Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Empagliflozin

Proprietary Product Name: Jardiance

Sponsor: Boehringer Ingelheim Pty Ltd

Date of CER: February 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
ACE	Angiotensin converting enzyme
ACR	Albumin creatinine ratio
AE	Adverse event
ANCOVA	Analysis of covariance model
ARB	Angiotensin receptor blocker
BI	Boehringer Ingelheim
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CI	Confidence interval
CV	cardiovascular
DBP	Diastolic blood pressure
DMC	Data monitoring committee
ECG	electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
FDA	Food and Drug Administration (USA)
FUS	Follow up set
FV	Final visit
HbA1c	Glycosylated haemoglobin
IXRS	Interactive voice and web response
LOCF	Last observation carried forward
LVOT	Last value on treatment

Abbreviation	Meaning
MACE	Major adverse cardiovascular event
MedDRA	Medical dictionary for drug regulatory activities
MI	Myocardial infarction
MMRM	Mixed model repeated measures
NCF	Non completers considered failures
NA	Not analysed
OC	Observed cases
OC-AD	Observed cases after discontinuation or rescue medication intake
OR	Original results
OS	On treatment set
PAOD	Peripheral arterial occlusive disease
PCI	Percutaneous coronary intervention
PPS	Per protocol set
SBP	Systolic blood pressure
SOP	Standard operating procedure
STEMI	ST elevation myocardial infarction
T2DM	Type 2 diabetes
TIA	Transient ischaemic event
UACR	Urine albumin creatinine ratio
ULN	Upper limit of normal
VTE	Venous thromboembolism

1. Introduction

This is a submission for:

1. extending the indications for Jardiance to include the *'prevention of cardiovascular deaths'.*
2. widen the usage in patients with renal impairment to include patients with moderate renal impairment (eGFR ≥ 30 mL/min/1.73 m^2).

1.1. Drug class and therapeutic indication

Empagliflozin is a sodium-glucose cotransport 2 inhibitor. It's main mechanism of action is to lower blood glucose levels in diabetes.

The approved indication is:

> '*Jardiance is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as:*
>
> - *Monotherapy.*
>
> *When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.*
>
> - *Add-on combination therapy.*
>
> *In combination with other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.'*

The proposed additional indication is:

> *'Prevention of cardiovascular events:*
>
> *Jardiance is indicated in patients with type 2 diabetes and high cardiovascular risk to reduce the risk of:*
>
> - *All-cause mortality by reducing cardiovascular death.*
> - *Cardiovascular death or hospitalisation for heart failure.'*

Comment: The population proposed for the new indication is not a new patient population but a subpopulation of those covered by the current indications.

Ideally, any treatment for type 2 diabetes improves not only glycaemic control (a surrogate marker of a risk factor for microvascular complications), but also other major causes of morbidity and mortality such as macrovascular disease and heart failure.

1.2. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

- empagliflozin 10 mg tablets
- empagliflozin 25 mg tablets

No new dosage forms or strengths are proposed.

1.3. Dosage and administration

The recommended starting dose of Jardiance is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycaemic control, the dose can be increased to 25 mg daily. Jardiance can be taken with or without food.

There are no new dosing instructions for the prevention of cardiovascular events.

2. Clinical rationale

Type 2 diabetes is a major risk factor for cardiovascular disease. It is estimated that 70 to 75% of all deaths in people with diabetes can be attributed to cardiovascular complications. The presence of both T2DM and cardiovascular disease is associated with increased morbidity and mortality. Despite a number of large clinical trials, there is minimal evidence that lowering blood glucose reduces the risk of cardiovascular events. There is a concern that intensive glucose lowering or the use of specific glucose lowering drugs can be associated with adverse cardiovascular outcomes, particularly in the elderly.

Compared to individuals without diabetes, those with diabetes have a higher prevalence of coronary artery disease, a greater extent of coronary ischemia, and are more likely to have myocardial ischemia and silent myocardial ischemia. In the Framingham Heart Study, the presence of diabetes doubled the age adjusted risk for cardiovascular disease in men and tripled it in women. In the Multiple Risk Factor Intervention Trial (MRFIT), among 5163 men who reported taking medication for diabetes, 9.7 % died from cardiovascular disease over a 12 year period, this compares to 2.6% of 342,815 men not taking medication for diabetes. This difference was independent on age, ethnic group, cholesterol level, systolic BP, and smoking. In addition to cardiovascular events, patients with type 2 diabetes have a high rate of asymptomatic coronary artery disease (as determined by the presence of coronary artery calcification (CAC) on electron beam CT scanning and inducible cardiac ischemia on stress imaging. Patients with type 2 diabetes have reduced myocardial flow reserve, a reflection of coronary vasodilator capacity, which is inversely related to glycaemic control. Silent ischemia in diabetes is thought to be caused at least in part by autonomic denervation of the heart.

The risk of heart failure in diabetes is increased 2.4-fold in men and 5-fold in women. It is associated with, but not entirely explained by, the presence of coronary artery disease. Other risk factors include age, duration of diabetes, poor glycaemic control and renal disease. Among patients with diabetes, those with heart failure have a greatly increased risk of death (around 10-fold) than those without. The 5-year survival rate for heart failure with diabetes is around 12.5%.

Most guidelines for diabetes suggest a therapeutic target goal for HbA1c should be 6.5 to 7%, however this can be difficult to achieve for many patients, particularly those with longstanding disease.

Apart from its ability to lower blood glucose through a decrease in renal glucose absorption, empagliflozin is associated with weight loss and a reduction in blood pressure without increases in heart rate. Empagliflozin also has favourable effects on markers of arterial stiffness and vascular resistance, visceral adiposity, albuminuria and plasma urate as well as increase in LDL and HDL. It increases rather than decreases glucagon.

The rational for the extension of indications for use to prevent cardiovascular disease comes from positive results from the EMPA-REG OUTCOME study.

The rational for widening the use of Jardiance in renal impairment comes from greater experience of the use of Jardiance in patients with moderate renal impairment in a clinical trial setting. In an analysis of patients in the EMPA-REG OUTCOME study with chronic kidney disease 3A (eGFR 45 to 60 mL/min/1.73 m^2) and 3B (eGFR 30 to 45mL/min/1.73 m^2), all CV and renal

benefits were also seen with similar effect sizes and safety profiles. In Study 1245.36, in patients with CKD 2 (eGFR 60 to 89 mL/min/1.73 m^2) and CKD3, beneficial effects in glycaemic control, body weight and blood pressure were shown.

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of SGLT2 with an IC_{50} of 1.3 nM. It is highly selective over SGLT1 and other glucose transporters. Empagliflozin improves glycaemic control in patients with T2DM by reducing glucose reabsorption. The amount of glucose removed by the kidney is dependent on the blood glucose concentration and GFR. Urinary glucose loss is accompanied by a reduction in body weight, presumably due to caloric loss. The glycosuria is also associated with a sustained and modest reduction in blood pressure.

2.1. Guidance

The trial design and analysis strategy for the EMPA-REG OUTCOME study was based on FDA and EMA diabetes guidance outcome documents.

The sponsor refers to the document:

- Guidance for industry: Diabetes mellitus: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (December 2008). Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research (CDER). 2008.

The evaluator used the guidance document:

- EMEA/CHMP/EWP/311890/2007: Guideline on the evaluation of medicinal products for cardiovascular disease prevention.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Study 1245.25: A Phase III, multicentre, international, randomised, parallel group, double blind cardiovascular safety study of BI 10773 (10 and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk. Otherwise referred to as 'the EMPA-REG OUTCOME trial'
- A Clinical Overview and Clinical Summary.

3.2. Paediatric data

There was no paediatric data submitted. empagliflozin is currently not registered for use in children.

In the EU, a paediatric investigation plan (PIP) waiver request for CV protection was submitted in December 2014. This was subsequently withdrawn based on information received from the PDCO/EMA in March 2015. The proposed indication in adults 'Reduction of cardiovascular morbidity in adults with type 2 diabetes mellitus who also have CV risk factors or established CV disease' was considered by PDCO to be covered by the condition 'Treatment of type 2 diabetes mellitus' in the already agreed PIP as the target population will not change.

In the USA, the sponsor does not have a paediatric plan under the paediatric research equity act in the USA. The sponsor submitted a request for a full waiver on 16 September 2015, and is under review. The sponsor does not have an 'agreed plan' as of yet.[1]

Children as young as 10 years do develop type 2 diabetes, most commonly when there are other risk factors such as obesity, family history and racial factors. Currently only metformin and insulin are approved for use in children. Although the investigation of the use of empagliflozin and other drugs for the management of type 2 diabetes is important, it is likely that glycaemic control and surrogate cardiovascular endpoints will be used in clinical trials. The age at which agents be used to treat other cardiovascular risk factors (such as obesity, hyperlipidaemia and hypertension) is not well established and tends to be based on surrogate markers, relatively short periods of follow up and extrapolation of adult data.

3.3. Good clinical practice

Prior to the start of Study 1245.25, the clinical trial protocol, patient review information leaflet, consent form and other documents were reviewed by the Independent Ethics Committee/Institutional Review Boards or each participating site. The IEC and IRBs met the requirements of the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice.

PharmacokineticsNo new data was submitted.

4. Pharmacodynamics

No new data was submitted.

5. Dosage selection for the pivotal studies

Randomisation of dosing was 1:1:1 to placebo, empagliflozin 10 mg and empagliflozin 25 mg.

The dosing guidelines in the PI suggest a starting dose of 10 mg and to up titrate the dose on the basis of poor glycaemic control. There were no significant dose effects for the prevention of 'cardiovascular events'.

The dosing used for the clinical trial and in the PI is acceptable for this proposed extension of indication.

6. Clinical efficacy

For the evaluation of clinical efficacy for:

'Improvement of cardiovascular events in patients with T2DM.'

6.1. EMPA-REG OUTCOME study

This was also published in the New England Journal of Medicine by Zinman et al (2015).

[1] FDA granted a full waiver of the Pediatric Research Equity Act requirements for empagliflozin for reducing cardiovascular risk on 10 December 2015.

6.1.1. Study design, objectives, locations and dates

The study was a randomised, double blind, placebo controlled trial to assess the effect of once daily empagliflozin (at a dose of either 10 mg or 25 mg) versus placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk against standard care. The study was an integral part of the ongoing safety assessment for regulatory authorities. The study took place from 26 August 2010 to 21 April 2015. Patients were treated at 590 sites in 42 countries. The date of report was 12 October 2015.

The trial was designed and overseen by a steering committee that included academic investigators and employees of the sponsor. Safety was reviewed by an independent academic data monitoring committee every 90 days. Cardiovascular outcomes and deaths were prospectively adjudicated by two clinical events committees.

The primary objective of this study was to determine non-inferiority (non-inferiority margin of 1.3, as per FDA Guidelines) of the treatment with 2 pooled doses of empagliflozin (10 mg once daily and 25 mg once daily) versus placebo on the composite of 3 major adverse cardiovascular events (3-point MACE; cardiovascular death, non-fatal stroke or nonfatal myocardial infarction) in patients with T2DM and increased cardiovascular risk. If non-inferiority of empagliflozin was established for the primary endpoint and for the key secondary endpoint (defined below), the hierarchical statistical analysis was to continue to evaluate the superiority of empagliflozin versus placebo for the primary endpoint and thereafter for the key secondary endpoints.

6.1.2. Inclusion and exclusion criteria

6.1.2.1. Inclusion criteria

The inclusion criteria included:

- Type 2 diabetes
- Age > 18 years
- BMI < 45 kg/m^2
- eGFR > 30 mL/minute/1.73 m^2
- Established cardiovascular disease defined as at least one of the following:
  - confirmed history of myocardial infarction more than 2 months prior to informed consent
  - evidence of multi vessel coronary artery disease in 2 or more major coronary vessels
  - evidence of a single vessel coronary artery disease with presence of a significant stenosis and either a positive non-invasive stress test or discharged from hospital with a documented diagnosis of unstable angina within 12 months prior to selection
  - last episode of unstable angina > 2 months prior to informed consent with evidence of coronary multi vessel or single vessel disease
  - history of ischemic or haemorrhagic stroke > 2 months prior to informed consent
  - presence of peripheral artery disease
- No glucose lowering agents for at least 12 weeks and had HbA1c of 7 to 9% or stable glucose lowering treatment and HbA1c of 7 to 10%

6.1.2.2. Exclusion criteria

The exclusion criteria included:

- Uncontrolled hyperglycaemia with a glucose level > 13.3 mmol/L after an overnight fast

- Acute coronary syndrome, stroke, TIA within 2 months or planned cardiac surgery or angioplasty within 3 months
- Liver disease
- eGFR < 30 mL/minute/1.73 m^2
- Bariatric surgery within 2 years and other gastrointestinal surgeries that induce chronic malabsorption
- Blood dyscrasia
- Medical history of cancer
- At risk of pregnancy
- On anti-obesity drugs
- Alcoholism

Comment: The study only recruited patients with T2DM and HbA1c > 7% (target HbA1c for most patients). Thus, all subjects recruited would be covered by the current indications for empagliflozin. The exclusion criteria included patients with extreme obesity very poor glycaemic control, and recent cardiovascular events. Thus, efficacy in these subgroups is uncertain. The inclusion criteria for cardiovascular risk would have selected those with macrovascular disease, not necessarily risk factor for heart failure.

6.1.3. Study treatments

A 2 week open label placebo ran to assess the willingness of patients to adhere to long-term treatment. Patients were randomised 1:1:1 to receive 10 mg empagliflozin, 25 mg empagliflozin, or placebo.

Background glucose lowering therapy was to be stable for the first 12 weeks (but was allowed to be intensified if the fasting level was > 13.3 mmol/L or reduced if needed). After Week 12, investigators could adjust glucose lowering to achieve local glycaemic targets and were encouraged to also treat other cardiovascular risk factors.

Visits were at Weeks 4, 8, 12, 16, 28, 40 and 52 weeks then at 14 week intervals. Patients who discontinued or withdrew for the study were to be followed up until the end of the study period. The expected treatment duration was 6 to 8 years based on the expected accrual period of 2 years and expected outcome treatment rate.

The protocol also encouraged the investigators to treat all other cardiovascular risk factors (lipid levels, blood pressure, micro/macroalbuminuria, unhealthy lifestyle, smoking) according to usual standard of care. In a high CV risk population this would imply use (if tolerated and not contraindicated) of statins, angiotensin converting enzyme (ACE) inhibitors, angiotensin II (ATII) receptor blockers, aspirin, beta-blockers, calcium channel blockers, and so on. This trial was to be conducted in the context of local or regional guidance for secondary cardiovascular prevention.

Comment: It is not entirely clear what training/experience the investigators who reviewed the patients had, what guidelines they used to step up treatment, and whether the patients saw their usual doctors as well and if the usual doctor was able to adjust medications. The intensity of treatment received in the study may have implications as to the external validity of the study results.

6.1.4. Efficacy variables and outcomes

The primary efficacy outcome was a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina.

Other secondary efficacy outcomes included: silent MI; heart failure requiring hospitalisation; new onset albuminuria (defined as UACR > 300 mg/g); composite microvascular outcome defined as initial retinal photocoagulation, vitreous haemorrhage, diabetes related blindness, new or worsening nephropathy. eGFR was calculated using the MDRD formula.

Additional exploratory endpoints included components of the macrovascular and microvascular composite endpoints, the composite endpoint of 'heart failure requiring hospitalisation or CV death', and all-cause mortality. Exploratory efficacy parameters included HbA1c, FPG (fasting plasma glucose), body weight, SBP (systolic blood pressure), and DBP (diastolic blood pressure).

A clinical event committee was established for the central adjudication of potential cardiovascular end points.

Comment: The large number of efficacy endpoints is noted. Neuropathy was not assessed. There was no physiological assessment of heart function.

6.1.5. Randomisation and blinding methods

Randomisation as centrally via a computer generated random sequence and interactive voice and web response system. It was stratified for HbA1c, BMI, eGFR and geographical area.

6.1.6. Analysis populations

Table 1. Analysis populations in the EMPA-REG OUTCOME study

Population	Abbreviation	Definition
Screened set	SCR	All patients screened for the trial with informed consent give and who completed at least 1 screening procedure at Visit 1
Randomised set	RS	All patients from the screened set who were randomised to study medication
Treated set	TS	All randomised patients who received at least 1 dose of study medication. This population was the basis of primary analysis
On treatment set	OS	Patients who received treatment for at least 30 days (cumulative). Events were considered that occurred not later than 30 days after last intake of the study medication or until the end of the entire trial
Full analysis set	FAS	All patients randomised, treated with at least 1 dose of medication and with a baseline HbA1c value

Population	Abbreviation	Definition
Treated set follow up	TS-FU	All patients in the TS for whom a follow up visit was performed between 28 and 50 days after last intake of study medication
Per Protocol set	PPS	All patients who were treated with at least 1 dose of study medication and did not have important protocol violations

6.1.7. Sample size

The trial continued until an adjudicated outcome event (a component of the 3-point MACE) had occurred in at least 691 patients.

The criteria used to determine this sample size included:

- A non-inferiority margin of 1.3 (based on FDA guidelines)
- One sided significance level of 2.5% ($\alpha = 0.025$)
- Power 90%
- Allocation ratio 2:1

The number of required events was independent of the accrual and follow up times and independent of the yearly event rate, however the number of patients to be randomised was dependent on these parameters. Based on an event rate of 1.5% per year, and 7000 patients randomised it was anticipated that the study would take 8 years to complete.

Comments: The study took less time to complete than expected, presumably because the patients selected were a high risk group with more cardiovascular events each year than anticipated.

6.1.8. Statistical methods

An independent external committee (clinical event committee) was established to adjudicate centrally and in a blinded fashion all fatal events and events suspected of stroke, MI, cardiac failure, and coronary revascularisation procedures. An independent data monitoring committee was established to monitor safety and advise the sponsor about whether to continue, modify or stop the trial. A steering committee was established to provide scientific leadership for the design and conduct of the study and interpretation of data.

The primary hypothesis was non-inferiority for the primary outcome with empagliflozin (pooled 10 mg and 25 mg) versus placebo, with a margin of 1.3 for the hazard ratio. A Haybittle Peto correction (0.0001) was used in view of an interim analysis.

For the primary analysis comparing the pooled doses of empagliflozin versus placebo, a Cox proportional hazards regression model of time to the first occurrence of CV death, non-fatal MI, or non-fatal stroke was performed with treatment (pooled empagliflozin versus placebo), age, sex, baseline categories of BMI (< 30 versus ≥ 30 kg/m^2), baseline HbA1c (< 8.5% versus ≥ 8.5%), baseline eGFR values (normal: eGFR ≥ 90 mL/min/1.73 m^2; mild impairment: 60 mL/min/1.73 m^2 ≤ eGFR ≤ 89 mL/min/1.73 m^2; and moderate/severe impairment: eGFR ≤ 59 mL/min/1.73 m^2) and geographical region as factors. The primary analysis was performed on the treated set (TS). Following the intent-to-treat (ITT) analysis principle, all events observed until trial termination were included in the analysis and patients were assigned to randomised treatment. The key secondary endpoint and additional secondary endpoints were analysed with a Cox proportional hazards model including the same factors as in the

primary analysis. Analyses of the secondary endpoints other than the key secondary endpoint were exploratory, there was no correction for multiple hypotheses testing.

A 4-step hierarchical testing strategy for the primary and key secondary endpoint was followed comparing pooled doses of empagliflozin versus placebo. If non-inferiority was established for the primary endpoint, non-inferiority was to be tested on the key secondary endpoint, both 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. Statistical tests as part of the hierarchical testing strategy were performed 1-sided, with a significance level of 0.0249.

Continuous endpoints: Data obtained on treatment until rescue therapy up to the planned week that could theoretically be achieved by all patients were included in this analysis. Descriptive statistics were calculated for the change from baseline based on OC and LOCF.

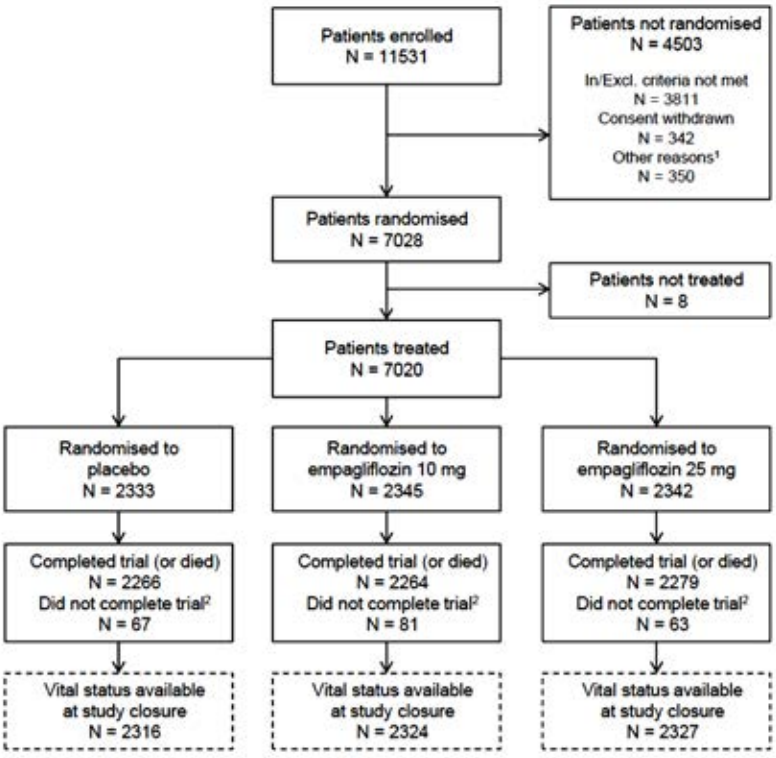
ANCOVA: The continuous further efficacy endpoints were analysed with ANCOVA using LOCF with treatment assigned as randomised. This model included effects accounting for sources of variation such as baseline BMI, baseline eGFR, and geographical region as fixed classification effects and baseline efficacy endpoints and HbA1c as linear covariates. The random error was assumed to be normally distributed.

MMRM: Change from baseline over time was assessed with a restricted maximum likelihood based MMRM approached.

6.1.9. Participant flow

Of the 7020 patients randomised to trial medication, 211 (3%) prematurely discontinued and data on the primary efficacy endpoint was not available. Vital status information was available for all but 53 patients (see Figure 1, below).

Figure 1. Overview of participant disposition



Overall, around 29.3% of subjects in the placebo group and 23.4% of subjects in the empagliflozin groups prematurely discontinued the study medication. This was due to an

adverse event in 13% of the placebo patients and 11.5% of the empagliflozin patients (see Table 2, below).

Table 2. Disposition of participants

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)
Enrolled/Screened patients					11531
Patients who started placebo run-in period					7610
Entered/Randomised patients[1]	2337	2347	2344	4691	7028
Not treated patients	4	2	2	4	8
Treated patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)	7020 (100.0)
Final vital status available	2316 (99.3)	2324 (99.1)	2327 (99.4)	4651 (99.2)	6967 (99.2)
Alive	2122 (91.0)	2187 (93.3)	2195 (93.7)	4382 (93.5)	6504 (92.6)
Dead	194 (8.3)	137 (5.8)	132 (5.6)	269 (5.7)	463 (6.6)
Lost to follow-up for vital status[2]	17 (0.7)	21 (0.9)	15 (0.6)	36 (0.8)	53 (0.8)
Prematurely discontinued trial[3]	67 (2.9)	81 (3.5)	63 (2.7)	144 (3.1)	211 (3.0)
Consent withdrawn	31 (1.3)	41 (1.7)	30 (1.3)	71 (1.5)	102 (1.5)
Site closure	25 (1.1)	30 (1.3)	26 (1.1)	56 (1.2)	81 (1.2)
Lost to follow-up for 3P-MACE	11 (0.5)	10 (0.4)	7 (0.3)	17 (0.4)	28 (0.4)
Prematurely discontinued trial med.	683 (29.3)	555 (23.7)	542 (23.1)	1097 (23.4)	1780 (25.4)
Adverse event	303 (13.0)	267 (11.4)	273 (11.7)	540 (11.5)	843 (12.0)
Study disease worsening	15 (0.6)	22 (0.9)	14 (0.6)	36 (0.8)	51 (0.7)
Other pre-exist. disease worsening	65 (2.8)	38 (1.6)	48 (2.0)	86 (1.8)	151 (2.2)
Other adverse event	223 (9.6)	207 (8.8)	211 (9.0)	418 (8.9)	641 (9.1)
Lack of efficacy[4]	11 (0.5)	1 (<0.1)	0	1 (<0.1)	12 (0.2)
Non-compliance with protocol	15 (0.6)	15 (0.6)	12 (0.5)	27 (0.6)	42 (0.6)
Lost to follow-up	15 (0.6)	9 (0.4)	6 (0.3)	15 (0.3)	30 (0.4)
Refused to continue trial medication[5]	172 (7.4)	118 (5.0)	122 (5.2)	240 (5.1)	412 (5.9)
Other reason	162 (6.9)	142 (6.1)	125 (5.3)	267 (5.7)	429 (6.1)
Study drug stopped, reason missing	5 (0.2)	3 (0.1)	4 (0.2)	7 (0.1)	12 (0.2)

6.1.10. Major protocol violations/deviations

The frequency of important protocol violations was low (2.1 to 2.8%). In 50 patients, important protocol violations led to exclusion.

6.1.11. Baseline data

Baseline characteristics were similar across all three groups (see Table 3, below). Overall, 71.5% of subjects were men. Most (72.4%) were White, 21.6% Asian and 5.1% were Black or African American. The mean age was 63.1 years (± 8.6 years) with 35.3% 65 to 74 years and 9.3% at least 75 years. A total of 439 (6.3%) were less than 50 years.

Table 3. Demographic data (Treatment set)

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

Of the enrolled patients, 75.6% had coronary artery disease, 23.3% had a history of stroke, and 20.8% had peripheral artery disease. Approximately 17% had two cardiovascular risk factors and 1% had three. The majority (57%) had been diagnosed with T2DM for more than 10 years. Only 1.8% were treatment naïve anti-hypoglycaemic drugs (see Table 4, below).

Table 4. Patients with cardiovascular high-risk factors

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)
Number of patients	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)	7020 (100.0)
Any CV high-risk factor	2307 (98.9)	2333 (99.5)	2324 (99.2)	4657 (99.4)	6964 (99.2)
Coronary artery disease (CAD)[1]	1763 (75.6)	1782 (76.0)	1763 (75.3)	3545 (75.6)	5308 (75.6)
Multi-vessel CAD	1100 (47.1)	1078 (46.0)	1101 (47.0)	2179 (46.5)	3279 (46.7)
History of MI	1083 (46.4)	1107 (47.2)	1083 (46.2)	2190 (46.7)	3273 (46.6)
Coronary artery bypass graft	563 (24.1)	594 (25.3)	581 (24.8)	1175 (25.1)	1738 (24.8)
Single-vessel CAD	238 (10.2)	258 (11.0)	240 (10.2)	498 (10.6)	736 (10.5)
History of ischaem./haemorrh. stroke	553 (23.7)	535 (22.8)	549 (23.4)	1084 (23.1)	1637 (23.3)
Peripheral artery disease	479 (20.5)	465 (19.8)	517 (22.1)	982 (21.0)	1461 (20.8)
CV high-risk factor categories					
Only CAD	1340 (57.4)	1398 (59.6)	1334 (57.0)	2732 (58.3)	4072 (58.0)
Only cerebrovascular disease	325 (13.9)	328 (14.0)	307 (13.1)	635 (13.5)	960 (13.7)
Only peripheral artery disease	191 (8.2)	195 (8.3)	217 (9.3)	412 (8.8)	603 (8.6)
2 of the 3 CV high-risk factors	414 (17.7)	375 (16.0)	427 (18.2)	802 (17.1)	1216 (17.3)
All 3 CV high-risk factors	37 (1.6)	37 (1.6)	39 (1.7)	76 (1.6)	113 (1.6)
No CV high-risk factor[2]	26 (1.1)	12 (0.5)	18 (0.8)	30 (0.6)	56 (0.8)

Table shows factors existing prior to signing informed consent (collected via tick boxes in the CRF).
Patients with missing information are not shown.
[1] CAD defined as any of the following: history of MI, coronary artery bypass graft, multi-vessel CAD, single-vessel CAD.
[2] These patients had no documented high CV risk. They were allowed to continue in the trial and were not excluded from the analyses because of this reason.

Comorbidities included hypertension in 91.4%, diabetic neuropathy in 31.3%, diabetic retinopathy in 22%, and diabetic nephropathy in 19.5%. Approximately 10% of patients were known (self-reported) to have heart failure (see Table 5, below).

Table 5. Patients with a diagnosis of cardiac failure at Baseline

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

Mean baseline HbA1c was 8.07%, with half of patients with values less than 8% and 17% with values greater than 9%. Mean BMI 30.6 kg/m^2. Blood pressure was well controlled in 61.3% at Baseline. Renal function was normal in 21.9%, 52.2% had mild renal impairment and 25.5% had severe renal impairment. UACR was normal in 59.4%, 28.7% had microalbuminuria and 11% had macroalbuminuria.

At Baseline, a large proportion of patients in the trial were taking other medication for cardiac disease or to reduce their cardiovascular risk. These included 80.7% of patients taking a renin-angiotensin inhibitor; 81% of patients taking a lipid lowering drug, mainly statins; and most

were taking an anti-platelet agent or anticoagulant. Sixty five percent of patients were taking beta blockers, 43.2% were taking diuretics and 2.8% were taking digoxin.

6.1.12. Results for the primary efficacy outcome

The mean observation times were 3.07 years in the placebo arm, 3.15 years in the empagliflozin 10 mg arm and 3.16 years in the empagliflozin 25 mg arm.

6.1.12.1. Primary and key secondary endpoint

A total of 772 patients had an adjudicated primary endpoint event: CV death, non-fatal myocardial infarction, or non-fatal stroke (3-point MACE). There were 490 patients (10.5%) with an event in the combined empagliflozin treatment group and 282 patients (12.1%) in the placebo group. The hazard ratio (HR) based on Cox regression for all empagliflozin versus placebo was 0.86 (95.02% CI 0.74, 0.99). This result was primarily driven by a lower frequency of CV death in the all-empagliflozin treatment group. No significant treatment difference was observed for non-fatal myocardial infarction or non-fatal stroke (which was numerically greater in the empagliflozin group) (see Tables 6 and 7, below).

A total of 932 patients had an adjudicated key secondary endpoint event, which was time to first occurrence of adjudicated CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina (4-point MACE). There were 599 patients (12.8%) reported with an event in the all-empagliflozin group and 333 patients (14.3%) in the placebo group.

The HR based on Cox regression for all empagliflozin versus placebo was 0.89 (95.02% CI 0.78, 1.01) (see Tables 6, 7 and 10 below).

These data demonstrate the following for all empagliflozin versus placebo, according to the pre-specified hierarchical testing strategy:

1. Non-inferiority for the primary endpoint (upper bound of the 95.02% CI below 1.3) was met.
2. Non-inferiority for the key secondary endpoint (upper bound of the 95.02% CI below 1.3) was met.
3. Superiority for the primary endpoint (upper bound of the 95.02% CI below 1.0) was met.
4. No superiority for the key secondary endpoint (upper bound of the 95.02% CI above 1.0) was shown.

Sensitivity analyses of the primary and key secondary endpoints for all empagliflozin versus placebo were all consistent with the main analyses, with similar hazard ratios.

Cardiovascular deaths represented about a third of all events of the 3-point MACE.

Table 6. Cox regression for time to 3-point MACE and 4-point MACE events, all empagliflozin versus placebo (Treatment set)

	Placebo	All empa
Total patients in TS, N (100%)	2333	4687
3-point MACE, N (%) [incidence rate/1000 y]	282 (12.1) [43.9]	490 (10.5) [37.4]
HR vs. placebo (95.02% CI)[1]		0.86 (0.74, 0.99)
(95% CI)		(0.74, 0.99)
p-value for HR≥1.3 (1-sided)		<0.0001
p-value for HR≥1.0 (1-sided)		0.0191
4-point MACE, N (%) [incidence rate/1000 y]	333 (14.3) [52.5]	599 (12.8) [46.4]
HR vs. placebo (95.02% CI)[1]		0.89 (0.78, 1.01)
(95% CI)		(0.78, 1.01)
p-value for HR≥1.3 (1-sided)		<0.0001
p-value for HR≥1.0 (1-sided)		0.0397

[1] Based on the reduced α level of 0.0249 resulting from the interim analysis

There was no difference in primary or secondary outcome variables based on dose of empagliflozin.

Table 7. Cox regression for time to first 3-point MACE and 4-point MACE, by empagliflozin dose

	Placebo	Empa 10 mg	Empa 25 mg
3-point MACE, N (%) [incidence rate/1000 y]	282 (12.1) [43.9]	243 (10.4) [37.1]	247 (10.5) [37.7]
HR vs. placebo (95% CI)		0.85 (0.72, 1.01)	0.86 (0.73, 1.02)
p-value		0.0668	0.0865
4-point MACE, N (%) [incidence rate/1000 y]	333 (14.3) [52.5]	300 (12.8) [46.6]	299 (12.8) [46.3]
HR vs. placebo (95% CI)		0.89 (0.76, 1.04)	0.88 (0.76, 1.03)
p-value		0.1451	0.1204

For all exploratory analyses, 2-sided p-values based on α level of 0.05 are shown.

Table 8. Number of patients with 3-point MACE events by component

	Placebo	All empa
Patients, N (100%)	2333	4687
Patients with event	282 (12.1)	490 (10.5)
CV death	107 (4.6)	143 (3.1)
Non-fatal MI	120 (5.1)	208 (4.4)
Non-fatal stroke	55 (2.4)	142 (3.0)

Patients could be reported with multiple events if a non-fatal MI and a non-fatal stroke occurred on the same day.

Table 9. NNT and ARR for primary efficacy endpoints and subcomponents

	Placebo N = 2333	Empagliflozin[1] N = 4687	RD, ARR	NNT Approximate over 3 years
3-point MACE	282 (12.1%)	490 (10.5%)	1.6%	62.5
4-point MACE	333 (14.3%)	599 (12.8%)	2%	50
CV death	107 (4.6%)	143 (3.1%)	1.5%	67

	Placebo N = 2333	Empagliflozin[1] N = 4687	RD, ARR	NNT Approximate over 3 years
Non-fatal MI	120 (5.1%)	208 (4.4%)	0.7%	143
Non-fatal stroke	55 (2.4%)	142 (3.0)	-0.6%	NNH = 167
All-cause morality	137 (5.9%)	172 (3.7%)	2.2%	45
HF requiring hospitalisation + CV death + HF death	91 (4.1%) 198 (8.5%) 104 (4.5%)	126 (2.7%) 265 (5.7%) 129 (2.8%)	1.4% 2.8% 1.7%	71 36 59

1) empagliflozin 10 or 25 mg. RD = Risk difference; ARR = Absolute risk reduction; NNT = Number needed to treat; NNH = Numbers needed to harm.

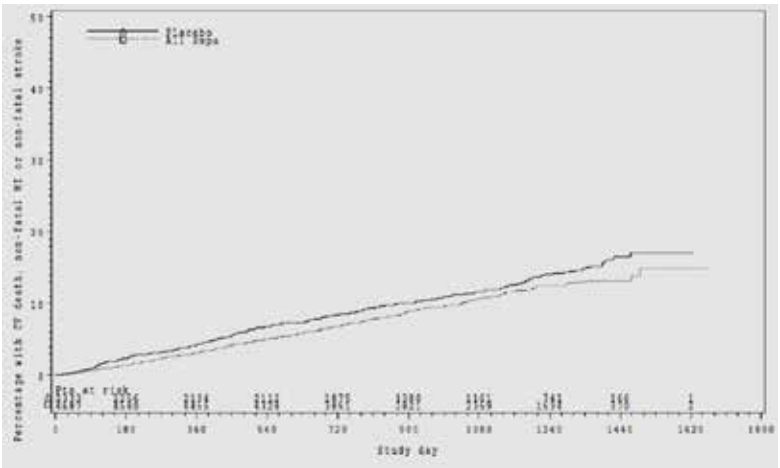
Although the relative risk reduction was around 14% for 3-point MACE and 11% for 4-point MACE, the absolute risk reduction was much smaller, 1.6% and 2% respectively.

Table 10. Number of patients with 4-point MACE events by component

	Placebo	All empa
Patients, N (100%)	2333	4687
Patients with event	333 (14.3)	599 (12.8)
CV death	104 (4.5)	142 (3.0)
Non-fatal MI	116 (5.0)	200 (4.3)
Non-fatal stroke	55 (2.4)	140 (3.0)
Hospitalisation for unstable angina	61 (2.6)	120 (2.6)

Note that these numbers for CV death, non-fatal MI and non-fatal stroke differ from to those for 3-point MACE (Table 11.1.1.1: 2) due to the additional component of hospitalisation for unstable angina.

Figure 2. Kaplan-Meier estimation of time to first 3-point MACE event

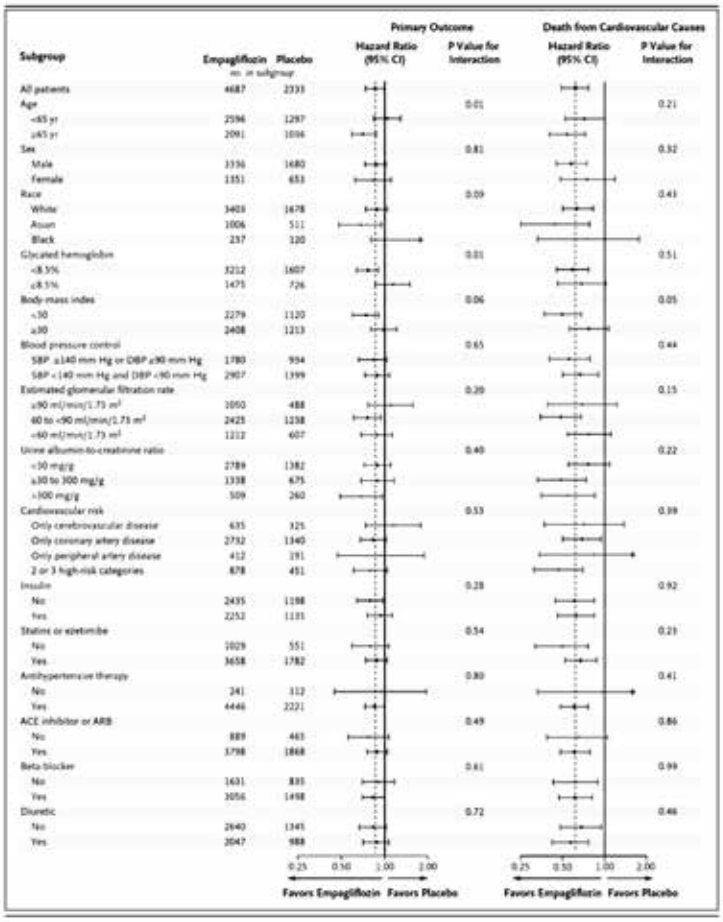


6.1.12.2. Subgroups

A nominal treatment by subgroup interaction p-value < 0.05 was observed for the parameters age, weight, history of hypertension and baseline HbA1c. Greater benefits were seen in those with prior coronary artery disease or a combination of cardiac risk factors than for cerebrovascular or peripheral vascular disease. However the subgroup analysis was not

adjusted for multiplicity testing and some subgroups were small. There was no significant treatment difference between patients treated with metformin at baseline and those without.

Table 11. Subgroup analysis



Source: New England Journal of Medicine by Zinman et al (2015).

Figure 3. Subgroup analysis for baseline HbA1c, time to CV death

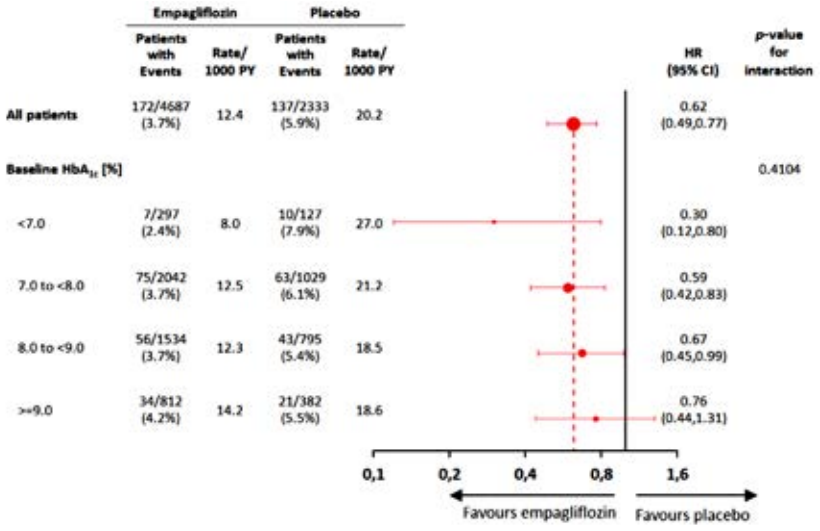
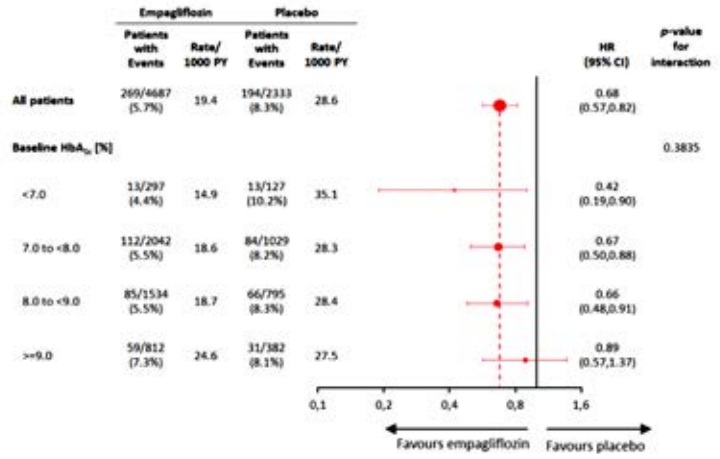
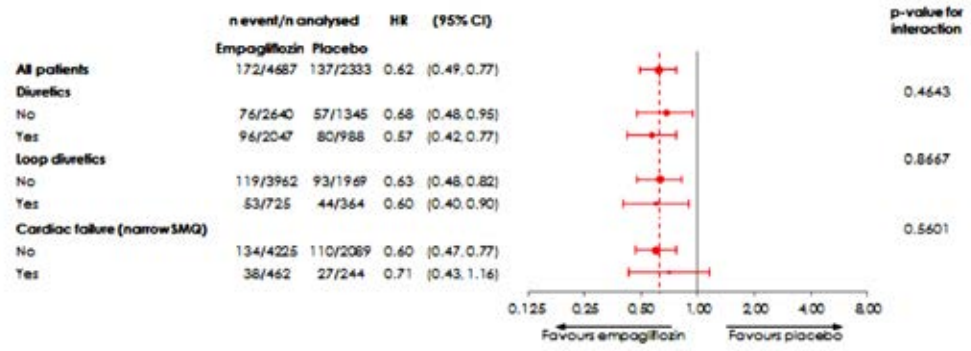


Figure 4. Subgroup analysis by baseline HbA1c: time to all-cause mortality



Patients with HbA1c < 7% in the placebo group had a higher rate of events than subjects with higher HbA1c in the placebo group. Empagliflozin was efficacious in improving the outcomes in this subgroup, however there were only 297 subjects in this group.

Figure 5. Subgroup analysis by baseline history of cardiac failure, time to first CV death



There was no significant difference in the outcomes CV death or hospitalisation for heart failure when patients with or without a history of heart failure or use of diuretics were compared.

6.1.13. Results for other efficacy outcomes

6.1.13.1. CV death and all-cause mortality

A total of 463 deaths occurred; the most common cause of death was cardiovascular (309 patients). The risk of CV death and of all-cause mortality was significantly lower in the empagliflozin treatment group than in the placebo group (see Tables 12 to 14, below). For both endpoints the separation of the event rates for empagliflozin and placebo started shortly after trial onset and was maintained throughout the trial (see Figure 2). The incidence rate of non-CV death was numerically lower in the all empagliflozin group than the placebo group. These results were confirmed for each individual dose group (with a similar extent of risk reduction) and across all subgroups by baseline characteristics including age, sex, renal function, glucose control, and baseline medication use.

Table 12. Cox regression for time to first CV death and all-cause mortality (Treatment set)

	Placebo	All empa
CV death, N (%) [incidence rate/1000 y]	137 (5.9) [20.2]	172 (3.7) [12.4]
HR vs. placebo (95% CI)		0.62 (0.49, 0.77)
p-value		<0.0001
All-cause mortality, N (%) [incidence rate/1000 y]	194 (8.3) [28.6]	269 (5.7) [19.4]
HR vs. placebo (95% CI)		0.68 (0.57, 0.82)
p-value		<0.0001
Non-CV death, N (%) [incidence rate/1000 y]	57 (2.4) [8.4]	97 (2.1) [7.0]
HR vs. placebo (95% CI)		0.84 (0.60, 1.16)

Table 13. Number of patients within the subcategories of CV death

	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)

Table 14. NNT and ARR for components of cardiovascular mortality

	ARR	NNT
Patients with CV Death	2.2%	45.5
Death due to acute MI	0.2%	500
Sudden death	0.5%	200
Death due to worsening heart failure	0.4%	240
Cardiogenic shock	0	-
Death due to stroke	0.2%	500

The greatest relative risk reduction was seen in the prevention of cardiovascular death, 38%. However the absolute risk reduction was much smaller, 2.2%. The small number of patients within each subgroup of cardiovascular deaths is noted. The most significant difference between groups was in the reduction in worsening of heart failure, but the number of patients was small 19 in the placebo group and 11 in the empagliflozin group. The cause of death was 'other' in 55/137 of the placebo patients, and 74/173 of those treated with empagliflozin. It is also unclear what cause the sudden cardiac deaths.

6.1.13.2. Myocardial infarction related endpoints

For the endpoints MI (fatal/non-fatal), non-fatal MI, and silent MI (secondary endpoint), no significant difference was observed between the empagliflozin and placebo groups. The same was observed for the endpoints hospitalisation for unstable angina and coronary revascularisation procedures. In each case, the results were consistent for the individual doses of empagliflozin.

Table 15. Cox regression for time to first MI related event

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
MI (fatal/non-fatal)[1]				
Analysed patients, N (100%)	2333	2345	2342	4687
Patients with event, N (%)	126 (5.4)	101 (4.3)	122 (5.2)	223 (4.8)
Incidence rate per 1000 years at risk	19.3	15.2	18.3	16.8
Hazard ratio vs. placebo (95% CI)		0.79 (0.61, 1.03)	0.95 (0.74, 1.22)	0.87 (0.70, 1.09)
p-value		0.0852	0.7141	0.2302
Non-fatal MI[1]				
Analysed patients, N (100%)	2333	2345	2342	4687
Patients with event, N (%)	121 (5.2)	96 (4.1)	117 (5.0)	213 (4.5)
Incidence rate per 1000 years at risk	18.5	14.4	17.6	16.0
Hazard ratio vs. placebo (95% CI)		0.79 (0.60, 1.03)	0.95 (0.74, 1.23)	0.87 (0.70, 1.09)
p-value		0.0769	0.7114	0.2189
Silent MI				
Analysed patients, N (100%)	1211	1174	1204	2378
Patients with event, N (%)	15 (1.2)	19 (1.6)	19 (1.6)	38 (1.6)
Incidence rate per 1000 years at risk	5.4	7.1	7.0	7.0
Hazard ratio vs. placebo (95% CI)		1.32 (0.67, 2.60)	1.24 (0.63, 2.45)	1.28 (0.70, 2.33)
p-value		0.4215	0.5282	0.4172
Hospitalisation for unstable angina				
Analysed patients, N (100%)	2333	2345	2342	4687
Patients with event, N (%)	66 (2.8)	69 (2.9)	64 (2.7)	133 (2.8)
Incidence rate per 1000 years at risk	10.0	10.4	9.5	10.0
Hazard ratio vs. placebo (95% CI)		1.03 (0.74, 1.45)	0.96 (0.68, 1.35)	0.99 (0.74, 1.34)
p-value		0.8509	0.7981	0.9706
Coronary revascularisation procedures				
Analysed patients, N (100%)	2333	2345	2342	4687
Patients with event, N (%)	186 (8.0)	154 (6.6)	175 (7.5)	329 (7.0)
Incidence rate per 1000 years at risk	29.1	23.5	26.7	25.1
Hazard ratio vs. placebo (95% CI)		0.81 (0.65, 1.00)	0.92 (0.75, 1.13)	0.86 (0.72, 1.04)
p-value		0.0536	0.4241	0.1135

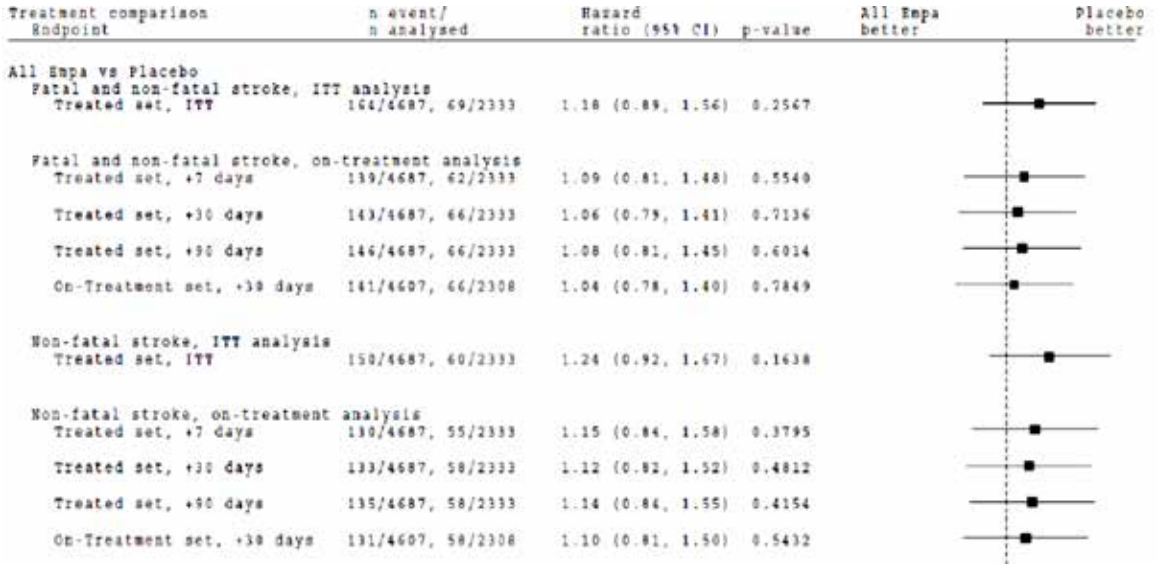
[1] Not including silent MI

There were numerically more silent MI (based on ECG criteria) than other types of cardiac ischemia in the empagliflozin groups. The sponsor has provided a number of reasons why silent MIs were not included in the 3-point MACE. The majority of modern cardiovascular trials do not include silent MI in the 3-point MACE. Although new pathogenic Q waves indicative of MI in asymptomatic patients who should be considered 'silent MI', ECG assessment alone a poor test for MI as silent Q waves can be transient in DM, they can recede after a true MI, and their prognostic value is unclear. There was no difference in the rate of the combined endpoint silent MI (ECG) or MI (fatal/nonfatal) between the placebo (incidence rate 48.5 per 1000 years at risk) and empagliflozin groups (45.7 per 1000 patient years at risk), HR 0.94 (95% CI 0.76, 1.15).

Cerebrovascular disease-related endpoints

For the endpoints stroke (fatal/non-fatal), non-fatal stroke, and TIA, there was no statistically significant difference was observed between the empagliflozin and placebo groups. However numerically, there were more strokes in the empagliflozin groups (see Figure 6).

Figure 6. Cox regression analysis for cerebrovascular events



6.1.13.3. Heart failure related endpoints

For the endpoints heart failure requiring hospitalisation (secondary endpoint), 'heart failure requiring hospitalisation or CV death (excluding fatal stroke)', and 'heart failure requiring hospitalisation or death from heart failure' a significantly lower risk was observed for the all-empagliflozin treatment group compared with the placebo group, (See Table 16, below). In each case the separation of the event rates for empagliflozin and placebo started shortly after at trial onset and was maintained throughout the trial. These results were confirmed for each individual dose group, with a similar extent of risk reduction. There was a consistent benefit of empagliflozin versus placebo for heart failure requiring hospitalisation and heart failure requiring hospitalisation or CV death (excluding fatal stroke) across all subgroups by baseline characteristics including age, sex, renal function, glucose control, and baseline medication use.

Table 16. Cox regression for time to first heart failure related event (Treatment set)

	Placebo	All empa
Heart failure requiring hospitalisation, N (%) [incidence rate/1000 y]	95 (4.1) [14.5]	126 (2.7) [9.4]
Hazard ratio vs. placebo (95% CI)		0.65 (0.50, 0.85)
p-value		0.0017
Heart failure requiring hospitalisation or CV death, N (%) [incidence rate/1000 y]	198 (8.5) [30.1]	265 (5.7) [19.7]
Hazard ratio vs. placebo (95% CI)		0.66 (0.55, 0.79)
p-value		<0.0001
Heart failure req. hosp. or death from heart failure, N (%) [incidence rate/1000 y]	104 (4.5) [15.8]	129 (2.8) [9.6]
Hazard ratio vs. placebo (95% CI)		0.61 (0.47, 0.79)
p-value		0.0002

Although the relative risk reduction in heart failure requiring hospitalisation or death from heart failure was 39%, the absolute risk reduction was 1.3%.

6.1.13.4. Microvascular endpoints

For the endpoint time to composite microvascular outcome, which consisted of nephropathy and diabetic retinopathy, a significantly lower risk was observed for the all-empagliflozin treatment group compared with the placebo group (see Table 17, below). There were 577 patients (14.0%) (incidence rate 52.8/1000 years) with an event in the all-empagliflozin group and 424 patients (20.5%) (incidence rate 83.6/1000 years) in the placebo group, with a hazard ratio of 0.62 (95% CI 0.54, 0.70; $p < 0.0001$). New or worsening nephropathy represented the

majority of the cases of the composite endpoint and thus largely influenced the result for this endpoint. Consistent observations were made for the individual empagliflozin dose groups. No significant treatment difference was observed for new onset of albuminuria or diabetic eye complications.

The improvement in microvascular endpoints was largely driven by improvement of renal disease.

Table 17. Cox regression analyses for composite microvascular endpoints (TS)

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
Composite microvascular outcome				
Analysed patients, N (100%)	2068	2057	2075	4132
Patients with event, N (%)	424 (20.5)	285 (13.9)	292 (14.1)	577 (14.0)
Incidence rate per 1000 years at risk	83.6	52.7	53.0	52.8
Hazard ratio vs. placebo (95% CI)		0.62 (0.53, 0.72)	0.62 (0.53, 0.71)	0.62 (0.54, 0.70)
p-value		<0.0001	<0.0001	<0.0001

There was no significant treatment difference for the endpoints retinal photocoagulation, vitreous haemorrhage, and diabetes related blindness.

6.1.13.5. Nephropathy endpoints

New or worsening nephropathy was a composite endpoint of:

1. New onset macroalbuminuria
2. Doubling of serum creatinine plus eGFR ≤ 45 mL/min/1.73m^2
3. Initiation of continuous renal replacement therapy
4. Death due to renal disease.

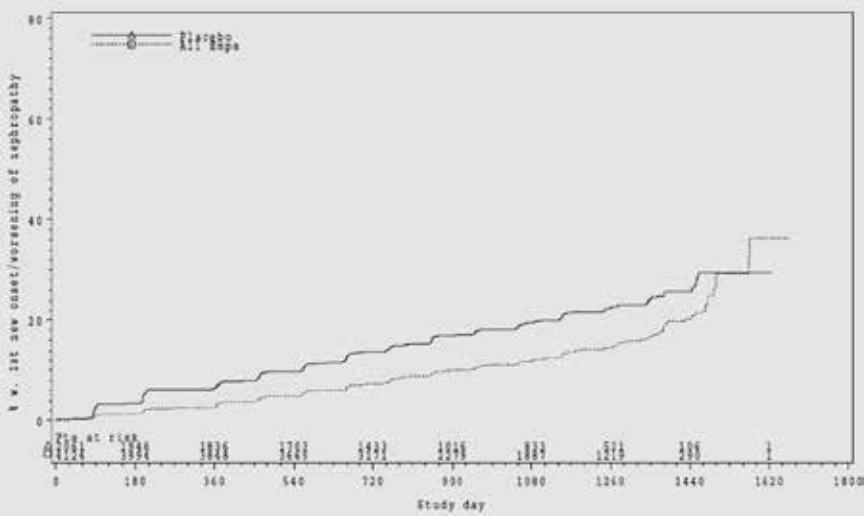
There was a significant reduction in risk in all components except for death due to renal disease (low numbers) compared to placebo, see Table 18 (below) and Figure 7. The relative risk reduction in new or worsening nephropathy was 39% and absolute risk reduction 6.1%.

Table 18. Cox regression analyses for nephropathy related endpoints (Treatment set)

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
New or worsening nephropathy				
Analysed patients, N (100%)	2061	2055	2069	4124
Patients with event, N (%)	388 (18.8)	261 (12.7)	264 (12.8)	525 (12.7)
Incidence rate per 1000 years at risk	76.0	47.9	47.6	47.8
Hazard ratio vs. placebo (95% CI)		0.61 (0.53, 0.72)	0.61 (0.52, 0.71)	0.61 (0.53, 0.70)
p-value		<0.0001	<0.0001	<0.0001
New or worsening nephropathy or CV death				
Analysed patients, N (100%)	2102	2078	2092	4170
Patients with event, N (%)	497 (23.6)	338 (16.3)	337 (16.1)	675 (16.2)
Incidence rate per 1000 years at risk	95.9	61.4	60.1	60.7
Hazard ratio vs. placebo (95% CI)		0.62 (0.54, 0.72)	0.61 (0.53, 0.70)	0.61 (0.55, 0.69)
p-value		<0.0001	<0.0001	<0.0001
New onset of macroalbuminuria (UACR >300 mg/g)[1]				
Analysed patients, N (100%)	2033	2037	2054	4091
Patients with event, N (%)	330 (16.2)	222 (10.9)	237 (11.5)	459 (11.2)
Incidence rate per 1000 years at risk	64.9	40.8	42.8	41.8
Hazard ratio vs. placebo (95% CI)		0.61 (0.52, 0.73)	0.64 (0.54, 0.75)	0.62 (0.54, 0.72)
p-value		<0.0001	<0.0001	<0.0001
Doubling of serum creatinine plus eGFR ≤45 mL/min/1.73m² [1]				
Analysed patients, N (100%)	2323	2323	2322	4645
Patients with event, N (%)	60 (2.6)	42 (1.8)	28 (1.2)	70 (1.5)
Incidence rate per 1000 years at risk	9.7	6.6	4.4	5.5
Hazard ratio vs. placebo (95% CI)		0.67 (0.45, 1.00)	0.44 (0.28, 0.69)	0.56 (0.39, 0.79)
p-value		0.0481	0.0004	0.0009
Initiation of continuous renal replacement therapy[1]				
Analysed patients, N (100%)	2333	2345	2342	4687
Patients with event, N (%)	14 (0.6)	3 (0.1)	10 (0.4)	13 (0.3)
Incidence rate per 1000 years at risk	2.1	0.4	1.5	1.0
Hazard ratio vs. placebo (95% CI)		0.21 (0.06, 0.74)	0.70 (0.31, 1.57)	0.45 (0.21, 0.97)
p-value		0.0146	0.3812	0.0409
Death due to renal disease[1, 2]				
Analysed patients, N (100%)	2333	2345	2342	4687
Patients with event, N (%)	0	3 (0.1)	0	3 (0.1)
Incidence rate per 1000 years at risk	0	0.4	0	0.2

[1] Component of 'new or worsening nephropathy'
[2] No hazard ratios were calculated, since the overall number of patients with event was lower than 7x the number of treatment groups.

Figure 7. Kaplan Meier graph for time to new onset or worsening of nephropathy



There was no significant difference in the prevalence of micro albuminuria between treatment groups. However, more patients in the empagliflozin arms had an improvement in albuminuria (see Table 19, below).

In those with micro albuminuria at baseline, there was an improvement in UACR with treatment with empagliflozin, however when treatment was stopped the UACR returned to baseline values (but remained less than the placebo group).

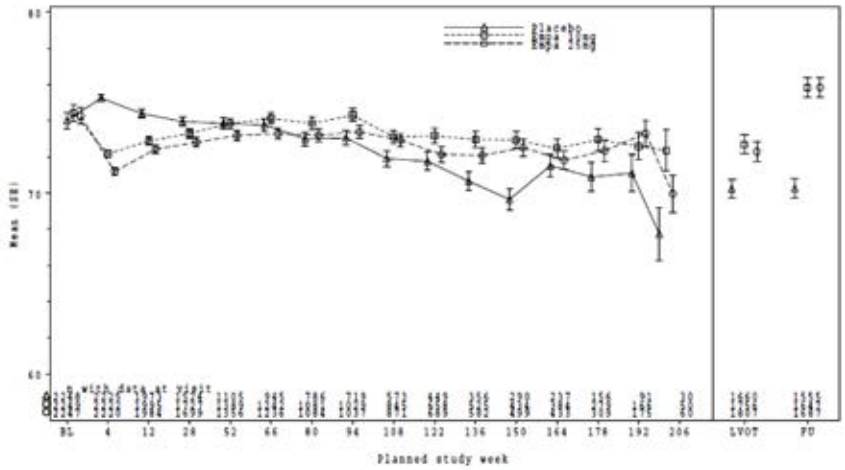
Table 19. Cox regression analyses for reversibility of albuminuria (Treatment set)

	Placebo	Empa 10 mg	Empa 25 mg	All Empa
New onset of sustained improvement to normoalbuminuria[1]				
Analysed patients, N (100%)	659	634	678	1312
Patients with event, N (%)	219 (33.2)	275 (43.4)	299 (44.1)	574 (43.8)
Incidence rate per 1000 years at risk	162.0	233.9	243.5	238.8
Hazard ratio vs. placebo (95% CI)		1.40 (1.18, 1.68)	1.45 (1.22, 1.72)	1.43 (1.22, 1.67)
p-value		0.0002	<0.0001	<0.0001
New onset of sustained improvement to normo- or microalbuminuria[2]				
Analysed patients, N (100%)	257	256	243	499
Patients with event, N (%)	74 (28.8)	126 (49.2)	122 (50.2)	248 (49.7)
Incidence rate per 1000 years at risk	155.2	295.6	313.8	304.2
Hazard ratio vs. placebo (95% CI)		1.78 (1.33, 2.37)	1.87 (1.39, 2.50)	1.82 (1.40, 2.37)
p-value		<0.0001	<0.0001	<0.0001

[1] In patients with microalbuminuria at baseline
[2] In patients with macroalbuminuria at baseline

In the placebo group there was a deterioration of eGFR with time, however eGFR remained more stable in those treated with empagliflozin (see Figure 8). eGFR increase when empagliflozin was stopped.

Figure 8. eGFR MMRM results over time (observed cases) with unadjusted last value on treatment and follow up value



6.1.13.6. Medication initiated during the trial

The study described the number of patients where antihypertensive, anticoagulants and lipid lowering drugs were introduced after Baseline. This summary does not capture medications ceased or changes in dosage. Of the TS, 51% of patients receiving placebo and 44.5% of those receiving empagliflozin received extra (or change in) hypertensive therapy. For anticoagulants, therapy was added in 30.3% and 28.6% respectively, and lipid lowering drugs 30.8% and 29.1% respectively.

Table 20. Use of rescue medication (FAS)

	Placebo	Empa 10 mg	Empa 25 mg
Number of patients, N (%)	(100.0)	(100.0)	(100.0)
Number of patients with any rescue medication	1265 (54.2)	777 (33.1)	745 (31.8)
Number of patients with increase[1] in dose of background medication	931 (39.9)	555 (23.7)	537 (22.9)
Number of patients with additional antidiabetic medication[1]	631 (27.0)	364 (15.5)	328 (14.0)
Insulin	221 (9.5)	110 (4.7)	87 (3.7)
DPP-IV inhibitor	151 (6.5)	106 (4.5)	88 (3.8)
Sulphonylurea	147 (6.3)	79 (3.4)	61 (2.6)
Metformin	96 (4.1)	69 (2.9)	60 (2.6)
GLP-1 agonist	51 (2.2)	22 (0.9)	31 (1.3)
Glitazone	60 (2.6)	17 (0.7)	29 (1.2)
A−glucosidase inhibitor	29 (1.2)	28 (1.2)	20 (0.9)
Glinide	26 (1.1)	11 (0.5)	14 (0.6)
Other antidiabetic medication	11 (0.5)	1 (<0.1)	4 (0.2)

[1] For 7 days or more

Note the increased prescribing of insulin and glitazones in the placebo arm. These drugs have been associated with salt and fluid retention and may have exacerbated any heart failure that was present.

Subgroup analysis by medications showed a numerically greater risk of primary outcome in those taking DPP-4 inhibitors at baseline. It is noted that the confidence interval is wide and p group for interaction was 0.06. The increased risk was driven by the endpoints CV death and stroke. Patients in the placebo arm who took DDP-4 inhibitors had a lower risk of events than those who did not take DDP-4 inhibitors. This may suggest DDP-4 inhibitors also had a CV protective effect.

6.1.13.7. Glycaemic control

There was an initial improvement in HbA1c in the empagliflozin groups of around 0.54 to 0.60 percentage points in the first 12 weeks, followed by a slow rise in parallel with the placebo group, see Figure 9 and Table 21 (below).

Figure 9. Adjusted mean HbA1c (%) over time, MMRM (Full analysis set, Observed cases)

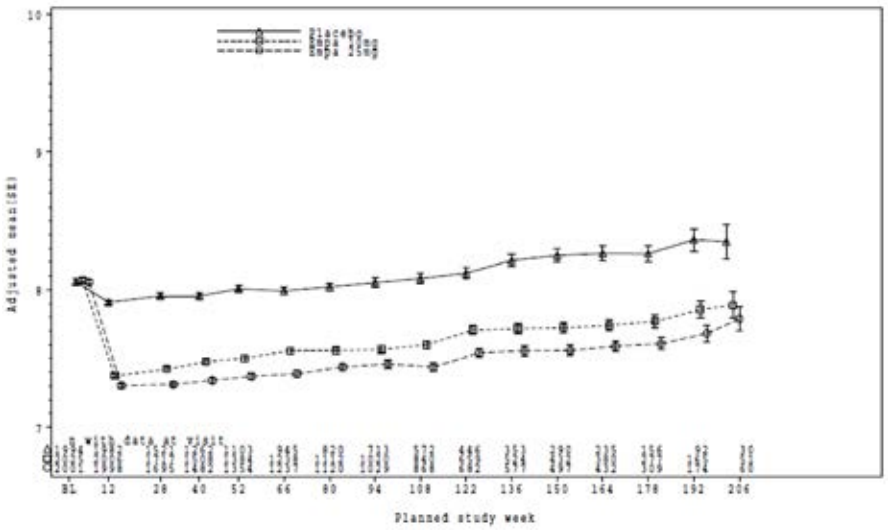


Table 21. Change in HbA1c (%) from Baseline, MMRM (FAS, Observed cases after discontinuation or rescue medication intake)

Visit/ treatment group	N[1]	Baseline HbA_{1c}, mean (SE)	Change from baseline, adjusted mean[2] (SE)	Difference from placebo	
				Adjusted mean[2] (SE)	95% CI
Week 12					
Placebo	2272	8.08 (0.02)	-0.11 (0.02)		
Empa 10 mg	2272	8.08 (0.02)	-0.65 (0.02)	-0.54 (0.02)	(-0.58, -0.49)
Empa 25 mg	2280	8.07 (0.02)	-0.71 (0.02)	-0.60 (0.02)	(-0.64, -0.55)
Week 94					
Placebo	1967	8.08 (0.02)	-0.08 (0.02)		
Empa 10 mg	2058	8.08 (0.02)	-0.50 (0.02)	-0.42 (0.03)	(-0.48, -0.36)
Empa 25 mg	2044	8.07 (0.02)	-0.55 (0.02)	-0.47 (0.03)	(-0.54, -0.41)

SE= standard error

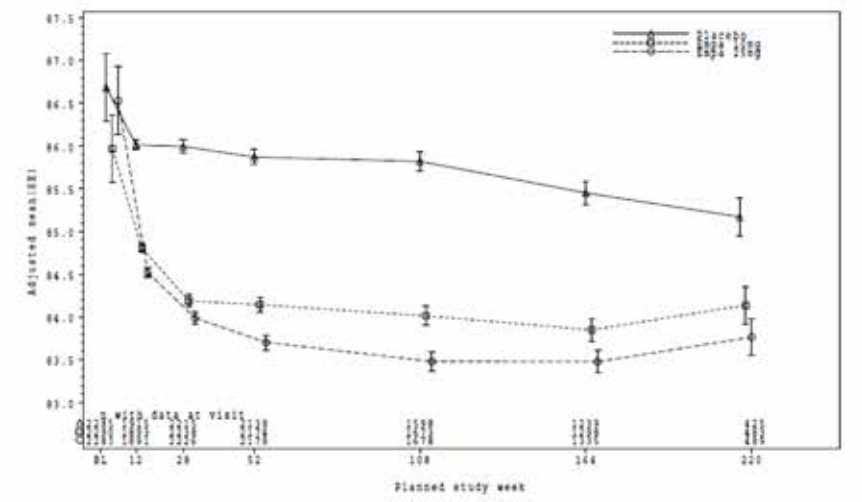
[1] Number of analysed patients

[2] MMRM model includes treatment, baseline HbA_{1c} (cont.), baseline BMI (cat.), baseline eGFR (cat.), week reachable for HbA_{1c}, geographical region, visit, visit by treatment interaction, and baseline HbA_{1c} by visit interaction.

6.1.13.8. Body weight and waist circumference

For both body weight and waist circumference the values in the placebo group remained relatively stable. In the empagliflozin groups, body weight decreased rapidly in the first 28 weeks then stabilised. It is noted that patients were only weighed annually after the first 52 weeks, and that there are less measurements contributing to the later data points (see Figure 7).

Figure 10. Adjusted mean body weight over time, MMRM (Treatment set, Observed cases after discontinuation or rescue medication intake)



Blood pressure

In the placebo group, systolic blood pressure remained stable throughout the study. In the empagliflozin groups, there was an initial reduction of systolic BP of around 7 mmHg at Week 16, followed by a gradual increase in systolic BP for the remainder of the study (see Figure 11. For diastolic BP, there was a reduction in BP in both placebo and empagliflozin groups for the duration of the study; this decrease was greater in the empagliflozin group (see Figure 12).

In relation to the proportion of patients achieving a target SBP< 140mmHg and DBP< 90mmHg, this was achieved by 40.1% of subjects in the empagliflozin group and 32% of those in the placebo group.

Figure 11. Adjusted mean SBP (mmHg) over time MMRM (Treatment set, Observed cases after discontinuation or rescue medication intake)

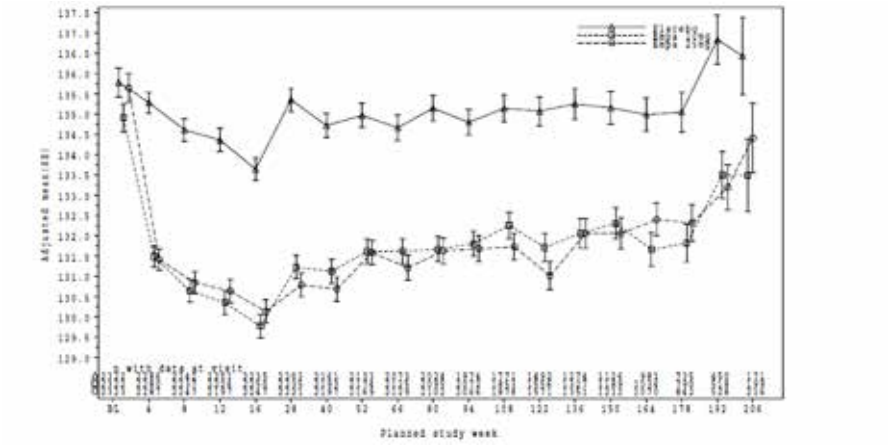
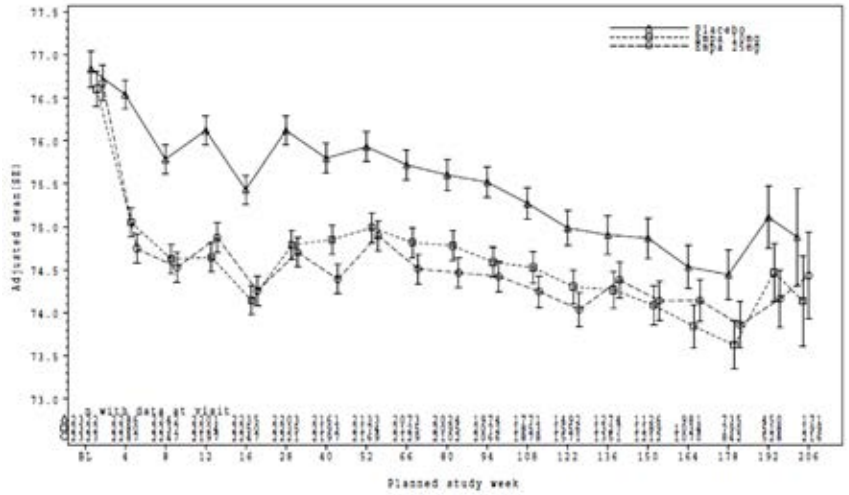


Figure 12. Adjusted mean DBP (mmHg) from Baseline over time-MMRM (Treatment set, Observed cases after discontinuation or rescue medication intake)



6.1.13.9. Subgroup analysis for efficacy in CRF with eGFR 30 to 45 mL/min/m²

The following number of patients had significant renal impairment and were used in this subgroup analysis

- eGFR 45 < 60 mL/min/1.73 m²: n = 1249
- eGFR 30 to 45 mL/min/1.73 m²: n = 543

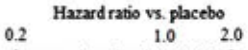
Improvements in cardiovascular outcomes were also observed in patients with eGFR < 60 mL/min/1.73 m². These were not statistically significant, however the small number of patients is noted, Figure 13.

The results for new or worsening nephropathy for patients with eGFR < 60 were also similar to the main study group, Figure 14.

There were no safety signals in patients with moderate renal impairment (see Table 22, below). However it is noted that patients with CKD had more serious adverse events than those without renal impairment.

Figure 13. Summary of CV death, mortality and heart failure related endpoints for all patients and patients with eGFR < 60 mL/min/1.73 m²

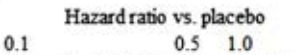
Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo HR	95% CI		p-value
CV death, all patients						
Placebo	137 (5.9)	20.2	--	--	--	--
All empa	172 (3.7)	12.4	0.62	0.49	0.77	<0.0001
Patients with eGFR <60 mL/min/1.73m²						
Placebo	48 (7.9)	27.2	--	--	--	--
All empa	75 (6.2)	21.1	0.78	0.54	1.12	0.1831
Patients with CKD 3A (eGFR 45 to <60 mL/min/1.73m²)						
Placebo	30 (7.2)	24.5	--	--	--	--
All empa	49 (5.9)	19.8	0.82	0.52	1.29	0.3950
Patients with eGFR <45 mL/min/1.73m²						
Placebo	18 (9.5)	33.2	--	--	--	--
All empa	26 (6.8)	24.0	0.71	0.39	1.30	0.2719
All-cause mortality, all patients						
Placebo	194 (8.3)	28.6	--	--	--	--
All empa	269 (5.7)	19.4	0.68	0.57	0.82	<0.0001
Patients with eGFR <60 mL/min/1.73m²						
Placebo	72 (11.9)	40.8	--	--	--	--
All empa	115 (9.5)	32.3	0.80	0.59	1.07	0.1345
Patients with CKD 3A (eGFR 45 to <60 mL/min/1.73m²)						
Placebo	45 (10.8)	36.8	--	--	--	--
All empa	68 (8.2)	27.5	0.76	0.52	1.11	0.1543
Patients with eGFR <45 mL/min/1.73m²						
Placebo	27 (14.3)	49.7	--	--	--	--
All empa	47 (12.3)	43.3	0.86	0.53	1.37	0.5183
Heart failure requiring hospitalisation or CV death (excluding fatal stroke), all patients						
Placebo	198 (8.5)	30.1	--	--	--	--
All empa	265 (5.7)	19.7	0.66	0.55	0.79	<0.0001
Patients with eGFR <60 mL/min/1.73m²						
Placebo	77 (12.7)	46.0	--	--	--	--
All empa	112 (9.2)	32.6	0.72	0.54	0.96	0.0237
Patients with CKD 3A (eGFR 45 to <60 mL/min/1.73m²)						
Placebo	48 (11.5)	41.1	--	--	--	--
All empa	71 (8.5)	29.7	0.74	0.51	1.07	0.1079
Patients with eGFR <45 mL/min/1.73m²						
Placebo	29 (15.3)	57.3	--	--	--	--
All empa	41 (10.8)	39.1	0.67	0.41	1.07	0.0953



Number of analysed patients with eGFR <60 mL/min/1.73m²: 607 in placebo, 1212 in all empagliflozin.
Number of analysed patients with eGFR 45 to <60 mL/min/1.73m²: 418 in placebo, 831 in all empagliflozin.
Number of analysed patients with eGFR <45 mL/min/1.73m²: 189 in placebo, 381 in all empagliflozin.

Figure 14. New or worsening nephropathy for all patients and patients with eGFR < 60 mL/min/1.73 m²

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo HR	95% CI		p-value
All patients						
Placebo	388 (18.8)	76.0	--	--	--	--
All empa	525 (12.7)	47.8	0.61	0.53	0.70	<0.0001
Patients with eGFR <60 mL/min/1.73m²						
Placebo	151 (30.4)	135.2	--	--	--	--
All empa	192 (19.5)	76.8	0.55	0.44	0.68	<0.0001
Patients with CKD 3A (eGFR 45 to <60 mL/min/1.73m²)						
Placebo	93 (27.3)	119.8	--	--	--	--
All empa	127 (18.0)	68.7	0.55	0.42	0.72	<0.0001
Patients with eGFR <45 mL/min/1.73m²						
Placebo	58 (37.2)	170.6	--	--	--	--
All empa	65 (23.6)	99.4	0.58	0.40	0.82	0.0022



Number of analysed patients with eGFR <60 mL/min/1.73m²: 497 in placebo, 983 in all empagliflozin.
Number of analysed patients with eGFR 45 to <60 mL/min/1.73m²: 341 in placebo, 707 in all empagliflozin.
Number of analysed patients with eGFR <45 mL/min/1.73m²: 156 in placebo, 276 in all empagliflozin.

Table 22. Summary of AE for patients with CKD 3 at Baseline

	Placebo		Empa 10 mg		Empa 25 mg	
	N (%)	Rate / 100 p-y	N (%)	Rate / 100 p-y	N (%)	Rate / 100 p-y
CKD 3 (eGFR 30 to <60 mL/min/1.73m^2), N	601 (100.0)		598 (100.0)		593 (100.0)	
Patients with any adverse event	571 (95.0)	262.31	544 (91.0)	178.37	544 (91.7)	184.94
Leading to discount. of study medication	163 (27.1)	12.39	145 (24.2)	10.59	128 (21.6)	9.27
Serious adverse events	318 (52.9)	31.75	271 (45.3)	24.39	269 (45.4)	24.96
Decreased renal function (SMQ)	84 (14.0)	6.32	62 (10.4)	4.45	71 (12.0)	5.20
Hepatic injury (SMQ)	27 (4.5)	1.94	21 (3.5)	1.44	24 (4.0)	1.68
Urinary tract infection (BIcMQ)	132 (22.0)	10.54	145 (24.2)	11.78	128 (21.6)	10.14
Genital infection (BIcMQ)	10 (1.7)	0.71	23 (3.8)	1.60	40 (6.7)	2.87
Confirmed hypoglycaemic AEs[1]	229 (38.1)	NA	194 (32.4)	NA	191 (32.2)	NA
Bone fracture (BIcMQ)	31 (5.2)	2.24	31 (5.2)	2.17	26 (4.4)	1.83
Volume depletion (BIcMQ)	48 (8.0)	3.55	44 (7.4)	3.12	35 (5.9)	2.49
Malignancy (BIcMQ)	33 (5.5)	2.36	39 (6.5)	2.71	28 (4.7)	1.95
Hypersensitivity (SMQ)	71 (11.8)	5.41	38 (6.4)	2.68	41 (6.9)	2.94
Venous embolic and thrombotic AEs (SMQ)	6 (1.0)	0.42	3 (0.5)	0.20	10 (1.7)	0.69

6.2. Evaluator's conclusions on clinical efficacy

6.2.1. The prevention of cardiovascular events

The EMPA-REG study was a large, multicentre, RCT initially designed as a non-inferiority study to assess the cardiovascular safety of empagliflozin in the management of patients with T2DM and poor glycaemic control. The methodology and conduct of the trial was robust. The primary end point was 3-point MACE. The main secondary endpoint was 4-point MACE. Additional secondary endpoints included the components of the MACE, hospitalisation for heart failure, causes of cardiovascular death, glycaemic control, BP, weight. Subgroup analysis was performed but was explorative in nature.

The main inclusion criteria were having T2DM with poor glycaemic control (HbA1c > 7%), eGFR > 30mL/min/m^2, and greater than one cardiac risk factor. The cardiac risk factors were mainly risk factors for macrovascular disease. It is noted that only 10% of patients had a documented history of heart failure at Baseline. There were no screening tests for cardiac function performed so the true prevalence may be different to this.

The study demonstrated that empagliflozin was non-inferior to placebo in the prevention of 3- and 4-point MACE, and also demonstrated superiority to placebo for combined 3-point MACE. On analysis of individual/component endpoints this was driven by a reduction in cardiovascular mortality and heart failure. The greatest relative risk reduction was in hospitalisation for heart failure, death due to heart failure but the number of events and absolute risk reduction was small.

There were more patients in the empagliflozin group who had silent MI. However no significant different when silent MI and all MI are considered together. The significance of the silent MI group could be questioned due to inability to prove ECG changes are due to infarction, and exclusion of a large number of patients in the analysis.

The reduction in cardiovascular mortality occurred early after the onset of the study, within 90 days, and persisted for the duration. It was largely attributed to a reduction in deaths due to worsening of heart failure. There was also a statistically significant reduction in hospitalisation due to heart failure. There was no significant difference in the rates of MI or coronary revascularisation procedures. There was no significant difference in the incidence of stroke or TIA between the empagliflozin and placebo groups. Numerically, there were more in strokes in the empagliflozin group, but more deaths due to stroke in the placebo group.

Treatment with empagliflozin resulted in a significant reduction in new onset and worsening or nephropathy and stabilisation of eGFR. There are plausible pathophysiological mechanisms by which the SGLT2 inhibitors may be beneficial to the kidney in patients with diabetes. In patients

with diabetes, hyperglycaemia leads to increased filtered glucose load at the proximal tubule and an increased SGLT2 mRNA expression. This causes more glucose and sodium reabsorption, reduced sodium delivery to the macular densa, less ATP, less vasoconstriction, and hyperfiltration. SGLT2 inhibitors have been shown to reverse this in animal and human trials, with an associated decrease then plateau of GFR (Skrtic 2015).

There was no significant difference in the development or progression of diabetic eye disease.

There was an initial improvement in HbA1c in the empagliflozin treatment group, flowed by a slow increase in HbA1c. Weight and SBP had a similar pattern. More patients in the placebo group received rescue medication for poor glycaemic control (50% compared with 34%), it is noted that there were more patients in the placebo group who commenced treatment with insulin, DDP-IV inhibitor, GLP-1 agonist or a glitazone. Some of these drugs are known to cause fluid retention and may have exacerbated any heart failure.

Although an improvement in cardiovascular mortality cannot be disputed, the absolute risk reduction is small (around 2%). There were a large number of patients who died from a cardiovascular event where the cause of the event was unknown. The greatest risk reduction appeared to be in the prevention of deterioration of heart failure and hospitalisation due to heart failure, but these numbers were small. Haemodynamic effects of empagliflozin in reducing pre- and after-load are likely to be responsible for this (Abdul-Ghani et al. 2016). This would not only reduce death due to heart failure from fluid overload, but also reduce the rate of sudden death from arrhythmia due to less 'stretch'. Unlike other diuretics, there was no increase in potassium, heart rate of uric acid. There does not appear to be a significant effect of the rate of macrovascular disease (MI, unstable angina, need for revascularisation procedures) between the two groups.

The cardiovascular benefits seen with empagliflozin are in addition to the use of other medications to reduce cardiovascular risk (that is, statins, ACE inhibitors or angiotensin reception blocked and/or beta blockers). This needs to be highlighted in the PI.

The investigators chose subjects with high cardiovascular risk defined as prior MI or coronary artery disease, evidence of stroke of peripheral vascular disease. However, having diabetes is also considered to be a cardiovascular risk. The absolute risk reduction in cardiovascular deaths would be lower in populations of lower baseline cardiovascular risk. A significant proportion of subjects with diabetes have silent cardiac ischemia. Heart failure in diabetes is thought to be multifactorial and not entirely explained by coronary artery disease. Other risk factors include age, duration of diabetes, use of insulin, ischemic heart disease, peripheral arterial disease, elevated serum creatinine, poor glycaemic control and microalbuminuria. The pathophysiology of heart failure in diabetes is related to not only coronary artery disease but also hypertension, diabetic cardiomyopathy and extracellular fluid volume expansion.

Of the other hypoglycaemic drugs: thiazolidinedione's, sulphonylureas and insulin have been associated with an increased risk of heart failure. The clinical trials of GLP-1 agonists and DDP-IV inhibitors have shown inconsistent results. Metformin has not been associated with an increased risk of heart failure. However from a physiological perspective, any drugs that cause hypoglycaemia have the potential to exacerbate heart failure by the physiological mechanism of sympathetic stimulation and also reduced energy substrate delivery to the myocardium.

The sponsor has proposed a new indication in T2DM for the prevention of cardiovascular death as the effects of empagliflozin are independent of the effects on glycaemic control. Evidence in support of this includes the early onset of changes in cardiac endpoints, lack of significant effect on cardiac mortality seen in other trials of glucose lowering therapy. This is reasonable. However, in the EMPA-REG study only 6% (424) of patient had HbA1c < 7%. Analysis of subgroups like these needs to be cautious, we cannot be sure that there was adequate randomisation for this subgroup, and the study was not powered for subgroup analysis. It is also noteworthy that there was an extra-ordinarily high rate of events in the placebo group.

Thus, although efficacy in patients with T2DM and poor glycaemic control has been satisfactorily established, efficacy in those who have reached their HbA1c target remains questionable.

The sponsor has proposed the words 'cardiovascular death' rather than 3-point MACE to be used in the indication based on the significant benefits seen on this endpoint. The sponsor's rationale was that it is an important and objective endpoint and statistically significant benefits were seen. Furthermore, there was no significant improvement in macrovascular outcomes, so the inclusion of other components of the 3-point MACE (MI or stroke) is potentially misleading. The evaluator considers it reasonable to include prevention of cardiac failure in the indication as there is reasonable evidence based on analysis of the secondary endpoints and knowledge of the mechanism of action of empagliflozin.

The sponsor included both 10 mg and 25 mg doses of empagliflozin in the efficacy analysis. This was pre-specified. The dose proposed for cardiovascular prevention is 10 mg, increasing to 25 mg in patients with poor glycaemic control. This is reasonable.

6.2.2. Use in renal failure

The improvement in HbA1c with empagliflozin in patients with impaired renal function was less than that observed in patients with normal renal function. However, in these patients, improved glycaemic control is probably less important than overall mortality. empagliflozin showed numerical trends towards efficacy in these endpoints. These were not statistically significant, most likely due to low patient numbers.

7. Clinical safety

7.1. Pivotal studies that assessed safety as a primary outcome

- EMPA-REG OUTCOME study

See Section 7 'Efficacy' above for the study methodology.

7.1.1. Safety variables and outcomes

Safety was assessed on the basis of adverse events that occurred during treatment or within 7 days after the last dose of a study drug.

Adverse events of special interest included hypoglycaemia (BGL < 3.9 mmol/L), UTI, genital infection, volume depletion, ARF, bone fracture, DKA and thromboembolic events.

Other safety outcomes included change from baseline in laboratory parameters, lipid profile, vital signs and ECG.

7.1.2. Results for the primary safety outcome

The trial was initially designed as a non-inferiority study to assess cardiovascular safety. This is described in the efficacy section. Any difference in the rates of cardiovascular and microvascular events are due to the use of adjudicated data for efficacy compared to adverse event data for safety.

7.2. Patient exposure

The mean observation time on treatment was 2.91 years in the placebo group and 2.96 years in the empagliflozin group. There were 3 patients who received empagliflozin for more than 260 weeks, 385 who received empagliflozin for greater than 208 weeks, and 2464 patients who received empagliflozin for more than 156 weeks (see Table 23, below).

Table 23. Patient exposure (Treatment set)

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

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

7.3. Adverse events

7.3.1. All adverse events (irrespective of relationship to study treatment)

Table 24. Overall summary of AE (Treatment set)

Category of AEs	Placebo			Empa 10 mg			Empa 25 mg		
	N	(%)	Rate/100 pt-yrs	N	(%)	Rate/100 pt-yrs	N	(%)	Rate/100 pt-yrs
Number of patients	2333	(100.0)		2345	(100.0)		2342	(100.0)	
Any AE	2139	(91.7)	178.67	2112	(90.1)	150.34	2118	(90.4)	148.36
Severe AEs [1]	592	(25.4)	NA	536	(22.9)	NA	564	(24.1)	NA
Investigator-defined drug-related AEs	549	(23.5)	11.33	666	(28.4)	14.15	643	(27.5)	13.38
AEs leading to discontinuation of study medication[2]	453	(19.4)	8.26	416	(17.7)	7.28	397	(17.0)	6.89
Serious AEs [3]	988	(42.3)	22.34	876	(37.4)	18.20	913	(39.0)	19.39
Fatal	119	(5.1)	2.06	97	(4.1)	1.61	79	(3.4)	1.31
Immediately life-threatening	44	(1.9)	0.77	53	(2.3)	0.89	60	(2.6)	1.00
Disabling/incapacitating	24	(1.0)	NA	18	(0.8)	NA	22	(0.9)	NA
Requiring hospitalisation	852	(36.5)	NA	751	(32.0)	NA	818	(34.9)	NA
Prolonging hospitalisation	74	(3.2)	NA	52	(2.2)	NA	67	(2.9)	NA
Congenital anomaly	0	(0.0)	NA	0	(0.0)	NA	0	(0.0)	NA
Other	173	(7.4)	NA	151	(6.4)	NA	147	(6.3)	NA
Other significant AEs[4] (according to ICH E3)	137	(5.9)	2.41	144	(6.1)	2.44	147	(6.3)	2.47

NA = not analysed
Exposure-adjusted incidence rates are presented where calculated, with rate per 100 patient years. For the time at risk, see source data indicated below.
[1] Worst intensity recorded
[2] Non-serious and serious AEs; includes AEs leading to permanent discontinuation of study medication; note, per CTP, patients could subsequently restart unless there was some underlying condition that discouraged its reintroduction
[3] A patient could be counted in more than 1 seriousness category.
[4] Nonserious AEs, as defined in Section 9.5.3.2.1

The rates of any AE and severe AE were slightly greater in the placebo than the empagliflozin treatment groups. However the rate of investigator defined drug related AE was greater in the empagliflozin groups than the placebo group (see Table 24, above).

The most common adverse events were related to infections and metabolic disorders. Urinary tract infections occurred in about 15% of patients. Hypoglycaemia was reported in around 29% of patients in the placebo and empagliflozin groups, hyperglycaemia was more common in the

placebo group (18.5%) than the empagliflozin groups (8.8% to 9.4%) (see Table 25, below). Oedema was less common in the empagliflozin (3.2% to 3.6%) than the placebo group (6.8%).

Table 25. Frequency of patients with confirmed hypoglycaemia adverse events by characteristics of hypoglycaemia

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
Number of patients	2333 (100.0)	2345 (100.0)	2342 (100.0)
Patients with confirmed hypoglycaemic AE [1]	650 (27.9)	656 (28.0)	647 (27.6)
Symptomatic	523 (22.4)	527 (22.5)	515 (22.0)
Asymptomatic	289 (12.4)	277 (11.8)	289 (12.3)
Severity (worst episode)			
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)
Symptomatic and plasma glucose <54 mg/dL [2]	259 (11.1)	257 (11.0)	265 (11.3)
Symptomatic and plasma glucose ≥54 and ≤70 mg/dL [2]	231 (9.9)	240 (10.2)	220 (9.4)
Asymptomatic and plasma glucose ≤70 mg/dL	124 (5.3)	126 (5.4)	132 (5.6)
Intensity (worst episode)			
Severe	43 (1.8)	38 (1.6)	33 (1.4)
Moderate	156 (6.7)	134 (5.7)	126 (5.4)
Mild	451 (19.3)	484 (20.6)	488 (20.8)
Action taken [1]			
Therapy required	329 (14.1)	304 (13.0)	326 (13.9)
Antidiabetic background medication changed [3]	70 (3.0)	82 (3.5)	69 (2.9)
Study medication discontinued [4]	2 (0.1)	4 (0.2)	1 (<0.1)
Requiring or prolonging hospitalisation	13 (0.6)	6 (0.3)	7 (0.3)
Minimum glucose level (worst episode)			
<54 mg/dL	404 (17.3)	404 (17.2)	415 (17.7)
≥54 and ≤70 mg/dL	246 (10.5)	251 (10.7)	231 (9.9)
>70 mg/dL	0	0	0
Not measured	0	1 (<0.1)	1 (<0.1)
Number of hypoglycaemic episodes per patient			
1 or 2	304 (13.0)	324 (13.8)	319 (13.6)
3 or 4	104 (4.5)	105 (4.5)	101 (4.3)
5 to 9	101 (4.3)	102 (4.3)	113 (4.8)
≥10	141 (6.0)	125 (5.3)	114 (4.9)

[1] Patients could be counted in more than 1 category
[2] No assistance required
[3] Due to the event, within 14 days
[4] Action taken with trial drug

7.3.2. Adverse events of special interest

Table 26. AESI (Treatment set)

AESI	Placebo		Empa 10 mg		Empa 25 mg	
Category of event	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Decreased renal function (SMQ)	155 (6.6)	2.77	121 (5.2)	2.07	125 (5.3)	2.12
AE leading to discontinuation	24 (1.0)	0.42	19 (0.8)	0.32	22 (0.9)	0.36
SAE	46 (2.0)	0.80	31 (1.3)	0.52	26 (1.1)	0.43
Hepatic injury (SMQ)	108 (4.6)	1.91	80 (3.4)	1.35	88 (3.8)	1.48
AE leading to discontinuation	8 (0.3)	0.14	7 (0.3)	0.12	6 (0.3)	0.10
SAE	5 (0.2)	0.09	9 (0.4)	0.15	8 (0.3)	0.13
AEs to end of 30-day FU	108 (4.6)	1.87	82 (3.5)	1.36	91 (3.9)	1.50
SAEs to end of 30-day FU	5 (0.2)	0.08	10 (0.4)	0.16	10 (0.4)	0.16
UTI (BIcMQ)	423 (18.1)	8.21	426 (18.2)	8.02	416 (17.8)	7.75
AE leading to discontinuation	10 (0.4)	0.17	22 (0.9)	0.37	19 (0.8)	0.31
SAE [1]	29 (1.2)	NA	24 (1.0)	NA	34 (1.5)	NA
Complicated UTI [2]	41 (1.8)	0.71	34 (1.4)	0.57	48 (2.0)	0.80
Genital infection (BIcMQ)	42 (1.8)	0.73	153 (6.5)	2.66	148 (6.3)	2.55
AE leading to discontinuation	2 (0.1)	0.03	19 (0.8)	0.32	14 (0.6)	0.23
SAE	3 (0.1)	0.05	5 (0.2)	0.08	4 (0.2)	0.07
Confirmed hypoglycaemia [3]	650 (27.9)	NA	656 (28.0)	NA	647 (27.6)	NA
Leading to discontinuation	2 (0.1)	NA	4 (0.2)	NA	1 (<0.1)	NA
Requiring assistance	36 (1.5)	NA	33 (1.4)	NA	30 (1.3)	NA
Bone fracture (BIcMQ)	91 (3.9)	1.61	92 (3.9)	1.57	87 (3.7)	1.46
AE leading to discontinuation	14 (0.6)	0.24	4 (0.2)	0.07	8 (0.3)	0.13
SAE	35 (1.5)	0.61	24 (1.0)	0.40	33 (1.4)	0.55
AEs up to trial termination [4]	105 (4.5)	1.61	105 (4.5)	1.58	98 (4.2)	1.47
Volume depletion (BIcMQ)	115 (4.9)	2.04	115 (4.9)	1.97	124 (5.3)	2.11
AE leading to discontinuation	7 (0.3)	0.12	1 (<0.1)	0.02	4 (0.2)	0.07
SAE	24 (1.0)	0.42	19 (0.8)	0.32	26 (1.1)	0.43
Malignancy (BIcMQ)	78 (3.3)	1.36	106 (4.5)	1.79	96 (4.1)	1.61
AE leading to discontinuation	29 (1.2)	0.50	46 (2.0)	0.77	36 (1.5)	0.60
AEs up to trial termination [4]	103 (4.4)	1.57	117 (5.0)	1.76	110 (4.7)	1.65
AEs after 6 months exposure [5]	65 (3.0)	1.41	91 (4.1)	1.90	70 (3.2)	1.44
AEs up to trial termination [4,5]	83 (3.8)	1.60	101 (4.6)	1.91	77 (3.5)	1.46
Hypersensitivity (SMQ)	197 (8.4)	3.59	158 (6.7)	2.75	181 (7.7)	3.14
AE leading to discontinuation	10 (0.4)	0.17	7 (0.3)	0.12	11 (0.5)	0.18
SAE	7 (0.3)	0.12	3 (0.1)	0.05	10 (0.4)	0.17
Venous embolic and thrombotic AEs (SMQ)	20 (0.9)	0.35	9 (0.4)	0.15	21 (0.9)	0.35
AE leading to discontinuation	2 (0.1)	0.03	0	0	2 (0.1)	0.03
SAE	13 (0.6)	0.23	5 (0.2)	0.08	19 (0.8)	0.31
Diabetic ketoacidosis (BIcMQ)	1 (<0.1)	0.02	3 (0.1)	0.05	1 (<0.1)	0.02
AE leading to discontinuation	0	0	2 (0.1)	0.03	0 (0)	0
SAE	0	0	3 (0.1)	0.05	1 (<0.1)	0.02

BIcMQ = BI customised MedDRA query; FU = follow-up; NA = not analysed; SMQ = standardised MedDRA query; UTI = urinary tract infection

Exposure-adjusted incidence rates are presented where calculated, with rate per 100 patient years. For the time at risk, see source data indicated below.

[1] Required or prolonged hospitalisation

[2] BIcMQ UTI (serious only), sub-BIcMQ pyelonephritis, and PT urosepsis

The only AESI that was significantly different between the treatment groups were genital infections, with a rate of 2.66 and 2.55 events per 100 patient years in the empagliflozin 10 mg and 25 mg groups respectively, compared to 0.73 events per 100 patient years in the placebo group. The reported event rate of decreased renal function showed less difference in the empagliflozin groups than would be anticipated from the results of the efficacy analysis (see Table 26, above).

There was no significant difference in the rate of UTI, DKA or hypoglycaemia between the placebo and empagliflozin groups. The rate of DKA is relatively low overall. The low rates of these problems compared to what has been described from post market surveillance may have been due increased surveillance and monitoring. Most episodes of hypoglycaemia were mild

and occurred on 1 to 2 occasions per patient. Hypoglycaemia was more common in patients with renal impairment and in those on sulphonylureas and/or insulin.

There were no signals related to hepatic injury, or bone fracture. The relatively short period of follow up may not have been sufficient to provide reliable data in relation to differences in bone metabolism or malignancy which can take some years to translate to a clinically detectable problem.

The frequency of hepatic injury events meeting the charter-specified criteria triggering adjudication was ≤ 1.0% in all treatment groups (empagliflozin 10 mg: 1.0%; empagliflozin 25 mg: 0.9%; placebo: 0.5%). In all cases of hepatic injury except 3 rated as 'possible', the relationship of these events to study medication was considered unlikely or indeterminate. Two cases in empagliflozin 10 mg group and 1 in empagliflozin 25 mg group were adjudicated as possibly related; these 3 cases were adjudicated as mild to moderate hepatic injury. Of note, all cases of other significant hepatic injury (11 patients on empagliflozin 10 mg; 9 patients on empagliflozin 25 mg; 4 patients on placebo), hepatic failure and fatal hepatic injury were adjudicated as unlikely to have a relationship to the study medication.

The frequency of reports of the AE volume depletion was similar in the empagliflozin and placebo groups. The risk of volume depletion was greater in those over 65 years, with a baseline GFR < 60 mL/min/1.73 m^2 and those using diuretics.

Table 27. Frequency of patients with volume depletion by subgroup

Sub-group variable	Subgroup category	Placebo			Empa 10 mg			Empa 25 mg		
		N	n (%)	Rate/ 100 pt-yrs	N	n (%)	Rate/ 100 pt-yrs	N	n (%)	Rate/ 100 pt-yrs
Age [years]	<50	142	4 (2.8)	1.19	154	3 (1.9)	0.76	143	8 (5.6)	2.09
	50 to <65	1155	41 (3.5)	1.41	1146	38 (3.3)	1.29	1153	46 (4.0)	1.56
	65 to <75	808	57 (7.1)	3.03	834	59 (7.1)	2.92	833	56 (6.7)	2.73
	≥75	228	13 (5.7)	2.57	211	15 (7.1)	3.19	213	14 (6.6)	2.93
Baseline eGFR [mL/min/ 1.73 m^2]	≥90	488	15 (3.1)	1.23	519	12 (2.3)	0.93	531	26 (4.9)	1.94
	60 to <90	1238	51 (4.1)	1.67	1221	58 (4.8)	1.87	1202	62 (5.2)	2.01
	45 to <60	418	33 (7.9)	3.48	420	34 (8.1)	3.31	411	25 (6.1)	2.47
	30 to <45	183	15 (8.2)	3.70	178	10 (5.6)	2.59	182	10 (5.5)	2.54
	<30	6	1 (16.7)	8.05	7	1 (14.3)	6.17	14	1 (7.1)	3.89
Use of loop diuretics[1]	Yes	364	30 (8.2)	3.69	343	37 (10.8)	4.92	382	38 (9.9)	4.45
	No	1969	85 (4.3)	1.76	2002	78 (3.9)	1.54	1960	86 (4.4)	1.72
Use of diuretics[1]	Yes	988	67 (6.8)	2.90	1036	66 (6.4)	2.65	1011	69 (6.8)	2.82
	No	1345	48 (3.6)	1.44	1309	49 (3.7)	1.47	1331	55 (4.1)	1.61
Use of ACE inhibitor/ ARB[1]	Yes	1868	97 (5.2)	2.16	1896	102 (5.4)	2.17	1902	109 (5.7)	2.30
	No	465	18 (3.9)	1.58	449	13 (2.9)	1.14	440	15 (3.4)	1.32

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; N = number of treated patients; n = number of patients in the subgroup with volume depletion

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data tables indicated below.

[1] At baseline

Overall, the frequency of malignancy was similar in the placebo and empagliflozin groups. However there was an imbalance towards more patients with bladder cancer and pancreatic cancer in the empagliflozin groups.

Table 28. Frequency of patients with malignancies

MedDRA HLT or MedDRA PT or medical topic	Placebo			Empa 10 mg			Empa 25 mg		
	N	%	Rate/100 pt-yrs	N	%	Rate/100 pt-yrs	N	%	Rate/100 pt-yrs
Number of patients	2333	100.0		2345	100.0		2342	100.0	
>6 months of cumulative exposure	2187	100.0		2216	100.0		2190	100.0	
Patients with malignancy AEs (SMQ)	103	4.4	1.57	117	5.0	1.76	110	4.7	1.65
>6 months of cumulative exposure	83	3.8	1.60	101	4.6	1.91	77	3.5	1.46
Malignancies of special interest									
HLT breast and nipple neoplasms malignant	4	0.2		5	0.2		3	0.1	
>6 months of cumulative exposure	3	0.1		4	0.2		3	0.1	
Bladder cancer [1]	5	0.2		3	0.1		9	0.4	
>6 months of cumulative exposure	4	0.2		3	0.1		7	0.3	
HLT renal neoplasms malignant	5	0.2		7	0.3		6	0.3	
>6 months of cumulative exposure	5	0.2		6	0.3		3	0.1	
Lung cancer [2]	15 [3]	0.6		14	0.6		10	0.4	
>6 months of cumulative exposure	11	0.5		12	0.5		6	0.3	
HLT skin melanomas (excl ocular)	3	0.1		4	0.2		4	0.2	
>6 months of cumulative exposure	2	0.1		4	0.2		3	0.1	
Other malignancies with a frequency of ≥0.2% in at least 1 treatment group, sorted by total patients with the specific malignancy									
PT basal cell carcinoma	19	0.8		17	0.7		15 [4]	0.6	
>6 months of cumulative exposure	16	0.7		14	0.6		10 [4]	0.5	
Colorectal cancer [5]	12	0.5		18 [6]	0.8		9	0.4	
>6 months of cumulative exposure	7	0.3		14	0.6		7	0.3	
HLT prostatic neoplasms malignant	12	0.5		12	0.5		11	0.5	
>6 months of cumulative exposure	9	0.4		12	0.5		8	0.4	
Squamous cell carcinoma of skin [7]	13	0.6		9	0.4		7	0.3	
>6 months of cumulative exposure	12	0.5		7	0.3		4	0.2	
Hematologic malignancy [8]	7	0.3		10	0.4		5	0.2	
>6 months of cumulative exposure	5	0.2		8	0.4		2	0.1	
HLT pancreatic neoplasms malignant (excl islet cell and carcinoid)	2	0.1		6	0.3		6	0.3	
>6 months of cumulative exposure	1	<0.1		5	0.2		3	0.1	
Hepatic cancer [9]	3	0.1		4	0.2		2	0.1	
>6 months of cumulative exposure	3	0.1		4	0.2		1	<0.1	
HLT oesophageal neoplasms malignant	4	0.2		2	0.1		0		
>6 months of cumulative exposure	4	0.2		2	0.1		0		
HLT laryngeal neoplasms malignant	0			0			5	0.2	
>6 months of cumulative exposure	0			0			3	0.1	

Exposure-adjusted incidence rate per 100 patient years is not shown for the specific malignancies because it was not calculated if several HLTs and/or PTs constituted the medical topic.

[1] Included HLTs bladder neoplasms malignant and PT transitional cell carcinoma

[2] Included HLTs non-small cell neoplasms malignant of the respiratory tract cell type specified and respiratory tract and pleural neoplasms malignant cell type unspecified NEC

[3] One patient (56708) reported with PT small cell carcinoma was included (medical review by BI: lung cancer)

[4] One patient (52589) reported with PT skin cancer was included (medical review by BI: basal cell carcinoma)

[5] Included HLTs colorectal and anal neoplasms malignancy unspecified and colorectal neoplasms malignant

[6] One patient (51298) reported with PT adenocarcinoma was included (medical review by BI: bowel adenocarcinoma with metastasis)

Table 29. Incidence rates for adverse events of UTI according to the BIcMQ for UTI with a frequency of > 0.3% (Treatment set)

MedDRA SOC	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	423 (18.1)	8.21	426 (18.2)	8.02	416 (17.8)	7.75
Infections and infestations	422 (18.1)	8.19	425 (18.1)	8.00	414 (17.7)	7.71
Urinary tract infection	352 (15.1)	6.70	347 (14.8)	6.38	347 (14.8)	6.34
Asymptomatic bacteriuria	30 (1.3)	0.52	28 (1.2)	0.47	14 (0.6)	0.23
Cystitis	23 (1.0)	0.40	35 (1.5)	0.59	34 (1.5)	0.57
Bacteriuria	14 (0.6)	0.24	11 (0.5)	0.18	5 (0.2)	0.08
Pyelonephritis chronic	10 (0.4)	0.17	4 (0.2)	0.07	6 (0.3)	0.10
Escherichia urinary tract infection	9 (0.4)	0.16	7 (0.3)	0.12	6 (0.3)	0.10
Pyelonephritis acute	6 (0.3)	0.10	7 (0.3)	0.12	1 (<0.1)	0.02
Pyelonephritis	4 (0.2)	0.07	3 (0.1)	0.05	10 (0.4)	0.17
Urinary tract infection fungal	3 (0.1)	0.05	12 (0.5)	0.20	15 (0.6)	0.25
Urosepsis	3 (0.1)	0.05	6 (0.3)	0.10	11 (0.5)	0.18
Urinary tract infection bacterial	3 (0.1)	0.05	7 (0.3)	0.12	4 (0.2)	0.07
Leading to discontinuation	10 (0.4)	0.17	22 (0.9)	0.37	19 (0.8)	0.31
Serious AEs[1]	29 (1.2)	NA	24 (1.0)	NA	34 (1.5)	NA

NA = not analysed

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

[1] Required or prolonged hospitalisation

There incidence of complicated UTI's was low, and the data is difficult to interpret due to unclear definitions of the individual components (thus an element of reporter bias). However there seems to be a trend of more urosepsis and fungal UTIs in the empagliflozin groups (see Table 29, above).

To investigate potential cases of urosepsis not reported with the PT, investigators performed a manual search and extracted data from the PT of sepsis, *E. coli* sepsis and septic shock. 4 additional cases were identified. The revised rate of urosepsis was higher in the empagliflozin 25 mg group (0.5%) than the placebo group (0.2%) and the empagliflozin 10 mg group (0.3%). Two patients with urosepsis and one patient with sepsis died, all treated with empagliflozin.

7.3.3. Treatment-related adverse events (adverse drug reactions)

There were more AE attributed to the to the study drug for the following symptoms: Dysuria, fungal genital infection, vulvovaginal candidiasis, pollakiuria, dysuria, nocturia, constipation, balanoprosthitis, vulvovaginal pruritis, and genital pruritis (see Table 30, below).

Table 30. Incidence rate for adverse events assessed as drug related by the investigators with a frequency of > 0.5% in any group at the PT level

MedDRA SOC	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	549 (23.5)	11.33	666 (28.4)	14.15	643 (27.5)	13.38
Metabolism and nutrition disorders	315 (13.5)	6.05	338 (14.4)	6.39	313 (13.4)	5.81
Hypoglycaemia	284 (12.2)	5.40	314 (13.4)	5.91	286 (12.2)	5.27
Hyperglycaemia	20 (0.9)	0.35	16 (0.7)	0.27	7 (0.3)	0.12
Infections and infestations	152 (6.5)	2.73	197 (8.4)	3.46	188 (8.0)	3.27
Urinary tract infection	120 (5.1)	2.13	119 (5.1)	2.04	107 (4.6)	1.82
Cystitis	8 (0.3)	0.14	12 (0.5)	0.20	17 (0.7)	0.28
Genital infection fungal	3 (0.1)	0.05	16 (0.7)	0.27	10 (0.4)	0.17
Vulvovaginal candidiasis	2 (0.1)	0.03	15 (0.6)	0.25	15 (0.6)	0.25
Renal and urinary disorders	75 (3.2)	1.32	107 (4.6)	1.85	123 (5.3)	2.11
Pollakiuria	15 (0.6)	0.26	34 (1.4)	0.57	31 (1.3)	0.52
Polyuria	9 (0.4)	0.16	25 (1.1)	0.42	25 (1.1)	0.42
Dysuria	9 (0.4)	0.16	16 (0.7)	0.27	16 (0.7)	0.27
Renal impairment	14 (0.6)	0.24	9 (0.4)	0.15	17 (0.7)	0.28
Nocturia	7 (0.3)	0.12	11 (0.5)	0.18	12 (0.5)	0.20
Investigations	56 (2.4)	0.98	56 (2.4)	0.95	78 (3.3)	1.32
Weight decreased	5 (0.2)	0.09	19 (0.8)	0.32	24 (1.0)	0.40
Lipase increased	15 (0.6)	0.26	2 (0.1)	0.03	11 (0.5)	0.18
Gastrointestinal disorders	26 (1.1)	0.45	43 (1.8)	0.72	58 (2.5)	0.98
Constipation	3 (0.1)	0.05	6 (0.3)	0.10	13 (0.6)	0.22
Nervous system disorders	23 (1.0)	0.40	27 (1.2)	0.45	42 (1.8)	0.70
Dizziness	11 (0.5)	0.19	8 (0.3)	0.13	18 (0.8)	0.30
General disorders and administration site conditions	19 (0.8)	0.33	26 (1.1)	0.44	33 (1.4)	0.55
Thirst	1 (<0.1)	0.02	4 (0.2)	0.07	12 (0.5)	0.20
Skin and subcutaneous tissue disorders	17 (0.7)	0.29	20 (0.9)	0.33	26 (1.1)	0.43
Pruritus	2 (0.1)	0.03	2 (0.1)	0.03	11 (0.5)	0.18
Reproductive system and breast disorders	12 (0.5)	0.21	65 (2.8)	1.10	59 (2.5)	0.99
Balanoposthitis	2 (0.1)	0.03	25 (1.1)	0.42	15 (0.6)	0.25
Vulvovaginal pruritus	2 (0.1)	0.03	12 (0.5)	0.20	20 (0.9)	0.33
Pruritus genital	3 (0.1)	0.05	12 (0.5)	0.20	12 (0.5)	0.20

7.3.4. Deaths and other serious adverse events

Overall, there were less deaths in the groups treated with empagliflozin. This is largely due to less deaths associated with cardiovascular disease (see Table 31, below).

Table 31. Incidence rates for adverse events leading to death with a frequency of > 0.2% at the PT level (Treatment set)

MedDRA SOC	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	119 (5.1)	2.06	97 (4.1)	1.61	79 (3.4)	1.31
Cardiac disorders	46 (2.0)	0.79	27 (1.2)	0.45	27 (1.2)	0.45
Myocardial infarction	11 (0.5)	0.19	12 (0.5)	0.20	9 (0.4)	0.15
Cardiac arrest	10 (0.4)	0.17	2 (0.1)	0.03	2 (0.1)	0.03
Acute myocardial infarction	7 (0.3)	0.12	3 (0.1)	0.05	6 (0.3)	0.10
Cardiac failure	5 (0.2)	0.09	3 (0.1)	0.05	1 (<0.1)	0.02
Cardio-respiratory arrest	4 (0.2)	0.07	4 (0.2)	0.07	2 (0.1)	0.03
General disorders and administration site conditions	26 (1.1)	0.45	26 (1.1)	0.43	14 (0.6)	0.23
Death	12 (0.5)	0.21	10 (0.4)	0.17	5 (0.2)	0.08
Sudden death	6 (0.3)	0.10	8 (0.3)	0.13	5 (0.2)	0.08
Cardiac death	3 (0.1)	0.05	4 (0.2)	0.07	2 (0.1)	0.03
Infections and infestations	15 (0.6)	0.26	8 (0.3)	0.13	6 (0.3)	0.10
Pneumonia	5 (0.2)	0.09	3 (0.1)	0.05	3 (0.1)	0.05
Septic shock	4 (0.2)	0.07	2 (0.1)	0.03	1 (<0.1)	0.02
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (0.6)	0.22	19 (0.8)	0.32	22 (0.9)	0.36
Lung neoplasm malignant	2 (0.1)	0.03	0	0	4 (0.2)	0.07
Respiratory, thoracic and mediastinal disorders	9 (0.4)	0.16	4 (0.2)	0.07	4 (0.2)	0.07
Respiratory failure	4 (0.2)	0.07	0	0	0	0

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

Table 32. Incidence rate for SAEs with a frequency of > 1.0% at the PT level (Treatment set)

MedDRA SOC	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	988 (42.3)	22.34	876 (37.4)	18.20	913 (39.0)	19.39
Cardiac disorders	398 (17.1)	7.52	320 (13.6)	5.69	332 (14.2)	5.92
Angina unstable	87 (3.7)	1.53	82 (3.5)	1.39	73 (3.1)	1.23
Cardiac failure	55 (2.4)	0.96	42 (1.8)	0.70	24 (1.0)	0.40
Myocardial infarction	47 (2.0)	0.82	50 (2.1)	0.84	44 (1.9)	0.73
Acute myocardial infarction	42 (1.8)	0.73	32 (1.4)	0.53	48 (2.0)	0.80
Coronary artery disease	46 (2.0)	0.80	21 (0.9)	0.35	29 (1.2)	0.48
Cardiac failure congestive	45 (1.9)	0.78	30 (1.3)	0.50	35 (1.5)	0.58
Angina pectoris	32 (1.4)	0.56	36 (1.5)	0.60	42 (1.8)	0.70
Atrial fibrillation	14 (0.6)	0.24	25 (1.1)	0.42	12 (0.5)	0.20
Infections and infestations	213 (9.1)	3.85	175 (7.5)	3.02	185 (7.9)	3.18
Pneumonia	53 (2.3)	0.92	41 (1.7)	0.69	38 (1.6)	0.63
Nervous system disorders	159 (6.8)	2.84	146 (6.2)	2.50	160 (6.8)	2.73
Cerebrovascular accident	31 (1.3)	0.54	46 (2.0)	0.77	37 (1.6)	0.61
Transient ischaemic attack	23 (1.0)	0.40	23 (1.0)	0.38	30 (1.3)	0.50
Vascular disorders	116 (5.0)	2.06	80 (3.4)	1.36	111 (4.7)	1.89
Peripheral arterial occlusive disease	23 (1.0)	0.40	28 (1.2)	0.47	30 (1.3)	0.50
General disorders and administration site conditions	94 (4.0)	1.65	80 (3.4)	1.35	74 (3.2)	1.24
Chest pain	28 (1.2)	0.49	32 (1.4)	0.54	33 (1.4)	0.55
Renal and urinary disorders	73 (3.1)	1.28	60 (2.6)	1.01	52 (2.2)	0.87
Acute kidney injury	32 (1.4)	0.56	26 (1.1)	0.43	19 (0.8)	0.31

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

7.3.5. Discontinuation due to adverse events

The summary of AE leading to treatment discontinuation included patients with AE documented by the investigator as leading to permanent discontinuation of the study drug. Patients who discontinued study medication for any reason could subsequently restart unless there was some underlying condition that discouraged reintroduction. More patients in the placebo group discontinued due to heart failure or cardiac arrest than in the placebo group. However more patients in the empagliflozin group discontinued due to stroke (see Table 33, below).

Table 33. Incidence rates for adverse events leading to discontinuation of study medication with a frequency of > 0.5% in any treatment group at PT (Treatment set)

MedDRA SOC	Placebo		Empa 10 mg		Empa 25 mg	
MedDRA PT	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients	2333 (100.0)		2345 (100.0)		2342 (100.0)	
Overall incidence	453 (19.4)	8.26	416 (17.7)	7.28	397 (17.0)	6.89
Cardiac disorders	111 (4.8)	1.94	75 (3.2)	1.26	78 (3.3)	1.30
Myocardial infarction	20 (0.9)	0.35	19 (0.8)	0.32	16 (0.7)	0.26
Acute myocardial infarction	17 (0.7)	0.29	14 (0.6)	0.23	15 (0.6)	0.25
Cardiac failure	16 (0.7)	0.28	9 (0.4)	0.15	5 (0.2)	0.08
Cardiac arrest	11 (0.5)	0.19	3 (0.1)	0.05	2 (0.1)	0.03
Angina unstable	8 (0.3)	0.14	15 (0.6)	0.25	9 (0.4)	0.15
Infections and infestations	71 (3.0)	1.24	78 (3.3)	1.31	57 (2.4)	0.95
Urinary tract infection	7 (0.3)	0.12	17 (0.7)	0.28	11 (0.5)	0.18
Pneumonia	14 (0.6)	0.24	10 (0.4)	0.17	7 (0.3)	0.12
Nervous system disorders	46 (2.0)	0.80	43 (1.8)	0.72	47 (2.0)	0.78
Cerebrovascular accident	6 (0.3)	0.10	12 (0.5)	0.20	12 (0.5)	0.20
Renal and urinary disorders	38 (1.6)	0.66	39 (1.7)	0.65	48 (2.0)	0.80
Renal impairment	10 (0.4)	0.17	10 (0.4)	0.17	16 (0.7)	0.26

Exposure-adjusted incidence rates are presented, with rate per 100 patient years. For the time at risk, see source data indicated below.

7.4. Laboratory tests

7.4.1. Liver function

The frequencies of patients with elevated liver enzyme values ≥ 3 x ULN were similar in both the empagliflozin groups (10 mg: 1.4%; 25 mg: 0.9%) and in the placebo group (1.5%). The frequencies of patients with elevated enzymes ≥ 5 x ULN were slightly higher for patients in the empagliflozin groups (10 mg: 0.7%; 25 mg: 0.6%) than for patients on placebo (0.3%).

Based on central laboratory data, 7 patients on empagliflozin (5 on 10 mg; 2 on 25 mg) and 2 patients on placebo were reported with the ALT and/or AST ≥ 3 x ULN with concomitant or subsequent total bilirubin ≥ 2 x ULN within 30 days after ALT/AST elevation. However, the maximum alkaline phosphatase (ALP) value in the 30-day period was ≥ 2 x ULN for 4 of these patients (3 on empagliflozin; 1 on placebo), thus not fulfilling the biochemical Hy's law. The remaining 5 patients had ALP < 2 x ULN (4 on empagliflozin 10 mg and 1 on placebo). In all cases there were underlying circumstances that resulted in adjudications of 'unlikely' for the relationship between the elevated liver enzymes and study medication.

7.4.2. Kidney function

See Efficacy section above.

7.4.3. Other clinical chemistry

There were no noteworthy changes in median values from baseline to the last value on treatment for patients on empagliflozin or patients on placebo for sodium, potassium, calcium, magnesium, chloride, phosphate, or bicarbonate.

There were more patients in the empagliflozin group (12.8% and 11.8%) compared to the placebo group (9.7%) with bicarbonate levels below the LLN. There were no noteworthy changes in median values from baseline to the last value on treatment for patients on empagliflozin or patients on placebo for AST, ALT, alkaline phosphatase, LDH, creatine kinase, and lipase.

7.4.4. Haematology

There were increases in haemoglobin, haematocrit, and RBC, for patients on empagliflozin compared with patients on placebo. At the end of the 30 day follow-up period, in both the empagliflozin 10 mg and empagliflozin 25 mg treatment groups the median values for haemoglobin and haematocrit had decreased from the value at the last visit on treatment compared with no change over this period for the placebo treatment group, see Table 34, below. The incidence rates of venous embolic and thrombotic AEs were comparable in both the empagliflozin and the placebo treatment groups. There was no noteworthy difference in median changes in WBC or platelets between the empagliflozin and placebo treatment groups.

Table 34. Median values for haematology parameters (Treatment set)

Parameter [units] Treatment group	Patients analysed	Baseline Median (Q1, Q3)	Last value on treatment Median (Q1, Q3)	Change from baseline to last value on treatment Median (Q1, Q3)
RBC [x10^6/µL]				
Placebo	2263	4.6 (4.3, 4.9)	4.7 (4.3, 5.1)	0.1 (-0.1, 0.3)
Empa 10 mg	2263	4.6 (4.2, 4.8)	5.1 (4.6, 5.4)	0.4 (0.2, 0.7)
Empa 25 mg	2248	4.6 (4.3, 4.9)	5.1 (4.6, 5.4)	0.4 (0.2, 0.7)
Haemoglobin [g/dL]				
Placebo	2263	13.5 (12.6, 14.4)	13.4 (12.3, 14.4)	-0.1 (-0.7, 0.6)
Empa 10 mg	2263	13.5 (12.5, 14.4)	14.3 (13.2, 15.4)	0.8 (0.1, 1.6)
Empa 25 mg	2249	13.5 (12.6, 14.4)	14.4 (13.4, 15.5)	0.9 (0.1, 1.6)
Haematocrit [%]				
Placebo	2258	41.2 (37.4, 44.5)	42.5 (38.6, 45.9)	1.3 (-1.4, 3.9)
Empa 10 mg	2255	41.2 (37.4, 45.2)	46.5 (41.7, 50.2)	5.2 (1.4, 7.8)
Empa 25 mg	2242	41.7 (37.4, 45.2)	46.5 (42.5, 50.4)	5.2 (1.4, 8.5)
WBC [x10^3/µL]				
Placebo	2263	6.9 (6.0, 7.9)	7.3 (6.2, 8.3)	0.3 (-0.4, 1.0)
Empa 10 mg	2263	6.9 (6.0, 8.1)	7.1 (6.2, 8.3)	0.2 (-0.5, 0.2)
Empa 25 mg	2248	6.9 (6.0, 8.0)	7.0 (6.2, 8.2)	0.2 (-0.5, 0.2)
Platelets [x10^3/µL]				
Placebo	2254	196 (175, 220)	202 (179, 229)	6 (-8, 19)
Empa 10 mg	2244	198 (176, 224)	198 (176, 224)	1 (-13, 15)
Empa 25 mg	2236	196 (175, 224)	198 (175, 224)	0 (-13, 14)

7.4.5. Lipids

There were increases in total cholesterol, HDL cholesterol, LDL cholesterol and non-HDL cholesterol in all treatment groups from baseline to Week 28 (see Table 35, below). Thereafter, values continued to increase slightly until Week 80. The increase was greater in the empagliflozin 25 mg group than in the empagliflozin 10 mg group, and increases were greater in both empagliflozin groups than in the placebo group. For LDL/HDL cholesterol ratio and triglycerides, there were only slight changes from baseline values until Week 80 and there were no noteworthy differences between the empagliflozin groups and placebo.

Table 35. Median values for lipid parameters (FS, Follow up)

Parameter [units] Treatment group	Patients analysed	Baseline Median (Q1, Q3)	Last value on treatment Median (Q1, Q3)	Follow-up value Median (Q1, Q3)	Change from baseline to follow-up Median (Q1, Q3)	Change from LVOT to follow-up Median (Q1, Q3)
Total cholesterol [mg/dL]						
Placebo	1668	154.29 (132.25, 180.20)	155.07 (132.25, 188.32)	154.29 (131.09, 185.23)	1.16 (-17.01, 20.11)	-1.93 (-15.08, 11.99)
Empa 10 mg	1773	157.39 (132.25, 187.16)	162.41 (137.28, 197.22)	159.32 (135.34, 189.48)	3.09 (-15.85, 22.82)	-3.09 (-18.95, 10.05)
Empa 25 mg	1824	154.29 (132.25, 185.23)	163.19 (139.21, 197.22)	160.09 (135.34, 190.26)	5.03 (-13.92, 24.75)	-4.64 (-18.95, 9.28)
HDL cholesterol [mg/dL]						
Placebo	1668	42.92 (35.96, 50.27)	42.92 (35.96, 51.04)	42.15 (35.96, 50.27)	0.00 (-4.25, 5.03)	0.00 (-3.87, 2.71)
Empa 10 mg	1773	42.92 (35.96, 51.04)	45.24 (37.12, 54.14)	44.08 (37.12, 52.98)	1.16 (-3.87, 6.19)	0.00 (-4.25, 3.09)
Empa 25 mg	1824	42.92 (37.12, 51.04)	45.24 (37.90, 54.14)	44.08 (37.90, 52.98)	1.93 (-3.09, 6.96)	0.00 (-4.25, 3.09)
LDL cholesterol [mg/dL]						
Placebo	1668	76.95 (59.16, 100.15)	78.11 (59.94, 106.34)	78.11 (59.16, 104.02)	0.77 (-13.92, 16.24)	-1.16 (-11.99, 9.28)
Empa 10 mg	1773	80.05 (59.94, 105.18)	84.30 (63.03, 109.05)	79.27 (61.10, 106.34)	1.16 (-15.08, 16.24)	-1.93 (-15.08, 8.12)
Empa 25 mg	1824	78.11 (59.94, 104.02)	83.14 (63.03, 111.56)	80.05 (62.26, 106.34)	2.32 (-12.76, 17.79)	-1.93 (-13.92, 8.89)
LDL/HDL cholesterol ratio						
Placebo	1668	1.83 (1.35, 2.40)	1.84 (1.36, 2.51)	1.81 (1.35, 2.52)	0.02 (-0.34, 0.42)	0.00 (-0.26, 0.24)
Empa 10 mg	1773	1.85 (1.36, 2.47)	1.87 (1.36, 2.51)	1.81 (1.32, 2.44)	-0.02 (-0.41, 0.35)	-0.03 (-0.32, 0.20)
Empa 25 mg	1824	1.82 (1.37, 2.47)	1.85 (1.39, 2.52)	1.81 (1.33, 2.40)	-0.01 (-0.38, 0.36)	-0.02 (-0.29, 0.25)
Non-HDL cholesterol [mg/dL]						
Placebo	1668	108.28 (88.17, 137.28)	111.37 (88.17, 141.92)	109.82 (87.39, 141.14)	1.16 (-16.24, 18.95)	-1.16 (-13.92, 11.21)
Empa 10 mg	1773	112.14 (87.39, 140.37)	116.01 (91.26, 147.33)	111.37 (89.33, 143.08)	1.93 (-16.24, 20.30)	-3.09 (-16.63, 9.28)
Empa 25 mg	1824	109.05 (88.17, 138.05)	116.20 (92.81, 149.27)	112.53 (90.10, 142.30)	2.32 (-15.85, 20.88)	-3.09 (-17.01, 10.05)
Triglycerides [mg/dL]						
Placebo	1668	139.95 (104.52, 201.06)	143.49 (102.75, 204.61)	144.38 (104.52, 202.83)	1.77 (-31.00, 37.20)	0.89 (-27.46, 25.69)
Empa 10 mg	1773	139.06 (100.09, 195.75)	143.49 (102.75, 204.61)	143.49 (101.86, 205.49)	3.54 (-29.23, 42.52)	-1.77 (-30.12, 25.69)
Empa 25 mg	1824	144.38 (106.29, 195.75)	146.15 (106.29, 207.26)	141.72 (101.86, 201.95)	0.00 (-31.89, 37.20)	-4.43 (-36.32, 23.91)

7.4.5.1. Free fatty acid, apo A1 and apo B

For free fatty acids and apo A1, there were slight increases from baseline to the last value on treatment for both empagliflozin groups and a slight decrease for the placebo group.

For apo B there were also increases from baseline to the last value on treatment for both empagliflozin groups and a similar but slightly lower increase for the placebo group.

7.4.5.2. Substrates

For uric acid, there were decreases in median values from baseline to the last value on treatment for patients on empagliflozin (10 mg: -0.43 mg/dL; 25 mg: -0.45 mg/dL) compared with patients on placebo (0.00 mg/dL). Median uric acid values at follow-up (30 days after the last dose of study medication) showed only a slight change from the last value on treatment in all treatment groups for all patients.

7.4.6. Urinalysis

There were no significant changes in either group on quantitative urinalysis parameters (urine pH, alpha-1 microglobulin, albumin, microalbumin creatinine ratio and alpha-1 microglobulin creatinine ratio). There were no significant changes in qualitative urinalysis variables nitrites, protein or ketones.

Most patients were negative for urine ketones throughout the study (empagliflozin 10 mg: 78.5%; empagliflozin 25 mg: 78.5%; placebo: 81.2%). No patient had levels of urine ketones categorised as 4+ as the worst value on treatment in any treatment group; 1 patient on placebo, 3 on empagliflozin 10 mg, and 2 on empagliflozin 25 mg had urine ketone levels of 3+ as their worst value on treatment. All other patients had trace amounts or 1+ or 2+ levels as their worst value on treatment.

7.4.7. Electrocardiograph

The frequencies of patients with AEs related to ECG findings were low and comparable in the empagliflozin and placebo treatment groups (empagliflozin 10 mg: 1.2%; empagliflozin 25 mg: 1.6%; placebo: 1.9%). The categorisations of QTcB and QTcF intervals at the end of treatment and changes from baseline at end of treatment were comparable across treatment groups, with few patients having a change in QTcB or QTcF interval of > 60 ms. Frequencies of patients with QT interval > 500 ms at the end of treatment were low and comparable in the empagliflozin and placebo treatment groups (empagliflozin 10 mg: 0.5%; empagliflozin 25 mg: 1.0%; placebo: 0.7%).

Silent MI was defined as the following ECG changes (it is unclear if this needed to be in the context of changes in cardiac enzymes):

- any Q wave in leads V2 to 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 to V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4 to 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.

There were more silent MIs in those treated with empagliflozin (38/2378) than those treated with placebo (15/1211).

7.4.8. Vital signs

There were very small clinically insignificant changes in HR.

7.5. Post-marketing experience

There have been concerns raised about the risk of DKA and urosepsis with empagliflozin and other SGLT2 inhibitors. This has led to statements on the TGA (and EMA and FDA) websites, a letter to health care professionals and updates to the PI.

7.6. Evaluator's overall conclusions on clinical safety

The safety profile in the study was consistent with the known safety profile of Empagliflozin.

The reported rates of DKA, genital infections and urosepsis were lower than have been reported in a post market setting. This is most likely due to increased vigilance of these problems and appropriate management in a clinical trial setting. The risk of these problems is likely to be increased in a real life setting.

There were high rates of hypoglycaemia (around 28%) in the placebo and empagliflozin groups.

There was a reduction in diastolic BP in both placebo and empagliflozin groups. This was greater in the empagliflozin group. There was a modest increase in Hb and haematocrit during the trial, possibly due to volume depletion. This may be significant given the numerical increased risk of non-haemorrhagic stroke. The sponsor performed intensive subgroup analysis looking at the rate of stroke in those on diuretics, those with increased haematocrit and those with signs of volume depletion. There were no significant interactions seen. However such analysis was exploratory and based on self-reported or subjective symptoms/signs.

More patients with renal impairment had serious adverse events in both empagliflozin and placebo groups.

A safety signal for amputation for another drug of this class (Canagliflozin) has recently been issued from interim results of a long-term safety study (CANVAS and CANVAS-R). There was no significant different in peripheral arterial disease in the EMPA-REG study. Possible reasons for the discrepancy include differences in reporting of adverse events, difference in populations studied, and shorter duration of the trial in the EMPA-REG study.

Overall, there was no significant difference in the frequency of malignancy between the placebo and empagliflozin groups. However, there was a discrepancy in the number of cases of bladder cancer and pancreatic cancer. But these numbers need to be interpreted with caution as the number of cases was small, and the number of subgroups large.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of empagliflozin for the prevention in 'the prevention of cardiovascular events' has been demonstrated in patients with T2DM, poor glycaemic control and macrovascular risk factors. This study has demonstrated the following benefits in this treatment group:

- Non-inferiority and superiority of Empagliflozin over placebo for 3-point MACE
- Non-inferiority for 4-point MACE
- Reduced cardiovascular mortality
- Reduced hospitalisation for heart failure
- Reduced worsening and new nephropathy
- No significant increased risk of hypoglycaemia

There was no statistically of clinically significant difference in the rate of MI, hospitalisation forangina, stroke or revascularisation procedures to support benefits on macrovascular disease. However it is acknowledged these were secondary endpoints and subject to statistical problems of multiplicity, compounded by small numbers. There was no statistically significant difference in retinopathy.

The benefits occurred early in the trial.

It is likely that the benefits are independent of glycaemic control.

8.2. First round assessment of risks

The risks of empagliflozin for the prevention of cardiovascular events are:

- A potential increase in the risk of stroke. This may be driven by a reduction in intravascular volume (higher haematocrit).
- A higher rate of serious adverse events in patients with moderate renal impairment.
- Increased risk of genital infections and urinary sepsis (known risks)

There was no evidence of benefit for MI, stroke, unstable angina, or revascularisation procedure.

8.2.1. Unknowns

Empagliflozin has not been studied in Indigenous people of Australia. This group have a high baseline risk of renal disease and infections, in particular STD. However, they also have a high rate of diabetes related morbidity and mortality. The benefit risk ratio may be different in this population.

Interactions encountered with other medications in the prevention of cardiovascular death. The study was not powered to determine if concomitant treatment with ACE inhibitors, B blockers, calcium channel blockers, or diuretics altered the efficacy.

8.3. First round assessment of benefit-risk balance

Overall, the risk benefit ratio for the current indications is favourable. The EMPA-REG study demonstrated that empagliflozin has advantages over other glucose lowering drugs in the reduction in cardiovascular mortality in T2DM.

In addition, there is sufficient evidence to support the efficacy and safety in patients with mild and moderate renal impairment.

9. First round recommendation regarding authorisation

9.1. Use to prevent cardiovascular events

The clinical evaluator would recommend approval for this indication. The Delegate may consider rewording of the indication with consideration to the following issues:

1. *Is the patient group (patients with type 2 diabetes and poor glycaemic control) different than the population of patients for which empagliflozin is currently indicated for?*

The sponsor has performed a large, well conducted, clinical study to support the safety and efficacy of empagliflozin in patients with T2DM and high cardiovascular risk. Unlike many other drugs used to treat T2DM, a reduction in cardiovascular death was demonstrated. Although patients in the empagliflozin arm also experienced an improvement in glycaemic control, weight and blood pressure, other studies that have examined the effects of improved glycaemic control on cardiovascular outcomes have not shown similar benefits. Thus, the effect of cardiovascular death is probably separate to its effect on glycaemic control. However, to include the prevention of cardiovascular death as a new indication would allow treatment with empagliflozin in patients with T2DM and adequate glycaemic control (HbA1c < 7%). This was not the primary aim of the study, thus the evidence for this relies upon results of subgroup analysis of a relatively small patient group with multiple possible confounding factors.

2. *The term high cardiovascular risk is not well defined in the PI,* and may be interpreted to mean different things to prescribers.

The clinical trial included patients with a history of coronary artery disease, cerebrovascular disease and peripheral vascular disease. Some may consider all patients with T2DM to have high

cardiovascular risk. The study results cannot be reliably extrapolated to a population with lower cardiovascular risk as this group will have a lower absolute risk reduction. The EU recommended using the inclusion criteria for the trial to better define the indication. However the evaluator is concerned about promoting the use of empagliflozin in patients with high risk of cerebrovascular and peripheral vascular disease (but lower risk of coronary artery disease) due to the imbalance in adverse events of stroke and amputation (for another drug in this class).

3. *There needs to be greater emphasis on the use of empagliflozin in the context of other measures to reduce cardiovascular risk (such as lipid lowering drugs, ACE inhibitors, aspirin, weight reduction and smoking cessation).*

Comparison to other drugs used for cardiovascular prevention: The sponsor has stated that the magnitude of the effect demonstrated in the EMPA-REG study is numerically similar to or greater than those seen in the outcome trials that established the use of statins or ACEi/ARBs (angiotensin converting enzyme inhibitor/angiotensin receptor blockers). In the Scandinavian Simvastatin Survival Study in patients with high CV risk, the risk of death was reduced by 30% with simvastatin compared with placebo, with an NNT of 30 to prevent 1 death in 5 years. Reported in 2000, the 'HOPE' study in patients with high CV risk demonstrated that ramipril (an ACEi) reduced the risk of death by 16% and CV death by 26%, with an NNT of 56 to prevent 1 death in 5 years.

The evaluator notes that the indications for ramipril include:

> *'treatment of hypertension;*
>
> *reducing the risk of myocardial infraction, stroke, cardiovascular death or the need for revascularisation procedures in patients 55 years of age or more who have clinical evidence of coronary artery disease, stroke or peripheral vascular disease;*
>
> *reducing the risk of myocardial infarction, stroke, cardiovascular death or revascularisation procedures in diabetic patients 55 years or more with one or more of the following risk factors: systolic blood pressure > 160 mmHg or diastolic BP > 90 mmHg (or on antihypertensive treatment), total cholesterol > 5.2mmol/L or HDL ,0.9mmol/L, current smoker, known microalbuminuria, and evidence or previous vascular disease.'*

In the pivotal clinical trials for the cardiovascular indications, hypertension was not a compulsory inclusion criteria (thus the hypertension indication would not have covered this patient group) and the improvement in cardiovascular outcomes were significant for all subcomponents of the 3-point MACE (cardiovascular death, MI and stroke).

The indications for simvastatin include:

> *'as an adjunct to diet for the treatment of hypercholesterolaemia;*
>
> *in patients at high risk of CHD (with or without hypercholesterolaemia) including patients with diabetes, history of stroke or other cerebrovascular disease, peripheral vascular disease, or with existing CHD to reduce the risk of cardiovascular death, major cardiovascular events including stroke and hospitalisation due to angina pectoris.'*

In the pivotal study for the cardiovascular outcomes, the baseline LDL was less than 2.6 mmol/L in about 17% and between 2.6 and 3.4 mmol/L in about 35%; for total cholesterol about 19% had levels less than 5.0 mmol/L and 38% had levels between 5 to 6.0 mmol/L (therefore would not have been covered by the hypercholesterolaemia indication). There were statistically significant benefits in mortality, CHD mortality, major vascular event composite measure, major coronary event composite measure, coronary revascularisation and hospitalisation for angina.

9.2. Use in moderate renal impairment

The EMPA-REG study included a relatively large group of patients with moderate renal impairment. In this group, there were more modest benefits in glycaemic control and cardiovascular events. A statistically significant improvement in the rate of new and worsening nephropathy was demonstrated. There were more serious adverse events in both the placebo and treatment arm of this subgroup. The evaluator would recommend relaxing the precautions around use in patients with moderate renal impairment.

10. Clinical questions

10.1. Additional expert input

- Cardiologist/ACPM:
  - Is this a clinically significant improvement in cardiovascular mortality?
  - What is the significance of the numerical increase in silent MI (ECG changes)?
- Renal physician/ACPM?
  - Do you consider the change in UACR and eGFR to be clinically significant?

10.2. Clinical questions

10.2.1. Pharmacokinetics

No questions.

10.2.2. Pharmacodynamics

No questions.

10.2.3. Efficacy

Q1) The proposed indication would include patients with T2DM with adequate and inadequate glycaemic control. Could the sponsor justify the use of empagliflozin in patients with adequate glycaemic control (that is, HbA1c < 7%).

10.2.4. Safety

Q2) What criteria were used to discontinue patients due to adverse events?

Q3) Was there any correlation between HbA1c and hypoglycaemia?

Q4) Do any animal studies suggest an association between empagliflozin and cancer? Have there been any signals for bladder or pancreatic cancer in previous clinical trials of empagliflozin or other SGLT2 inhibitors?

Q5) Have any clinical trials with empagliflozin demonstrated an increased risk of amputations or peripheral vascular disease?

11. Second round evaluation of clinical data submitted in response to questions

11.1. Efficacy

11.1.1. Question 1

The proposed indication would include patients with T2DM with adequate and inadequate glycaemic control. Could the sponsor justify the use of empagliflozin in patients with adequate glycaemic control (that is, HbA1c < 7%)?

11.1.1.1. Sponsor's response

In the study, 6% of patients had a HbA1c of < 7% at baseline. Subgroup analysis was performed on those subjects with a HbA1c < 7% at baseline and showed consistent results with the main study. The HR for CV events was 0.3 (95% CI 0.12, 0.8), all-cause mortality 0.42 (95% CI 0.19, 0.9), time to heart failure requiring hospitalisation or CV death 0.44 (95% CI 0.22, 0.89). The p-value for the interaction between HbA1c and outcome was not significant.

The sponsor states that the beneficial effect of empagliflozin cannot be explained by the modest glucose control achieved in Trial 1245.25 as the study was designed for glycaemic equipose. The sponsor has also stated that the beneficial effects were seen soon after the start of the study, thus unlikely to be attributed to glycaemic control.

11.1.1.2. Evaluator's comment

In the EMPA-REG study, the beneficial effects of empagliflozin on cardiovascular events were seen across the range of HbA1c levels, with no significant interaction between HbA1c and cardiovascular events. Approximately 6% of patients had a HbA1c of < 7% at baseline. However these patients must have a HbA1c of > 7% at some stage to qualify for the study.

A HbA1c of > 6.5% is now a valid diagnostic criteria for diabetes. The study did not address whether treatment with empagliflozin in these patients will improve cardiovascular outcomes, however the current indications would include this group of patients. The efficacy and safety of empagliflozin in this group of patients is unknown.

11.2. Safety

11.2.1. Question 2

What criteria were used to discontinue patients due to adverse events?

11.2.1.1. Sponsor's response:

Discontinuation of study drug due to an adverse event (AE) was at the discretion of the investigator. Permanent study drug discontinuation was only justified when clear, persistent contraindications arose. The following subcategories of AEs leading to discontinuation were collected on the case report form:

- Unexpected worsening of disease under study
- Unexpected worsening of other pre-existing disease
- Other adverse event

During the treatment period, patients were allowed to stop treatment and then subsequently re-start treatment (temporary discontinuation of study medication). Patients with temporary discontinuation of study medication were included in the analysis of patients with AEs leading to treatment discontinuation. All outcome events in the trial, including those with an onset after

the premature discontinuation of trial medication, were included for the assessment following the intention to treat (ITT) analysis principle.

11.2.1.2. Evaluator's comment

There were more treatment discontinuations due to heart failure in the placebo group with more treatment discontinuations due to stroke in the Empagliflozin group. Early treatment discontinuation due to AE would reduce the number of further AE.

11.2.2. Question 3

Was there any correlation between HbA1c and hypoglycaemia?

11.2.2.1. Sponsor's response

No correlation was found between the occurrence of hypoglycaemia and baseline HbA1c in the trial. Namely, there were similar overall frequencies of confirmed hypoglycaemic adverse events (AEs) across the patient subgroups by baseline HbA1c, and there were no notable differences across treatments in the overall patient population and also in the subgroups. The frequency of patients with symptomatic events with plasma glucose less than < 54 mg/dL (3 mmol/L) was also comparable between treatments. Few patients had hypoglycaemic events requiring assistance, with similar frequencies across treatments in the baseline HbA1c subgroup.

Table 36. Patients with confirmed hypoglycaemic adverse events by baseline HbA1c category (Treatment set)

Baseline HbA_{1c} category	Confirmed hypoglycaemic AE	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)
All patients	Patients	2333 (100.0)	2345 (100.0)	2342 (100.0)
	Confirmed hypoglycaemic AE	650 (27.9)	656 (28.0)	647 (27.6)
	Symptomatic + PG <54 mg/dL	259 (11.1)	257 (11.0)	265 (11.3)
	Required assistance	36 (1.5)	33 (1.4)	30 (1.3)
<7.5%	Patients in subgroup	596 (100.0)	618 (100.0)	635 (100.0)
	Confirmed hypoglycaemic AE	154 (25.8)	162 (26.2)	155 (24.4)
	Symptomatic + PG <54 mg/dL	68 (11.4)	61 (9.9)	66 (10.4)
	Required assistance	4 (0.7)	6 (1.0)	7 (1.1)
7.5% to 8.5%	Patients in subgroup	1090 (100.0)	1066 (100.0)	1051 (100.0)
	Confirmed hypoglycaemic AE	314 (28.8)	313 (29.4)	293 (27.9)
	Symptomatic + PG <54 mg/dL	123 (11.3)	128 (12.0)	119 (11.3)
	Required assistance	19 (1.7)	19 (1.8)	14 (1.3)
>8.5%	Patients in subgroup	647 (100.0)	660 (100.0)	655 (100.0)
	Confirmed hypoglycaemic AE	182 (28.1)	181 (27.4)	199 (30.4)
	Symptomatic + PG <54 mg/dL	68 (10.5)	68 (10.3)	80 (12.2)
	Required assistance	13 (2.0)	8 (1.2)	9 (1.4)

Confirmed hypoglycaemic adverse events were defined as all symptomatic and asymptomatic hypoglycaemic adverse events with a plasma glucose value of ≤70 mg/dL (3.9 mmol/L) or where assistance was required.
PG = plasma glucose; empa = empagliflozin

11.2.2.2. Evaluator's comment

This is acceptable

11.2.3. Question 4

Do any animal studies suggest an association between empagliflozin and cancer? Have there been any signals for bladder or pancreatic cancer in previous clinical trials of empagliflozin or other SGLT2 inhibitors?

11.2.3.1. Sponsor's response

In a 2-year carcinogenicity study in the mouse, there was an increase in renal adenomas and carcinomas given empagliflozin 1000 mg/kg/day, but not at lower doses. These effects were thought to be unlikely to occur in humans as they were associated with a metabolic pathway not present in humans and at a much higher dose.

In a 2-year carcinogenicity study in the rat, treatment related vascular proliferative lesions of the mesenteric lymph nodes were observed at 700 mg/kg/day in male rats but not lower doses. These tumours are common in rats and not thought to be relevant to humans.

No drug related tumours occurred in female animals. There were no empagliflozin related neoplasms in the urinary bladder or pancreas.

There has been no correlation between the use of empagliflozin and bladder or pancreatic cancer in previous clinical trials. The sponsor analysed data from the SAF-52 data set which includes 4588 patients treated with empagliflozin 10 mg, 5520 patients treated with empagliflozin 25 mg and 5599 patients treated with comparators. It also included data from the sponsor's global drug safety system and a literature search.

The overall frequencies of bladder cancer were similar across treatment groups, empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0.2% and comparator group 0.1% and for the patients with malignancy with an onset of 6 months or later after start of treatment empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0.1% and in the comparator group 0.1%.

The overall frequencies of pancreatic cancer were low and similar across treatment groups: empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0.1% and comparator group 0.1%, and for the patients with malignancy with an onset of 6 months or later after start of treatment empagliflozin 10 mg 0.1%, empagliflozin 25 mg 0.1% and in the comparator group 0.1%.

In relation to the other SGLT2 inhibitors, dapagliflozin has shown an imbalance for human bladder cancer.

11.2.3.2. Evaluator's comment

The cell of origin in renal and bladder cancer are different. It appears unlikely that the increased risk of renal cancer in male rodents treated with high doses of empagliflozin is significant. However, it is highly relevant that there was a potential signal for bladder cancer for dapagliflozin.

The evaluator is uncertain of the significance of the numerical increase in the number of bladder and pancreatic cancer in the EMPA-REG study. There is insufficient collaborative data to deny a signal may exist. However, the magnitude of effect seems to be small. The impact of SGLT2 inhibitors on malignancy needs ongoing vigilance.

11.2.4. Question 5

Have any clinical trials with empagliflozin demonstrated an increased risk of amputations or peripheral vascular disease?

11.2.4.1. Sponsor's response

The sponsor conducted a thorough analysis of the lower limb amputations in the clinical trials with empagliflozin containing products. The results of the conducted analysis did not suggest an increased risk of lower limb amputations with empagliflozin. The sponsor has stated that no increased risk of peripheral arterial occlusive disease (PAOD) with empagliflozin was identified, however there were numerically more in the empagliflozin groups than the placebo group (and peripheral arterial disease was an exclusion criteria).

In Phase II and III clinical trials, only one single AE for amputation was recorded. The low number was explained by the sponsor as a feature of the terminology used for reporting (amputation considered a procedure). The sponsor then did a broader search with a number of related terms. Despite the efforts made by the sponsor, the data has a number of limitations due to problems capturing data that may not have been reliably recorded or coded. Most (87.5%) of cases were from the EMPA-REG outcome study.

Table 37. Number of patients with lower limb amputations after the first study drug intake in the EMPA-REG study

Treatment arm	All cases of lower limb amputation
Empagliflozin 10 (N=2345)	42 (1.79%)
Empagliflozin 25 (N=2342)	47 (2.01%)
Placebo (N=2333)	44 (1.89%)
Overall (N=7020)	**133 (1.89)**

Table 38. Selected baseline conditions of patients with amputations after the first study drug intake and overall study population in the EMPA-REG study

Treatment arm	Population	Patients with PAOD	Patients with DPN	Patients with diabetic foot	History of amputation
Empagliflozin 10	With amputation (N=42)	24 (57%)	28 (67%)	19 (45%)	14 (33%)
	Overall population (N=2345)	485 (20.7%)	735 (31.3%)	127 (5.4%)	See Table S4: 4
Empagliflozin 25	With amputation (N=47)	36 (77%)	28 (60%)	21 (45%)	13 (28%)
	Overall population (N=2342)	533 (22.8%)	735 (31.4%)	136 (5.8%)	See Table S4: 4
Placebo	With amputation (N=44)	35 (80%)	24 (55%)	23 (52%)	10 (23%)
	Overall population (N=2333)	492 (21.1%)	727 (31.2%)	145 (6.2%)	See Table S4: 4
Overall	With amputation (N=133)	**95 (71%)**	**80 (60%)**	**63 (47%)**	**37 (28%)**
	Overall population (N=7020)	**1510 (21.5%)**	**2197 (31.3%)**	**408 (5.8%)**	**See Table S4: 4**

In the EMPA-REG study, the rate of amputations was low and not significantly different between the empagliflozin and placebo arms. Most patients with amputations had other risk factors.

Table 39. Trigger event of the lower limb amputations in the EMPA-REG study

Treatment	Ischemic event	Infection	DPN, Diabetic foot	Trauma	Ischemia or Diabetic foot
Empagliflozin 10 (N=2345)	26 (1.11%)	15 (0.64%)	9 (0.38%)	0	35 (1.49%)
Empagliflozin 25 (N=2342)	28 (1.20%)	14 (0.60%)	7 (0.30%)	2 (0.09%)	34 (1.45%)
Placebo (N=2333)	27 (1.16%)	16 (0.69%)	7 (0.30%)	0	33 (1.41%)
Overall (N=7020)	**81 (1.15%)**	**45 (0.64%)**	**23 (0.33%)**	0	**102 (1.45%)**

The triggering event for all amputations was similar across the placebo and empagliflozin groups.

A review of the events of peripheral arterial occlusive disease was performed in SAF-42: the safety dataset representing the broadest randomized, placebo-controlled safety pool of clinical trial data in patients with T2DM. A total of 12,620 randomised and treated patients were included in SAF-42, of which 4221 patients received empagliflozin 10 mg, 4196 patient empagliflozin 25 mg and 4203 patients received placebo. The total exposure of patients being

randomised to empagliflozin 10 mg dose was 7781.9 patient years and to empagliflozin 25 mg dose was 7753.5.

The overall frequency and exposure adjusted incidence rate of the event 'Peripheral artery occlusive disease' was slightly higher in empagliflozin groups: 43 (1.0%) or 0.55/100 PY for empagliflozin 10 mg, and 48 (1.1%) or 0.62/100 PY for Empagliflozin 25 mg compared to placebo group: 34 (0.8%) or 0.46/100 PY. The majority of the cases were reported from the EMPA-REG study.

As with the pooled safety set, in the EMPA-REG study, the event 'Peripheral arterial occlusive disease' was reported with higher incidence rate in empagliflozin groups compared to placebo: 0.69/100 PY for 10 mg, 0.75/100 PY for 25 mg versus 0.58/100 PY for placebo.

To further explore the difference in the incidence rate of the PT 'PAOD', the applicant performed a post-hoc analysis of the medical concept of PAOD using customized MedDRA query.

Table 40. Frequency of PAOD adverse events

	Placebo N=2333		Empa 10 mg N=2345		Empa 25 mg N=2342	
	n (%)	Rate /100 PYs	n (%)	Rate /100 PYs	n (%)	Rate /100 PYs
Total	**87 (3.7)**	**1.54**	**92 (3.9)**	**1.56**	**103 (4.4)**	**1.75**
Peripheral arterial occlusive disease	33 (1.4)	0.58	41 (1.7)	0.69	45 (1.9)	0.75
Intermittent claudication	16 (0.7)	0.28	23 (1.0)	0.38	30 (1.3)	0.50
Peripheral vascular disorders	21 (0.9)	0.36	14 (0.6)	0.23	10 (0.4)	0.17
Peripheral artery stenosis	8 (0.3)	0.14	6 (0.3)	0.10	11 (0.5)	0.18
Femoral artery occlusion	1 (<0.1)	0.02	4 (0.2)	0.07	6 (0.3)	0.10
Peripheral coldness	3 (0.1)	0.05	4 (0.2)	0.07	3 (0.1)	0.05
Arterial occlusive disease	0	0	2 (0.1)	0.03	3 (0.1)	0.05
Iliac artery occlusion	1 (<0.1)	0.02	0	0	2 (0.1)	0.03
Peripheral artery restenosis	1 (<0.1)	0.02	2 (0.1)	0.03	0	0

11.2.4.2. Evaluator's comment

The response is satisfactory. The EMPA-REG study provided the most reliable data regarding AE of amputations and peripheral vascular disease of all of the clinical trials involving empagliflozin.

There was no imbalance observed for the number of amputations, however the reliability of this data is questioned due to amputations not being a pre-specified safety endpoint. There was a numerically greater number of AE related to peripheral vascular occlusive disease in the empagliflozin group.

The evaluator would recommend a warning about the risk of PVD in the PI and RMP due to safety signal from the CANVAS study and imbalance in PVD reported in the EMPA-REG study.

11.2.5. Question 6

The interactions of empagliflozin with other medications in the prevention of cardiovascular events may warrant further evaluation.

11.2.5.1. Sponsor's response

The cardiovascular benefits with empagliflozin in the trial 1245.25 have been consistently observed across a wide range of pre-specified subgroups, including antidiabetic and other baseline medications. Further insights into the interactions of empagliflozin and other medications in the prevention of cardiovascular events are beyond the scope of this trial.

11.2.5.2. Evaluator's comment

The evaluator agrees that further evaluation of the interaction between medications and events are beyond the scope of the trials. There were some discordant findings in the event rates with different medications which may justify further evaluation in other clinical trials

11.3. RMP

1. The sponsor has agreed to add DKA as an important identified risk.
2. The sponsor has not agreed to include stroke as a potential risk. The following reasons were given: There was no significant difference observed between empagliflozin and stroke (fatal/non-fatal); there was no increase in treatment emergent strokes; there was no increase in recurrent, disabling or fatal strokes, TIA was not increased for empagliflozin, there was no evidence in the trial of a diuretic effect of empagliflozin and stroke.

Comment: The evaluator does not believe that this is significant justification. There were numerically more strokes in the empagliflozin group and more treatment discontinuation due to stoke in the empagliflozin groups. Although this was not statistically significant- the study was not powered for subgroup analysis. The fact that the HR for stroke approached 1 with increasing number of days since ceasing empagliflozin would infer that as patients hydration improved after the excessive diuresis from empagliflozin stopped, the risk of stroke decreased. It is not surprising the trial did not find an association between hydration status and stroke as mild dehydration can be difficult to detect clinically with a variety of signs, particularly in the elderly and particularly if the dehydration is chronic.

3. The sponsor has agreed to add Indigenous Australians as Missing Information.
4. Off label use in T1DM and paediatrics is included in the RMP.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

12.1.1. Cardiovascular events

The benefits of empagliflozin for the prevention of cardiovascular death have been described above.

The second round response has not changed the evaluator's views on the efficacy.

There is some uncertainty about the cardiovascular protection in patients with HbA1c < 7% as these patients represented only a small subset of patients in the EMPA-REG study and are likely to have a history of previous period of poor glycaemic control. Efficacy in patients with recent onset T2DM is unknown.

12.1.2. Use in renal impairment

The efficacy of empagliflozin is dependent upon renal function. The evidence from use in renal impairment suggests less improvement in HbA1c, but similar improvement in cardiovascular events in patients with severe renal impairment. In addition there are additional benefits in terms of prevention of deterioration of renal disease.

Comment: Dapagliflozin is contraindicated in patients with eGFR < 60 mL/min and canagliflozin contraindicated in patients with eGFR < 45 mL/min. The

contraindications for use in renal impairment relate to concerns about efficacy rather than based on safety or increased exposure due to reduced elimination.

There has been a recent safety communication from the FDA in relation to cases of acute renal injury in patients taking dapagliflozin and canagliflozin.

12.2. Second round assessment of risks

The risks associated with the use of empagliflozin have been better characterised as a result of the EMPA-REG study.

There is also some uncertainty about whether the term 'high cardiovascular risk' needs further defining. This is probably better mentioned in the precautions section; that is how well the results can be extrapolated to patients with higher/lower risk than those in the study. Possibilities may include factors similar to the inclusion/exclusion criteria for the study. There are possible safety signals for PVD and stroke, does extra care need to be given to patients with pre-existing PVD or cerebrovascular disease.

It is uncertain whether the SGLT2 inhibitors may lead to an increased risk of PVD, stroke or bladder cancer. These potential risks should be included in the RMP and PI.

12.3. Second round assessment of benefit-risk balance

Overall, the risk/benefit balance for the use of empagliflozin in patients with T2DM and poor glycaemic control for cardiovascular prevention is positive.

13. Second round recommendation regarding authorisation

The evaluator would recommend approval of:

1. Extension of indication to include the prevention of cardiovascular events:

   'Jardiance is indicated in patients with type 2 diabetes mellitus and high cardiovascular risk to reduce the risk of:

   - *All-cause mortality by reducing cardiovascular death*
   - *Cardiovascular death or hospitalisation for heart failure*

   To prevent cardiovascular events, Jardiance should be used in conjunction with other measures to reduce cardiovascular risk in line with the current standard of care.

   Note: Benefits in patients with recent onset T2DM and HbA1c < 7% has not been established.'

2. Extension of use in patients with severe renal disease, by changing the contraindication to eGFR < 30mL/min/1.73 m^2.

14. References

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