo N=2333	**All Empa N=4687**
	N (%)	**N (%)**
High Level Term		
- Hypoglycemic conditions NEC	686 (29.4%)	1370 (29.2%)
- Upper respiratory tract infections	492 (21.1%)	973 (20.8%)
- Urinary tract infections	387 (16.6%)	769 (16.4%)
- Musculoskeletal and connective tissue pain and discomfort	344 (14.7%)	678 (14.5%)
- Ischemic coronary artery disorders	255 (10.9%)	489 (10.4%)
- Lower respiratory tract and lung infections	286 (12.3%)	486 (10.4%)
- Hyperglycemic conditions NEC	432 (18.5%)	425 (9.1%)
- Neurological signs and symptoms NEC	163 (7.0%)	384 (8.2%)
- Pain and discomfort NEC	181 (7.8%)	375 (8.0%)
- Vascular hypertensive disorders NEC	216 (9.3%)	340 (7.3%)
- Gastrointestinal atonic and hypomotility disorders NEC	155 (6.6%)	304 (6.5%)
- Diarrhea (excl infective)	175 (7.5%)	298 (6.4%)
- Non-site specific injuries NEC	139 (6.0%)	293 (6.3%)
- Influenza viral infections	167 (7.2%)	287 (6.1%)
- Renal failure and impairment	182 (7.8%)	287 (6.1%)
- Bladder and urethral symptoms	96 (4.1%)	279 (6.0%)
- Joint related signs and symptoms	138 (5.9%)	268 (5.7%)
- Coughing and associated symptoms	162 (6.9%)	252 (5.4%)
- Fungal infections NEC	71 (3.0%)	240 (5.1%)

	Placebo N=2333	All Empa N=4687
	N (%)	N (%)
- Bacterial infections NEC	127 (5.4%)	236 (5.0%)
- Nausea and vomiting symptoms	126 (5.4%)	236 (5.0%)
- Asthenic conditions	134 (5.7%)	233 (5.0%)
- Headaches NEC	133 (5.7%)	230 (4.9%)
- Infections NEC	127 (5.4%)	221 (4.7%)
- Gastrointestinal and abdominal pains (excl oral and throat)	126 (5.4%)	211 (4.5%)
- Diabetes mellitus (incl subtypes)	185 (7.9%)	199 (4.2%)
- Cataract conditions	124 (5.3%)	193 (4.1%)
- Breathing abnormalities	133 (5.7%)	193 (4.1%)
- Edema NEC	188 (8.1%)	181 (3.9%)
- Anemias NEC	129 (5.5%)	178 (3.8%)
- Renal function analyses	119 (5.1%)	172 (3.7%)

Source: Reviewer generated using JReview and the ADAE ADSL datasets

e. Laboratory Findings

Descriptive statistics for selective laboratory parameters is presented below. Laboratory evaluations of hepatic and renal functions are described under renal safety.

Electrolytes:

No significant change in median values from baseline to last value on treatment was reported for any of these laboratory tests.

The Applicant identified patients with possible clinically significant abnormalities (PCSA) by treatment, defined as follows:

- 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 proportion of patients who experienced 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.

Hematology:

In the original NDA review for empagliflozin, an 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 is not clear that hemoconcentration resulted 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 patients treated with empagliflozin compared to placebo. 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 was noted.

Significant rises in hemoglobin and hematocrit, defined as a hemoglobin >18 g/dL, or a hematocrit >55 were overall rare. However, more patients in the empagliflozin group were observed to have experience significant rises in these paramaters than in placebo. This is consistent with previous findings and is currently labeled.

Serum lipids:

In the original empagliflozin NDA review, several dose-dependent changes of unknown clinical significance were noted in serum 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.

Baseline values for lipid parameters were similar between the treatment groups. Small, dose-dependent increases were observed for total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and non-HDL cholesterol (Table 34). The clinical significance of these changes remains unclear.

Table 34: Changes in lipid parameters from Baseline to Week 80

	Placebo	Empa 10	Empa 25
Baseline mean (mg/dL)			
• Total cholesterol (SE)	161.82 (0.91)	163.59 (0.96)	163.29 (0.91)
• HDL (SE)	44.02 (0.24)	44.67 (0.25)	44.51 (0.25)
• LDL (SE)	84.85 (0.75)	86.22 (0.78)	85.61 (0.75)
• Triglycerides (SE)	170.28 (2.54)	168.32 (2.72)	172.23 (2.83)
• non-HDL cholesterol (SE)	117.79 (0.89)	118.93 (0.93)	118.78 (0.90)
Week 28 adjusted mean change from baseline (mg/dL)			
• Total cholesterol (SE)	3.59 (0.83)	6.23 (0.78)	7.98 (0.79)
• HDL (SE)	0.12 (0.18)	1.51 (0.17)	2.03 (0.17)
• LDL (SE)	2.57 (0.68)	4.26 (0.65)	5.59 (0.65)
• Triglycerides (SE)	6.01 (2.39)	2.61 (2.26)	0.64 (2.27)
• non-HDL cholesterol (SE)	3.50 (0.81)	4.68 (0.77)	5.96 (0.77)
Week 52 adjusted mean change from baseline (mg/dL)			
• Total cholesterol (SE)	4.62 (0.98)	7.88 (0.88)	9.05 (0.89)
• HDL (SE)	0.17 (0.20)	1.63 (0.19)	2.15 (0.19)
• LDL (SE)	3.21 (0.81)	5.27 (0.73)	6.07 (0.74)
• Triglycerides (SE)	6.23 (2.71)	5.08 (2.45)	5.92(2.48)
• non-HDL cholesterol (SE)	4.47 (0.95)	6.21 (0.86)	6.91 (0.87)
Week 80 adjusted mean change from baseline (mg/dL)			
• Total cholesterol (SE)	5.97 (1.13)	8.23 (1.00)	10.44 (1.00)
• HDL (SE)	0.73 (0.24)	1.71 (0.21)	2.39 (0.21)
• LDL (SE)	3.94 (0.94)	5.17 (0.82)	6.50 (0.82)
• Triglycerides (SE)	5.03 (3.26)	8.34 (2.84)	9.33 (2.84)
• non-HDL cholesterol (SE)	5.26 (1.11)	6.49 (0.97)	8.09 (0.97)

SE = standard error; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol

Source: Adapted from Table 15.3.2.4.1.1: 1, Table 15.3.2.4.2.1: 1, Table 15.3.2.4.3.1: 1, Table 15.3.2.4.5.1: 1, and Table 15.3.2.4.6.1: 1 of the study report for study 1245.25

f. Vital Signs

Blood pressure changes are discussed above in "Observed differences between treatment arms".

Heart rate (HR):

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. Also, 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.

CARDIOLOGY CONSULT REVIEW – EXECUTIVE SUMMARY

Memorandum

FROM: Karen A. Hicks, M.D., Medical Officer
Division of Cardiovascular and Renal Products

John Lawrence, Ph.D., Biostatistician
Division of Biometrics I

THROUGH: Aliza Thompson, M.D., Team Leader
Division of Cardiovascular and Renal Products

H. M. James Hung, Ph.D.
Director, Office of Biometrics I

Norman L. Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products

TO: Michael White, RPM
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II

Andreea Ondina Lungu, M.D., Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II

SUBJECT: Cardiovascular Findings in sNDA 204629 S-008, Empagliflozin Cardiovascular Outcome Trial (EMPA-REG OUTCOME)

DATE RECEIVED: December 15, 2015

DATE COMPLETED: May 5, 2016

NOTE: For the Advisory Committee Meeting Briefing Package, only the Executive Summary of the Consult is included.

1. Executive Summary

Jardiance® (Empagliflozin) is a sodium-glucose co-transporter 2 (SGLT2) inhibitor and new molecular entity that was approved by the FDA on August 1, 2014 and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). By inhibiting SGLT2, empagliflozin (BI 10773) reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose hence increases urinary glucose excretion. The approval letter included a postmarketing requirement for the applicant to conduct

> "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."

On November 4, 2015, the Division of Metabolism and Endocrinology Products (DMEP) received an efficacy supplement (NDA 204629/S-008) with the results of Study 1245.25 intended to address this requirement titled "A Phase III, Multicenter, International, Randomised, 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" known as the EMPA-REG OUTCOME® Trial. DMEP has requested input from the Division of Cardiovascular and Renal Products (DCaRP) on the cardiovascular findings and proposed labeling changes. Specifically, the applicant has proposed a new indication "to reduce the risk of 1) all-cause mortality by reducing the incidence of cardiovascular death and 2) cardiovascular death or hospitalization for heart failure" in "adult patients with T2DM and high cardiovascular risk."

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. Study duration was a median of 3.1 years.

The primary endpoint was the time to first occurrence of major adverse cardiovascular (CV) events defined as adjudicated CV death, nonfatal myocardial infarction (MI), and nonfatal stroke, herein described as 3-point MACE (3-P MACE). The key secondary endpoint was the time to first occurrence of MACE+ defined as adjudicated CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina, herein described as 4-point MACE (4-P MACE).

The primary endpoint tested the hypothesis that empagliflozin (pooled doses of 10 mg and 25 mg) was noninferior to placebo for 3-P MACE based on a margin of 1.3 for the hazard ratio. If non-inferiority was established for the primary endpoint, non-inferiority was to be tested on the key secondary endpoint (4-P MACE), again based on a margin

of 1.3. If non-inferiority was established for the key secondary endpoint, superiority for the primary endpoint was to be tested. If established, superiority for the key secondary endpoint was to be tested.

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).

Below, we discuss the efficacy findings as they relate to each of the following outcomes/endpoints.

1) Major adverse cardiovascular events
2) Cardiovascular death and all-cause mortality
3) Hospitalization for heart failure and other heart failure-related endpoints

1) Major Adverse Cardiovascular Events

Myocardial Infarctions

As previously noted, the primary endpoint for the trial was a composite endpoint that included CV death, nonfatal MI, and nonfatal stroke. The primary endpoint finding was driven by the treatment effect on CV death. In contrast, there was no effect on nonfatal stroke (in fact the point estimate of the HR was > 1). Although the findings for nonfatal MI numerically favored the empagliflozin arms, findings related to treatment effects on silent MIs, as well as missing data, complicate interpretation of these data.

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. At this time, it is unclear whether the exclusion of silent MIs from the primary endpoint represents a late change to the protocol (Amendment 3 dated December 29, 2011).[10] Regardless, the discrepancy merits further consideration. It is possible that a number of factors related to how MIs were identified and assessed in the trial contributed to this discrepancy.

- The trial used an algorithm for silent MIs (and patients who would not be included in the analysis) that likely did not identify all potential events; that said, it's not clear that the algorithm would have led to a differential ascertainment of events in the different arms.
- We found that the data on time to event for silent MIs was not reliable because in some cases, the silent MI changes were also present on earlier 12-lead electrocardiograms (ECGs); this could have added noise to the endpoint.

[10] In contrast to later versions of the protocol, earlier versions of the protocol did not explicitly exclude silent MIs from the primary endpoint. We are still seeking clarification on how many events accrued before this date. For a timeline of key trial dates and changes to the protocol and statistical analysis plans, see Appendix B.

- There was no oversight by the CEC of these events; again, this could have contributed to noise; and
- Some patients in the trial did not have an ECG performed at baseline prior to study drug initiation; again, it's not clear that this would have led to differential ascertainment.

There are arguments for and against including silent MIs in the overall adjudication of MIs in CV outcome trials, and some CV outcome trials include them in the overall adjudication of MIs, while others do not. For the most part, studies have demonstrated that "silent Q wave MIs" can account for "9-37% of all non-fatal MI events" and are associated with a "significantly increased mortality risk"[11] (1-5). Hence, regardless of whether these events were included in the prior endpoint, given their prognostic importance, we believe it is important to consider these events when interpreting the data on MACE events.

Another issue that should be considered is the amount of missing data. It is important to note that 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 or 3-P MACE are known. There were also 74 subjects with potential MACE nonfatal events that could not be assessed by the Clinical Event Committee (CEC), including 30 placebo subjects, 26 empagliflozin 10 mg subjects, and 18 empagliflozin 25 mg subjects. We encourage the primary review division to conduct further analyses exploring the impact of missing data on the primary endpoint findings, if they have not already done so.

In conclusion, considering the totality of the data including the stroke findings, the silent MI findings, and the missing data, we do not believe that the trial provides substantial evidence that empagliflozin lowers the risk of MACE, and specifically, strokes and MIs. As discussed below, we do, however, believe the trial provides substantial evidence that empagliflozin reduces the risk of CV death.

2) Cardiovascular Death and All-Cause Mortality

Based on the findings in the EMPA-REG OUTCOME® trial, the applicant is seeking claims for CV death and all-cause mortality. Compared to placebo, pooled empagliflozin doses demonstrated a 38% reduction in the risk of CV death (HR 0.62; 95% CI 0.49, 0.77) and a 32% reduction in the risk of all-cause mortality (HR 0.68; 95% CI 0.57, 0.82). As previously discussed, CV death was a component of the primary and key secondary composite endpoint.

[11] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, and White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. ESC/ACCF/ AHA/WHF Expert Consensus Document. Third Universal Definition of Myocardial Infarction. J Am Coll Cardiol, 2012;60(16):1581-1598.

In the EMPA-REG OUTCOME® trial, “all deaths not attributed to the specified categories above and not attributed to a non-cardiovascular cause” were presumed to be CV deaths and part of the CV mortality endpoint. Although we generally presume that undetermined causes of death are CV deaths, how these events will be handled in the analysis should be prespecified before a trial begins, and the stipulation here is that in any well-run clinical trial, the number of undetermined deaths should be few (7). We note that in the EMPA-REG OUTCOME® trial, the categorization of these events as CV deaths was not made until late in the trial (i.e., reflected a late change to the Trial Statistical Analysis Plan [TSAP]). Moreover, there were many undetermined causes of death in the trial. Of the 463 deaths in the trial, 124 deaths (71 empagliflozin, 53 placebo) were defined as “fatal events not assessable” (i.e., undetermined deaths) and were presumed to be CV deaths. Thus, these deaths, which may or may not have been CV deaths, comprise 124/309 (40.1%) of all CV deaths and 124/463 (26.8%) of all deaths in the trial.

We discussed the larger issue with CEC experts (i.e., what one should expect in terms of the number of undetermined causes of death in a CV outcome trial). In some CEC experiences, undetermined deaths may account for approximately 14% of all deaths in large acute coronary syndrome (ACS)/atrial fibrillation trials. In other CEC experiences, undetermined deaths could comprise < 5% of deaths. However, if a trial included a patient who was “dead in bed” as an undetermined death, this category could apply to 10-20% of all deaths. For the most part, these cases should be sudden cardiac deaths, but if the patient has not been seen ≤ 24 hours, then the deaths would be undetermined. All vital status only deaths are unknown, may comprise 20-30% of deaths in a particular trial, and may not be a reflection of trial quality. For example, if subjects were lost or not followed and a vital status search were not conducted, there would be few vital status only/undetermined deaths, but deaths would be missed. If there were a large level of incomplete data and a vital status search was conducted, the number of undetermined deaths could be high. If a trial had a low level of missing data and vital status was evaluated, then there would be small numbers of undetermined deaths.

Our sense is that the missing data in this trial likely stems from how the trial was designed, and, specifically, the forms that were used to capture information on events. The investigator endpoint reporting form in this trial captured information on the date of the event but not the time and instructed investigators to check a box indicating that a particular endpoint event had occurred. In particular, the form did not include information that would be pertinent to the particular endpoint event or check boxes for criteria needed to fulfill a particular endpoint definition. It is also unclear whether study personnel used standard questions when inquiring about subjects who died in the trial. In general, documentation of the time of the event is important for the adjudication of virtually every endpoint event. Documenting when symptoms began and when cardiac troponins (cTn) were obtained in relation to the symptoms is critical for the adjudication of MI. Documenting the duration of symptom persistence may be also be used in some trials to determine whether a subject experienced a transient ischemic attack (TIA) or an ischemic stroke. In addition, patients usually have numerous comorbid conditions, and

understanding the timing of events and treatments administered can help to determine the cause of death for fatal events.

All of that said, sensitivity analyses excluding these 124 cases still demonstrated a statistically significant reduction in the risk of 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); hence, we believe the finding is reliable. It is important to note that the empagliflozin finding on CV death was driven by treatment effects on 3 components including undetermined deaths, worsening heart failure (HF), and sudden death. As a result, we do not have a good understanding of the mechanism by which empagliflozin is improving mortality.

3) Hospitalization for Heart Failure and Other Heart Failure-Related Endpoints

In addition to requesting a claim for all-cause mortality and CV death, the applicant is requesting a claim related to hospitalization for HF and a composite of CV death (excluding fatal stroke) or hospitalization for HF. According to the applicant, compared to placebo, pooled empagliflozin doses reduced the risk of HF requiring hospitalization by 35% (HR 0.65; 95% CI 0.50, 0.85). Pooled empagliflozin doses also reduced the risk of HF requiring hospitalization or CV death (excluding fatal stroke) by 34% (HR 0.66; 95% CI 0.55, 0.79). As previously noted, hospitalization for HF and other HF-related endpoints were not included in a plan to control the overall Type 1 error; hence, all of these analyses are exploratory.

During the trial, the CEC also made key changes to the hospitalization for HF definition which resulted in what could be considered a "soft" endpoint. Version 6 of the Charter dated February 18, 2012 changed the HF requiring hospitalization 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." Version 8(a) of the Charter dated April 4, 2014 also updated the hospitalization for HF definition to include "initiation of *oral diuretic*, intravenous diuretic, inotrope, or vasodilator therapy" or "uptitration of *oral diuretic*, intravenous therapy, if already on therapy."

Based on the new definition, initiation or uptitration of an *oral* diuretic and an overnight stay in the emergency room were sufficient to meet the criteria for a HF hospitalization. Given how the endpoint was defined, it is possible that some of the events that were categorized as "HF" may not have reflected HF. Moreover, the trial enrolled a broad population of patients and it is difficult to assess whether patients who had HF were receiving optimal guideline-directed medical and device therapy for HF or whether patients who had a history of HF had HF with a reduced ejection fraction (EF) or a preserved EF. In contrast to typical HF trials, this trial did not collect baseline information on EF or New York Heart Association (NYHA) Functional Classification. Because of its diuretic effect, it is certainly plausible that empagliflozin could reduce the

risk of HF hospitalization (in patients with a preserved or reduced EF); however, we believe this hypothesis should be confirmed in a well-designed and well conducted trial in patients with HF.

Conclusion

In conclusion, we believe that the data demonstrate that empagliflozin reduces the risk of CV death in adult patients with type 2 diabetes mellitus who are at high CV risk. Because hospitalization for HF and other HF-related endpoints were not included in a plan to control the overall Type 1 error rate, as well as other concerns related to how well the trial was designed to assess effects on HF hospitalization, we do ***not*** recommend approval of empagliflozin to reduce the risk of either 1) hospitalization for HF; or 2) a composite of CV death (excluding fatal stroke) or hospitalization for HF. Finally, we note that, in general, we rarely give indications for reducing the risk of all-cause mortality in CV outcome trials because this endpoint is typically driven by CV death.

We look forward to further discussion of the issues raised in this consult at the Advisory Committee Meeting.

12. References

1. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, and White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. ESC/ACCF/AHA/WHF Expert Consensus Document. Third Universal Definition of Myocardial Infarction. J Am Coll Cardiol. 2012;60(16):1581-1598.

2. Chaitman BR, Hardison RM, Adler D, Gebhart S, Grogan M, Ocampo S, Sopko G, Ramires, Schneider D, Frye RL. Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Study Group. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: Impact of treatment strategy on cardiac mortality and myocardial infarction. Circulation. 2009;120:2529-2540.

3. Burgess DC, Hunt D, Zannino D, Williamson E, Davis TME, Laakso M, Kesaniemi YA, Zhang J, Sy RW, Lehto S, Mann S, Keech AC. Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Eur Heart J. 2010;31:92-99.

4. Sheifer SE, Manolio TA, Gersh BJ. Unrecognized myocardial infarction. Ann Intern Med. 2001;135:801-811.

5. Toma M, Fu Y, Ezekowitz JA, McAlister FA, Westerhout CM, Granger C, Armstrong PW. Does silent myocardial infarction add prognostic value in ST-elevation myocardial infarction? Insights from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial. Am Heart J. 2010;160:671-677.

6. Alexander JH, Harrington RA, Bhapkar M, Mahaffey KW, Lincoff AM, Ohman EM, Klootwijk P, Pahlm O, Henden B, Deckers JW, Simoons ML, Califf RM, Wagner GS. Prognostic Importance of New Small Q Waves following Non-ST-Elevation Acute Coronary Syndromes. Am J Med. 2003;115;613-619.

7. Hicks KA, Hung H.M. James, Mahaffey KW, Mehran RW, Nissen SE, Stockbridge NL, Targum SL, Temple R on behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials. Draft Definitions for CDISC, August 20, 2014.

NEPHROLOGY CONSULT REVIEW

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products

Date: April 29, 2016
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Tzu-Yun McDowell[12], Senior Clinical Analyst, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Team Leader
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Michael White, Regulatory Project Manager, Division of Metabolism and Endocrinology Products
Subject: Renal findings in the EMPA-REG OUTCOME trial

Background

Empagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor approved August 1, 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. As has been the practice for diabetes drugs, the approval letter included a postmarketing requirement to conduct "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." Previous clinical trials suggested an increased risk of acute kidney injury, so the postmarketing study was also to include an assessment of "the 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."

On November 4, 2015, the Division of Metabolism and Endocrinology Products (DMEP) received an efficacy supplement (sNDA 204629) containing the results of the EMPA-REG OUTCOME Trial, the trial conducted to address the postmarketing requirement. DMEP has requested input from the Division of Cardiovascular and Renal Products (DCRP) on the renal findings and proposed labeling changes.

Materials Reviewed

1. Clinical Trial Report
2. Original protocol and amendments 1 through 4
3. Clinical Event Committee charter
4. Statistical analysis plans dated August 24, 2012 and May 21, 2015
5. Applicant's response to clinical information requests submitted February 3, 2016 and March 25, 2016
6. Current empagliflozin prescribing information
7. Draft revised prescribing information submitted March 31, 2016
8. Selected case Report Forms (CRFs) and narratives

[12] Dr. McDowell conducted data analyses where noted.

Overview of Protocol[13]

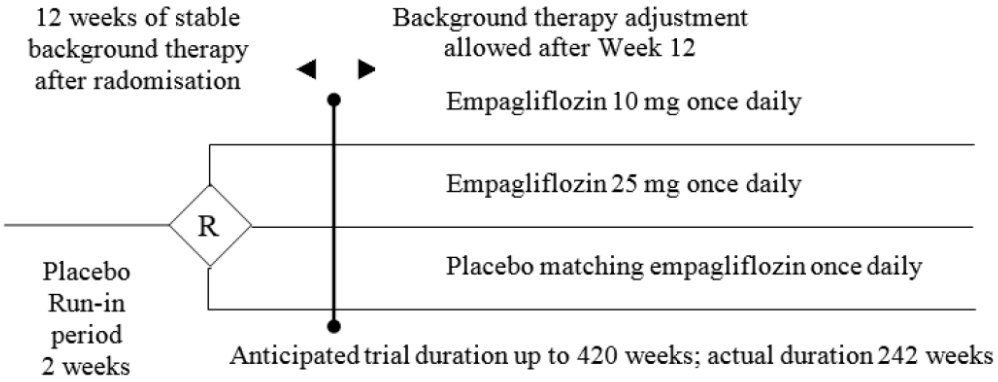
The EMPA-REG OUTCOME trial was a randomized, double-blind, event-driven cardiovascular safety trial conducted between July 20, 2010 and April 13, 2015. In total, 7028 patients with type 2 diabetes mellitus (T2DM) and increased cardiovascular risk were randomized 1:1:1 to empagliflozin 10 mg once daily (n=2347), empagliflozin 25 mg once daily (n=2344), or placebo (n=2337). The primary objective was to determine non-inferiority of treatment with empagliflozin (pooling the 10 mg and 25 mg dose groups) versus placebo on cardiovascular outcomes. If non-inferiority was established, then superiority would be tested.

Trial design

Figure 1**Figure** shows an overview of the trial design. In brief, all subjects initially entered a 2-week, open-label, placebo run-in period. Subjects who successfully completed the run-in and still met eligibility criteria were then randomized. Randomization was stratified by HbA1c, BMI, region, and renal impairment at screening (normal: eGFR≥ 90 ml/min; mild impairment: 60 ml/min ≤ eGFR≤ 89 ml/min; and moderate impairment: 30 ml/min ≤ eGFR≤ 59 ml/min).

According to the protocol, pre-existing background diabetes therapy was to remain unchanged for 12 weeks after randomization unless changes were medically necessary. Investigators were also encouraged "to treat all other CV [cardiovascular] risk factors (lipid levels, blood pressure, micro/macroalbuminuria, unhealthy lifestyle, smoking) according to an optimal level of standard of care. In a high CV risk population this usually implies liberal use (if tolerated and not contraindicated) of statins, ACE inhibitors, AT-II receptor blockers, aspirin, beta-blockers, calcium channel blockers, etc. This should be conducted in the context of local or regional guidance for secondary CV prevention."

Figure 1: Overview of Study Design



Renal-Related Eligibility Criteria

The eligibility criteria were not designed to identify subjects with diabetic nephropathy (i.e., subjects were not required to have a reduced eGFR or albuminuria at baseline and there was no exclusion for other etiologies of kidney disease). The eligibility criteria pertinent to the renal findings are:

Key Inclusion Criteria

1. Diagnosis of T2DM.

[13] Except where noted, the description of the protocol is based on Protocol Version 5.0 dated October 15, 2013.

2. Age ≥18 years (for Japan: age ≥20 years; for India: age ≥18 years and ≤65 years).
3. HbA1c of ≥7.0% and ≤10% at screening for patients on background therapy or HbA1c of ≥7.0% and ≤ 9.0% for drug-naïve patients.
4. High cardiovascular risk according to protocol-defined criteria.

Key Exclusion Criteria

1. Uncontrolled hyperglycemia with a glucose level >240 mg/dL after an overnight fast during placebo run-in and confirmed by a second measurement (not on the same day).
2. Impaired renal function defined as GFR <30 mL/min/1.73m^2 (MDRD formula) during screening and/or run in phase.

Overview of Renal Monitoring

Visits were conducted at 4, 8, 12, 16, 28, 40, and 52 weeks, and thereafter at 14 week intervals until the end of study visit, and 30 days after the end of study visit. Patients who prematurely discontinued study drug were to be followed up until the end of the trial using the same visit schedule.

Creatinine and urine albumin-to-creatinine ratio (UACR) were measured 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; at the end of study visit; and 30 days after the end of study visit. At the same time points, urine dipstick was performed locally. The timing of urine collection (e.g., first morning void) was not specified.

Patients who consented after approval of protocol amendment 3 dated December 30, 2011 also had cystatin C drawn at randomization; Weeks 4, 12, 28, and 52; then every year until the end of study visit; at the end of study visit; and 30 days after the end of study visit.

Decreased renal function was a "protocol-specified significant adverse event" defined as "creatinine value shows a ≥ 2 fold increase from baseline and is above the upper limit of normal."

Renal Endpoints

The protocol was amended four times as shown in the Appendix. The renal endpoints were substantially modified with amendment 2[14] and key details regarding the renal endpoints were first defined in the final statistical analysis plan submitted after the trial ended. No renal endpoints were specified within a plan to control the overall Type 1 error rate in any version of the protocol or statistical analysis plan.

In the final protocol, secondary renal "safety" endpoints included occurrence and time to first occurrence of:

- 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,

[14] Based on the applicant's March 25, 2016 submission, nearly 85% of subjects were enrolled after amendment 2, and a majority of primary endpoint events occurred after the amendment.

- 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.

Various combinations of the renal endpoints above were included in the final protocol as "further miscellaneous endpoints." No renal endpoints were adjudicated, but the Clinical Endpoint Committee Charter included "renal causes" as one category of "non-cardiovascular death." The charter did not define "renal causes."

Ascertainment of Renal-Related Events

As previously noted, the applicant is seeking claims in Section 14 related to the "new or worsening nephropathy" component of the composite microvascular outcome (i.e., "*the risk of new or worsening nephropathy (defined as onset of macroalbuminuria, doubling of serum creatinine, and initiation of renal replacement therapy (i.e., hemodialysis)) was significantly reduced in empagliflozin group compared to placebo*") including a table showing event rates, hazard ratios, and p-values for the individual components. The applicant is also seeking claims in Section 14 related to analyses of changes in albuminuria (i.e., "*JARDIANCE compared with placebo showed a significantly higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria*"). Neither the protocol nor statistical analysis plan specified processes for identifying or confirming potential renal events for these analyses. In a February 3, 2016 submission, the applicant provided additional detail regarding how potential renal events were defined and identified for these analyses:

New Onset of Macroalbuminuria

Cases of new onset of macroalbuminuria were identified as any UACR >300 mg/g after first study drug intake. Subjects with a UACR >300 mg/g at baseline (defined as the last measurement before or on first drug intake) or with missing baseline or post-baseline data were excluded.

Reviewer's comment: The endpoint captures any UACR value >300 mg/g in subjects with a UACR ≤300 mg/g at baseline and would include small, transient, and/or reversible changes.

Doubling of Serum Creatinine

Doubling of serum creatinine events were identified by any single post-baseline creatinine measurement of ≥2x baseline with an eGFR ≤45 mL/min/1.73m^2 on the same date. Patients missing a baseline or post-baseline creatinine measurement were excluded.

Reviewer's comment: The endpoint requires only a single creatinine measure without requiring confirmation that the decline in renal function persisted after a specified time period. As such, it would capture both acute, reversible changes in renal function (i.e., acute kidney injury) and chronic, irreversible changes in renal function (i.e., the development or progression of chronic kidney disease).

Initiation of "Continuous Renal Replacement Therapy"

Initiation of "continuous renal replacement therapy" events were identified through the adverse event and concomitant medication datasets. Patients with "continuous renal replacement therapy" at baseline (before first trial medication) were excluded.

Reviewer's comment: In trials of diabetic nephropathy, one component of the endpoint is often progression to end-stage disease defined by initiation of chronic dialysis (i.e., dialysis that is ongoing after a specified period of time), renal transplant, or a sustained eGFR <15

mL/min/1.73m^2. In the EMPA-REG trial, it is not obvious what events the applicant intended to capture with the "continuous renal replacement therapy" endpoint as defined, but it is possible that they included cases of acute kidney injury that were reversible. See the results section for a review of identified events.

Renal Death

"Fatal Renal Disease" was identified as:

- Patients that died due to a non-CV death, and
- Patients who had an eGFR <10 mL/min/1.73m^2 at any time OR who had "any fatal renal charter" identified by selecting "the AEs of interest" "Acute renal failure without dialysis with nephropatic syndrome" with an outcome of "fatal."
- Excluding patients with a record of dialysis within 14 days of death identified in the adverse event and concomitant medication datasets using the preferred term "dialysis."

Reviewer's comment: It is not obvious how the above criteria were selected to identify cases of renal death. Although there is no standardized definition of "renal death," it is generally defined as a death occurring after a patient refuses or a physician withholds renal replacement therapy (i.e., initiation of chronic dialysis or renal transplantation) or in cases where dialysis is unavailable. The definition often excludes deaths due to another primary process and/or when another cause is adjudicated (e.g., sepsis, end-stage heart failure, malignancy). Given the complexity in this definition, we generally recommend that renal death be adjudicated with explicit rules for adjudication. Although the Clinical Endpoint Committee Charter included "renal causes" as one category of "non-cardiovascular death," the charter did not further define "renal causes." Regardless, it does not appear that the applicant used the adjudicated data for purposes of this endpoint. See the results section for a review of the identified "renal deaths."

Sustained Normo- or Microalbuminuria

According to the Clinical Trial Report, the "further miscellaneous endpoint" of sustained normo- or microalbuminuria was defined as two consecutive measurements fulfilling the condition of normo-albuminuria (<30 mg/g) or microalbuminuria (≤300 mg/g) at least 4 weeks apart in subjects with baseline macroalbuminuria (>300 mg/g).

Statistical Analysis Plan for Renal-Related Endpoints

Adjustment for Multiplicity

No renal-related endpoints were included in plans to control the overall Type 1 error rate. According to the protocol and statistical analysis plan, "all secondary analyses (except for the analysis of the key secondary endpoint) are of exploratory nature and no correction for multiple hypothesis testing will be made."

Secondary Endpoint Analysis

The secondary renal endpoints were analyzed using a Cox proportional hazards regression model of time to the first occurrence of the event with factors for treatment (pooled empagliflozin vs. placebo), age, sex, baseline categories of BMI (<30 vs. ≥30 kg/m^2), baseline HbA1c (<8.5% vs. ≥8.5%), baseline eGFR (normal: eGFR ≥90 mL/min; mild impairment: 60 mL/min ≤ eGFR ≤89 mL/min; and moderate/severe impairment: eGFR ≤59 mL/min), and geographic region (North America [including Australia and New Zealand], Latin America, Europe, Africa, and Asia).

Analysis of Continuous Variables

For continuous variables, change over time was evaluated with a restricted maximum likelihood based mixed model repeated measures (MMRM) approach with the fixed, categorical effects of treatment, week, treatment-by-week interaction, with the covariates of baseline efficacy endpoint,

baseline HbA1c, baseline BMI, baseline eGFR, geographical region, and baseline efficacy endpoint-by-week interaction and baseline HbA1c-by-week interaction. Any data obtained on treatment until rescue therapy (Observed Cases analysis) were used.

Renal-related Results

Baseline Subject Characteristics

Key baseline characteristics were generally balanced between the treatment arms (Table **1**). Approximately 20% of subjects were reported by the investigators to have diabetic nephropathy at baseline, although over 25% had an eGFR <60 mL/min/1.73m^2 and 40% had albuminuria. Most were on a RAS blocker.

Table 1: Key renal-related baseline characteristics

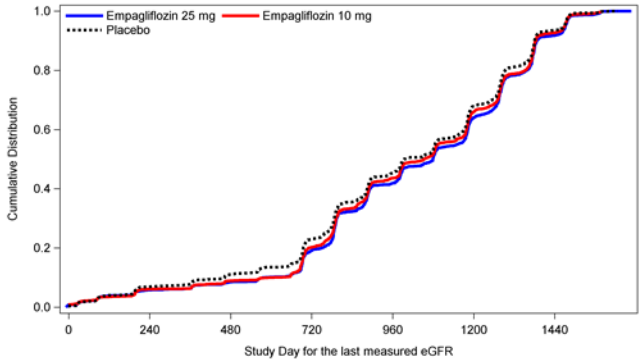
	Empagliflozin (n=4687)	**Placebo (n=2333)**
Age (mean [SD])	63.1 (8.6)	63.2 (8.8)
Male	336 (71%)	1680 (72%)
Medical History		
Hypertension	4266 (91%)	2153 (92%)
DM Nephropathy	904 (19%)	467 (20%)
RAS Blocker	4018 (86%)	2007 (86%)
eGFR (mean [SD] mL/min/1.73m^2)	74.2 (22)	73.8 (21)
≥90	1050 (22%)	488 (21%)
60-<90	2423 (52%)	1238 (53%)
45-<60	831 (18%)	418 (18%)
30-<45	360 (8%)	183 (8%)
<30	21 (0.4%)	6 (0.3%)
UACR Category (mg/g)		
<30	2789 (60%)	1382 (59%)
30-≤300	1338 (29%)	675 (29%)
>300	509 (11%)	260 (11%)

Source: Applicant, Clinical Trial Report, Tables 10.4.1:1, 10.4.3:1, 10.4.5:1. Appendix 16.1.9.2, Table 4.2.

Disposition

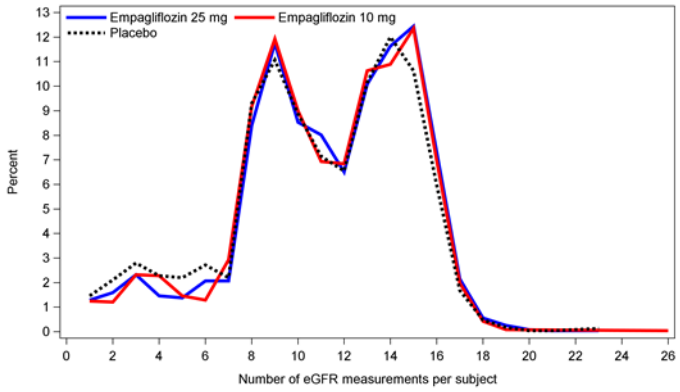
Overall, 7020 (99.9%) randomized subjects were treated with study drug. The duration of follow-up related to renal function was similar between the treatment arms as shown in Figure **2** and Figure 3.

Figure 2: Time to last eGFR measurement



Source: Analyses by Dr. McDowell, dataset *adrenim.*

Figure 3: Number of eGFR measurements per subject



Source: Analyses by Dr. McDowell, dataset *adrenim.*

Analyses of Renal-related Endpoints

The results for the albuminuria-based endpoints and the microvascular composite outcome and its components are shown in Table 2. As previously noted, renal endpoints of interest were re-defined during the trial, not specified in detail, and not tested within a plan to control the overall Type 1 error rate. There was no difference between treatment arms in the rate of new onset albuminuria or the eye-related components of the microvascular composite outcome. The empagliflozin group had nominally fewer cases of new onset macroalbuminuria and more cases of "sustained improvement to normo- or microalbuminuria" as defined by the applicant. The empagliflozin group had nominally fewer microvascular composite outcome events driven by the "new or worsening nephropathy" component, which was driven primarily by cases of new onset macroalbuminuria.

Table 2: Results of renal endpoints

Endpoint	**Empagliflozin n/N (%)**	**Placebo n/N (%)**	**Hazard Ratio (95% CI; p-value)**
New onset albuminuria[1]	1430/2779 (51.5)	703/1374 (51.2)	0.95 (0.87, 1.04; 0.25)
New onset macroalbuminuria[2]	459/4091 (11.2)	330/2033 (16.2)	0.62 (0.54, 0.72; <0.01)
Sustained improvement to normo- or microalbuminuria[3]	248/499 (49.7)	74/257 (28.8)	1.82 (1.40, 2.37; <0.01)
Microvascular composite	577 (14.0)	424 (20.5)	0.62 (0.54, 0.70; <0.01)
- Retinal photocoagulation	41/4687 (0.9)	29/2333 (1.2)	0.69 (0.43, 1.12; 0.13)
- Vitreous hemorrhage	30/4687 (0.6)	16/2333 (0.7)	0.93 (0.51, 1.71; 0.81)
- Diabetes-related blindness	4/4687 (0.1)	2/2333 (0.3)	--
- New or worsening nephropathy	525/4124 (12.7)	388/2061 (18.8)	0.61 (0.53, 0.70; <0.01)
New onset macroalbuminuria	459/4091 (11.2)	330/2033 (16.2)	0.62 (0.54, 0.72; <0.01)
Doubling of serum creatinine	70/4645 (1.5)	60/2323 (2.6)	0.56 (0.39, 0.79; <0.01)
Continuous renal replacement therapy	13/4687 (0.3)	14/2333 (0.6)	0.45 (0.21, 0.97; 0.04)
Renal death	3/4687 (0.1)	0	--

Source: Applicant, Clinical Trial Report, Tables 11.1.2.8.1: 1 and 11.1.2.8.2: 2.
[1]Includes subjects without albuminuria at baseline.
[2]Includes subjects without macroalbuminuria at baseline.
[3]Includes subjects with macroalbuminuria at baseline. Not a specified secondary endpoint.

Doubling of Serum Creatinine

As noted previously, the doubling of serum creatinine endpoint required only a single post-baseline serum creatinine value ≥2x baseline with an eGFR ≤45 mL/min/1.73m^2 on the same date without requiring confirmation that the decline in renal function persisted after a specified time period. As a result, the endpoint might capture both acute, reversible changes in renal function (i.e., acute kidney injury) and chronic, irreversible changes in renal function (i.e., development or progression of chronic kidney disease). To explore this issue, we looked for a confirmatory creatinine value ≥2x baseline and ≤45 mL/min/1.73m^2 at any time ≥30 days following an initial event. As shown in Table 3, we confirmed the decline in fewer than half of subjects with an event, suggesting that many of the initial events may have been cases of acute kidney injury. We did not specify a time window for confirmation, and the median time to confirmation was approximately 3 months (range 30 days to 2 years); therefore, it is likely that some of the "confirmed" events were cases of recurrent acute kidney injury.

Table 3: Doubling of serum creatinine events, unconfirmed and confirmed

	Empagliflozin N=4645	**Placebo N=2323**
Doubling of serum creatinine	70 (1.5)	60 (2.6)
Event confirmed at ≥ 30 days	25 (0.5)	29 (1.2)

Source: Analysis by Dr. McDowell, datasets *adtte*, *adlb*, and *adrenim.*

Continuous Renal Replacement Therapy

The definition of "continuous renal replacement therapy" was not clear, so we reviewed the narratives and CRFs for a random selection of 5 of the 27 identified events. As described below, four were cases of acute kidney injury requiring temporary dialysis and one was a case of acute kidney injury for which a dialysis catheter was placed but the subject died before receiving dialysis. While acute kidney injury events requiring dialysis are clinically significant, they do not represent the "end-stage" disease that is typically captured in efficacy endpoints for trials of diabetic nephropathy.

- Subject 50025 (empagliflozin 25 mg): Patient developed severe sepsis following aortic valve replacement surgery complicated by acute kidney injury requiring temporary dialysis. Based on the CRF, it appears the patient initiated chronic dialysis approximately two years later, although this is not captured in the narrative. The "continuous renal replacement therapy" event date reflects the acute dialysis.
- Subject 50302 (placebo): Patient developed acute kidney injury with hyperkalemia requiring dialysis for one day.
- Subject 50426 (placebo): Patient was admitted with "terminal systolic and diastolic heart failure," "underwent dialysis for the event of cardiac failure and end stage renal failure," and died the following day "due to the event cardiac failure."
- Subject 51464 (empagliflozin 25 mg): Patient was hospitalized for unstable angina and experienced "a progression of the kidney failure after angioplasty" requiring dialysis for one day.
- Subject 64686 (empagliflozin 10 mg): Patient was admitted with inoperable mesenteric ischemia complicated by severe lactic acidosis and acute kidney injury. A dialysis catheter was placed "in anticipation of potential post-operative dialysis (this was never used)." The patient died the same day. Neither the narrative nor CRF state that the subject received dialysis.

Renal Death

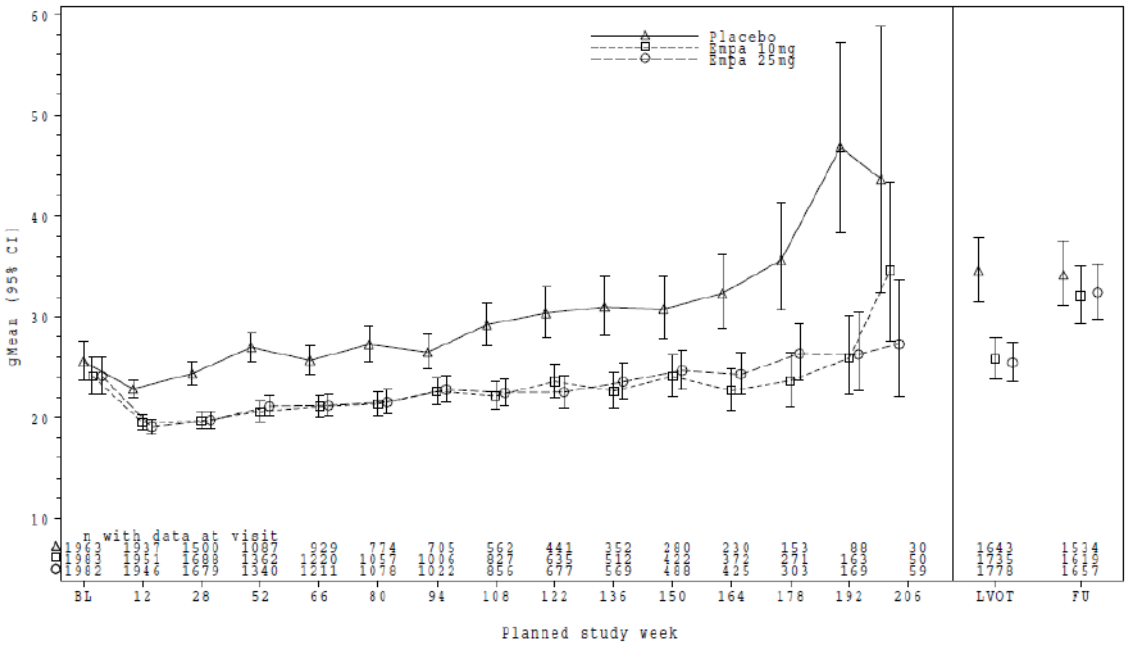
The definition of "renal death" was not clear, so we reviewed the narratives and CRFs for the three identified events, which all occurred in the empagliflozin 10 mg treatment arm. As noted below, the CEC attributed only one death in the trial to renal failure.

- Subject 51232: Patient was diagnosed with "severe dehydration, severe secondary renal failure with hypernatremia, and severe multiorganic failure." According to the narrative, ongoing events included disorientation, cough, and shortness of breath. "Her vitals, laboratory, and diagnostic examinations during the events were not reported." She was treated with fluid, ciprofloxacin, and furosemide. "She did not receive any therapy for the event multiorganic failure." She subsequently died from "dehydration and secondary renal failure with hypernatraemia which caused multiorganic failure." The CEC attributed this event to pneumonia (Source: dataset *adcec*).
- Subject 61835: Patient "was diagnosed with severe congestive heart failure secondary to end stage renal disease secondary to chronic kidney disease due to uncontrolled hypertension." According to the narrative, dialysis was advised, the subject refused, and she subsequently died "due to the event hypertensive nephropathy." No details were provided regarding renal function or other diagnostic evaluations at the time of the event. This appears to be the only event in the trial that the CEC attributed to renal failure.
- Subject 66563: Patient was diagnosed with hepatocellular carcinoma and declined treatment. He subsequently began vomiting and developed progressive renal failure. "The patient was not dialysed due to the patient's haemodynamic instability" and the subject subsequently died. The CEC attributed this event to liver cancer (Source: dataset *adcec*).

Changes in Renal Function, Albuminuria, Blood Pressure, and Weight

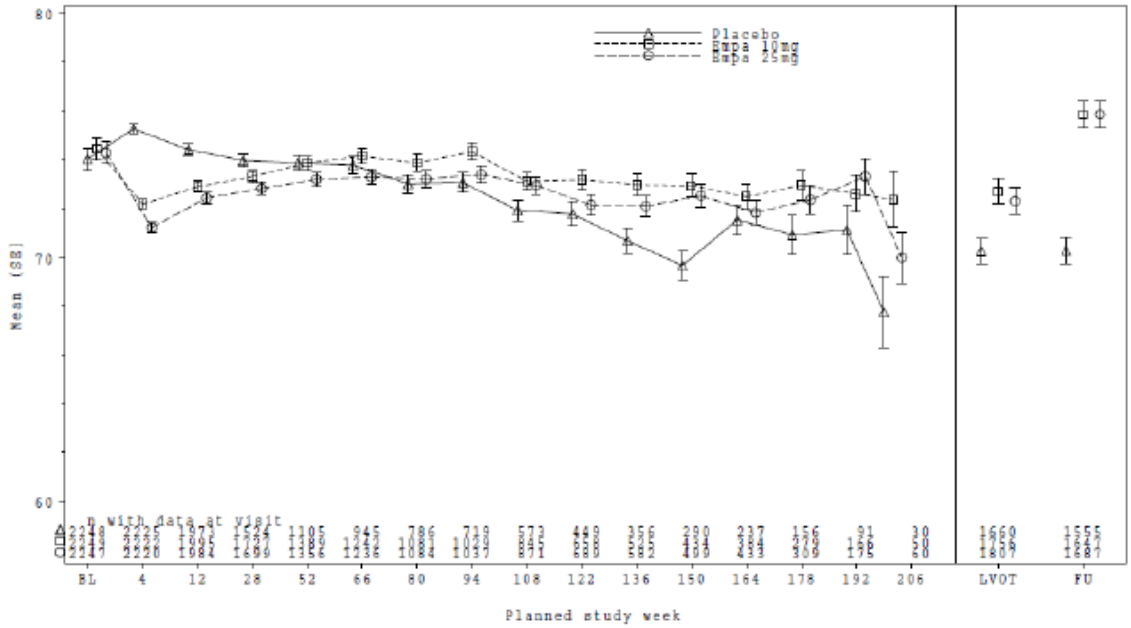
According to the applicant's analyses, UACR, eGFR, and systolic blood pressure all decreased in the initial weeks of treatment with empagliflozin (Figure 4, Figure 5, and Figure 6). Following discontinuation of empagliflozin, both UACR and eGFR increased from the last value on treatment (LVOT) to the follow-up assessment (FU) (Figure 4, Figure 5). Collectively, these findings suggest an acute, hemodynamic effect of empagliflozin on renal function and albuminuria. As shown in Figure 4, UACR appears to be similar between the empagliflozin and placebo groups following study drug discontinuation. The mean eGFR appears to be higher in the empagliflozin groups following study drug discontinuation (Figure 5); however, interpretation of this finding is complicated by the substantial amount of missing data.

Figure 4: Urine albumin-to-creatinine (mg/g) MMRM results over time



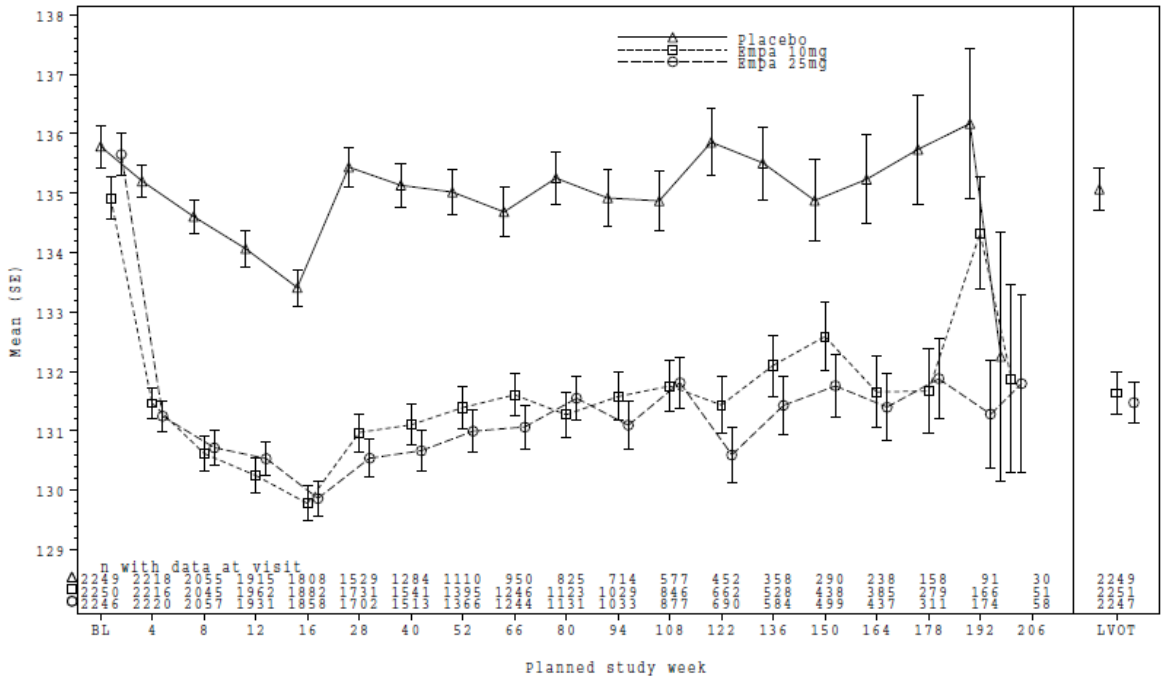
Source: Applicant, Clinical Trial Report, Figure 11.1.2.8.2:3.

Figure 5: eGFR (mL/min/1.73m^2) MMRM results over time



Source: Applicant, Clinical Trial Report, Figure 11.1.2.8.3:1.

Figure 6: Systolic blood pressure (mmHg) MMRM results over time



Source: Applicant, Clinical Trial Report, Figure 15.2.4.3.5.2:3.

Additional Safety Analyses

To further assess renal safety, the applicant 1) summarized renal adverse events using a narrow SMQ for acute renal failure and 2) summarized the "protocol-specified significant adverse event" of "creatinine value shows a ≥ 2 fold increase from baseline and is above the upper limit of normal." There was no difference in the number of narrow SMQ events of acute renal failure, SAEs, or events leading to study drug discontinuation by treatment group (Table 4) or by baseline eGFR category (not shown). A renal "protocol-specified significant adverse event" was reported for 2.1%, 1.4%, and 0.9% of placebo, empagliflozin 10 mg, and empagliflozin 25 mg subjects, respectively (Source: Applicant, Clinical Trial Report, Table 15.3.2.3.1.5:1).

Table 4: Incidence of narrow MedDRA SMQ acute renal failure events

	Placebo (N=2333) n (%)	**Empagliflozin 10mg (N=2345) n (%)**	**Empagliflozin 25mg (N=2342) n (%)**
Overall incidence	155 (6.6)	121 (5.2)	125 (5.3)
Renal impairment	77 (3.3)	73 (3.1)	73 (3.1)
Renal failure	42 (1.8)	23 (1.0)	31 (1.3)
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)
Azotaemia	1 (<0.1)	1 (<0.1)	4 (0.2)
Acute prerenal failure	2 (0.1)	1 (<0.1)	0
Anuria	1 (<0.1)	0	1 (<0.1)
Nephropathy toxic	0	0	1 (<0.1)
Oliguria	1 (<0.1)	0	0
Prerenal failure	0	0	1 (<0.1)
Leading to discontinuation	24 (1)	19 (0.8)	22 (0.9)
SAE	46 (2)	31 (1.3)	26 (1.1)

Source: Applicant, Clinical Trial Report, Table 12.1.3.2:1.

Consult Questions

1. Comment on the overall study as it relates to its adequacy with regard to evaluating the effectiveness of empagliflozin as a treatment for "nephropathy" or as a treatment to preserve renal function (i.e., study population, design, selected endpoints, etc.)?

   DCRP Response: *The applicant has proposed efficacy claims in Section 14 of the label for the "new or worsening nephropathy" component of the composite microvascular outcome defined as: a) new onset of macroalbuminuria; b) doubling of serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73m^2; c) need for continuous renal replacement therapy; or d) death due to renal disease. The applicant has also proposed claims in Section 14 related to changes in albuminuria.*

   It is important to note that these endpoints differ from those typically used to establish the efficacy of drugs intended to treat diabetic nephropathy, which are generally designed to assess a treatment's effect on the irreversible loss of renal function (i.e., progression of chronic kidney disease). The practice to date has been to conduct the trials in patients with more advanced renal disease compared with the population enrolled in this trial, to enrich for patients who are more likely to progress to end stage disease. The practice has also been to define the endpoint as a composite of: a) a confirmed doubling of serum creatinine or, more recently, a confirmed 40% decline in eGFR; b) progression to end-stage disease defined as the need for chronic dialysis (i.e., dialysis that is ongoing after a specified time period), renal transplant, or a sustained eGFR <15 mL/min/1.73m^2. Sometimes the endpoint also includes renal death, cardiovascular death, or all-cause mortality. To date, the Agency has not accepted on-treatment effects on albuminuria as a surrogate for clinical outcomes in diabetic nephropathy, in part because therapies can have acute and reversible pharmacologic effects on albuminuria that may differ from their long-term effects on the irreversible loss of renal function and underlying disease progression.

   The "new or worsening nephropathy" component of the composite microvascular outcome was not well-designed to capture treatment effects on the irreversible loss of renal function. Key issues include:

   1. *The "new or worsening nephropathy" component of the microvascular composite outcome was largely driven by cases of new onset of macroalbuminuria, which accounted for over 85% of events. As defined, the new onset macroalbuminuria component could capture small, transient, and/or reversible changes in albuminuria of uncertain clinical significance. In fact, there was no difference in albuminuria between the placebo and empagliflozin arms following discontinuation of study drug, suggesting a hemodynamic effect rather than a direct effect on the underlying disease process.*
   2. *The doubling of serum creatinine component did not require confirmation after a specified time period to ensure that the decline in renal function was chronic in nature, rather than acute. We were unable to confirm the decline in renal function at ≥30 days after the event for at least half of the cases, suggesting that many of the events identified represented acute kidney injury.*
   3. *The "continuous renal replacement therapy" component was not well-designed to capture progression to end-stage disease, as evidenced by the fact that all 5 randomly selected cases reviewed were cases of acute kidney injury, one of which did not undergo dialysis.*

   The applicant is seeking additional claims based on analyses of "sustained normo- or microalbuminuria in patients with baseline macroalbuminuria"; as noted above, the

observed treatment effects on albuminuria appear to be hemodynamic in nature and reversible with discontinuation of study drug.

In addition to issues related to endpoint definitions, we note that the renal endpoints were re-defined during the trial and that key aspects of the endpoints were either defined after trial completion, but reportedly before database lock, or were not defined prospectively. Finally, no renal-related endpoints were included in plans to control the overall Type 1 error rate because, as the applicant noted, the endpoints "are of exploratory nature and no correction for multiple hypothesis testing will be made." As such, we consider the analyses to be exploratory.

Regarding the study population, as noted above, the eligibility criteria did not identify a population with pre-existing diabetic nephropathy (i.e., subjects were not required to have a reduced eGFR or albuminuria at baseline and there was no exclusion for other etiologies of kidney disease). In addition, subjects were not required to be on a maximum tolerated dose of an ACE inhibitor or ARB, although nearly all were reported to be on a RAS blocker at baseline. These are relatively minor issues and would not necessarily be barriers to a renal-related claim, absent the issues noted above.

2. In section 5.2 of the label (Warnings and Precautions), and section 6 (Adverse Reactions), the applicant proposes to eliminate or change class labeling language describing and mitigating risks of acute renal function changes with product initiation. The rationale being that although a decrease in renal function is observed acutely after initiation of empagliflozin, this finding reverses somewhat with continued treatment and is reversible with product withdrawal. Do you believe the submitted data support removal of this language from one or more section of the label?

DCRP Response: *We do not believe the submitted data support removal of language related to renal safety from the label (i.e., removal of the Warning and Precaution "Impairment in Renal Function" or language related to renal safety in Section 6). No difference was noted in narrow SMQ acute renal failure events or in the "protocol-specified significant adverse event" of "creatinine value shows a ≥ 2 fold increase from baseline and is above the upper limit of normal"; however, such events would be relatively severe and such analyses would not necessarily identify an imbalance in less severe acute kidney injury events that are still clinically significant and may require adjustments in therapy or other interventions. In addition, we note that the "protocol-specified significant adverse event" does not clearly distinguish between acute and chronic changes in renal function. Based on its mechanism of action, empagliflozin results in an osmotic diuresis and can contribute to volume depletion and acute kidney injury, although this may not translate into longer term impacts on renal function. We note a parallel with renin-angiotensin system blockers such as captopril, irbesartan, and losartan, drugs indicated for the treatment of diabetic nephropathy that also carry precautions regarding impaired renal function. Given the totality of the available data, we believe the Warning and Precaution related to the risk of acute kidney injury should remain in the label; however, given the longer-term eGFR data, it may be reasonable to add a statement to indicate that, in the population as a whole, data on the longer-term effects on renal function are reassuring.*

Appendix: Amendments to protocol and statistical analysis plan (SAP) related to renal endpoints

Amendment # and Date	Summary
Original Protocol May 10, 2010	• Renal endpoints included "Further secondary CV-endpoints" of "the occurrence of and time to…the incidence of microalbuminuria and the progression of microalbuminuria to macroalbuminuria from baseline to end of trial."
Amendment #1 September 22, 2010	• No substantive changes to renal endpoints.
Amendment #2 April 22, 2011	• Separated albuminuria-related endpoints into 1) microalbuminuria and 2) progression of microalbuminuria to macroalbuminuria from baseline to end of trial where macroalbuminuria is defined as an UACR > 300 mg/g. • Added composite microvascular outcome as a secondary endpoint defined as: o Need for retinal photocoagulation o Vitreous hemorrhage o Diabetes-related blindness o New or worsening nephropathy defined as: a) new onset of macroalbuminuria; or b) doubling of serum creatinine level accompanied by an eGFR (MDRD) ≤ 45 mL/min/1.73m^2; or c) need for continuous renal replacement therapy o Death due to renal disease • Added individual components of the composite microvascular outcome as "other tertiary endpoints."
Amendment #3 December 29, 2011	• Defined new onset albuminuria as UACR ≥30 mg/g. • Moved death due to renal disease from a component of the composite microvascular endpoint to the definition of "new or worsening nephropathy." • Added cystatin C measurement for patients enrolled after local approval of the protocol amendment.
Original SAP August 24, 2012	• Listed renal endpoints as outlined in protocol. • Defined new onset microalbuminuria as ACR ≥30 mg/g and new onset macroalbuminuria as ACR ≥300 mg/g.
Amendment #4 October 15, 2013	• Under Section 7.3: Planned Analyses, added "For new or worsening nephropathy as well as death due to renal disease, an intent-to-treat similar to the primary analysis for MACE will be performed."
Final SAP May 21, 2015	• Re-defined macroalbuminuria as ACR >300 mg/g. • Stated that doubling of serum creatinine level refers to baseline serum creatinine, i.e., last value prior to first drug intake and requires an eGFR value of ≤45 mL/min/1.73m^2 in the same sample. • Stated that death due to renal disease requires all of the following conditions: o Patient had an eGFR <10 mL/min/1.73m^2 at any time or had experienced one event of broad standardized MedDRA query acute renal failure (including nephrotic syndrome) considered as leading to death by the investigator. o One of two conditions: o Patient was not on dialysis at any time from start of randomization, or o Patient was on dialysis, but has stopped this and last dialysis occurred 14 days before the date of death (in order to fulfil this requirement there must not be any adverse event or concomitant therapy related to dialysis with stop date > death date – 14 days) o Patient did not die from CV death • Stated that "definitions of…continuous renal replacement therapy and dialysis are stored in PDMAP." • Added "further miscellaneous endpoints" including various combinations of the components of the composite microvascular outcome and CV death and exploratory analyses of change in eGFR and albuminuria.

Amendment # and Date	Summary
	• Stated that time to first occurrence of “new onset of albuminuria” or “new onset of macroalbuminuria” or “doubling of serum creatinine level” is determined by the date of the first ACR or serum creatinine measurement that fulfills the condition.

NEUROLOGY CONSULT REVIEW

FDA CDER Division of Neurology Products (DNP)
Consultation for the Division of Metabolism and Endocrine Products (DMEP)

From:	Jody E Green, Medical Officer DNP OND-I
Through:	John R. Marler, MD, Team Leader Billy Dunn, MD, Division Director DNP OND-I
To:	Michael White, Regulatory Project Manager DMEP OND-II
Subject:	Neurology Consultation NDA 204629-S-008
Name of Drug:	Jardiance (empagliflozin)
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date Consult Assigned:	December 14, 2015
Desired Completion Date:	April 22, 2016
Date Consult Completed:	May 5, 2016

1. Overview

The Division of Metabolism and Endocrine Products (DMEP) has consulted the Division of Neurology Products (DNP) for an evaluation of cerebrovascular safety of empagliflozin, a newly approved selective SGLT-2 inhibitor, used in the treatment of type 2 diabetes mellitus (T2DM) in conjunction with diet and exercise. The drug can be used as monotherapy with lifestyle changes or along with other diabetic treatments such as other oral medication or injectable insulin. This issue has recently been evaluated in the 1245.25 trial, the EMPA-REG OUTCOME trial fulfilling PMR 2755-4. This study was designed to determine CV safety in a cohort of patients with T2DM with high CV risk with the possibility of showing cardioprotection. The multinational, randomized, controlled, double-blind, parallel group study compared two doses of empagliflozin to placebo in 7025 subjects. The primary endpoint was event-based, the achievement of 3-point MACE, a composite endpoint used in trials evaluating cardioprotection. The 3-point MACE included cardiovascular death [death from stroke and heart disease], nonfatal myocardial infarction and nonfatal stroke. In this study, at completion, the Hazard Ratio (HR) for achieving non-fatal stroke was found to be elevated, 1.24 (95% CI 0.92, 1.67 p = 0.1638), although the drug did meet its endpoint in preventing 3-point MACE with HR of 0.86 (95% CI 0.74, 0.99 p = 0.0382) and preventing cardiovascular death with HR 0.62 (95% CI 0.49, 0.78 p < 0.0001), according to the sponsor. The imbalance seen in non-fatal stroke events during the study, although a nonstatistically

significant finding, was of some concern. Previously it had been noted that there was a slight increase in stroke in the first 60 days after initiating therapy in the one year trial leading to the approval of empagliflozin. Additionally in a meta-analysis evaluating other SGLT-2 inhibitors, canagliglozin and dapagliflozin, the HR for stroke was found to be elevated for both products, 1.46 and 1.21, respectively. As a result of these findings DMEP sought an opinion on the following issues:

1. If the findings are chance or real
2. If the temporal relationship of the drug initiation to the stroke is of importance
3. If the dose response sheds any light on the occurrence
4. If the type or nature of the stroke could be consistent with a known drug effect such as hypotension or hemoconcentration

This review will evaluate the stroke-related events that comprise part of the primary outcome related to the proposed label change requested by the sponsor. This product's indication and requested label change will be the subject of an Advisory Meeting in June, 2016.

2. Documents Reviewed

- Clinical Study Report
- Protocol with 4 Amendments
- Sample Case Report forms
- Statistical methods interim analysis plan 8/24/2012, 521/2015
- Steering committee meetings
- CECN meeting minutes
- Data monitoring committee meetings
- CEC Charter
- Applicant's response to Information Requests dated 8/10/15, 8/14/15, 9/19/15, 12/16/15, 12/17/15, 12/17/15, 12/18/15, 1/19/15, 1/26/15, 2/4/16, 3/4/16, 3/21/16, 3/22/16, 3/24/16, 3/23/16, 3/28/16, 3/30/16/ 3/31/16/ 4/1/16, 4/5/16, 4/7/16, 4/7/16, 4/8/16, 4/18/16
- Datasets to include ADCEC, ADTTE, ADAE, SDTM.CE, SDTM.SUPPCE, SUPPAE
- Statistical analysis plans dated August 24, 2012 and May 21, 2015
- Draft revised prescribing information submitted March 31, 2016
- Literature

3. Background

3.1 Treatment of diabetes

T2DM affects over 21 million Americans and is one of the most common of chronic health conditions. In 2010 it was found to be the seventh leading cause of mortality in the US. Specifically mortality due to cardiovascular conditions is about 1.7 times higher in adults with diabetes than in those without

diabetes. Both mortality and complications can be related to the macrovascular complications of the disease as well as microvascular complications of the disease. The relationship between blood sugar control and the microvascular complications of diabetes is better delineated than with macrovascular complications such as large vessel stroke. In 2007 after a meta-analysis of 42 studies for another product, rosiglitazone, showed an odds ratio for myocardial infarction of 1.43 in those treated with drug compared to those treated with placebo, followed by another large study with the product that did not show this risk compared to standard agents, the FDA mandated that all new drugs for diabetes needed to be monitored with a PMR assessing cardiovascular outcomes. (Ghosh) This trial was a direct outcome of the 2008 FDA "Guidance for Industry, Diabetes Mellitus Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes," which covered recommendations for cardiovascular safety in the pre-approval and post- approval period for drugs and biologics used to treat T2DM. Even without cardiovascular safety signals during Phase II/III development, it was required that evidence be provided to rule out unacceptable cardiovascular risk, such as in a long-term cardiovascular trial. The Guidance allowed for adaptive trial design to use accumulating data to decide how to modify aspects of the trial while it was ongoing without compromising the integrity of the study as long as the outcome measures were preplanned. If unblinded analyses of the data were performed, Type I error had to be controlled for. Additionally the patients enrolled in these long-term safety trials were to be similar to those who might use the product; that is, include those with high risk. Patients should include those with relatively advance disease, elderly patients, and patients with renal impairment. Patients would also be expected to have other co-morbid illnesses, preferentially those being treated such as dyslipidemia, hypertension, heart disease and stroke. An endpoint such as MACE or Major Adverse Cardiovascular Events composite endpoint was found to be useful to help minimize trial size. Since some of the cardiovascular endpoints of interest, such as stroke, are sufficiently infrequent, use of a composite endpoint kept the sample size down while still evaluating cardiovascular risk. Secondary endpoints could be evaluated, but only with adjustments for multiplicity to control for Type I error. Outcomes needed to be adjudicated in a blinded fashion. The EMPA-REG OUTCOME trial 1245.25 is the first completed large scale trial to evaluate adjudicated CV outcome events in high CV risk patients. If approved with an indication of reducing CV mortality in those with T2DM, this would be a major paradigm shift in treating diabetes and its complications.

3.2 Currently available drugs in the same class

Empagliflozin is one of three marketed SGLT2 inhibitors; all three oral medications are administered once a day. As a class, the drugs have a modest effect on controlling blood sugar. The first in class, canagliflozin, was approved by the FDA in March, 2013. Dapagliflozin followed in January, 2014 and empagliflozin in August, 2014. All are approved for the treatment of T2DM and significantly lower HbA1c both as a single agent and in combination with other anti-diabetes products.

The drugs are thought to work by lowering the threshold for glucose excretion by the kidney. This particular class of medication, SGLT2 inhibitors, serves as a transporter 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. In addition to increasing urinary glucose excretion, they lower the plasma glucose level independently from the effects of insulin. Hypoglycemia is less common

with these products than with insulin, but can occur. The increased excretion of glucose is thought to help with weight control.

3.3 The product

Empagliflozin is available by prescription in the United States as a single drug or as a component of a fixed-dose combination product. Two doses are approved, 10 mg and 25 mg. It is suggested that dosing be started once a day with the 10 mg dose and in patients tolerating the product the dose can be advanced. The drug is not indicated in those with severe renal impairment, end-stage renal disease, or dialysis as well as those who are hypersensitive to it.

Pharmacokinetics

The pharmacokinetics of empagliflozin demonstrates that after oral administration, the peak plasma concentration is 1.5 hours after dosing. The elimination half-life was estimated to be 12.4 hours after oral dosing. In those with mild, moderate, and severe renal impairment empagliflozin did increase peak plasma levels as did those with mild, moderate, and severe hepatic impairment.
Pharmacodynamics

Pharmacodynamics

The pharmacodynamics effects of this drug are many. The drug's primary effect is thought to be increasing renal excretion of glucose and lowering blood sugar. The renal excretion of glucose occurs immediately and was found to be maintained over a 4 week treatment period. A substantial reduction in the HbA1c level takes about 6 weeks to occur and about 18 weeks to plateau. In addition to increasing the renal excretion of glucose and lowering blood sugar, other effects seen include weight loss, better blood pressure control, diuresis, uric acid reduction, hemoconcentration. The mean change in the systolic blood pressure for pressures ≥ 130/80 mmHg was found to be lowered by 5 mm Hg for those on 25 mg of empagliflozin and by 3.9 mmHg for those on 10 mg empagliflozin which plateaued by week 24.

Reviewer's Comment

Empagliflozin is a diuretic, and as such, causes increased urination, some decrease in blood pressure with related symptoms such as dizziness and falls. There may also be an increase in yeast infections and urinary tract infections and a decrease in blood sugar and increase in hematocrit. It is possible that patients and their health care providers may have been unblinded in the study due to the adverse events associated with empagliflozin, but most likely randomization minimized the effects of any unblinding. Additionally many of the adverse events associated with this product are common in diabetics such as increased urination, increased urinary tract infections.

3.4 Indication sought

Currently empagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The sponsor requests adding to the label an indication "in adults with T2DM and high cardiovascular risk to reduce the risk of all-cause mortality by reducing the incidence of cardiovascular death and to reduce the risk of cardiovascular death or hospitalization for heart failure." This will be a novel indication for a selective SGLT-2 inhibitor and if granted, it will be the first in class to receive this indication.

3.5 CEC, DMC, Steering Committee, their function, their charters

Study oversight:

A project based **Data-Monitoring Committee (DMC)** independent from the sponsor guided the clinical safety and critical endpoints and recommended to the sponsor if they should continue, stop, or modify the trial. The DMC monitored several empagliflozin trials simultaneously for safety in addition to this trial. They advised the sponsor if the trial needed to be modified or stopped due to safety issues. A **Steering Committee** was established to provide scientific leadership for the design and conduct of the trial as well as the interpretation of data. The **Clinical Event Committee (CEC)** was an independent external committee established to centrally adjudicate the events that occurred in the study in a blinded fashion under a charter. The CEC charter described how stroke, myocardial ischemia, myocardial infarction, cardiac failure, coronary revascularization, stroke, were to be evaluated as well as specific events of cancer and hepatic events. If the CEC saw problems in data collection that impaired the ability to adjudicate cases they discussed issues with the sponsor and potentially amended their charter.

CEC Charter Definitions established April 1, 2010

Transient Ischemic Attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemic without acute infarction.

Stroke

Stroke is defined as the rapid onset of new persistent neurological deficit attributed to an obstruction in cerebral blood flow and or cerebral hemorrhage with no apparent non-vascular cause such as trauma, tumor or infection. If neuroimaging studies are available they will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown based on the findings or absence of visual imaging.

- Duration of deficit is ≥ 24 hours (excluding therapeutic intervention)
- Available neuroimaging studies can support diagnosis
- Confirmation either by a neurological specialist, or brain image or lumbar puncture

Changes to the CECN Charter with target date November 11, 2011

1. Time of events added to the CEC Charter suggested to be added so that TIAs could be distinguished from stroke. This was added to the CECN case cover form, although it was not information directly collected on the Outcome form.
2. Remove hemorrhagic transformation from Hemorrhagic stroke category
3. Update ischemic stroke to include hemorrhagic transformation
4. Change how amaurosis fugax is described
5. Right facial paresis was added as a PT trigger term
6. Onset date of outcome event was agreed on by CEC when the CEC did not agree with the Investigators. If there was a disagreement, members could vote on if they agreed with the date within 5 days

Change to the CECN Charter May 22, 2014

1. Hematoma removed as a cause of stroke to conform to FDA Guidance.

3.6 Adjudication process

This is the basic path that outcome events went through from event until the final adjudication.

1. Collect AE at routine monitoring within 24 if in person and within 48 hours if over the phone. The list of triggering events or preferred terms (PT) that were used to search for stroke outcome events among study participants is found in Appendix 9.1.
2. Collect source documents included using a third party locator within days to weeks of the event. Local Clinical Monitors and CRAs put together a CEC package where an outcome determination was made. Staff was to make three documented attempts to locate the patient and arrange for follow-up. If allowed by local law, the site staff could check information in the public domain or other allowable sources to track down the patient. If the patient was unavailable it was permissible to contact the designated individual on the patient contact form including family member, neighbor, personal physician or other. Patients who discontinued were specifically instructed to contact the site in the case of a cardiovascular outcome that might qualify such as a primary outcome or key secondary outcomes such as non-fatal stroke, non-fatal MI, or hospitalization for unstable angina. Sometimes several outcome determinations were made for a single event, particularly for longer events. The CEC recommended that symptoms for any particular event be followed no longer than 14 days, but in the case of stroke could be followed for 30 days to make a determination regarding an outcome.
3. CEC reviewed the packets and determined if the outcome is death. If further source documents are needed for adjudication, they were requested.
4. If death was the outcome, then it was adjudicated to be due to CV cause or due to nonCV cause. Most deaths were assumed to be CV given the entry criteria of the study. If no determination could be made then the outcome was "not assessable." For those CV deaths attributed to stroke, the convention was that the death was counted as stroke if stroke occurred at the outset. If the death occurred in someone with a complex medical condition where it was difficult to sort out if the primary event was cardiogenic shock, worsening of heart failure or other cause, then this most likely would be counted as CV death, not assessable.
5. Non-fatal events were next adjudicated into several categories if there was adequate documentation. A non-fatal event could be designated stroke if there was evidence of a neurologic examination such as on a discharge summary, or autopsy evidence. The stroke was then characterized as ischemic, hemorrhagic or non-assessable based on the results of visual imaging or lumbar puncture. If there was no visual imaging or lumbar puncture the stroke was called "non-assessable."
6. If information was available regarding disability from the stroke, this was recorded, but not at any fixed time during the course of the illness.
7. Onset date of outcome event was determined and agreed upon by CEC when the CEC did not agree with the Investigators.

Death due to stroke

On July 4, 2013 the DMC acknowledged that there were problems determining the cause of death in patients and they made a suggestion to streamline the collection of source documents to verify the causes of death by updating the CEC Charter. One patient for example had 4 causes of death determined on different days and another had two causes of death determined on different days. The sponsor was advised to collect and bundle the causes of death to be submitted so that the endpoint committee could confirm the date of the primary event and the cause. They stated that one primary cause of death must be made based on the principal condition and not based the immediate mode of death. Due to the strict cut off there was a greater likelihood that an event leading to death more than 14 days after the initial event would be adjudicated as a non-fatal separate event and this could underestimate the

number of deaths. If this were to occur, the initial event such as a stroke and a second event such as a fatal event could be considered as two separate events if the documentation of the source documents supported this, and only the first event, the stroke would count toward the outcome. It was suggested that the DMC team reconcile the cause of death in a monthly panel meeting rather than let a longer period of time go by. The suggestions made to streamline collection and determination of cause of death required an update to the CEC Charter.

Examples of adjudications
Case 30638
A patient had a neurological event that was thought to be a stroke and was treated with tPA. The symptoms were dysarthria and quadriparesis that resolved with tPA administration. Imaging studies were reported as normal. Since event was less than 24 hours it was unclear how the condition should be arbitrated for this case as well as for future cases. It was determined that this was a stroke.

Case 2557 retinal ischemia was the PT. In order for stroke to be diagnosed there would have to be a description of hemianopia and a physical examination which was lacking. This was labeled event not assessable.

To give some idea of the scope of the CEC's task in May 2014 there were a total of 2537 events where source information was collected. Of these 2210 events were adjudicated and 1160 outcome events were confirmed; 562 were confirmed 3-point MACE outcomes and 168 were fatal.

Reviewer's Comments
In general the sponsor appears to have done a reasonable job culling through PT terms to find possible stroke events. (See Appendix 9.3) A total of 10 randomly selected CEC adjudication packets were reviewed for either fatal or non-fatal stroke and in each case the adjudication appeared reasonable and abiding by the CEC charter. (See Appendix 9.2) Despite the care that the adjudication panel took to sort through the provided source documents, much of the material was incomplete and determining outcome events was not always straightforward. If several events occurred in close proximity to each other, a judgment had to be made which was the principal condition, and this might mean that death was sometimes not counted when it followed a protracted illness such as non-fatal stroke.

4. Protocol and SAP

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

Important dates
Protocol dated: May 10, 2010
First randomization: September 15, 2010
Last randomization: April 19, 2013
Trial discontinuation April 21, 2015

Design of the Trial

The EMPA-REG OUTCOME trial was a randomized, double-blind, multinational, parallel group event driven study with 7020 treated patients divided among three treatment arms in patients with type 2 diabetes. In this cardiovascular study the impact of treatment with empagliflozin vs standard of care on centrally adjudicated major cardiovascular events was assessed. The patients all had standard care including the management of diabetes, hypertension, and high cholesterol and were randomized 1:1:1 placebo, empagliflozin 10 mg, empagliflozin 25 mg. After screening, patients underwent a 2-week, open-label, placebo run-in period before randomization. After randomization the visits were at weeks 4, 8, 12, 16, 28, 40, and 52 weeks and thereafter every 14 weeks until the end of the study. The end of study visit (EOS) was to take place within 7 days of a scheduled visit after the last dose of study medication for patients who prematurely discontinued or when the study ended. A follow-up visit was planned for 30 days after the EOT visit. This was felt to be adequate as the pharmacodynamics effect of empagliflozin only extended to about 3 days after the last dose. If patients discontinued therapy after the third visit, they were to stay in the study and have visits according to the study schedule. There visits could be over the phone rather than in person. This was also the case for those too ill to return.

Patients were randomized and stratified using a computer-generated random-sequence and interactive voice- and Web response system according to the following stratification scheme. Since the HbA1c and the eGFR were not anticipated to change rapidly the baseline values were used as covariates in the analysis model.

- HbA1c values at screening <8.5% and ≥8.5%
- Baseline BMI < 30 and ≥ 30
- eGFR for renal impairment at screening (normal: eGFR ≥90 ml/min, mild impairment: 60 ml/min ≤ eGFR ≤89 ml/min and moderate impairment: 30 ml/min ≤ eGFR ≤59 ml/min)
- Geographic region (North America, Latin America, Europe, Africa and Asia)

Reviewer's Comments

This study was crafted as a safety trial where adverse events were collected in a less strictly defined fashion compared with an efficacy trial designed to test a specific endpoint or hypothesis. No formal clinical assessments were performed at the time of the outcome event and information collected was based on what was available, rather than a prescribed set of information, such as a brain CT scan or a neurological or disability examination with specific proximity to the event in question. For an endpoint like death, this qualitative approach might be reasonable, as the endpoint is based on a definitive event; but for an endpoint like non-fatal stroke the endpoint may well be uninterpretable based on the paucity of rigorous information gathered. Regional differences in stroke recognition, concomitant drug treatment, imbalances in co-morbid conditions such as atrial fibrillation, may compromise interpretation of the stroke events. One can say little about stroke pathology, such as if the events are due to large vessel disease or lacunar strokes, given the inconsistency in visual imaging obtained. Additionally, no disability measures were obtained at the beginning and end of the trial, so it if unclear if disabling strokes were prevented or if less death from stroke resulted in more disabled patients. Death may have been underestimated in patients that had a protracted illness with an earlier qualifying event.

Study Duration:

Randomization lasted until 691 events were adjudicated. A total of 7028 patients were randomized. The sponsor anticipated that it would take 420 weeks to complete the study but in fact it was complete in 242 weeks.

Study population:

Patients were treated at 590 sites from 42 countries. Eligible patients had T2DM and had a body-mass index of < 45 and an estimated glomerular filtration rate (eGFR) of at least 30 ml/minute/1.73 m^2 of body-surface area. All had established cardiovascular disease. History of ischemic or hemorrhagic stroke, unstable angina were allowable as long as they occurred at least two months prior to screening, but were not allowable within two months prior to the signing of the informed consent. Presence of documented peripheral vascular disease, or numerous factors associated with coronary artery disease were also allowable. The protocol allowed for investigators to treat all other cardiovascular risk factors as needed according to the standard of care. Many patients were on statins, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, aspirin, beta-blockers, calcium channel blockers. Patients who were on glucose-lowering therapy, had to have been at a stable dose for at least 12 weeks before randomization with a glycated hemoglobin level of 7-10% or received no glucose-lowering agent for at least 12 weeks before randomization and had a glycated hemoglobin level between 7-9%.

Study treatment:

There were 5 treatment phases in the study, screening, placebo run-in, study treatment phase, post-treatment, post-study which was 1 day after the patient's end of trial visit. During the treatment phase subjects were allowed to go off treatment, and did, and then were allowed to re-start treatment. As stated by the sponsor, this could happen not at all or happen repeatedly over the course of the several year study as it could be anticipated that the control of blood sugar frequently requires adjustments in management. There was strict accounting of stops and starts of medication or other therapies during the trial. In the first 12 weeks of the trial background glucose-lowering drugs were to remain unchanged unless an individual had a BS > 240 mg/dL or a low BS requiring reduction in medication, but after 12 weeks other modifications were more common. For the analysis of AEs temporary discontinuations were ignored and exposures were considered to be from the first dose to the last dose.

Primary and Key Secondary Endpoint:

The primary endpoint was the time to first occurrence of the 3-point MACE, a composite of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction. The key secondary endpoint was the time to first occurrence of the 4-point MACE which included hospitalization for unstable angina pectoris to 3-point MACE.

Statistical plan:

Subjects were randomized to empagliflozin 10 mg, 25 mg, and placebo in a 1:1:1 fashion. The primary objective was to determine noninferiority for the primary outcome for pooled doses of empagliflozin compared to placebo with a margin of 1.3 for the HR. A four-step hierarchical-testing strategy for the pooled empagliflozin group versus the placebo group was performed as described in Appendix 9.4. The non-inferiority margin was based on the FDA Guidance for Industry-Diabetes Mellitus- Evaluating

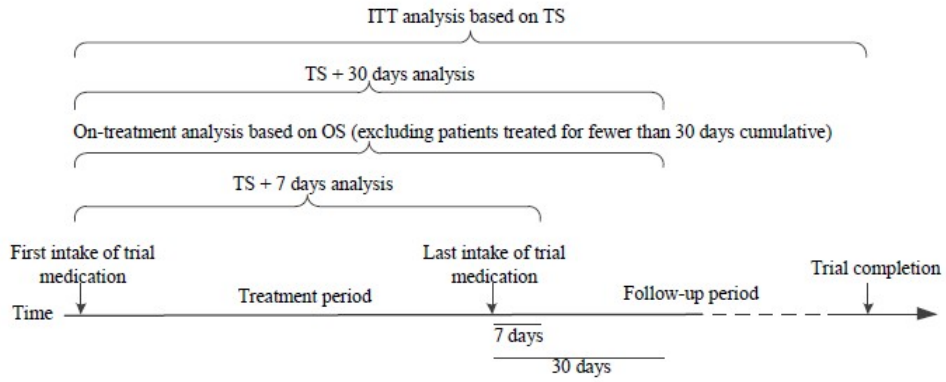
Cardiovascular Risk in New Antidiabetic Therapies to treat Type 2 Diabetes (p105 reference). If non-inferiority was established, the trial was allowed to proceed to determine superiority.

Analyses were based on a Cox proportional-hazards model, with study group, age, sex, baseline body-mass index, baseline glycated hemoglobin level, baseline eGFR, and geographic region as covariate factors. Estimates of cumulative-incidence function were corrected for death as a competing risk except for death from any cause, for which Kaplan–Meier estimates were presented. Because of the declining numbers of patients at risk, cumulative-incidence plots were truncated at 48 months.

Analysis Sets

The primary analysis was the **Treated set (TS),** those randomized subjects who received at least one dose of medication, (safety population) and not the intent to treat (ITT) population. An analysis was also performed for those **on treatment set (OS)** who received study medication for at least 30 cumulative days. The outcome event had to occur no later than the end of the trial or within 30 days of the subject's last dose, whichever occurred first. Patients who did not meet the endpoint were censored either at 30 days after their last intake of study medication or at the end of their observation. Various other sensitivity analyses were performed on the TS population. These included evaluating the TS population considering events only up to 7 days, 30 days and 90 days after treatment cessation to try and get a better look at those on treatment close to the time of the event.

Figure 1 Schematic representation of the observation time in the different analyses



Jardiance s-008 Figure 9.7.1.3:1 page 108/14090

5. Efficacy Findings related to Stroke Events

Overview

The analyses described here were performed by the sponsor unless otherwise indicated. The CEC adjudicated all events that were thought to be due to stroke and transient ischemic attack. Time to the first occurrence of such an event was needed to be used as components of the primary endpoint 3-point MACE. Patients who did not have such events were censored at the end of the study or at the end of the individual observation period. Additionally **tertiary cardiovascular endpoints** were assessed and these

were the occurrence of and time to each of several events including non-fatal stroke, TIA, all-cause mortality. Additionally, independent from the outcome of the event adjudication, all-cause mortality was assessed as the occurrence of any new onset of a fatal AE and the time to the first onset of a fatal AE.

Exposure

A total of 7020 patients were randomized and treated with medication during this trial. Of those 97.0% completed the trial even though 25.4% did prematurely discontinue treatment. Treatment discontinuation on placebo was 29.3% and on all doses of empagliflozin 23.4%. The mean length of time that patients were observed in the study was 2.91 years (SD 0.82) on placebo and 2.96 (SD 0.89) on e empagliflozin. Approximately 90% of patients were exposed to medication for at least a year and approximately 50% for three years. Exposure was based on first day of medication to last day of medication and did not include accounting for the days when treatment was held, for example for adverse events such as hypoglycemia.

Concomitant Medication

According to the sponsor patients did have many medication changes introduced after starting this trial. As outcome events took place sporadically, at random times compared to visits where concomitant medications were checked, an analysis was not performed to determine changes in the medications of those with stroke before their event. Visits could be an infrequent as every 14 weeks. Table 1 gives a summary of the medication changes that took place during the trial.

Table 1 Patients with medications 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)
Lipid-lowering drugs	719 (30.8)	673 (28.7)	693 (29.6)	1366 (29.1)
Anticoagulants	708 (30.3)	663 (28.3)	677 (28.9)	1340 (28.6)
Antidiabetic medications	736 (31.5)	484 (20.6)	429 (18.3)	913 (19.5)

Source data: [c02695839, Tables 15.1.4.3: 5 and 15.2.4.3.8: 8]

Demographic and Baseline Characteristics of the Stroke population

The subset of those who had “stroke-like events” (TIA, nonfatal stroke, and fatal stroke) was evaluated for baseline and demographic features to compare this group to the study population at large. There were 285 subjects in the TS population that had adjudicated stroke events (fatal + nonfatal). Baseline demographics were similar for many features including sex, race, history of hypertension, peripheral vascular disease. Those who had stroke events were older (mean 67.5 SD 8.8) than the average patient in the study (mean 63.1 SD 8.6), a difference of 4.2 years. There were highly significant differences between the two populations for other demographic features such as duration of diabetes beyond 10

years, history of CAD, history of stroke, and well controlled hypertension. The average stroke patient had diabetes longer than 10 years in 66.7% compared with 57.1% without stroke ($p < .0001$). They had a greater history of CAD at baseline, 91.2% in those with stroke and 75.6% in those without stroke ($p < 0.0001$). Additionally they had a greater history of prior stroke in 38.6% compared with those without stroke, 23.3% ($p < .0001$) and more well controlled hypertension was found in those without stroke 61.3% than in those with stroke, 49.8% ($p < .0001$).

Those of Hispanic ethnicity were significantly less likely to have stroke in this study. A total of 18.0% of the study population was Hispanic and yet they represented 9.5% of those who had stroke events. Those from Latin America represented 15.4% of the population in the study but only 5.9% of the events. Those in North America represented 19.9% of the treated population, but had 24.4% of the events. In Africa which only provided 4.5% of the study population there were 9.0% of the events. The numbers with stroke events in Europe and Asia appeared proportional to those enrolled in the study.

Table 2 Demographic or baseline characteristics for all patients in TS population compared with all with stroke-like event (stroke fatal, stroke nonfatal and TIA)

Demographic or baseline variable		All patients	All patients with stroke-like events
Treated patients N (%)		7020 (100%)	285 (100%)
Sex	Male	5016 (71.5%)	210 (73.7%)
	Female	2004 (28.5%)	75 (26.3%)
Race	White	5081 (72.4%)	203 (71.5%)
	Asian	1517 (21.6%)	64 (22.5%)
	Black	357 (5.1%)	15 (5.3%)
	Am Ind/Alaska	54 (0.8%)	2 (0.1%)
	Haw/Pacific	10 (0.1%)	0
Ethnicity	Not Hispanic	5747 (81.9%)	258 (90.5%)
	Hispanic	1265 (18.0%)	27 (9.5%)
Region	Europe	2885 (41.1%)	216 (42.4%)
	North America	1394 (19.9%)	124 (24.4%)
	Asia	1347 (19.2%)	93 (18.3%)
	Latin America	1081 (15.4%)	30 (5.9%)
	Africa	313 (4.5%)	46 (9.0%)
Age yrs	Mean (SD)	63.1 (8.6)	67.5 (8.8)
Time since diagnosis N (%)	≤ 1 yr	180 (2.6%)	5 (1.8%)
	<1-5 yrs	1083 (15.4%)	35 (12.3%)
	>5 -10 yrs	1746 (24.9%)	55 (19.3%)
	>10 years	4011 (57.1%)	190 (66.7%)
Hypertension hx baseline		6419 (91.4%)	277 (92.2%)
SBP < 140 and DBP < 90 mmHg		4306 (61.3%)	142 (49.8%)
CAD hx baseline		5308 (75.6%)	260 (91.2%)
Stroke hx baseline		1637 (23.3%)	110 (38.6%)
PVD hx baseline		1461 (20.8%)	63 (22.1%)
eGFR (MDRD) category n(%)			
≥90 mL/min/1.73m2		1538 (21.9%)	57 (20.0%)
60 to <90 mL/min/1.73m2		3661 (52.2%)	132 (46.2%)

45 to <60 mL/min/1.73m2	1249 (17.8%)	68 (23.9%)
30 to <45 mL/min/1.73m2	543 (7.7%)	27 (9.5%)
<30 mL/min/1.73m2	27 (0.4%)	1 (0.04%)

Sponsor's response to IR 4/1/2016 Table 1 p 5-6

The sponsor was additionally asked to provide a breakdown of those with a baseline history of atrial fibrillation, anticoagulant use, antiplatelet use and aspirin use in the study. There was an imbalance of baseline atrial fibrillation; a total of 11.6% of those assigned to empagliflozin and 5.8% of those assigned to placebo. Despite this, only 88.4% of those on empagliflozin were being treated with anticoagulants and 97.1% of those on placebo. There was also less antiplatelet agent use and aspirin use on those treated with empagliflozin compared to placebo.

Table 3 Baseline information on patients with stroke (fatal and nonfatal) in the study - TS

Demographic or baseline info	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All Empa N (%)
Total with stroke (fatal + nonfatal)	69 (100.0)	85 (100.0)	79 (100.0)	164 (100.0)
Atrial fibrillation [1]	4 (5.8)	8 (9.4)	11 (13.9)	19 (11.6)
Anticoagulant use	67 (97.1)	76 (89.4)	69 (87.3)	145 (88.4)
Antiplatelet agent use [2]	64 (92.8)	73 (85.9)	64 (81.0)	137 (83.5)
Aspirin use	57 (82.6)	70 (82.4)	60 (75.9)	130 (79.3)

[1] Based on PT Atrial fibrillation
[2] Platelet aggregation inhibitors excl. heparin

Sponsor's response to IR 04/18/2016

Reviewer's Comment
Stroke patients in the study were older, had diabetes longer, had more risk factors including prior history of CAD, stroke, atrial fibrillation, and more poorly controlled hypertension compared to the general population of the study. Despite the increased incidence of baseline medical risk factors, patients may have been undertreated, at least with anticoagulants and antiplatelet agents.

Fatal Stroke

All causes of death were adjudicated by the CEC and sorted into those that were cardiovascular which included those due to stroke. The following Table 4 describes those with adjudicated death. Of the 27 deaths due to adjudicated stroke, 11 were on placebo and 16 were on empagliflozin, without evidence of significant treatment effect (p = 0.410).

Table 4 Patients (n, %) with adjudicated death events in trial, by subgroup- TS

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
Patients, N (100%)	2333	2345	2342	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)

CSR

Jardiance CSR-S-008 Table 11.1.2.2.1:2

One question to be raised is, if some of the fatal events deemed "not assessable" were due to stroke. An information request dated April 5, 2016 addressed the issue of the "not assessable" deaths and how CV not assessable deaths were distinguished from non-CV causes of death. A further delineation was made. In the analysis of the 309 patients with CV death, a total of 129 had "other cardiovascular death- fatal event not assessable". The sponsor stated that they abided by the rules of the CEC in making determinations. In their summary five cases were deemed fatal and due to other CV causes. These included patients that died after surgery such as CABG, from digoxin toxicity for arrhythmia, and pulmonary embolism. Those 124 who had CV death not assessable tended to be those who died out of the hospital without hospital records limiting the availability of ECG, echocardiogram and other testing. Those with a PT event called fatal stroke may have had only a death certificate without further documentation. Table 5 shows the reason for non-assessable determinations for the study. According to the sponsor's analysis eight of the CV deaths not assessable may have been due to stroke but lacked sufficient documentation (see Table 6). As noted by Warlow, "death certificate information is easily available, but not very accurate …. and cannot reliably distinguish even the most basic pathological types of stroke (eg. ischaemic stroke or innercranial hemorrhage). …But, at least mortality gives some idea of the (stroke) burden."

Reviewer's Comment – In retrospect, reduction in all deaths in those at high cardiovascular risk would have been easier to validate as a primary endpoint of the study. Assigning causation of death in very sick patients where records are compiled and analyzed well after the event by third-hand observers has intrinsic problems. It must be remembered that the patients who entered this study were at high-risk for vascular events, and without other obvious health issues, a vascular cause of death is most likely, though not necessarily well documented.

Table 5 Reasons for non-assessable determinations of death

	placebo (n=53)	Empa 10mg (n=34)	Empa 25mg (n=37)
i. Found dead in bed/home, informed by family.	10	6	18
ii. Death certificate or proof of death available	19	20	11
iii. Autopsy	0	0	0
iv. Limited or no medical records, but suggestive history	29	14	12

Sponsor's response to IR 4/5/2016 Table 2 page 3/48

Table 6 Not assessable and assessable CV deaths thought to be due to stroke

Cerebrovascular accident	Placebo n	Empa 10 mg n	Empa 25 mg n	Empa all n
Assessable events	11	9	7	16
Not assessable events	3	3	2	5
Total possible fatal stroke events	14	12	9	21

Sponsor's response to IR 4/5/2016 summary related to stroke from Listing 20.2.3

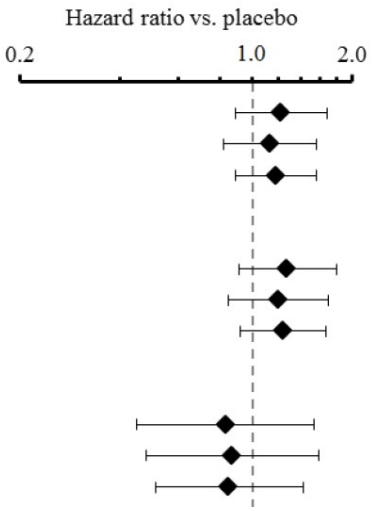
Reviewer's Comment
According to the Cardiovascular Endpoints Data Standards, "any noise introduced by slight misclassifications of events will not bias the results towards one arm or another, but may mask a true difference in effectiveness or safety." The fact that about a third of the deaths due to stroke could not be definitely attributed to stroke, but likely were strokes, would not have favored drug over placebo, but could certainly underestimate the number of fatal strokes that took place in this study.

Nonfatal stroke

Despite the significant effects seen for CV death and all-cause mortality, non-fatal adjudicated stroke was not reduced for those treated with empagliflozin nor were all adjudicated strokes, fatal and non-fatal as seen in Table 7. The HR for non-fatal stroke was 1.24 (95% CI 0.92-1.67) and the HR for combined fatal and non-fatal stroke was 1.18 (95% CI 0.89-1.56) in the TS population. Though the incidence rates and hazard ratios were increased, there was not a statistically significant difference between treatment and placebo. The sponsor also did sensitivity analyses that confirmed the main analysis in the TS population up to treatment stop + 7 days, + 30 days, + 90 days and those in the OS population + 30 days. TTS +7 day sensitivity analysis is the analysis that most reflects those that were still on treatment at the time of the outcome event. All of these sensitivity analyses showed no significant difference between empagliflozin and placebo, and the hazard ratio shifted closer to 1 in these analyses when compared with the main TS analysis (see Table 8)

Table 7 Summary of cerebrovascular disease-related endpoints TS population

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
Stroke (fatal/non-fatal)						
Placebo	69 (3.0)	10.5	--	--	--	--
Empa 10 mg	85 (3.6)	12.7	1.22	0.89	1.68	0.2119
Empa 25 mg	79 (3.4)	11.8	1.13	0.82	1.56	0.4594
All empa	164 (3.5)	12.3	1.18	0.89	1.56	0.2567
Non-fatal stroke						
Placebo	60 (2.6)	9.1	--	--	--	--
Empa 10 mg	77 (3.3)	11.5	1.27	0.91	1.79	0.1593
Empa 25 mg	73 (3.1)	10.9	1.20	0.85	1.69	0.2954
All empa	150 (3.2)	11.2	1.24	0.92	1.67	0.1638
Transient ischaemic attack (TIA)						
Placebo	23 (1.0)	3.5	--	--	--	--
Empa 10 mg	19 (0.8)	2.8	0.83	0.45	1.53	0.5603
Empa 25 mg	20 (0.9)	2.9	0.87	0.48	1.58	0.6357
All empa	39 (0.8)	2.9	0.85	0.51	1.42	0.5368



Jardiance s-008 Clinical overview Table 4.2.5:1 p 20/53

Table 8 Summary of stroke events in TS population –up to treatment stop + 7 days

Treatment	Number treated	Patients with event	Incidence	Comparison with placebo		p value
		N (%)	/1000 pt-yr	HR	95% CI	
		Stroke (fatal/non-fatal) – up to treatment stop + 7 days				
Placebo	2333	62 (2.7%)	10.8			
Empa 10 mg	2345	72 (3.1%)	12.1	1.14	0.81, 1.60	
Empa 25 mg	2342	67 (2.9%)	11.2	1.05	0.75, 1.49	
All empa	4687	139 (3.0%)	11.7	1.09	0.81, 1.48	0.554
		Non-fatal stroke – up to treatment stop + 7 days				
Placebo	2333	55 (2.4%)	9.6			
Empa 10 mg	2345	67 (2.9%)	11.3	1.19	0.83, 1.70	
Empa 25 mg	2342	63 (2.7%)	10.5	1.11	0.78, 1.60	
All empa	4687	130 (2.8%)	10.9	1.15	0.84, 1.58	0.380

Jardiance S-008 CSR From sponsor's analysis provided in Table 11.1.2.4.1:1 page 182/14090

Classification of stroke, disability from stroke, recurrence of stroke after adjudicated event

Although the sponsor attempted to obtain information about stroke type and disability as a result of stroke, it was not a requirement for this study, it was inconsistently collected, and hence was not further evaluated by this reviewer. It is noted that initially those with hematoma were adjudicated as having had a stroke, but later when the definition of stroke was refined to conform to the FDA Guidance, hematoma was excluded. This led to 13 cases being dismissed as previously adjudicated non-fatal strokes and attributed instead to an adverse event of traumatic hematoma not contributing to an outcome event.

Since there was a trend toward an increase in strokes in patients in the trial on treatment compared with those on placebo, once they had their first adjudicated event, how likely was it for study participants to have a second stroke event, or other vascular event, for that matter? The sponsor did evaluate those who may have had further strokes after a first adjudicated event.

Table 9 Frequency n (%) of patients with number of adjudicated stroke events that had further stroke events- TS

	Placebo [N (%)]	Empa 10mg [N (%)]	Empa 25mg [N (%)]	All Empa [N (%)]
Number of patients in analysis set	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)
1 event	61 (2.6)	79 (3.4)	72 (3.1)	151 (3.2)
Non-fatal stroke	52 (2.2)	71 (3.0)	66 (2.8)	137 (2.9)
Fatal stroke	9 (0.4)	8 (0.3)	6 (0.3)	14 (0.3)
2 events	6 (0.3)	5 (0.2)	6 (0.3)	11 (0.2)
Non-fatal stroke, Non-fatal stroke	5 (0.2)	4 (0.2)	5 (0.2)	9 (0.2)
Non-fatal stroke, Fatal stroke	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
3 events	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
Non-fatal stroke, Non-fatal stroke, Non-fatal stroke	1 (<0.1)	1 (<0.1)	1 (<0.1)	2 (<0.1)
4 events	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Non-fatal stroke, Non-fatal stroke, Non-fatal stroke, Fatal stroke	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Jardiance s-008 CSR Table 8.2.5 Statistical analysis section 16.1.9.2 p 142628

Reviewer's Comment

Although the data suggests that further stroke events that were captured when subjects remained in the study after a primary outcome event were no more likely on drug than on placebo as seen in Table 8. It is noted that all events after the first event were not adjudicated, but this is still reassuring to see.

Relationship of 1st stroke event to initiation of empagliflozin

A total of 1.1% of patients on either empagliflozin or placebo had stroke events, either fatal or non-fatal in the first year of use of the product as seen in Table 10. By approximately 600 days the stroke events in those on empagliflozin were greater than those on placebo.

Table 10 Cox regression for time to first non-fatal stroke, empagliflozin 10 mg, empagliflozin 25 mg vs. placebo in TS

	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	2333	2345	2342
Number of analysed patients	2333	2345	2342
Number of patients with event [N(%)]	60 (2.6)	77 (3.3)	73 (3.1)
Time at risk for event [years]	6580.4	6669.1	6711.5
Incidence rate [patients with events per 1000 years at risk]	9.1	11.5	10.9
Comparison vs Placebo*			
Hazard ratio		1.27	1.20
95% confidence interval		(0.91,1.79)	(0.85,1.69)
p-value		0.1593	0.2954
Time to event [days]**			
2.5% quantile	883	704	855
5.0% quantile	NC.	NC.	NC.
7.5% quantile	NC.	NC.	NC.
10.0% quantile	NC.	NC.	NC.
Patients with events [%]**			
1 year	1.1	1.1	1.1
2 years	2.0	2.6	2.1
3 years	2.8	3.5	3.4
4 years	2.9	3.9	3.8

* Based on a Cox regression model with terms for age (p=0.0525), sex (p=0.5213), basel. BMI cat. (p=0.0900), basel. HbA1c cat. (p=0.0832), basel. eGFR cat. (p=0.1003), geographical region (p=0.0101) and treatment (p=0.3531).
** Based on Kaplan-Meier estimates.
NC. = Not calculated.

Jardiance s-008 CSR Table 15.2.4.1.3:2 p 1448/14090

The sponsor was asked to determine the frequency of non-fatal stroke in 30 day time intervals for the first six months of the trial. As seen in Table 11, the incidence of non-fatal stroke was greater in those on empagliflozin 10 mg or 25 mg compared to placebo over the first 90 days of treatment. Clinicians were encouraged not to change other medications during the first 12 weeks of the trial, and this early in the trial most patients would still be on study medication. An imbalance in events early on in the first 90 days was seen for those on empagliflozin compared to placebo.

Table 11 Frequency [n (%)] of non-fatal stroke by time interval- TS

	Placebo	Empa 10mg	Empa 25mg	All Empa
Number of patients in analysis set	2333	2345	2342	4687
Day >0 to 30 days				
Number of patients at risk*, N(%)	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)
Number of patients with event, N(%)	0	2 (0.1)	1 (<0.1)	3 (0.1)
Hazard rate**	0	0.000028	0.000014	0.000021
>30 days to 60 days				
Number of patients at risk*, N(%)	2329 (100.0)	2340 (100.0)	2339 (100.0)	4679 (100.0)
Number of patients with event, N(%)	1 (<0.1)	3 (0.1)	4 (0.2)	7 (0.1)
Hazard rate**	0.000014	0.000043	0.000057	0.000050
>60 days to 90 days				
Number of patients at risk*, N(%)	2323 (100.0)	2329 (100.0)	2331 (100.0)	4660 (100.0)
Number of patients with event, N(%)	2 (0.1)	4 (0.2)	1 (<0.1)	5 (0.1)
Hazard rate**	0.000029	0.000057	0.000014	0.000036
>90 days to 120 days				
Number of patients at risk*, N(%)	2309 (100.0)	2320 (100.0)	2325 (100.0)	4645 (100.0)
Number of patients with event, N(%)	4 (0.2)	2 (0.1)	2 (0.1)	4 (0.1)
Hazard rate**	0.000058	0.000029	0.000029	0.000029
>120 days to 180 days				
Number of patients at risk*, N(%)	2296 (100.0)	2311 (100.0)	2315 (100.0)	4626 (100.0)
Number of patients with event, N(%)	9 (0.4)	1 (<0.1)	5 (0.2)	6 (0.1)
Hazard rate**	0.000066	7.224 x10^-6	0.000036	0.000022

	Placebo	Empa 10mg	Empa 25mg	All Empa
>180 days to 360 days				
Number of patients at risk*, N(%)	2278 (100.0)	2303 (100.0)	2303 (100.0)	4606 (100.0)
Number of patients with event, N(%)	13 (0.6)	14 (0.6)	16 (0.7)	30 (0.7)
Hazard rate**	0.000032	0.000034	0.000039	0.000037

Sponsor's response to IR 4/18/2016

Dose Effect

As seen in Table 10 there were more strokes that occurred on empagliflozin 10 mg than on the 25 mg dose, but the difference was not statistically significant. The incidence rate/1000 years was 11.5 for empagliflozin 10 mg (p= 0.1593) and the incidence rate/1000 years was 10.9 for empagliflozin 25 mg dose (p = 0.2954). Additionally, as seen in Table 4, the death rate from stroke was marginally increased on the 10 mg dose (9, 0.4%) compared with the higher dose (7, 0.3%), but not significantly. Figure 2 demonstrates how similar time to first event was for the 10 mg and 25 mg doses of empagliflozin compared to placebo.

Figure 2 Kaplan-Meier estimate of the time to first non-fatal stroke, empagliflozin 10 mg, empagliflozin 25 mg, and placebo –TS

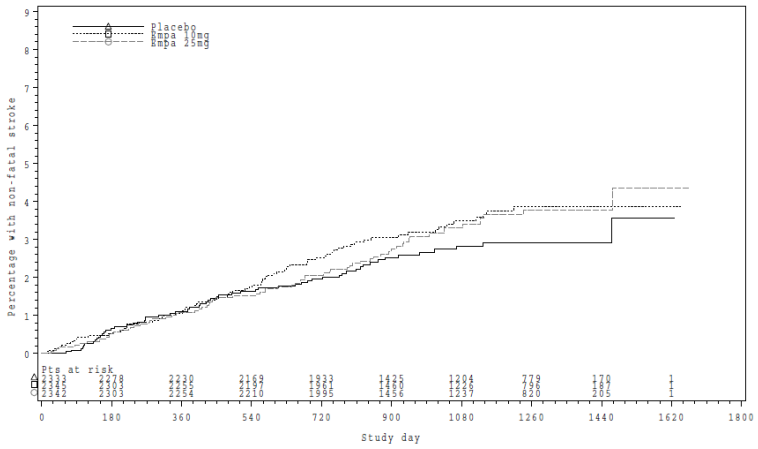


Figure 15.2.4.1.3: 2 Kaplan-Meier est. of time to first non-fat. stroke, indiv. empa doses vs placebo - treated set

Jardiance s-008 CSR Figure 15.2.4.1.3:2

Subpopulations

Subgroup analyses were assessed to see if there were any outliers or groups driving the study results that might shed light on treatment response. It must be noted that the subgroup analyses were not adjusted for multiplicity and the study was not powered to assess subgroup response for stroke- fatal and nonfatal. The subgroup analyses by region, sex, race, ethnicity, baseline HgA1c level, time since T2DM diagnosis were reviewed for those with first stroke. Most of the analyses were consistent with the primary analysis and are not discussed here; further discussion will be confined to those analyses that had findings inconsistent with the primary analysis.

The two demographic factors that appeared to interact with treatment effect according to the sponsor, were time since diagnosis of T2DM > 5-10 years (HR 1.26, 95% CI 0.66, 2.40, p = 0.4788) which was not statistically significant and baseline HgA1c ≥ 8.5 (HR 2.13, 95% CI 1.23, 3.74, p = 0.0084) which was statistically significant.

A further subgroup analysis was done for the 5 regions that participated in the study. Data from Africa could not be analyzed as the sample size and number of events was too small. Results from North America (HR 0.82, 95% CI 0.46, 1.45, p = 0.49) and Asia (HR of 1.08, 95% CI 0.60, 1.95, p = 0.798) showed

little difference in treatment response to empagliflozin or placebo. Those from Latin America had less chance of having a stroke on empagliflozin (HR 0.44, 95% CI 0.18, 1.07, p = 0.07), but they were only 15.4% of the population. Europe was notable, however, as 41.1% of patients in the study were from Europe and the HR was 2.04, 95% CI 1.26, 3.29, p = 0.0035 as demonstrated in Table 12 and Figure 3.

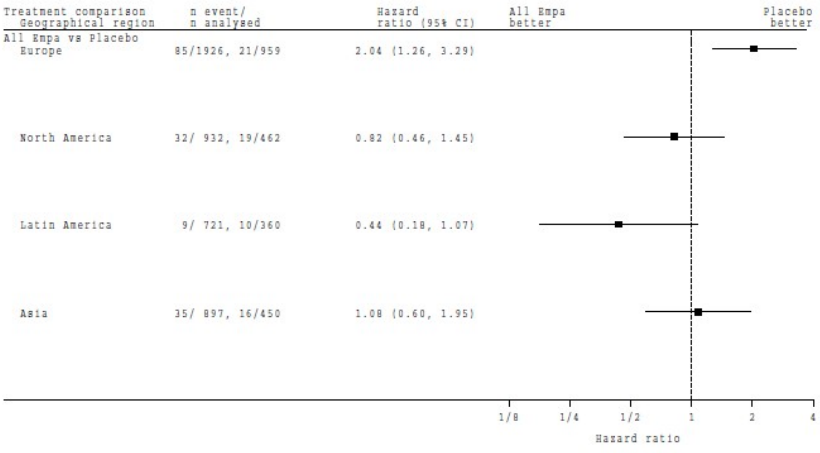
Table 12 Cox regression for time to first stroke by geographic region pooled empagliflozin vs placebo - TS

Subgroup Description	Placebo	All Empa
Geographical region: Europe		
Number of patients in analysis set	959	1926
Number of analysed patients	959	1926
Number of patients with event [N(%)]	21 (2.2)	85 (4.4)
Incidence rate [patients with events per 1000 years at risk]	7.8	15.7
Comparison vs Placebo*		
Hazard ratio		2.04
95% confidence interval		(1.26,3.29)
p-value		0.0035
Geographical region: North America		
Number of patients in analysis set	462	932
Number of analysed patients	462	932
Number of patients with event [N(%)]	19 (4.1)	32 (3.4)
Incidence rate [patients with events per 1000 years at risk]	15.2	12.3
Comparison vs Placebo*		
Hazard ratio		0.82
95% confidence interval		(0.46,1.45)
p-value		0.4940
Geographical region: Latin America		
Number of patients in analysis set	360	721
Number of analysed patients	360	721
Number of patients with event [N(%)]	10 (2.8)	9 (1.2)
Incidence rate [patients with events per 1000 years at risk]	9.9	4.4
Comparison vs Placebo*		
Hazard ratio		0.44
95% confidence interval		(0.18,1.07)
p-value		0.0704

* Based on a Cox regression model with terms for age (p=0.0106), sex (p=0.6103), basel. BMI cat. (p=0.0185), basel. HbA1c cat. (p=0.3051), basel. eGFR cat. (p=0.2245), treatment (p=0.7193), geographical region (p=0.0482) and treatment by geographical region interaction (p=0.0098).
313 patients were excluded as they were in groups with <14 events.

Jardiance -008 CSR Appendix 16.1.9.2 page 16,250/42,035 and Table 7.4.1.24.6.3 of IR April 1, 2016

Figure 3 Forest plot of the Cox regression HR (95% CI) of time to first stroke in geographic region pooled empagliflozin vs. placebo in the TS



Sponsor's response to IR dated April 1, 2016 Figure 7.4.1.24.6.1 page 48/143

Reviewer's Comment
It is reassuring that world-wide, with the exception of Europe, use of empagliflozin was not associated with an increased incidence of stroke. The disproportionate number of strokes on empagliflozin compared to placebo appears to be driven by the statistically significant results from European subjects. It is unclear what factors might be operative with European subjects that might have been related to the increased incidence there. It might be that the baseline characteristics of the patients were not well matched in Europe. It may be that patients and their physicians were unblinded by the side effects of the product, and this lead to treatment differences. The sponsor reported that fewer medications were prescribed after study entry in those being treated with empagliflozin and this may have had a more deleterious effect on those suspected to be on treatment.
It might be worthwhile to check to see if Europeans were outliers for other outcome events or adverse events. Having a better understanding of why stroke events were considerably higher in Europe could possibly shed some light on labeling recommendations. Although subgroup analyses are usually post-hoc and need to be interpreted with caution as studies are not usually powered to reliably assess the subgroup, in this case the study population was large and the subgroup represented 41.1% of the population, and the findings appear to have impacted the nonfatal stroke outcome.

6. Consultant Questions

In the EMPA-REG Outcome trial, the nonfatal stroke component of the composite primary endpoint of 3-point MACE has a hazard ratio (HR) of 1.24. Is this a chance finding?

Yes, the increase in the non-fatal stroke rate observed in those who received either dose of empagliflozin compared to those who received placebo is likely due to chance and not to treatment with empagliflozin.

In this study, empagliflozin was found to have a significant effect over placebo for the primary endpoint, the 3-point MACE, where the HR was 0.86 (95% CI 0.74, 0.99, p = 0.0382) for the pooled empagliflozin compared with placebo. Additionally, as reported by the sponsor, there were significant findings for two out of the three measures that comprised the primary composite endpoint namely the reduction in all CV death (including fatal stroke) and the reduction in non-fatal myocardial infarction, but not for non-fatal stroke. Non-fatal strokes appeared to be increased in those on each dose of empagliflozin as well as the pooled doses of empagliflozin where the HR was 1.24 (95% CI 0.92, 1.67, 0.1638, p = 0.1638), a trend but not a statistically significant finding.

Unfortunately, the design of the study does not permit one to have confidence in the nonfatal stroke outcome. As pointed out, the population from Europe who constituted more than 40% of the study population appeared to be having strokes driving the event rate. When the European patients are excluded from the analysis the HR approaches 1, that is, treatment with empagliflozin and placebo are no different with regard to stroke. Additionally there may have been substantial differences in disease management for those on empagliflozin compared to placebo perhaps as a result of unbinding due to side effects. Detailed records were not kept for medication changes, but the sponsor noted that those on empagliflozin tended to have less new medications introduced after starting the study (as seen in Table 1) more than those on placebo and this may have had a negative impact. Additionally, vital signs and laboratory tests were done at visits not necessarily in close proximity to stroke events. Drug exposure to the study medication, empagliflozin also may have been different, as intermittent interruptions in treatment were not accounted for and may have been unbalanced between treatment groups. Small interruptions in therapy were not thought to be infrequent due to possible episodes of hypoglycemia, and these episodes may have been more frequent on empagliflozin.

One other factor to consider is that patients did not have a baseline neurologic examination or brain CT nor were they chronically followed neurologically unless they had an overt event. It maybe that due to the practice of medicine throughout the world, small stroke events may not have come to recognition or events considered TIAs may have actually been strokes. While the study may have been reasonably designed to capture disabling or long-lasting strokes, it may not have captured smaller events such as lacunar events picked up only radiographically (similar to silent MIs). While decreased recognition of smaller less disabling events events may not have favored either arm of the trial, it may have led to a misestimate of nonfatal stroke.

Finally, after an outcome event, further strokes did occur and these were not adjudicated events, nor do they enter into the primary time to event analysis. That means for example that someone who had a myocardial infarction was censored and the stroke that they had that followed would not be counted toward the primary endpoint. A subsequent stroke would only be considered an adverse event, perhaps also leading to an underestimation of the true non-fatal stroke rate.

The results might be more meaningful from a stroke perspective if disability measurements had been obtained at baseline and at the end of the study. It would be important to know that in addition to a reduction in fatal strokes that there was not an increase in those with disabling nonfatal strokes compared with placebo. In summary, if there was a relationship between the use of empagliflozin and the severity of strokes that occurred, or the type of stroke that occurred, the design of the study does not easily permit one to sort this out.

Is the temporal relationship of drug initiation to the stroke of importance?

No. There was a small increase in both nonfatal and fatal strokes in the first 90 days of therapy on empagliflozin compared to placebo, but the numbers are few overall and represent a small fraction of those with stroke as an outcome event in the study.

At 90 days, early in the trial, most patients were still on study medication and had not yet had many of their other drugs adjusted, as clinicians had been advised not to change other medications for the first 12 weeks. An increase in events could have been related to treatment with empagliflozin. By the end of the first year strokes were more balanced between those on drug and those on placebo with an incidence of 1.1% of the study population. By approximately 600 days, those on empagliflozin appeared to have more strokes then those on placebo. One would not have expected many strokes in the first 90 days of the study, and there were very few on placebo.

Does the dose response shed any light on the occurrence of stroke?

Although there is a very modest trend of more strokes on empagliflozin 10 mg than on 25 mg, there is no statistically significant difference between the two doses of empagliflozin. The lack of significant and consistent dose response, either positive or negative suggests that the drug has no significant effect on stroke incidence.

Is the type or nature of stroke events consistent with a known drug effect such as hypotension or hemo-concentration?

Neither hypotension nor hemoconcentration are known common risk factors for stroke, particularly if they are mild in nature and not acute.

Citations in the literature typically refer to more extreme cases and not to the modest changes in BP and hematocrit seen with this drug. According to the drug label for empagliflozin, the drug, an osmotic diuretic, may cause volume depletion, as well as other adverse reactions related to volume depletion, such as decreased systolic blood pressure, dehydration, hypotension, hypovolemia, orthostasis hypotension and syncope. According to an sNDA cross-disciplinary team leader review dated August 3, 2014 by Dr. William Chong, age over 65 and diuretic at baseline were both risk factors that increased volume depletion. Mean blood pressure changes were only noted to be < 5 mmHg. Mild changes in hematocrit were also noted and appeared to be dose dependent.

Hypotension, especially orthostatic hypotension was one of many risk factors addressed in a meta-analysis published by Xin. In this paper eight published articles were reviewed that consisting of 64,782 participants with a mean follow-up of 15.2 years where 3657 stroke events occurred. In this meta-analysis there was an increased risk for stroke with a HR= 1.19, 95% CI 1.08-1.30 in those with orthostatic hypotension independent of conventional risk factors, but the orthostatic blood pressure changes were great, a reduction in SBP of ≥ 20 mm Hg or a reduction in DBP of ≥ 10 mm Hg within 3 minutes from supine to standing. In the present study orthostasis was not routinely evaluated, nor is it possible to determine if this may have been disproportionately present in those patients who presented with early stroke as orthostatic measurements were not obtained.

With rare exception, hypotension without orthostasis is not reported as a risk factor for stroke; instead hypertension has been identified as a significant cause of stroke, and control of BP is usually a goal of care of those at risk for stroke. In the recent ACCORD study the effects of intensive blood-pressure control in those with T2DM was assessed in 4733 patients. Patients were randomly assigned to intensive blood pressure treatment with a goal of targeting a SBP of less than 140 mm Hg or standard therapy aiming for a SBP of less than 140 mm Hg. The primary outcome was the 3-point MACE and follow-up was for a year. After a year, the mean SPB was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard-therapy group. One of the prespecified secondary outcomes in this study was stroke. Although the primary endpoint, 3-point MACE, was not significantly reduced with intensive therapy, the annual rate of stroke was reduced with intensive therapy, 0.32% in the intensive therapy group and 0.53% in the standard-therapy group with a HR of 0.59 (95% CI, 0.39-0.89, p = 0.01) (ACCORD study group). This post-hoc analysis suggests that stroke incidence is lessened by better control of blood pressure and not increased. In another study, a meta-analysis of the effects of intensive blood-pressure lowering on cardiovascular outcomes (Xie) in a review of 14 trials with a total of 43,483 participants, there were a total of 1099 stroke events and more intensive blood pressure lowering regimens were associated with a 22% reduction in stroke (95% CI 10-32). Hence, in general, lowering the blood pressure has a beneficial effect on reducing stroke, not causing stroke.

Pertaining to hemoconcentration, this also would be a most uncommon cause of stroke. Mild increases in hematocrit were noted with this drug and appeared to be dose dependent, but lab work was not done at the time of stroke events. Hemoglobin levels and risk of stroke was assessed many years ago in the Framingham Study where they prospectively evaluated a population of 5185. Of those, there were 152 documented strokes over 16 years. They found that although an elevated hemoglobin level appeared to be associated with increased stroke risk when adjustments for multiplicity were made (smoking and hypertension); the effect of increased hemoglobin was modest and not statistically significant. In the Framingham study elevated hematocrits were levels over 15 mg in men and 14 mg in

women. (Kannel) Others have described increase risk of stroke in those with polycythemia vera, but those who have this condition may have a number of pathophysiological processes leading to a propensity for thrombosis and hypertension such as increased erythropoietin production by the ischemic kidney. Yet others have described sustained hemoconcentration in patients with chronic atrial fibrillation (Yamada) putting them at greater risk for stroke. While all of these mechanisms are intriguing, they are unlikely to play a significant role here. A meaningful assessment of the effect of hemoconcentration cannot be made as the risk factors for stroke are typically multifactorial and there are too many confounding factors in this study to isolate hemoconcentration as playing a significant role.

8. References

ACCORD study group, Effects of Intensive Blood-Pressure control in T2DM. *NEJM*, 2010; 362: 1575-1585.

Al-Rubeaan, KA, Al-Hussain, F, et al Ischemic Stroke and its risk factors in a Registry-based large cross-sectional diabetic cohort in a country facing a diabetes epidemic. *Journal of Diabetes Research*, 2016; Jan: 1-9.

Caveney, E A Review of FDA Guidance Understanding the FDA Guidance on assessing cardiovascular risks for new antidiabetic therapies www.quintiles.com

Ghosh, RK, Bandyopadhyay, D et al Cardiovascular outcomes of sodium-glucose co-transporter 2 inhibitors: A comprehensive review of clinical and preclinical studies. *International Journal of Cardiology* 2016; 212: 29-36.

Guidance for Industry Diabetes Mellitus – Evaluating Cardiovscular Risk in New Antidiabetic Therapies to treat Type 2 Diabetes. December, 2008 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf

Hicks, KA, Hung, J et al Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials, Draft Definitions for CDISC. August 20, 2014.

Lai, CL, Kuo, RNC, et al Risk of Ischemic Stroke during the initiation period of α blocker therapy among in older men. *CMAJ*, March 1, 2016: 255-260.

Kannel, WB Gordon, T, Wolf, P, and P McNamara Hemoglobin and the risk of cerebral infarction: The Framingham Study. *Stroke* 1972; 3: 409-420.

Kalra, S One Small Step for Empagliflozin, One Giant Leap for Diabetology *Diabetes Therapy*,.2015; 6: 405-409.

O'Donnell, MJ, Xavier, D et al Risk factors for ischemic and intracerebral hemorrhage stroke in 22 countries (the INTERSTROKE study): a case-control study. *The Lancet* 2010; 376: 112-123.

Warlow, CP, Epidemiology of Stroke. *Stroke* 1998; 352: 1-4.

Whalen, K, Miller, S, St. Onge, E The Role of Sodium-Glucose Co-Transporter 2 Inhibitors in the Treatment of Type 2 *Diabetes Clinical Therapeutics*. 2015; 37: 1150-1166.

Wolf PA, Abbott RD, Kannel WB Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991; 22: 983-8.

Xie, X, Atkins, E et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systemic review and meta-analysis. *The Lancet*, 2016; 387: 435-443.

Yamada, H et al Sustained Hemoconcentration in patients with chronic atrial fibrillation, a potential risk for stroke and thromboembolic complications A Retrospective Study *Japanese Heart Journal.* 1998; Nov: 715-720.

Yamaji T, IShibashi M, Nakaoka H, et al Possible role for atrial natriuretic peptide in polyuria associated with paroxysmal atrial arrhythmias. *Lancet* 1985; 1: 1211.

Zinman, B et al Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovascular Diabetology* 2014; 13:102: 1-8.

Zinman, B et al Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *NEJM* 2015; 373: 2117-28.

9. Appendices

9.1 List of Triggering Events (SMQ Cerebrovascular Disorder) used to look for stroke events

Agnosia	Amaurosis fugax
Angiogram cerebral abnormal	Aphasia
Balint's syndrome	Basal ganglia haemorrhage
Basal ganglia infarction	Basal ganglia stroke
Basilar artery occlusion	Basilar artery stenosis
Basilar artery thrombosis	Blood brain barrier defect
Brachiocephalic artery occlusion	Brain stem haemorrhage
Brain stem infarction	Brain stem ischaemia
Brain stem microhaemorrhage	Brain stem stroke
Brain stem thrombosis	Capsular warning syndrome
Carotid aneurysm rupture	Carotid angioplasty
Carotid arterial embolus	Carotid arteriosclerosis
Carotid artery aneurysm	Carotid artery bypass
Carotid artery disease	Carotid artery dissection
Carotid artery insufficiency	Carotid artery occlusion
Carotid artery stenosis	Carotid artery stent insertion
Carotid artery stent removal	Carotid artery thrombosis
Carotid endarterectomy	Central pain syndrome
Cerebellar artery occlusion	Cerebellar artery thrombosis
Cerebellar embolism	Cerebellar haematoma
Cerebellar haemorrhage	Cerebellar infarction
Cerebellar ischaemia	Cerebellar microhaemorrhage
Cerebral amyloid angiopathy	Cerebral aneurysm ruptured syphilitic
Cerebral arteriosclerosis	Cerebral arteriovenous malformation haemorrhagic
Cerebral arteritis	Cerebral artery embolism
Cerebral artery occlusion	Cerebral artery stenosis
Cerebral artery thrombosis	Cerebral circulatory failure
Cerebral gas embolism	Cerebral haematoma
Cerebral haemorrhage	Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal	Cerebral haemosiderin deposition
Cerebral hypoperfusion	Cerebral infarction
Cerebral infarction foetal	Cerebral ischaemia
Cerebral microangiopathy	Cerebral microhaemorrhage
Cerebral revascularisation	Cerebral septic infarct
Cerebral small vessel ischaemic disease	Cerebral thrombosis
Cerebral vasoconstriction	Cerebral venous thrombosis
Cerebrovascular accident	Cerebrovascular accident prophylaxis
Cerebrovascular arteriovenous malformation	Cerebrovascular disorder
Cerebrovascular insufficiency	Cerebrovascular spasm
Cerebrovascular stenosis	Charcot-Bouchard microaneurysms
Congenital cerebrovascular anomaly	Congenital hemiparesis

CSF bilirubin positive	Diplegia
Dural fistula	Dysarthria
Embolic cerebral infarction	Embolic stroke
Foetal cerebrovascular disorder	Haemorrhage intracranial
Haemorrhagic cerebral infarction	Haemorrhagic stroke
Haemorrhagic transformation stroke	Hemiparesis
Hemiplegia	Inner ear infarction
Internal carotid artery kinking	Intra-cerebral aneurysm operation
Intracerebral haematoma evacuation	Intracranial aneurysm
Intracranial haematoma	Intracranial venous sinus thrombosis
Intraventricular haemorrhage	Intraventricular haemorrhage neonatal
Ischaemic cerebral infarction	Ischaemic stroke
Lacunar infarction	Lateral medullary syndrome
Meningorrhagia	Millard-Gubler syndrome
Monoparesis	Monoplegia
Moyamoya disease	Paralysis
Paralysis flaccid	Paraparesis
Paraplegia	Paresis
Post procedural stroke	Post stroke depression
Precerebral artery occlusion	Putamen haemorrhage
Quadriparesis	Quadriplegia
Red blood cells CSF positive	Reversible ischaemic neurological deficit
Ruptured cerebral aneurysm	Sneddon's syndrome
Spastic paralysis	Spastic paraplegia
Spinal artery embolism	Spinal artery thrombosis
Spinal cord haemorrhage	Spinal epidural haemorrhage
Spinal haematoma	Spinal vascular disorder
Spinal vessel congenital anomaly	Stroke in evolution
Subarachnoid haemorrhage	Subarachnoid haemorrhage neonatal
Subdural haemorrhage	Subdural haemorrhage neonatal
Superficial siderosis of central nervous system	Superior sagittal sinus thrombosis
Susac's syndrome	Thalamic infarction
Thalamus haemorrhage	Thrombotic cerebral infarction
Thrombotic stroke	Transient ischaemic attack
Transverse sinus thrombosis	Vascular encephalopathy
Vasculitis cerebral	Vertebral artery dissection
Vertebral artery occlusion	Vertebral artery stenosis
Vertebral artery thrombosis	Vertebrobasilar dolichoectasia
Vertebrobasilar insufficiency	Visual midline shift syndrome
Wallenberg syndrome	
MedDRA 14.1	

VIIth nerve paralysis	
MedDRA 14.1	

9.2 Ten randomly selected Neurology CEC packets reviewed to overview adjudication process

Patient number	Preferred Term	Determination	Determination
50065	Left MCA Stroke with shower of emboli	Non-fatal stroke Ischemic stroke	CT L ACA distribution hypodensity suggestive of infarction and MRI multiple small white matter lesions with enhancement suggest embolic source, narrative provided, AE event form
51410	Ischemic Stroke	Non-fatal stroke Ischemic stroke	CT without hemorrhage, Discharge summary
51465	Stroke	Non-fatal stroke Subacute ischemic stroke	Discharge summary CT ischemic stroke
52399	Stroke, ischemic	Non-fatal stroke Ischemic infarction	Neurologic exam in stroke unit, CT described in hospital discharge summary, two lesions, looked old
53113	Ischemic Stroke	Non-fatal stroke Not assessable	Discharge summary which stated patient had a right side hemiparesis, no CT available
53136	Infarction of brain with hemiparesis	Non-fatal stroke Ischemic infarction	Discharge summary stated cerebral infarction CT brain showed ischemic infarction
53401	Ischemic stroke	Nonfatal stroke Ischemic infarction	Discharge summary MRI showed ischemic stroke
53901	Massive hemorrhagic stroke	Fatal stroke Hemorrhagic infarction	Discharge summary CT shows large hemorrhagic stroke
57091	Fatal stroke	Fatal stroke Ischemic infarction	Hospital records and clinical summary
57346	Ischemic stroke	Non-fatal stroke Ischemic infarction	Discharge summary and CT brain

From Sponsor's response to IR 3/21/2016

9.3 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.

Jardiance s-008 CSR Table 9.7.1.2:1 page 106

APPENDIX

Appendix 1: CEC Event Definitions (v9.0)

6.3 CLINICAL EVENT DEFINITIONS – CEC CARDIOLOGY (CECC)

In this section clinical event definitions are provided for the following adjudication endpoints:

- Cardiovascular death including Presumed Cardiovascular Death
- Non-Cardiovascular death
- Myocardial infarction (non-fatal)
- Hospitalisation for unstable angina
- Stent thrombosis
- Heart Failure Requiring Hospitalization
- Coronary Revascularization Procedures

The definitions are based on draft recommendations of the Centre for Drug Evaluation and Research (CDER) – Division of Metabolism and Endocrinology Products (2).

In many cases, data are collected on subjects in clinical trials at a level where definitions can be applied objectively. However, if there are limited or missing data, the Clinical Event Committee Cardiology (CECC) for the clinical trial should adjudicate events based on their clinical expertise and the totality of the evidence.

Please note: not all of these adjudication endpoints will be used as endpoints for the cardiovascular risk analysis. The statistical analysis including primary and secondary endpoints are described in the respective Cardiovascular Risk Analysis Plan or Trial Statistical Analysis Plan (for CV outcome studies).

6.3.1 Cardiovascular Death

The cause of death will be determined by the principal condition that caused the death, not the immediate mode of death. CECC members will review all available information and use their clinical expertise to adjudicate the cause of death. Nevertheless, all deaths not attributed to the categories of cardiovascular death and not attributed to a non-cardiovascular cause, are presumed cardiovascular deaths and as such are part of the cardiovascular mortality endpoint. For fatal events the onset date of the event leading to death should be reported by the committee.

Study sites should provide death certificates for all patients who have died. However, if a death certificate is the only information available for review besides the patient profile in

the clinical trial database, the CEC may decide not to use this information as a cause of death if another etiology appears to be more plausible.

The following definitions will be used for the adjudication of fatal cases:

Sudden cardiac death

Sudden Cardiac Death refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths:

- Witnessed and instantaneous without new or worsening symptoms
- Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms
- Witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic)
- Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology
- Un-witnessed death and there is no conclusive evidence of another, non-cardiovascular, cause of death. (i.e. presumed cardiovascular death, information regarding the patient's clinical status within the week preceding death should be provided)

Sudden Death due to Acute Myocardial Infarction (MI type 3)

Sudden death occurring up to 14 days after a documented acute myocardial infarction [verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus] and where there is no conclusive evidence of another cause of death.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death due to Heart Failure or Cardiogenic Shock

Refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death.

New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

  Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for more than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

  - Cool, clammy skin or
  - Oliguria (urine output < 30 mL/hour) or
  - Altered sensorium or
  - Cardiac index < 2.2 L/min/m2

  Cardiogenic shock can also be defined in the presence of SBP ≥ 90 mm Hg or for a time period of less than one hour if the blood pressure measurement or the time period is influenced by the presence of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour.

  The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study endpoint.

  This category will include sudden death occurring during an admission for worsening heart failure.

Death due to Stroke, Cerebrovascular event (FDA Stroke Team Definition): refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by complication of the stroke.

Death due to Other Cardiovascular Causes: death must be due to a fully documented cardiovascular cause not included in the above categories (e.g. dysrythmia, pulmonary embolism, or cardiovascular intervention). Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

6.3.2 NON-Cardiovascular Death

Non-cardiovascular death is defined as any death not covered by cardiac death or vascular death. The CEC will be asked to indicate the most likely cause of non-cardiovascular death on their voting form. Examples of non-cardiovascular death are: pulmonary causes, renal causes, gastrointestinal causes, infection (including sepsis), non-infectious (e.g., systemic inflammatory response syndrome (SIRS)), malignancy (i.e., new malignancy, worsening of prior malignancy), hemorrhage (not intracranial), accidental/trauma, suicide, noncardiovascular organ failure (e.g., hepatic failure) or non-cardiovascular surgery.

6.3.3 Myocardial Infarction (non-fatal)

6.3.3.1 Criteria for Acute Myocardial Infarction

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria A to C meets the diagnosis for myocardial infarction.

A. Spontaneous MI (type 1, see 6.3.3.2)

To identify a type 1 myocardial infarction, patients should demonstrate spontaneous symptoms of myocardial ischemia unprovoked by supply/demand inequity, together with at least one of the following criteria:

- **Cardiac Biomarker elevation** Troponin is the preferred marker for use to adjudicate the presence of acute myocardial infarction. At least one value should show a rise and/or fall above the lowest cut-point providing 10% imprecision (typically the upper reference limit for the troponin run per standard of clinical care). Creatine kinase-MB is a secondary choice to troponin; a rise of CK-MB above the local upper reference limit would be consistent with myocardial injury.
- **ECG changes consistent with new ischemic changes**
    - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]*
    - Development of pathological Q waves in the ECG**

*ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):

ST elevation:

New ST elevation at the J-point in two contiguous leads with the cut-off points:

≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads

ST depression and T-wave changes:

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio > 1.

**Pathological Q waves:

- 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)

- **Imaging evidence of new non-viable myocardium or new wall motion abnormality**

B. "Demand" related (type 2) myocardial infarction (see 6.3.3.2)

Patients with type 2 MI should be considered with similar diagnostic criteria as a type 1 MI, however type 2 MI should be considered present when myocardial ischemia and infarction are consequent to supply/demand inequity, rather than a spontaneous plaque rupture and coronary thrombosis.

C. Percutaneous Coronary Intervention-Related Myocardial Infarction (type 4a/4b, see 6.3.3.2)

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL (Troponin or CK-MB > 3 x 99th percentile URL) are consistent with PCI-related myocardial infarction.

If the cardiac biomarker is elevated prior to PCI, a ≥ 20% increase of the value in the second cardiac biomarker sample within 24 hours of the PCI and documentation that

cardiac biomarker values were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI is also consistent with PCI-related myocardial infarction.

Symptoms of cardiac ischemia are not required.

D. Coronary Artery Bypass Grafting-Related Myocardial Infarction (type 5)

For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevation of cardiac biomarkers above the 99th percentile URL within 72 hours of the procedure is indicative of peri-procedural myocardial necrosis. By convention, an increase of biomarkers greater than 5 x 99th percentile URL (Troponin or CK-MB > 5 x 99th percentile URL) plus

- either new pathological Q waves in at least 2 contiguous leads on the electrocardiogram that persist through 30 days or new LBBB or
- angiographically documented new graft or native coronary artery occlusion or
- imaging evidence of new loss of viable myocardium is consistent with CABG-related myocardial infarction.

If the cardiac biomarker is elevated prior to CABG, a ≥ 20% increase of the value in the second cardiac biomarker sample within 72 hours of CABG and documentation that cardiac biomarker values were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI plus either new pathological Q waves in at least 2 contiguous leads on the electrocardiogram or new LBBB, angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium is consistent with a peri-procedural myocardial infarction after CABG.

Symptoms of cardiac ischemia are not required.

6.3.3.2 Clinical Classification of Acute Myocardial Infarction

For each acute myocardial infarction (MI) identified by the CEC, a Type of MI will be assigned using the following guidelines:

- **Type 1**

  Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

- **Type 2**

  Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

- **Type 3**

  Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

- **Type 4a**

  Myocardial infarction associated with PCI

- **Type 4b**

  Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

- **Type 5**

  Myocardial infarction associated with CABG

6.3.4 Hospitalization for Unstable Angina

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.

Unstable angina requiring hospitalization is defined as:

1. No elevation in cardiac biomarkers (cardiac biomarkers are negative for myocardial necrosis). Note: according to conventional assays or contemporary sensitive assays

   AND

2. Clinical Presentation (one of the following) with cardiac symptoms lasting ≥ 10 minutes and considered to be myocardial ischemia on final diagnosis

   - Rest angina or

- New-onset (< 2 months) severe angina (Canadian Cardiovascular Society Grading Scale* (or CCS classification system) classification severity ≥ III) or

- Increasing angina (in intensity, duration, and/or frequency) with an increase in severity of at least 1 CCS class to at least CCS class III

AND

3. Requiring an unscheduled visit to a healthcare facility and overnight admission

AND

4. At least one of the following:

   a. New or worsening ST or T wave changes on ECG. ECG changes should satisfy the following criteria for acute myocardial ischemia in the absence of LVH and LBBB:

      ST elevation

      New transient (known to be < 20 minutes) ST elevation at the J-point in two contiguous leads with the cut-off points:

      - ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads

      ST depression and T-wave changes

      New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent Rwave

      or

      R/S ratio > 1.

   b. Evidence of ischemia on stress testing with cardiac imaging

   c. Evidence of ischemia on stress testing with angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery **or**

      initiation/increased dosing of antianginal therapy.

   d. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery

Class	Description of Stage
Class I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.
Class III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
Class IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."

*Grading of Angina Pectoris According to Canadian Cardiovascular Society Classification:

6.3.5 Stent Thrombosis

6.3.5.1 Stent Thrombosis: Timing

Type	Timing
Acute stent thrombosis	*0 to 24 hours after stent implantation
Subacute stent thrombosis	>24 hours to 30 days after stent implantation
Late stent thrombosis †	>30 days to 1 year after stent implantation
Very late stent thrombosis †	>1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheterization laboratory.

*Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30days) will be used in the remainder of this document.

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

6.3.5.2 Definitions of Definite, Probable, and Possible Stent Thrombosis

• Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

1. Acute onset of ischemic symptoms at rest

2. New ischemic ECG changes that suggest acute ischemia

3. Typical rise and fall in cardiac biomarkers

   (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)

   Note: according to conventional assays or contemporary sensitive assays

4. Nonocclusive thrombus

   Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream

5. Occlusive thrombus

   TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis

   Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

- Probable Stent Thrombosis

  Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

  a. Any unexplained death within the first 30 days§

  b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

- Possible Stent Thrombosis

  Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of trial followup.

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis

6.3.6 Heart Failure requiring Hospitalization

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 (HF) requiring hospitalization is defined as an event that meets the following criteria:

a. 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).

   AND

b. Clinical manifestations of heart failure including at least one of the following:

   New or worsening

   - dyspnea
   - orthopnea
   - paroxysmal nocturnal dyspnea
   - edema
   - pulmonary basilar crackles
   - jugular venous distension
   - new or worsening third heart sound or gallop rhythm, or
   - radiological evidence of worsening heart failure.

   AND

c. Additional/Increased therapy

   1. Initiation of oral diuretic, intravenous diuretic, inotrope, or vasodilator therapy

2. Uptitration of oral diuretic, intravenous therapy, if already on therapy

3. Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

Changes in biomarker (e.g., brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

6.3.7 Coronary Revascularization Procedure

A coronary revascularization procedure is defined as either coronary artery bypass graft surgery (CABG) or a percutaneous coronary intervention (PCI) (e.g., angioplasty, coronary stenting). CABG is defined as the successful placement of at least one conduit with either a proximal and distal anastomosis or a distal anastomosis only. PCI is defined as successful balloon inflation with or without stenting and the achievement of a residual stenosis <50%. The balloon inflation and/or stenting could have been preceded by device activation (e.g., angiojet, directional coronary atherectomy, or rotational atherectomy).

In case the procedure leads to a myocardial infarction (type 4a, 4b or 5), the event will be adjudicated as the myocardial infarction.

6.4 CLINICAL EVENT DEFINITIONS – CEC NEUROLOGY (CECN)

In this section clinical event definitions are provided for the following adjudication endpoints:

- TIA
- Stroke

6.4.1 Transient Ischemic Attack (TIA)

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

6.4.2 Stroke

Stroke is defined as the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable

lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown.

6.4.2.1 Diagnosis of Stroke

For the diagnosis of stroke, the following 4 criteria should be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:
    - Change in level of consciousness
    - Hemiplegia
    - Hemiparesis
    - Numbness or sensory loss affecting one side of the body
    - Dysphasia/Aphasia
    - Hemianopia (loss of half of the field of vision of one or both eyes)
    - Other new neurological sign(s)/symptom(s) consistent with stroke

    *If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation

2. Duration of a focal/global neurological deficit ≥24 hours

    OR

    < 24 hours if

    - this is because of at least one of the following therapeutic interventions:

        a. Pharmacologic (i.e., thrombolytic drug administration)

        b. Non-pharmacologic (i.e., neurointerventional procedure (e.g. intracranial angioplasty))

    or

    - available brain imaging clearly documents a new hemorrhage or infarct

    or

    - the neurological deficit results in death

3. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)
4. Confirmation of the diagnosis by at least one of the following:*
    a. Neurology or neurosurgical specialist
    b. Brain imaging procedure (at least one of the following):
    - CT scan
    - MRI scan
    - Cerebral vessel angiography
    c. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

*if a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus will be mandatory.

If the acute focal signs represent a worsening of a previous deficit, these signs must have either

- Persisted for more than one week, or
- persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

6.4.2.2 Classification of Stroke

Strokes are sub-classified as follows:

- Ischemic (Non-hemorrhagic)

  A stroke caused by an arterial obstruction due to either a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. 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).

- Hemorrhagic

  A stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral

hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage.

- Not assessable

  The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed.

Appendix 2: Trigger event definition for liver events

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

Appendix 3: WHO causality categories for assessing relationship between event and study drug

oncAAC Category	WHO-UMC Causality term	WHO-UMC Assessment Criteria
Possibly related to study drug	Certain	• Event or laboratory abnormality, with plausible time relationship to study drug intact • Cannot be explained by disease or other drugs • Response to withdrawal plausible • (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Possibly related to study drug	Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to study drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possibly related to study drug	Possible	• Event or laboratory test abnormality, with reasonable time relationship to study drug intake • Could also be explained by disease or other drugs • Information on study drug withdrawal may be lacking or unclear
Not related to study drug	Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Not assessable	Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Not assessable	Unassessable/ Unclassifiable	• Report suggesting adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

oncAAC = oncology assessment and adjudication committee; WHO-UMC = World Health Organization-Uppsala Monitoring Centre

Appendix 4: Excerpt from sample case report form

Boehringer Ingelheim Patient
Investigator
Trial 1245_0025 Blank page ☐

ADVERSE EVENTS / OUTCOME EVENTS

Event _____ **(Spell out single event name)**

Start date _____ **If AE is ongoing, mark this box** ☐
End date _____

All outcome events related to an adverse event should be entered on this e-CRF adverse event page. Outcome events reported at Visits 3 - to the end of the trial should NOT be reported on the SAE paper form or sent to drug safety but should still be reported as a serious adverse event on this e-CRF adverse event page. If the outcome event occurred before randomisation (Visit 1 or 2) these events should be reported on the SAE paper form and sent to drug safety.

Was this an Outcome Event?

☐ 0=No ☐ 1=Yes If yes is ticked, select all outcome events that apply below:

- ○ Cardiovascular death (including fatal stroke and fatal myocardial infarction).
- ○ Non fatal myocardial infarction
- ○ Non fatal stroke
- ○ Hospitalisation for unstable angina pectoris **If ticked, enter date below
- ○ Hospitalisation for cardiac heart failure **If ticked, enter date below
- ○ Transient ischemic attack
- ○ Silent Myocardial Infarction

If hospitalization for unstable angina pectoris or hospitalization for cardiac heart failure is ticked, please fill in the date: **Date of hospitalisation _____

Was PCI or CABG performed? ☐ 0=No ☐ 1=Yes Date of procedure _____

Therapy for event
☐ 0=No
☐ 1=Yes, enter drug or non-drug therapy on the Concomitant Therapy form.

Intensity of event
Indicate the most severe intensity
☐ 1=Mild
☐ 2=Moderate
☐ 3=Severe

Action taken with trial drug due to AE?
☐ 1=Neither discontinued nor reduced
Includes temporary discontinuation of 7 days or LESS and re-introduction at previous dose; Includes NA
☐ 2=Dose permanently reduced
☐ 3=Drug discontinued
Includes discontinuation of 7 consecutive days or MORE and re-introduction at previous dose

Was event serious?
☐ 0=No ☐ 1=Yes
Please indicate below the criteria that qualified the event as serious.
(Select all that apply)

- ○ Results in death
- ○ Immediately life threatening
- ○ Persistent or significant disability/incapacity
- ○ Requires hospitalisation
- ○ Prolongs hospitalisation
- ○ Congenital anomaly/birth defect
- ○ Other comparable medical criteria (specify under description)

☐ 3=No, but significant
(as defined in the Trial Protocol as AE of Special Interest)

Book ALL VISITS5 Patient Status Page 1.1
Version AE (v10, 01-NOV-2013) Approved by
On

Boehringer Ingelheim
Patient
Investigator
Trial 1245_0025 Blank page ☐

Outcome of event
☐ 1=Recovered
☐ 2=Not yet recovered
☐ 3=Sequelae
☐ 4=Fatal
☐ 5=Unknown

Causal relationship between the event and the trial drug
Medical judgement considering all relevant factors, including pattern of reaction, temporal relationship, positive dechallenge or re-challenge, confounding factors such as co-medicaton, co-diseases and relevant history.
☐ 0=No
☐ 1=Yes

Follow-up status for AEs not yet recovered at end of trial
This field is left blank if an end date is given and the Outcome is recovered. If 2 is selected, the date that the monitor and the investigator agree should be entered in the description field below.
☐ 1=Lost to follow-up
☐ 2=Follow-up sufficient

Description of the event if necessary

Hypoglycaemic event ☐ 0=No ☐ 1=Yes

If YES, please record information below

All symptomatic hypoglycaemic events, all asymptomatic events with glucose levels less than 3.0 mmol/L (or less than 54 mg/dL) and all asymptomatic hypoglycaemic events that are considered as Adverse Events by the investigator have to be recorded on this page.

If Hypoglycaemic event happens more than once in the same day, please record each event separately and be sure to record the start time.

Start time ☐

Blood glucose
☐ 0= No: measured
☐ 1= <3.0 mmol/L (<54 mg/dL)
☐ 2= >=3.0 and <=3.9 mmol/L (>=54 and <=70 mg/dL)
☐ 3= >3.9 mmol/L (>70 mg/dL)

Any Symptoms?
☐ 0=No
☐ 1=Yes (Typical symptoms of hypoglycaemia)
*If yes, please specify if the below mentioned symptoms occurred

Did one or both occur? ☐ 1=Seizures ☐ 2=Coma ☐ 3=Seizures and coma

Assistance required? ☐ 0=No (Event requiring the assistance of another person to actively administer
☐ 1=Yes carbohydrate, glycagon or other resuscitative actions)

Appendix 5: Sample case cover form for adjudication - Cardiology

CEC CARDIOLOGY - CASE COVER, VOTING AND DECISION FORMS

Boehringer Ingelheim
biDIA Program

CECC CASE COVER FORM

Seq Number ☐☐☐

Subject # ☐☐☐☐☐☐

Case Cover Form

BI Trial No. ☐☐☐☐ _ ☐☐☐☐

Investigator reported name of event	MedDRA AE Preferred Term Code	Onset Date dd/mmm/yyyy

Did the subject experience a Fatal Event? ☐ No ☐ Yes

Re-Adjudication of Trigger Event? ☐ No ☐ Yes

If yes, reason for re-adjudication: _____

_____

Source *(Please specify the test(s) that confirmed the event):*

- ☐ SAE Form / Narrative
- ☐ Autopsy Result
- ☐ Death/Hospital Summary
- ☐ Admission History
- ☐ Discharge Summary
- ☐ Clinical Course
- ☐ Lab Values (including cardiac biomarkers, units, normal ranges, myocardial necrosis and myocardial infarction limits)
- ☐ ECGs
- ☐ Echocardiography
- ☐ Szintigraphy
- ☐ Procedure Reports (cardiac catheterization, PCI, CABG)
- ☐ CT Scan
- ☐ MRI
- ☐ Chest X-Ray
- ☐ Other, please specify: _____
- ☐ Other, please specify: _____
- ☐ Other, please specify: _____
- ☐ No Source records available, please specify reason: _____

ACI 17/NOV/2011 Version 03

Note: Revisions to Appendices will not be considered formal amendments to the charter. Approvals for Appendices will be collected separately on the ACT "Sponsor Signature of Approval" Form.

Boehringer Ingelheim
biDIA Program

CECC VOTING FORM

Seq Number ☐☐☐

Subject # ☐☐☐☐☐☐

BI Trial No. ☐☐☐☐ _ ☐☐☐☐

After careful review of the event documentation, please provide your vote below.

☐ **Not assessable.** *(There was not enough information to determine. If checked, do not answer questions below)*

Did the subject experience a Cardiovascular endpoint event(s)?

☐ **No** → If Fatal, what was the cause of the event? _____

☐ **Yes** → Indicate event(s) by referencing the code list below.

FATAL Cardiovascular endpoint events
01 Acute Myocardial Infarction 02 Sudden Death 03 Worsening Heart Failure 04 Cardiogenic Shock
05 Cerebrovascular Event 06 Other Cardiovascular Causes, Specify:

NON-FATAL Cardiovascular endpoint events
07 Acute MI Type 1 08 Acute MI Type 2 09 Acute MI Type 4a 10 Acute MI Type 4b 11 Acute MI Type 5
12 PCI 13 CABG 14 Definite Stent Thrombosis 15 Probable Stent Thrombosis 16 Possible Stent Thrombosis
17 Non-Assessable Stent Thrombosis 18 Hospitalization for Heart Failure 19 Hospitalization for Unstable Angina

1. ☐☐ → **If 06 Specify:** _____
   → **Indicate Event Onset Date*:** ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*
2. ☐☐ → **If 06 Specify:** _____
   → **Indicate Event Onset Date*:** ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*
3. ☐☐ → **If 06 Specify:** _____
   → **Indicate Event Onset Date*:** ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*
4. ☐☐ → **If 06 Specify:** _____
   → **Indicate Event Onset Date*:** ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*
5. ☐☐ → **If 06 Specify:** _____
   → **Indicate Event Onset Date*:** ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*

**For Non-Fatal Cardiovascular Event Codes #18 and #19, the date of hospital admission should be recorded for "Event Onset Date".*

Comments (optional): _____

Committee Member ID Number 0 0

☐ By checking this box, I certify that my name is correct as printed below and I have reviewed this event.

Member Name: **DR. [INSERT NAME HERE]** Date: ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*
PLEASE PRINT

ACI 17/NOV/2011 Version 03

Note: Revisions to Appendices will not be considered formal amendments to the charter. Approvals for Appendices will be collected separately on the ACI "Sponsor Signature of Approval" Form.

Boehringer Ingelheim
biDIA Program

CECC VOTING MEMBER XX VOTING FORM

Seq Number ☐☐☐

Subject # ☐☐☐☐☐☐

BI Trial No. ☐☐☐☐ _ ☐☐☐☐

After careful review of the event documentation, please provide your vote below.

☐ **Not assessable.** *(There was not enough information to determine. If checked, do not answer questions below)*

Did the subject experience a Cardiovascular endpoint event(s)?

☐ **No** → If Fatal, what was the cause of the event? _____

☐ **Yes, subject has experienced the following Cardiovascular endpoint event(s):**

☐ Subject has experienced the following Fatal Cardiovascular endpoint event:

☐ Acute Myocardial Infarction ☐ Sudden Death ☐ Worsening of Heart Failure ☐ Cardiogenic Shock

☐ Cerebrovascular Event ☐ Other Cardiovascular Causes: _____

Event Onset Date: ☐☐ day ☐☐☐ month ☐☐☐☐ year

☐ Subject has experienced the following Non-Fatal Cardiovascular endpoint event(s):

☐ Acute Myocardial Infarction: → ☐ Spontaneous (Type 1) ☐ Secondary to Ischemia (Type 2)
☐ PCI related (Type 4a) ☐ Stent Thrombosis (Type 4b) ☐ CABG related (Type 5)

Event Onset Date: ☐☐ day ☐☐☐ month ☐☐☐☐ year

☐ Coronary Revascularization Procedures: → ☐ PCI ☐ CABG

Event Onset Date: ☐☐ day ☐☐☐ month ☐☐☐☐ year

☐ Stent Thrombosis: → ☐ Definite ☐ Probable ☐ Possible ☐ Not Assessable

Event Onset Date: ☐☐ day ☐☐☐ month ☐☐☐☐ year

☐ Hospitalization for Heart Failure → Event Onset Date: ☐☐ day ☐☐☐ month ☐☐☐☐ year

☐ Hospitalization for Unstable Angina → Event Onset Date: ☐☐ day ☐☐☐ month ☐☐☐☐ year

**For Hospitalization for Heart Failure/Unstable Angina, the date of hospital admission should be recorded for "Event Onset Date".*

Comments (optional): _____

Committee Member ID Number ☐☐

☐ By checking this box, I certify that my name is correct as printed below and I have reviewed this event.

Member Name: _____ (PLEASE PRINT) Date: ☐☐ day ☐☐☐ month ☐☐☐☐ year

ACI 24/MAR/2014 Version 03

Please note: The format of the Voting Form has been revised in order to enable efficient generation of decisions. Any cases adjudicated within the ACI AIMS 3.1 system will use the new voting format.

Note: Revisions to Appendices will not be considered formal amendments to the charter. Approvals for Appendices will be collected separately on the ACI "Sponsor Signature of Approval" Form

Boehringer Ingelheim
biDIA Program

CECC CASE DECISION FORM

Seq Number ☐☐☐

Subject # ☐☐☐☐☐☐

BI Trial No. ☐☐☐☐ _ ☐☐☐☐

Investigator reported name of event	MedDRA AE Preferred Term Code	Onset Date dd/mmm/yyyy

After careful review, the committee has confirmed the following:

☐ **Event is not assessable.**

☐ **Subject did not experience a Cardiovascular endpoint event.**

→ If Fatal, what was the cause of the event? _____

☐ **Subject did experience a Cardiovascular endpoint event.**

☐ Subject has experienced the following Fatal Cardiovascular endpoint event:

→ ☐ Acute Myocardial Infarction ☐ Sudden Death ☐ Worsening of Heart Failure ☐ Cardiogenic Shock
☐ Cerebrovascular Event ☐ Other Cardiovascular Causes: _____

→ Event Onset Date: ☐☐ (day) ☐☐☐ (month) ☐☐☐☐ (year)

☐ Subject has experienced the following Non-Fatal Cardiovascular endpoint event(s):

☐ Acute Myocardial Infarction: → ☐ Spontaneous (Type 1) ☐ Secondary to Ischemia (Type 2)
☐ PCI related (Type 4a) ☐ Stent Thrombosis (Type 4b) ☐ CABG related (Type 5)

→ Event Onset Date: ☐☐ (day) ☐☐☐ (month) ☐☐☐☐ (year)

☐ Coronary Revascularization Procedures: → ☐ PCI ☐ CABG

→ Event Onset Date: ☐☐ (day) ☐☐☐ (month) ☐☐☐☐ (year)

☐ Stent Thrombosis: → ☐ Definite ☐ Probable ☐ Possible ☐ Not Assessable

→ Event Onset Date: ☐☐ (day) ☐☐☐ (month) ☐☐☐☐ (year)

☐ Hospitalization for Heart Failure → Event Onset Date: ☐☐ (day) ☐☐☐ (month) ☐☐☐☐ (year)

☐ Hospitalization for Unstable Angina → Event Onset Date: ☐☐ (day) ☐☐☐ (month) ☐☐☐☐ (year)

Comments (Record any CEC comments):

Decision Date: ☐☐ (day) ☐☐☐ (month) ☐☐☐☐ (year) **ACI Initials:** _____

ACI 17/NOV/2011 Version 03

Note: Revisions to Appendices will not be considered formal amendments to the charter. Approvals for Appendices will be collected separately on the ACI "Sponsor Signature of Approval" Form

Appendix 6: Sample case cover form for adjudication - Neurology

CEC NEUROLOGY – CASE COVER, VOTING AND DECISION FORMS

Boehringer Ingelheim
biDIA Program

CECN CASE COVER FORM

Seq Number ☐☐☐

Subject # ☐☐☐☐☐☐

Case Cover Form

BI Trial No. ☐☐☐☐ __ ☐☐☐☐

Investigator reported name of event	MedDRA AE Preferred Term Code	Onset Date dd/mmm/yyyy

Did the subject experience a Fatal Event? ☐ No ☐ Yes

Re-Adjudication of Trigger Event? ☐ No ☐ Yes

If yes, reason for re-adjudication: _____

Does the uploaded source documentation contain information stating symptom duration?
(i.e. the source indicates if symptoms did or did not last more than 24 hours?)

☐ Yes
☐ No → please specify reason: _____
☐ NA *(for ACI internal use only)*

Source *(Please specify the test(s) that confirmed the event):*

☐ SAE Form / Narrative
☐ Autopsy Result
☐ Death/Hospital Summary
☐ Admission History
☐ Discharge Summary
☐ Clinical Course
☐ Neurology Consult
☐ Angiography
☐ CT Scan
☐ MRI
☐ MR Angiography
☐ Duplex Scan (Transthoracic and/or Transesophageal echocardiograms)
☐ Surgery
☐ Other, please specify: _____
☐ Other, please specify: _____
☐ Other, please specify: _____
☐ No Source records available, please specify reason: _____

ACI 26/AUG/2014 Version 03

Note: Revisions to Appendices will not be considered formal amendments to the charter. Approvals for Appendices will be collected separately on the ACI "Sponsor Signature of Approval" Form.

Boehringer Ingelheim
biDIA Program

CECN VOTING FORM

Seq Number ☐☐☐

Subject # ☐☐☐☐☐☐

BI Trial No. ☐☐☐☐ __ ☐☐☐☐

After careful review of the event documentation, please provide your vote below.

☐ **Not assessable.** *(There was not enough information to determine. If checked, do not answer questions below)*

1. Did the subject experience a Neurological endpoint event(s)?

☐ **No**
→ If Fatal, what was the cause of the event? _____

☐ **Yes**

→ **Fatal Neurological Endpoint Event:**

Check the primary cause of the event: *(check only one box)*

☐ Ischemic stroke
☐ Hemorrhagic stroke
☐ Type of stroke is Not Assessable

Indicate Fatal Event Onset Date: ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*

→ **Non-Fatal Neurological Endpoint Event:**

Check the primary cause of the event: *(check only one box)*

☐ Ischemic stroke
☐ Hemorrhagic stroke
☐ TIA
☐ Type of stroke is Not Assessable

Indicate Non-Fatal Event Onset Date: ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*

Comments (optional):

_____

_____

Committee Member ID Number 0 0

☐ By checking this box, I certify that my name is correct as printed below and I have reviewed this event.

Member Name: **DR. [INSERT NAME HERE]** (PLEASE PRINT) Date: ☐☐ *day* ☐☐☐ *month* ☐☐☐☐ *year*

ACI 22/NOV/2011 Version 03

Note: Revisions to Appendices will not be considered formal amendments to the charter. Approvals for Appendices will be collected separately on the ACI "Sponsor Signature of Approval" Form.

Boehringer Ingelheim
biDIA Program

CECN DECISION FORM

Seq Number ☐☐☐

Subject # ☐☐☐☐☐☐

BI Trial No. ☐☐☐☐ __ ☐☐☐☐

Investigator reported name of event	MedDRA AE Preferred Term Code	Onset Date dd/mmm/yyyy

After careful review, the committee has confirmed the following:

☐ **Event is not assessable.**

☐ **Subject did not experience a Neurological endpoint event.**

→ If Fatal, what was the cause of the event? _____

☐ **Subject did experience a Neurological endpoint event(s).**

→ Subject has experienced a Fatal Neurological endpoint event with a primary cause of:

- ☐ Ischemic stroke
- ☐ Hemorrhagic stroke
- ☐ Type of stroke is Not Assessable

Indicate Fatal Event Onset Date: ☐☐ ☐☐☐ ☐☐☐☐ (day month year)

→ Subject has experienced a Non-Fatal Neurological endpoint event with a primary cause of:

- ☐ Ischemic stroke
- ☐ Hemorrhagic stroke
- ☐ TIA
- ☐ Type of stroke is Not Assessable

Indicate Non-Fatal Event Onset Date: ☐☐ ☐☐☐ ☐☐☐☐ (day month year)

Comments (Record any CEC comments):

_____

_____

Decision Date: ☐☐ ☐☐☐ ☐☐☐☐ (day month year) **ACI Initials:** _____

ACI 22/NOV/2011 Version 03

Note: Revisions to Appendices will not be considered formal amendments to the charter. Approvals for Appendices will be collected separately on the ACI "Sponsor Signature of Approval" Form.