15 December 2016
EMA/11728/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jardiance

International non-proprietary name: empagliflozin

Procedure No. EMEA/H/C/002677/II/0014

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ACEi	Angiotensin converting enzyme inhibitors
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BMI	Body mass index
BP	Blood pressure
CEC	Clinical Event Committee
CI	Confidence interval
CKD	Chronic kidney disease
CTR	Clinical trial report
CV	Cardiovascular
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eGFR	(Estimated) glomerular filtration rate
EMA	European Medicines Agency
Empa	Empagliflozin
FAS	Full analysis set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
HbA1c	Glycosylated haemoglobin
HDL	High-density lipoprotein
HLT	High level term
HR	Hazard ratio
ITT	Intent to treat
LDL	Low-density lipoprotein
LLN	Lower limit of normal

LOCF	Last observation carried forward
MACE	Major adverse cardiovascular events
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for drug regulatory activities
MI	Myocardial infarction
MMRM	Mixed model repeated measures
OC	Observed cases
OC-AD	Observed cases after discontinuation or after rescue medication intake
OS	On-treatment set
PT	Preferred term
RAAS	Renin angiotensin aldosterone system
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT	Sodium-dependent glucose co-transporter
SMQ	Standardised MedDRA query
SOC	System organ class
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TIA	Transient ischaemic attack
TS	Treated set
UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 9 November 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Modification of the indication for Jardiance to reflect new data on cardiovascular outcomes based on study 1245.25 (EMPA-REG OUTCOME).
In addition, the Marketing authorisation holder (MAH) took the opportunity to make some editorial changes.

Furthermore, the PI is brought in line with the latest QRD template.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0211/2015on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP not yet completed as some measures were deferred

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Hans Hillege Co-Rapporteur: Bart Van der Schueren

The Rapporteur appointed by PRAC was:

PRAC Rapporteur: Dolores Montero

Timetable	Dates
Submission date	9 November 2015
Start of procedure:	28 November 2015
CHMP Rapporteur Assessment Report	22 January 2016
CHMP Co-Rapporteur Assessment Report	22 January 2016
PRAC Rapporteur Assessment Report	1 February 2016
Updated PRAC Rapporteur Assessment Report	4 February 2016
PRAC Outcome	11 February 2016
CHMP members comments	N/A
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 February 2016
Request for supplementary information (RSI)	25 February 2016
Submission	21 April 2016
CHMP Rapporteur Assessment Report	27 May 2016
PRAC Rapporteur Assessment Report	27 May 2016
Updated PRAC Rapporteur Assessment Report	2 June 2016
PRAC Outcome	07 June 2016
CHMP members comments	13 June 2016
Updated CHMP Rapporteur Assessment Report	16 June 2016
2nd Request for Supplementary information	23 June 2016
Submission	12 August 2016
PRAC Rapporteur's preliminary Assessment Report circulated on:	22 August 2016
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
CoRapporteur's preliminary assessment report on the MAH's responses circulated on	31 August 2016
PRAC Outcome	02 September 2016
CHMP members comments	05 September 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	08 September 2016
An Oral explanation took place on:	14 September 2016

Timetable	Dates
3rd Request for Supplementary information	15 September 2016
Request for clock stop extension	10 October 2016
MAH Submission	14 November 2016
Procedure re-start	16 November 2016
PRAC (RMP) Assessment Report	18 November 2016
PRAC members comments	N/A
Updated PRAC Rapporteur's Assessment Report	N/A
CoRapporteur's preliminary assessment report on the MAH's responses circulated on	29 November 2016
PRAC Outcome	01 December 2016
CHMP Members comments	05 December 2016
Updated CoRapporteur's Assessment Report	08 December 2016
CHMP Opinion	15 December 2016

2. Scientific discussion

2.1. Introduction

Diabetes mellitus is an increasingly prevalent disease. Recent estimates suggest that the number of people worldwide with diabetes is currently 382 million and is expected to reach at least 592 million within the next 25 years. The most common form is type 2 diabetes mellitus (T2DM), which is characterized by insulin resistance, impaired insulin secretion, and increased glucose production by the liver.

Type 2 diabetes is frequently associated with comorbidities that exacerbate cardiovascular (CV) risk, such as obesity and hypertension. The risk of CV disease is increased approximately 2 to 4-fold in adults with diabetes. The risk of heart failure is increased more than 2-fold in patients with T2DM, and heart failure in these patients is associated with a poor prognosis. Recommended strategies for reducing CV risk in patients with T2DM include glucose management, lipid lowering, blood pressure (BP) control, smoking cessation, and weight loss [R14-0344]. There is a clear association between microvascular complications such as albuminuria and an increased risk of CV events in patients with T2DM, and improved glycaemic control has been associated with a reduction in microvascular events. However, the impact of reducing blood glucose and the potential benefit of specific glucose-lowering agents on CV events in patients with T2DM remains unclear and highly controversial. Thus, there is a strong clinical need to identify antihyperglycaemic agents that are safe and can potentially reduce cardiovascular and microvascular complications.

Empagliflozin is a novel, orally administered, potent, and selective SGLT-2 inhibitor developed by Boehringer Ingelheim (BI). Empagliflozin is currently indicated for treatment of type 2 diabetes mellitus in conjunction with diet and exercise, as monotherapy or as add-on therapy to other oral antidiabetic treatments or insulin. Empagliflozin 10 mg and 25 mg once daily is approved in more than 50 countries including the EU and the US.

In this application, the proposed new indications, as initially proposed by the applicant, are to reduce the risk of all-cause mortality by reducing CV deaths and to reduce the risk of CV death or hospitalisation for heart

failure, in patients with T2DM and high CV risk. The proposed indications are based on the results from the EMPA-REG OUTCOME (trial 1245.25).

2.2. Non-clinical aspects

No new non- clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided a justification for not submitting an environmental assessment update.

As the target population and the maximum daily dose (25 mg) are not changed as a result of this variation, the CHMP agrees that the ERA submitted with the initial MAA remains valid for the current type II variation.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of empagliflozin. Empagliflozin is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

In this dossier, (only) the results of the cardiovascular outcome trial are presented. In this outcome trial, limited PK data were collected. The design of the trial is discussed below under clinical efficacy.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

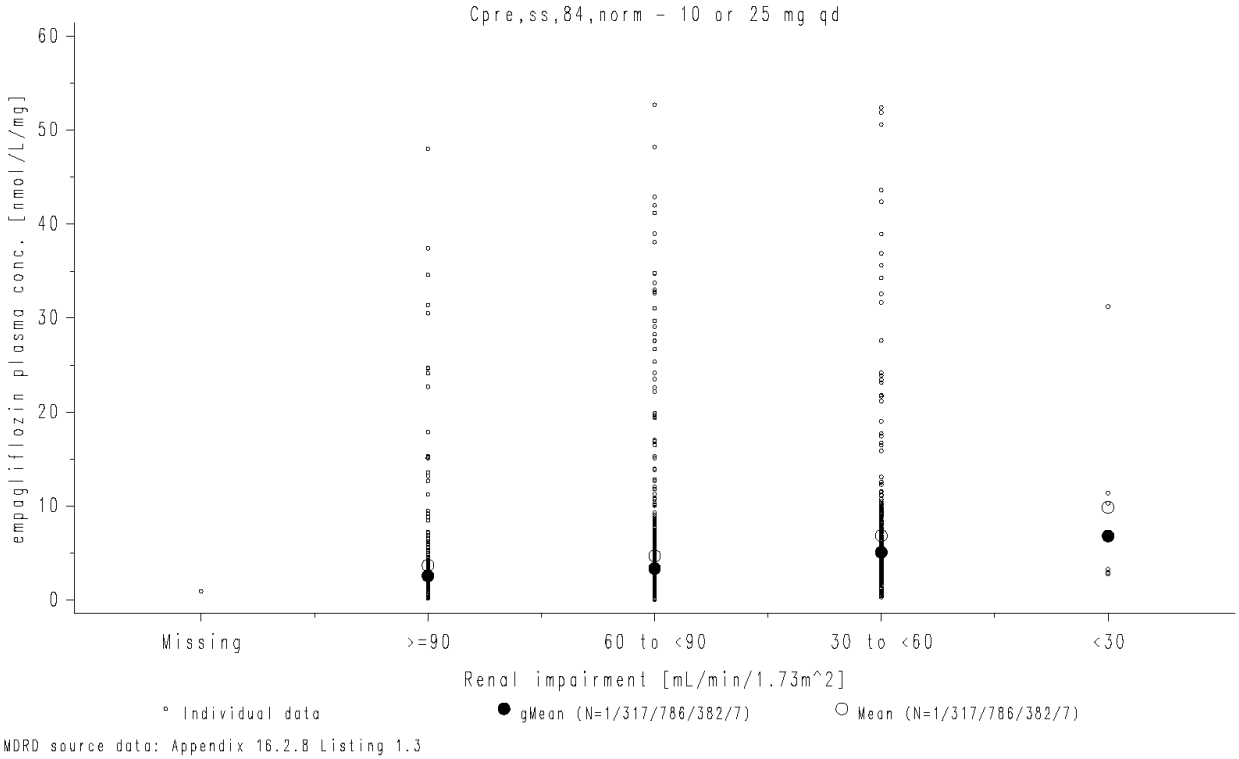
Limited pharmacokinetic data were collected during the EMPA-REG trial. No changes to the product documentation are proposed.

Steady-state morning trough concentrations of empagliflozin were evaluated on Days 85 and 364. In this study patients were treated with Empagliflozin 10mg or 25mg once daily. Empagliflozin trough concentrations were similar within each dose group at both time points indicating that steady-state concentrations of empagliflozin were maintained during the course of the trial. The increase in empagliflozin exposure with dose was roughly proportional to dose.

Empagliflozin exposures were generally similar in men and women at both dose levels. There were no relevant changes in empagliflozin exposure with an increase in gender, age or body weight. No specific trends were observed by geographic region or country. There were no major differences in exposure in different races or ethnicities. Empagliflozin exposure increased with a decrease in renal function. These findings are consistent with the results of the previous population pharmacokinetic analysis.

In subjects with renal insufficiency, dose-normalised geometric mean plasma trough concentrations are increased up to 2.8 fold in patients with severe renal impairment compared to patients with a normal renal function (Figure 1). These results are in line with the previously observed higher AUCss of empagliflozin in patients with renal impairment as reflected in the current SmPC.

Figure 1. Comparison of dose normalised plasma through concentrations of empagliflozin after multiple oral administration in patients by renal impairment.



MDRD source data: Appendix 16.2.8 Listing 1.3

2.3.3. Pharmacodynamics

No specific pharmacodynamic data were submitted. For results regarding HbA1c and FPG, please refer to the section on Further Efficacy endpoints (see section 2.4.1).

Mechanism of action

The current SmPC contains information about the regulation of glucose by empagliflozin. However, the proposed CV prevention indication likely has another mode of action that is not directly related to glycaemic control. This is even more relevant in subjects with renal insufficiency, where the effect on glycaemic control was limited but the effect for CV prevention is preserved.

2.4. Clinical efficacy

In this application, a single trial is submitted (EMPA-REG, 1245.25). This trial is discussed below and summarised in Table 16.

2.4.1. Main study

Title of Study

A Phase III, multicentre, international, randomised, parallel group, double blind cardiovascular safety study

of BI 10773 (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk. The EMPA-REG OUTCOME Trial.

Methods

Study participants

The study was performed in patients with T2DM and high cardiovascular risk who had insufficient glycaemic control despite diet and exercise and were either treatment-naïve (drug-naïve) or receiving any antidiabetic background therapy.

The inclusion criteria specify a population at high risk for CV events, specified by the combination of T2DM and a history of CV disease, defined as at least one of the following:

- confirmed history of myocardial infarction (MI) (>2 months prior to informed consent);
- evidence of coronary artery disease (in ≥2 major coronary arteries or single vessel coronary artery disease (significant stenosis with positive non-invasive stress test or with previous hospitalisation for unstable angina); last episode of unstable angina >2 months prior to informed consent);
- history of ischaemic or haemorrhagic stroke (>2 months prior to informed consent);
- presence of peripheral artery disease (symptomatic or not).

Patients could only be included if glycaemic control was insufficient (HbA1c 7-9% for treatment-naïve patients, 7-10% for patients already on glucose-lowering therapy).

Contrary to the current SmPC of Jardiance, subjects with moderate renal insufficiency (eGFR between 30 and 60 ml/min 1.73m^2) were fully eligible for all treatments.

Treatments

Empagliflozin was administered in 10 mg or 25 mg doses once daily and compared to placebo. The study treatment is in line with the current SmPC of Jardiance for subjects with normal renal function or mild renal impairment (eGFR > 60 ml/min 1.73m^2).

However, according to the SmPC for subjects with moderate renal insufficiency (eGFR between 45 and 60 ml/min 1.73m^2) only the 10 mg dose should be used and therapy should not be initiated. Therapy should be withdrawn if the eGFR remains below 45 ml/min 1.73m^2.

All patients received trial medication on top of standard-of-care treatment, which could be adapted if indicated. Background antidiabetic medication was to be kept stable in the first 12 weeks but could be changed thereafter to achieve standard of care according to investigator's discretion and local guidelines.

Objectives

The primary objective of this event-driven study was to determine non-inferiority (with a non-inferiority margin of 1.3) and subsequently superiority of empagliflozin treatment (2 pooled doses, 10 mg once daily and 25 mg once daily) vs. placebo based on the composite of 3 major adverse cardiovascular events (MACE): cardiovascular death, non-fatal stroke, or non-fatal MI in patients with T2DM and increased cardiovascular risk. The procedure guaranteed control of the type 1 error.

Outcomes/endpoints

The primary endpoint was the time to first occurrence of 3-point MACE (major adverse cardiovascular events; composite of any of the following: cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction). The key secondary endpoint was the time to first occurrence of 4-point MACE (cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction, or hospitalisation for unstable angina pectoris).

These events were prospectively adjudicated using pre-specified definitions by an independent clinical events committee (CEC), blinded to treatment allocation.

In addition, around 40 secondary and other endpoints were analysed.

Sample size

The primary hypothesis originally aimed to assess the non-inferiority of empagliflozin versus placebo based on a non-inferiority margin of 1.8 for the hazard ratio but later this was amended (see below) to a non-inferiority margin of 1.3 for the hazard ratio. Assuming a non-inferiority margin of 1.3 and 90% power, with a significance level of 0.025 (one-sided), with the empagliflozin and placebo patients in 2:1 ratio, a minimum of 691 events were required to achieve the primary aim of the trial (using a Haybittle-Peto boundary that preserved 0.0249 of the alpha for the final analysis). The trial would continue until a minimum of 691 patients had experienced an adjudicated primary outcome event.

While the number of required events was independent of the accrual and follow-up time and independent of the yearly event rates, the number of patients to be randomised was dependent on these parameters. To obtain the minimum 691 events, based on 7000 patients, assuming an accrual period of 24 months, a yearly event rate of 1.5%, and a randomisation rate of 3500 patients/year, the trial duration was anticipated to be just under 8 years. The planned treatment duration of the patients was therefore up to 8 years, with approximately 8 years (approximately 420 weeks) as the planned total duration of trial. With a minimum of 691 events, the trial would have at least 80% power to detect a hazard ratio of 0.785 (corresponding to a 21.5% risk reduction in cardiovascular outcome events) for the primary endpoint.

Randomisation

Patients were randomly assigned to 1 of the 3 treatment groups (empagliflozin 10 mg; empagliflozin 25 mg; placebo) in a 1:1:1 ratio. Randomisation was stratified in a balanced ratio for HbA1c (<8.5 or ≥8.5% at screening), BMI (<30 or ≥30 kg/m2 at randomisation), geographical regions (North America, Latin America, Europe, Africa, and Asia), and renal function at screening (normal: eGFR ≥ 90 mL/min/1.73m2; mild impairment: eGFR 60 to ≤89 mL/min/1.73m2; moderate impairment: eGFR 30 to ≤59 mL/min/1.73m2).

Blinding (masking)

The placebo run-in period of this trial was performed open-label, i.e. both the investigator and the patient knew that the patient received placebo during the run-in period. The randomised period of this trial was performed double-blind according to current standards. The interim analysis was performed by a separate team.

Statistical methods

For confirmatory testing, the hazard ratio (HR) of empagliflozin (10 mg and 25 mg combined; designated as "all empagliflozin" in the document) to placebo was to be analysed with a Cox proportional hazards regression model. Non-inferiority on the primary endpoint was to be tested based on the non-inferiority margin of 1.3 and the overall significance level of alpha=0.025 (1-sided). If non-inferiority for the primary endpoint could be established for the 1.3 margin, non-inferiority would be tested for the key secondary endpoint based on the same margin. If non-inferiority was established for both endpoints, superiority was to be tested for the primary endpoint and then the key secondary endpoint. The significance level of the final analysis was slightly adapted due to an interim analysis of the trial data.

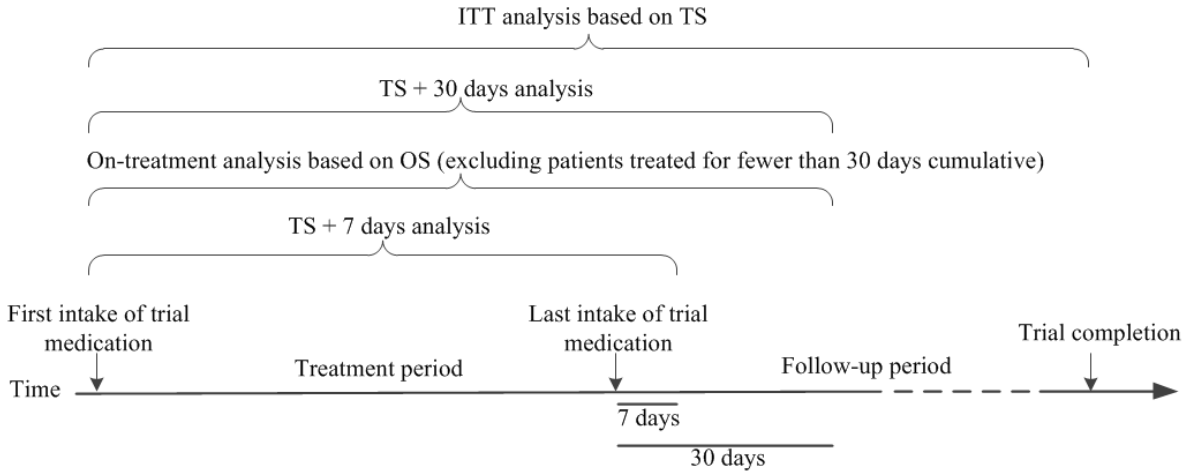
The primary and key secondary endpoints were tested for non-inferiority and superiority using a 4-step hierarchical testing strategy, which will protect the overall type I error. The non-inferiority margin was set at 1.3.

A number of additional secondary and further endpoints related to CV safety and microvascular safety were analysed in an **exploratory** manner, based on adjudicated events, reported adverse events, or laboratory

data. These included the components of the composite CV and microvascular endpoints as individual endpoints, as well as a composite of heart failure requiring hospitalisation or CV death, all-cause mortality, and a composite of new or worsening nephropathy.

The main analysis for each endpoint followed the "intent-to-treat (ITT)" principle, using the treated set (TS) and including all events up to individual trial completion. In addition, on-treatment analyses for CV endpoints based on the "treatment-emergent" principle were performed using the on-treatment set (OS, included only patients with at least 30 days of cumulative treatment and considered only events up to 30 days after treatment stop). Furthermore, analyses using the TS with various lengths of follow-up time (such as 7 or 30 days) after treatment stop were performed for CV endpoints (see Figure 2 below).

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



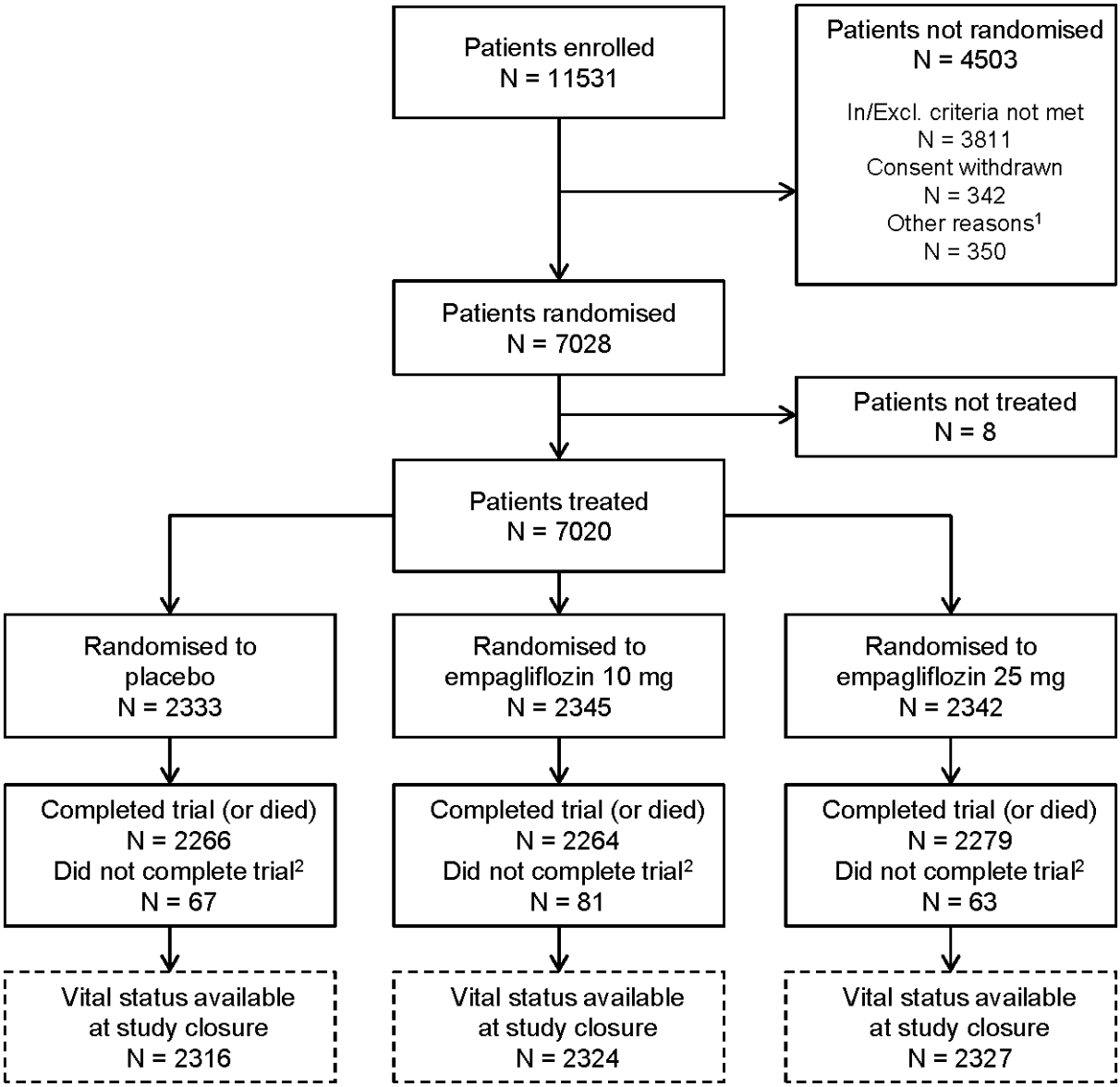
The primary analysis will be on the ITT population and performed with a Cox proportional hazards model, stratified by age, sex, baseline categories of BMI, baseline HbA1c, baseline eGFR values and geographical region, performed on the ITT population. This is considered standard for time to event endpoints. For sensitivity analyses, the primary endpoint was further tested in the on-treatment set and the per-protocol set. Secondary and exploratory time-to-event endpoints used the same analysis model as the primary endpoint. UACR and eGFR were analysed with the mixed model repeated measures approach (MMRM), using the observed data. Other categorical endpoints were analysed using an ANCOVA model with LOCF. An interim analysis was performed in 2012 to provide data for a cardiovascular meta-analysis submitted in the initial marketing application. The overall type I error rate was maintained at a one-sided significance level of 0.025 using a Haybittle-Peto correction, resulting in α=0.0001 for the interim analysis and 0.0249 for the final analysis, to protect the overall type I error at 0.025 one-sided.

Results

Participant flow

Of the 7020 patients treated with randomised trial medication, 97.0% of the patients completed the trial. Vital status information at the end of the trial was available for all but 53 patients (0.8%). Disposition in terms of trial completion and the availability of vital status was balanced across the 3 treatment groups (Figure 3). The proportions of patients who prematurely discontinued trial medication were higher in the placebo group than in the empagliflozin groups; the most frequent reasons were adverse events (placebo: 13.0%; empagliflozin 10 mg: 11.4%; empagliflozin 25 mg: 11.7%).

Figure 3. Overview of patient disposition – SCR



Recruitment

This trial was a multi-centre trial conducted globally. A total of 11531 patients signed informed consent, i.e. were screened or enrolled, at 609 centres in 42 countries in Africa, Asia, Europe, North America, Latin America and Australia/New Zealand (the last 2 countries were grouped with North America for the purpose of the analyses). The first patient was enrolled into this trial on 26 Aug 2010. The last on-site visit of a patient took place on 13 Apr 2015. The last contact date with any patient in the trial was 21 Apr 2015.

The majority of randomised patients came from Europe (41.1%) and North America (19.8%).

Conduct of the study

This trial was conducted according to the original trial protocol dated 10 May 2010 and its revisions. There were 4 global protocol amendments leading to 4 global protocol revisions (dated 22 Sep 2010, 22 Apr 2011, 29 Dec 2011, 15 Oct 2013).

With amendment nr 3, prior to the interim analysis, the non-inferiority margin was reduced from 1.8 to 1.3 and the sample size increased accordingly from 4000 to 7000 patients to meet regulatory requirements. The required number of events increased from 137 to 691. The anticipated treatment duration of the patients was changed from 3-4 years to 6-8 years.

Also with amendment nr 3, the primary endpoint was reworded to make it clear that silent MI was not included in the definition (time to the first occurrence of MACE-3).

Baseline data

Demographics and baseline characteristics were well balanced across the 3 treatment groups. For brevity, only overall data are shown and no breakdown per group (Table 1).

Of note, slightly fewer patients in the placebo group compared to 'all empagliflozin' reported a history of recurrent or chronic urinary tract infection (5.6% v 6.7%).

In the placebo group, more medications were introduced during the trial, especially antidiabetic (31.5% placebo v. 19.5% empagliflozin) and anti-hypertensive (51.0% v 44.5%).

Table 1. Demographic and baseline data of the study population – TS

Demographic or baseline variable	All patients
Total treated patients, N (%)	7020 (100.0)
Sex, N (%)	
Male	5016 (71.5)
Female	2004 (28.5)
Race [1], N (%)	
White	5081 (72.4)
Asian	1517 (21.6)
Black/African American	357 (5.1)
Amer. Indian/Alaska Native	54 (0.8)
Ethnicity, N (%)	
Not Hispanic/Latino	5747 (81.9)
Hispanic/Latino	1265 (18.0)
Region, N (%)	
Europe	2885 (41.1)
North America	1394 (19.9)
Asia	1347 (19.2)
Latin America	1081 (15.4)
Africa	313 (4.5)
Age category, N (%)	
<50 years	439 (6.3)
50 to <65 years	3454 (49.2)
65 to <75 years	2475 (35.3)
≥75 years	652 (9.3)
Age [years], mean (SD)	63.1 (8.6)
Time since diagnosis of T2DM, N (%)	
≤1 year	180 (2.6)
>1 to 5 years	1083 (15.4)
>5 to 10 years	1746 (24.9)
>10 years	4011 (57.1)

Demographic or baseline variable	All patients
eGFR (MDRD) category, N (%)	
≥90 mL/min/1.73m^2	1538 (21.9)
60 to <90 mL/min/1.73m^2	3661 (52.2)
45 to <60 mL/min/1.73m^2	1249 (17.8)
30 to <45 mL/min/1.73m^2	543 (7.7)
<30 mL/min/1.73m^2	27 (0.4)
CV risk	
With CV high-risk factor, N (%)	6964 (99.2)
Coronary artery disease	5308 (75.6)
History of stroke	1637 (23.3)
Peripheral artery disease	1461 (20.8)
HbA_{1c} [%], mean (SD)	8.07 (0.85)
FPG [mg/dL], mean (SD)	152.9 (43.8)
BMI [kg/m^2], mean (SD)	30.62 (5.26)
History of hypertension, N (%)	6419 (91.4)
SBP <140 and DBP <90 mmHg, N (%)	4306 (61.3)
UACR category, N (%)	
Normal (<30 mg/g)	4171 (59.4)
Microalbuminuria (30 to 300 mg/g)	2013 (28.7)
Macroalbuminuria (>300 mg/g)	769 (11.0)
Medication use at baseline, N (%)	
Antidiabetic background medication	6891 (98.2)
Metformin	5193 (74.0)
Insulin	3387 (48.2)
Sulphonylurea	3006 (42.8)
DPP-IV inhibitor	796 (11.3)
Antihypertensives	6667 (95.0)
Lipid-lowering drugs	5684 (81.0)
Anticoagulants	6252 (89.1)

Assessor's note: for brevity, only overall data shown and no breakdown per group.

Numbers analysed

Several analysis sets were defined for the various analyses in this trial. An overview of the number of patients in each analysis set is provided in the table below. The treated set (TS) was used for the primary analysis. It comprised all randomised patients who received at least 1 dose of study medication and thus excluded 8 randomised but not treated patients.

Table 2. Patient analysis sets

	Placebo N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	All empa N (%)	Total N (%)
Randomised set (RS)	2337	2347	2344	4691	7028
Treated set (TS), (% of RS)	2333 (99.8)	2345 (99.9)	2342 (99.9)	4687 (99.9)	7020 (99.9)
Full analysis set (FAS), (% of TS)	2333 (100.0)	2344 (100.0)	2341 (100.0)	4685 (100.0)	7018 (100.0)
Per-protocol set (PPS), (% of TS)	2316 (99.3)	2332 (99.4)	2322 (99.1)	4654 (99.3)	6970 (99.3)
On-treatment set (OS), (% of TS)	2308 (98.9)	2306 (98.3)	2301 (98.2)	4607 (98.3)	6915 (98.5)
Treated set follow-up (TS FU), (% of TS)	1668 (71.5)	1773 (75.6)	1824 (77.9)	3597 (76.7)	5265 (75.0)
Pharmacokinetic set, (% of RS)	928 (39.7)	953 (40.6)	954 (40.7)	1907 (40.7)	2835 (40.3)

The RS, TS, FAS, PPS and OS all included at least 98.2% of randomised patients in each group and thus largely overlap.

According to the disposition of patients, 1780 (25.4%) of patients prematurely discontinued trial medication. In line with the ITT principle these patients were followed up and remained in the trial. The results in these patients were consistent with the on-treatment and per protocol analyses.

Outcomes and estimation

Primary endpoint: 3-point MACE

The primary endpoint (3-point MACE) was the time to first occurrence of CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), or non-fatal stroke. The primary analysis based on the TS showed superiority of "all empagliflozin" treatment to placebo (Table 3).

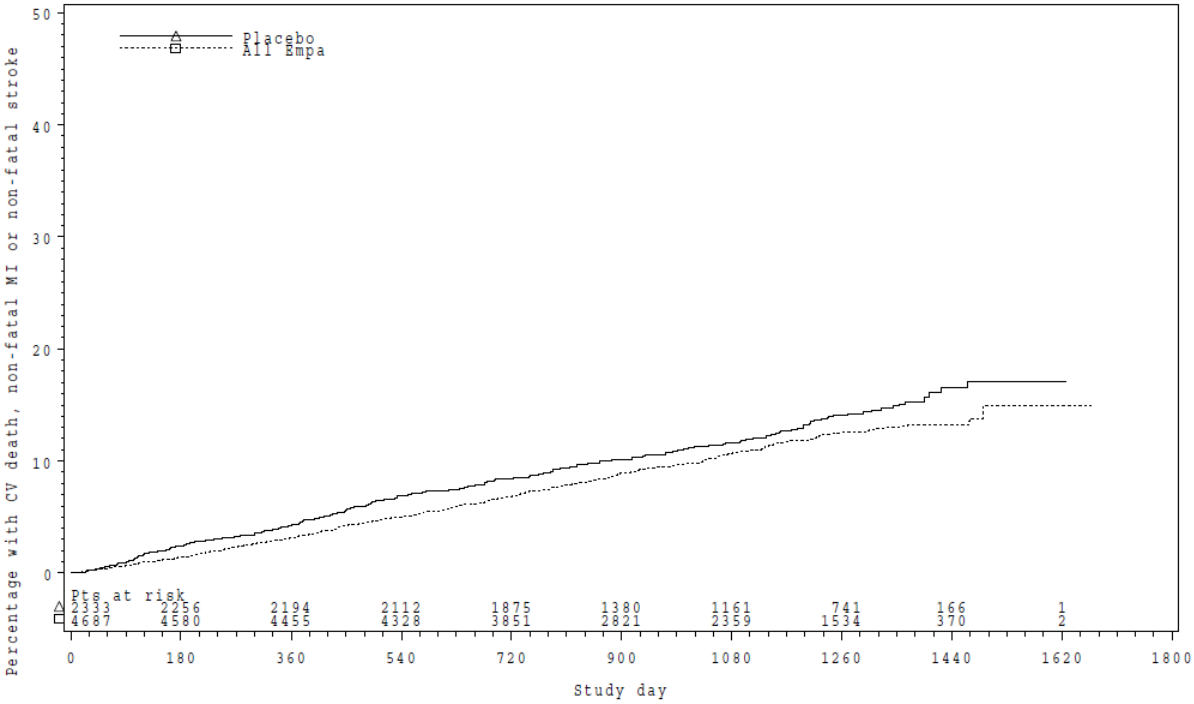
Table 3. Cox regression for time to first 3-point MACE, all empagliflozin vs. placebo – TS and PPA

	Placebo	All empa
Treated Set (TS)		
Analysed patients, N (100%)	2333	4687
Patients with event, N (%)	282 (12.1)	490 (10.5)
Incidence rate per 1000 years at risk	43.9	37.4
Hazard ratio vs. placebo	--	0.86
(95.02% CI) [1]		(0.74, 0.99)
(95% CI)		(0.74, 0.99)
p−value for HR≥1.3 (1-sided)		<0.0001
p−value for HR≥1.0 (1-sided)		0.0191
p−value (2-sided)		0.0382
Per protocol analysis (PPA)		
Patients with event, N (%)	278/2316 (12.0)	487/4654 (10.5)
HR (95% CI)		0.86 (0.75, 1.00)
p−value (2-sided)		0.0519

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

The Kaplan-Meier estimates for time to first 3-point MACE are shown in Figure 4 below.

Figure 4. Kaplan-Meier estimates of time to first 3-point MACE, all empagliflozin vs. placebo – TS



Exploratory analyses were performed for the individual empagliflozin doses. The results were consistent with those for "all empagliflozin", with no relevant differences observed between the 2 doses. The similarity of the hazard ratio point estimate of "all empagliflozin" and the 2 doses supports the robustness of the primary analysis. Due to the smaller sample size (thus a loss of statistical power) in the analysis for the individual doses, the p-values of empagliflozin 10 mg or 25 mg vs. placebo treatment were not significant (p>0.05; Table 4 below).

Table 4. Cox regression for time to first 3-point MACE, empagliflozin doses vs. placebo – TS

	Placebo	Empa 10 mg	Empa 25 mg
Treated set (TS)			
Analysed patients, N (100%)	2333	2345	2342
Patients with event, N (%)	282 (12.1)	243 (10.4)	247 (10.5)
Incidence rate per 1000 years at risk	43.9	37.1	37.7
Hazard ratio vs. placebo (95% CI)	--	0.85 (0.72, 1.01)	0.86 (0.73, 1.02)
p-value		0.0668	0.0865

The primary analysis based on TS described above included all events until individual trial completion, following the ITT principle. Results from the sensitivity and additional analyses (such as on-treatment analysis and analysis based on the per-protocol set) were generally consistent with the results of the primary analysis, but in the per protocol analysis statistical significance was not reached (Table 3 and Table 5 below).

The breakdown of the first event for 3-point MACE indicated that the lower frequency of 3-point MACE for empagliflozin was primarily due to the lower frequency of CV death (Table 6 below). Assessments of the

time to first events for each MACE component as individual outcome endpoint are described in the sections below, and confirmed a reduction in CV death with empagliflozin treatment.

Table 5. Cox regression for time to first 3-point MACE event up to treatment stop + 30 days – OS, TS

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

Source data: [c02695839, Tables 15.2.1.2: 1, 15.2.1.2: 2, 15.2.1.2: 5, 15.2.1.2: 6]

Table 6. Patients with the first confirmed 3-point MACE event by component – TS

	Placebo	**Empa 10 mg**	**Empa 25 mg**	**All empa**
Patients, N (100%)	2333	2345	2342	4687
Patients with 3-point MACE, N (%)	282 (12.1)	243 (10.4)	247 (10.5)	490 (10.5)
CV death	107 (4.6)	78 (3.3)	65 (2.8)	143 (3.1)
Non-fatal MI	120 (5.1)	92 (3.9)	116 (5.0)	208 (4.4)
Non-fatal stroke	55 (2.4)	75 (3.2)	67 (2.9)	142 (3.0)

Patients could be reported with multiple events if these occurred on the same day.

The results for **subgroup analyses** of the primary endpoint are summarised in the figures 5, 6 and 7 below. The results for subgroups show good consistency with the overall primary endpoint.

Figure 5. Primary endpoint (MACE-3) subgroups for demographic characteristics

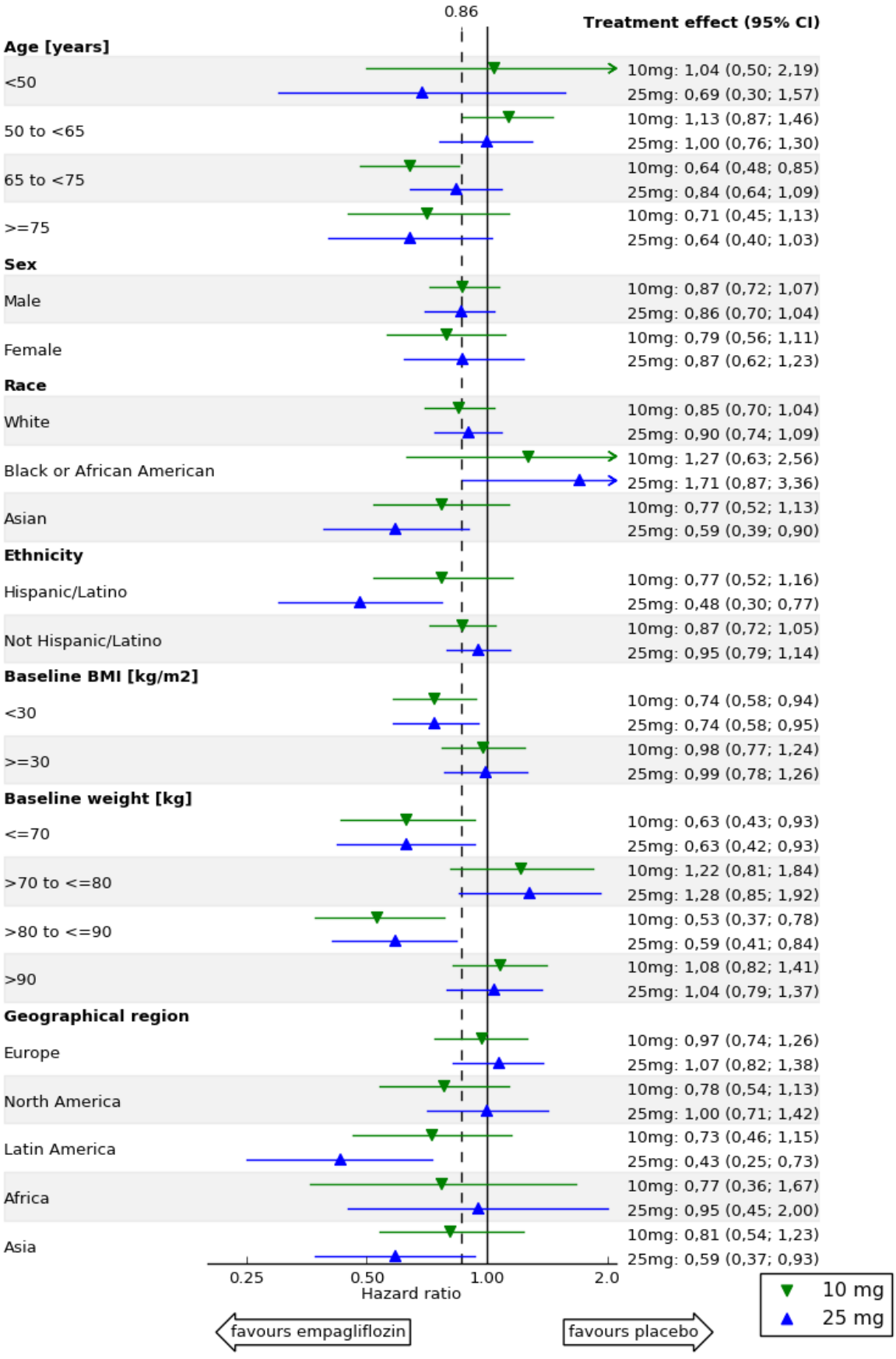


Figure 6. Primary endpoint (MACE-3) subgroups for baseline disease characteristics

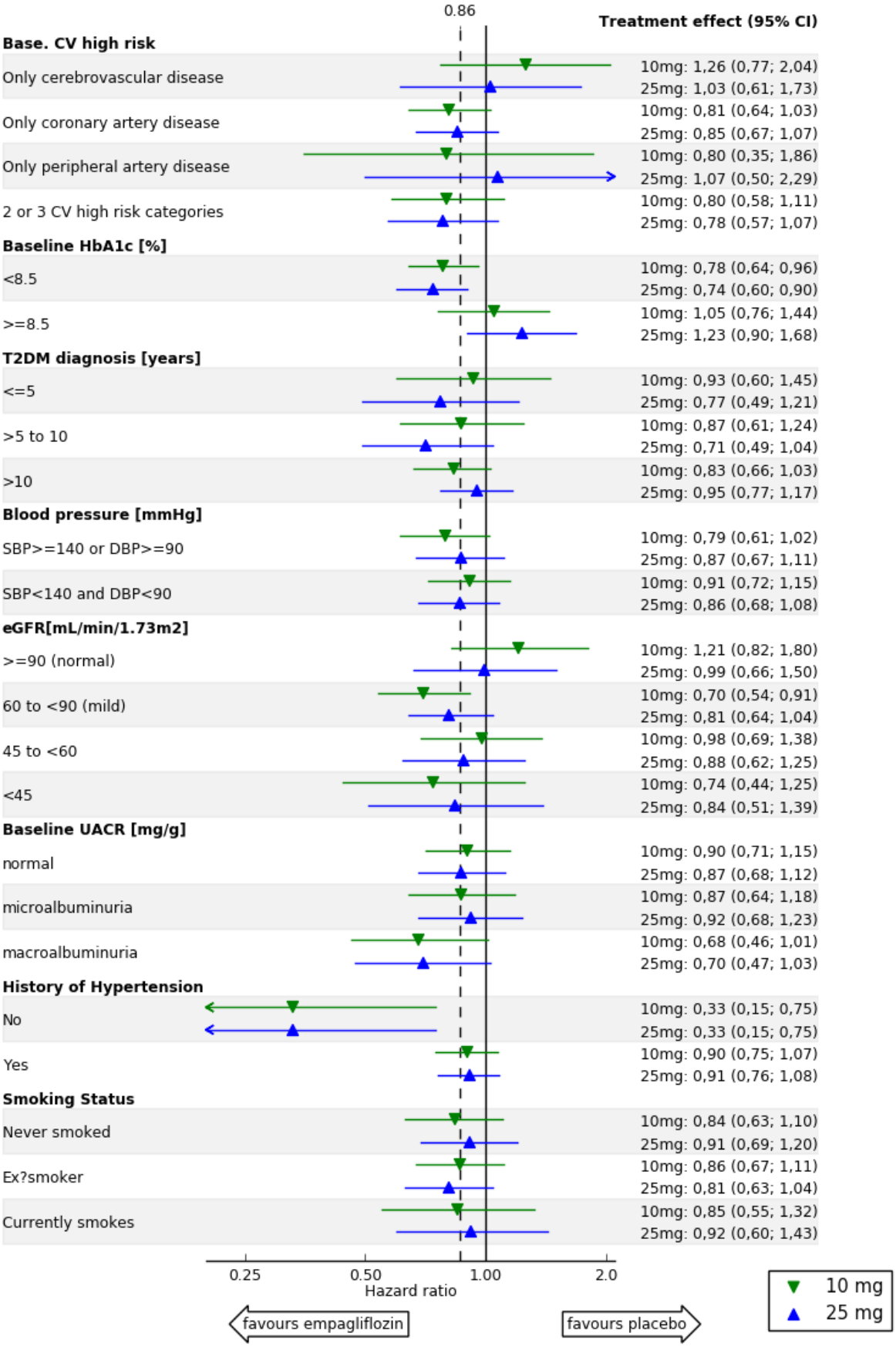
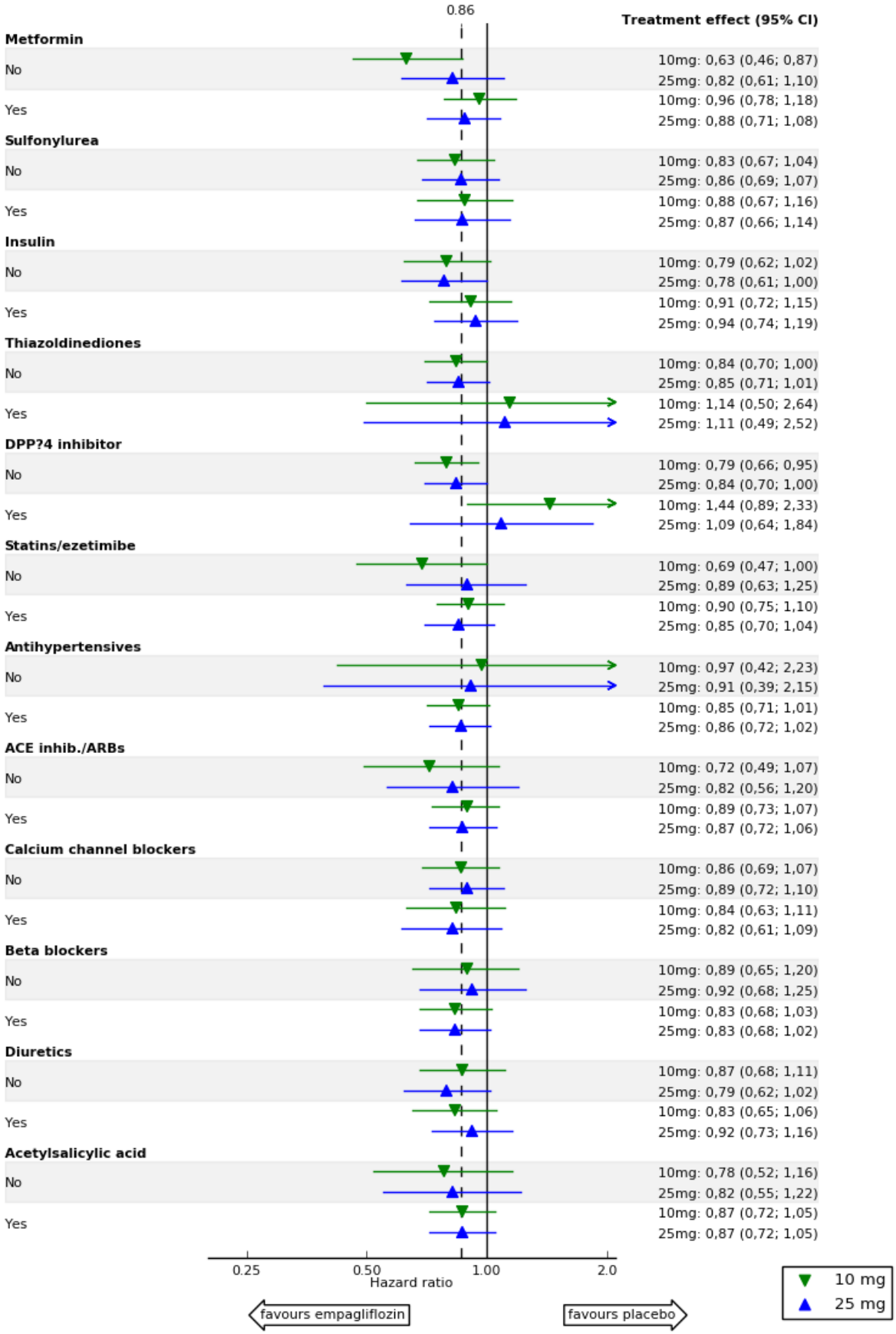


Figure 7. Primary endpoint (MACE-3) subgroups for baseline medication



Key secondary endpoint: 4-point MACE

The key secondary endpoint (4-point MACE) was the time to first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for unstable angina pectoris. Empagliflozin (doses pooled) was non-inferior, but not superior, to placebo based on this endpoint (Table 7 below). The result of the additional component in the 4-point MACE, hospitalisation for unstable angina pectoris, showed no significant difference between empagliflozin and placebo treatment.

Table 7. Cox regression for time to first 4-point MACE, empagliflozin vs. placebo – TS

	Placebo	Empa 10 mg	Empa 25 mg	**All empa**
Analysed patients, N (100%)	2333	2345	2342	4687
Patients with event, N (%)	333 (14.3)	300 (12.8)	299 (12.8)	599 (12.8)
Incidence rate per 1000 years at risk	52.5	46.6	46.3	46.4
Hazard ratio vs. placebo	--	0.89	0.88	0.89
(95.02% CI) [1]				(0.78, 1.01)
(95% CI)		(0.76, 1.04)	(0.76, 1.03)	(0.78, 1.01)
p−value for HR≥1.3 (1−sided)		<0.0001	<0.0001	<0.0001
p−value for HR≥1.0 (1−sided)		0.0726	0.0602	0.0397
p−value (2-sided)		0.1451	0.1204	0.0795

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

The results from the analyses of the individual empagliflozin doses vs. placebo were consistent with those for "all empagliflozin", with no relevant differences observed between the 2 doses. Results from all sensitivity analyses were consistent with the results of the main analysis following the ITT principle.

Component: CV death (and all-cause mortality)

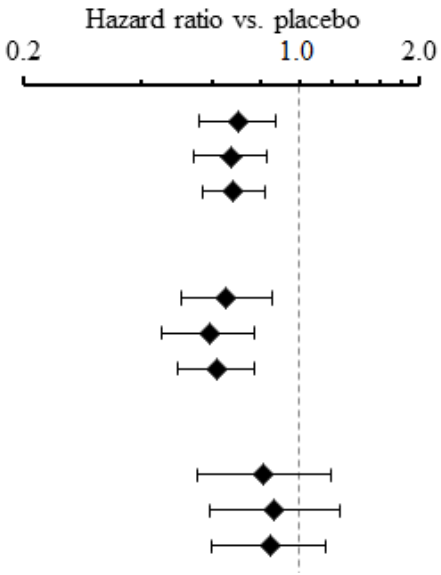
The risk of CV death and all-cause mortality was significantly reduced in the "all empagliflozin" group and the individual dose groups compared with the placebo group. There were no obvious differences between the two empagliflozin dose groups. The majority of all deaths were CV deaths, but also non-CV death was numerically reduced in the empagliflozin groups compared with the placebo group (Table 8 below). The additional analyses using an on-treatment approach showed results consistent with the main analyses following the ITT analysis principle. Also, an analysis for time to all-cause mortality assuming all 36 patients lost to follow up in the empagliflozin groups as deceased further confirmed the robustness of the main analysis (HR 0.77, 95% CI 0.65 to 0.93; *post hoc*). The analyses of subgroups (including by age, sex, renal function, glucose control and medication use at baseline; performed for CV death and all-cause mortality *post hoc*) showed consistent results across all subgroups.

The most prevalent categorisation of the CV deaths were "other CV death", including fatal events deemed not assessable by the CEC (129 of 309 patients with CV death), followed by sudden deaths (91) and worsening of heart failure (30). The majority of the non-CV deaths at system organ class (SOC) level were benign, malignant and unspecified neoplasms (incl. cysts and polyps; 69 of 154 patients with non-CV deaths) and infections and infestations (37).

For both CV death and all-cause mortality, the separation of the event rates between empagliflozin and placebo started shortly after trial onset and was maintained throughout the trial (Figure 8).

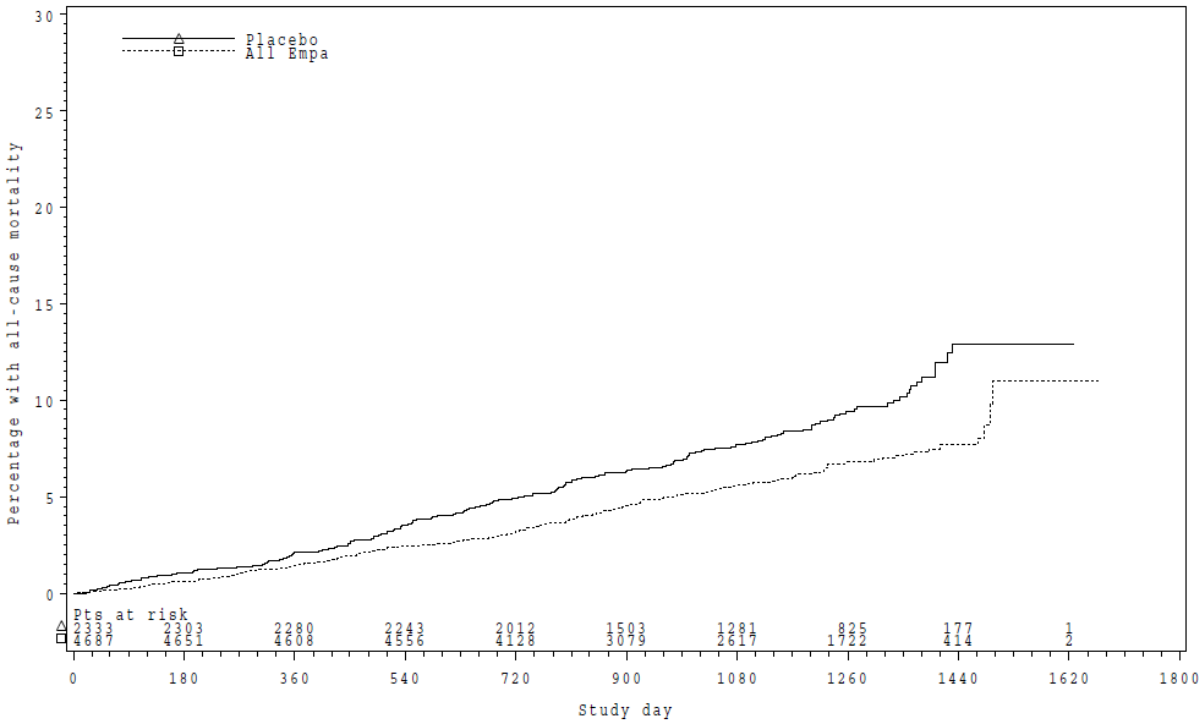
Table 8. Summary of endpoints of death - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo HR	95% CI		p-value
All-cause mortality						
Placebo	194 (8.3)	28.6	--	--	--	--
Empa 10 mg	137 (5.8)	19.8	0.70	0.56	0.87	0.0013
Empa 25 mg	132 (5.6)	19.0	0.67	0.54	0.83	0.0003
All empa	269 (5.7)	19.4	0.68	0.57	0.82	<0.0001
CV death						
Placebo	137 (5.9)	20.2	--	--	--	--
Empa 10 mg	90 (3.8)	13.0	0.65	0.50	0.85	0.0016
Empa 25 mg	82 (3.5)	11.8	0.59	0.45	0.77	0.0001
All empa	172 (3.7)	12.4	0.62	0.49	0.77	<0.0001
Non-CV death						
Placebo	57 (2.4)	8.4	--	--	--	--
Empa 10 mg	47 (2.0)	6.8	0.81	0.55	1.20	0.2909
Empa 25 mg	50 (2.1)	7.2	0.86	0.59	1.26	0.4400
All empa	97 (2.1)	7.0	0.84	0.60	1.16	0.2852



For the graph: the diamond indicates the HR and the bars 95% CIs for the HR of empagliflozin vs. placebo.

Figure 8. Kaplan-Meier estimates of time to all-cause mortality, all empagliflozin vs. placebo – TS

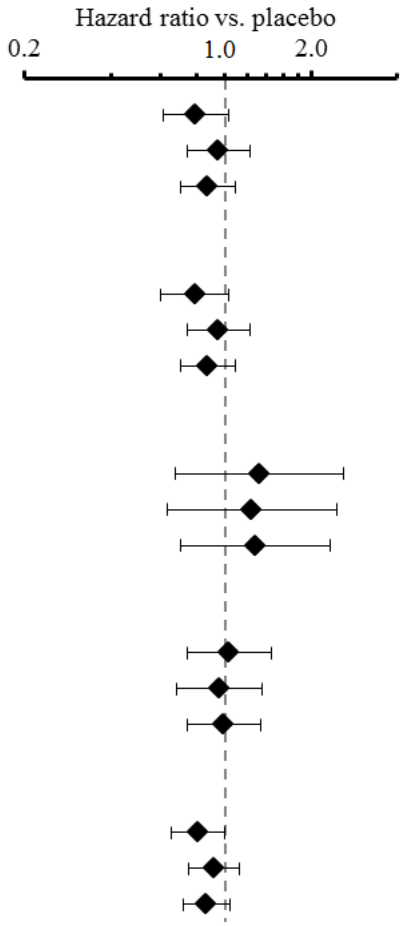


Component: Myocardial infarction (MI)-related outcomes

For all MI-related endpoints, no significant difference was observed between empagliflozin and placebo (Table 9).

Table 9. Summary of MI-related endpoints - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
MI (fatal/non-fatal)						
Placebo	126 (5.4)	19.3	--	--	--	--
Empa 10 mg	101 (4.3)	15.2	0.79	0.61	1.03	0.0852
Empa 25 mg	122 (5.2)	18.3	0.95	0.74	1.22	0.7141
All empa	223 (4.8)	16.8	0.87	0.70	1.09	0.2302
Non-fatal MI [1]						
Placebo	121 (5.2)	18.5	--	--	--	--
Empa 10 mg	96 (4.1)	14.4	0.79	0.60	1.03	0.0769
Empa 25 mg	117 (5.0)	17.6	0.95	0.74	1.23	0.7114
All empa	213 (4.5)	16.0	0.87	0.70	1.09	0.2189
Silent MI [2]						
Placebo	15 (1.2)	5.4	--	--	--	--
Empa 10 mg	19 (1.6)	7.1	1.32	0.67	2.60	0.4215
Empa 25 mg	19 (1.6)	7.0	1.24	0.63	2.45	0.5282
All empa	38 (1.6)	7.0	1.28	0.70	2.33	0.4172
Hospitalisation for unstable angina						
Placebo	66 (2.8)	10.0	--	--	--	--
Empa 10 mg	69 (2.9)	10.4	1.03	0.74	1.45	0.8509
Empa 25 mg	64 (2.7)	9.5	0.96	0.68	1.35	0.7981
All empa	133 (2.8)	10.0	0.99	0.74	1.34	0.9706
Coronary revascularization procedures						
Placebo	186 (8.0)	29.1	--	--	--	--
Empa 10 mg	154 (6.6)	23.5	0.81	0.65	1.00	0.0536
Empa 25 mg	175 (7.5)	26.7	0.92	0.75	1.13	0.4241
All empa	329 (7.0)	25.1	0.86	0.72	1.04	0.1135



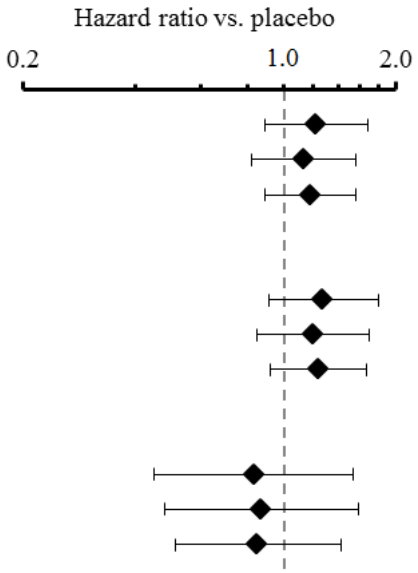
[1] Non-fatal MI did not include 'silent MI' unless these events were reported by investigators and confirmed as MI by central adjudication committee.
[2] Events reported here as 'silent MI' are based only on ECG findings.

Component: Stroke and Cerebrovascular disease-related outcomes

For stroke (fatal/non-fatal), non-fatal stroke, and transient ischaemic attack (TIA), no significant difference was observed between empagliflozin and placebo (Table 10). Strokes were classified into ischaemic, haemorrhagic, and type not assessable by the CEC neurology. The majority of confirmed strokes were ischaemic.

Table 10. Summary of cerebrovascular disease-related endpoints - TS

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



Although not statistically significant, the hazard ratio point estimate for stroke was above 1. Therefore stroke results were further investigated. In the TS analysis including all events up to individual trial completion, the Kaplan-Meier estimates showed almost no difference between empagliflozin (both doses) and placebo in the probability of stroke up to Day 600; thereafter, empagliflozin 10 mg started to separate from placebo, and empagliflozin 25 mg after about Day 900 (Figure 9). For patients in Europe, the differences are larger and the separation appears earlier (around Day 180) for both doses (Figure 10).

When analysing treatment-emergent stroke using a cut-off for the observation period after treatment stop (7, 30, 90 days after treatment stop on TS; 30 days after treatment stop on OS; see Figure 2), the results showed no significant differences between empagliflozin and placebo, and the hazard ratio point estimate shifted towards unity when compared with the analysis of all events following the ITT analysis principle (Figure 10). The difference between empagliflozin and placebo in the ITT analysis was largely caused by more events occurring beyond 90 days after treatment stop in the empagliflozin groups (10 mg: 11 patients with stroke; 25 mg: 7 patients) than in the placebo group (3 patients).

In the subgroup analyses of time to first stroke, a nominal treatment-by-subgroup interaction p-value <0.05 was observed for the parameters baseline HbA_{1c} and geographic region.

Figure 9. Time to first stroke

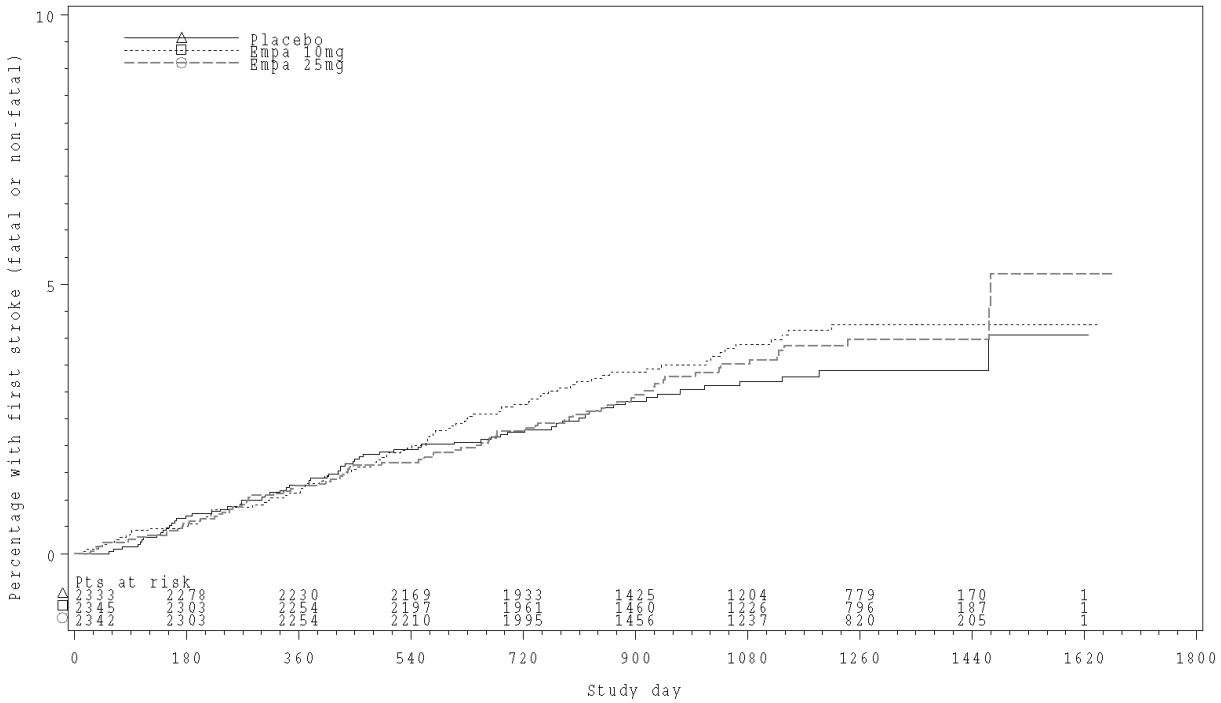


Figure 10. Time to first stroke in Europe.

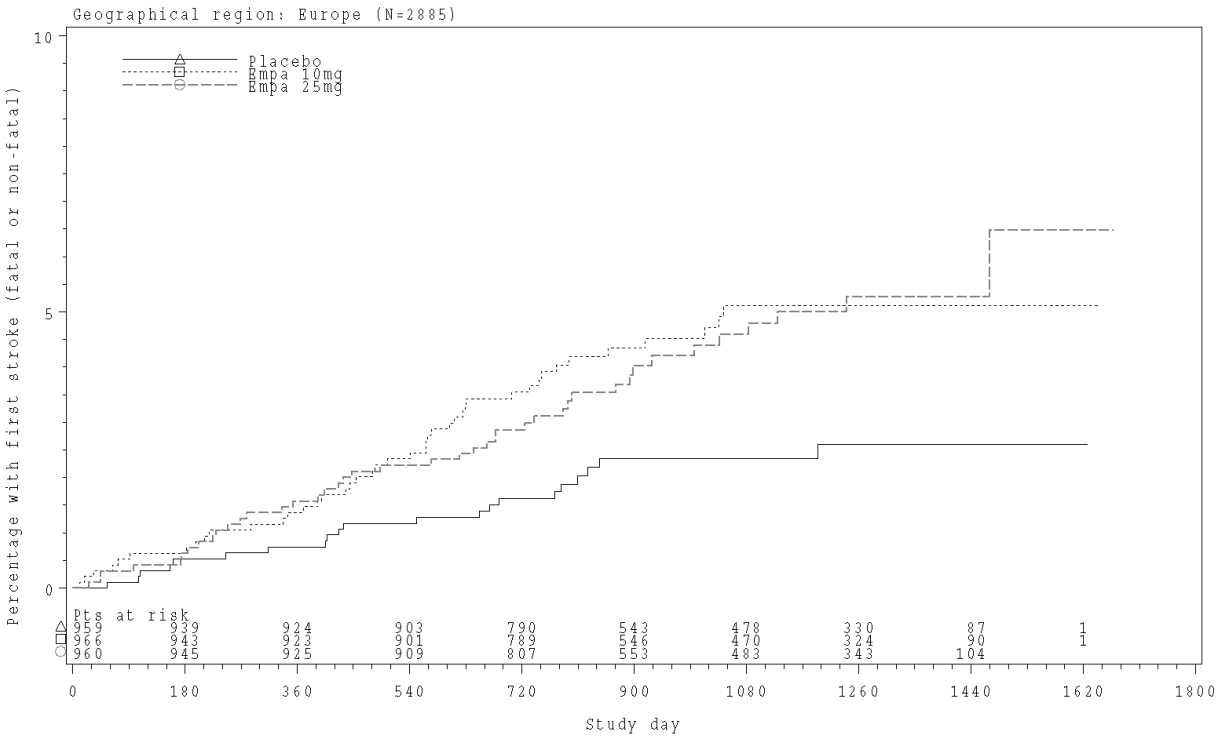
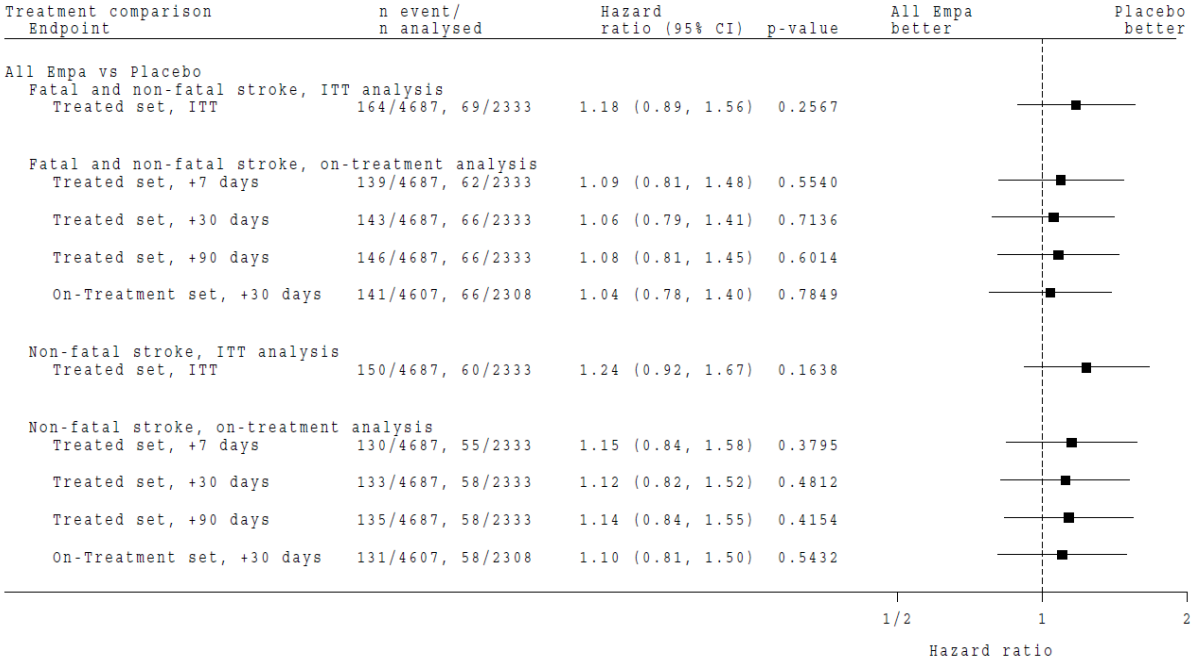


Figure 7.4.1.24.6.6 Kaplan-Meier est. of time to first stroke by geographical region (5 cat.), indiv. empa vs placebo - treated set

Figure 11. Overview of Cox regression analyses for stroke and non-fatal stroke, all empagliflozin vs. placebo

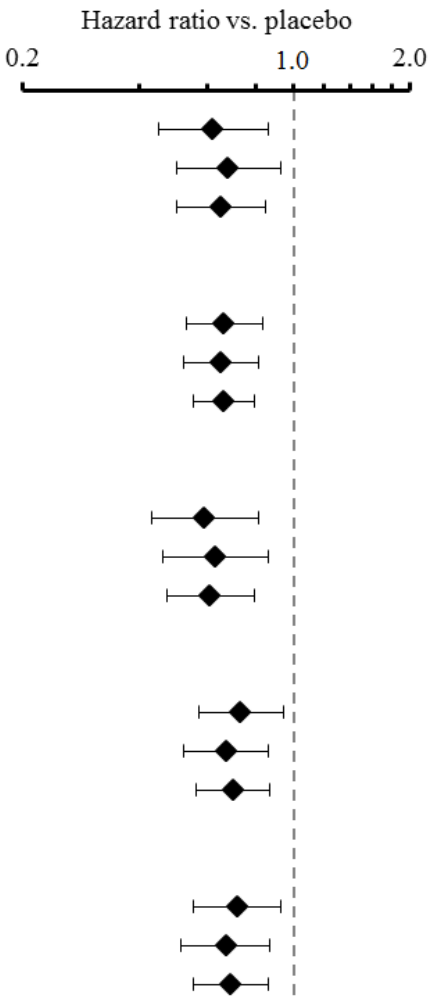


Heart failure-related outcomes

Heart failure endpoints were analysed in exploratory manner. The risk was reduced in the "all empagliflozin" group and the individual dose groups compared with the placebo group. There were no obvious differences between the 2 empagliflozin dose groups (Table 11). The additional analyses using an on-treatment approach showed results consistent with the main analyses which followed the ITT principle. The analyses of subgroups (including by age, sex, renal function, glucose control, cardiac failure based on SMQ, diuretics and other medication use at baseline; performed for the first 2 heart failure endpoints) showed consistent results across all subgroups. Moreover, the frequencies of patients with AEs requiring hospitalisation (a criterion for SAE) were numerically lower in the empagliflozin groups (10 mg: 32.0%; 25 mg: 34.9%) than placebo (36.5%)

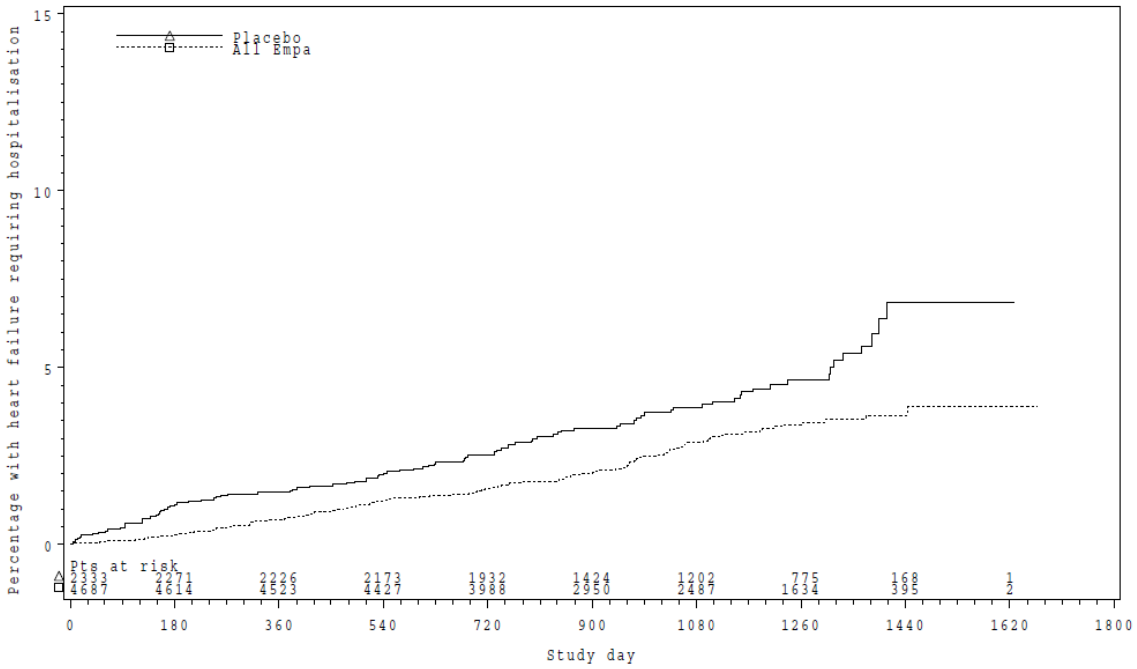
Table 11. Summary of heart failure-related endpoints - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
Heart failure requiring hospitalisation						
Placebo	95 (4.1)	14.5	--	--	--	--
Empa 10 mg	60 (2.6)	8.9	0.62	0.45	0.86	0.0044
Empa 25 mg	66 (2.8)	9.8	0.68	0.50	0.93	0.0166
All empa	126 (2.7)	9.4	0.65	0.50	0.85	0.0017
Heart failure requiring hospitalisation or CV death (excluding fatal stroke) [1]						
Placebo	198 (8.5)	30.1	--	--	--	--
Empa 10 mg	133 (5.7)	19.8	0.66	0.53	0.83	0.0002
Empa 25 mg	132 (5.6)	19.5	0.65	0.52	0.81	0.0001
All empa	265 (5.7)	19.7	0.66	0.55	0.79	<0.0001
Heart failure requiring hospitalisation or death from heart failure						
Placebo	104 (4.5)	15.8	--	--	--	--
Empa 10 mg	62 (2.6)	9.2	0.59	0.43	0.81	0.0010
Empa 25 mg	67 (2.9)	9.9	0.63	0.46	0.86	0.0034
All empa	129 (2.8)	9.6	0.61	0.47	0.79	0.0002
Cardiac failure based on SMQ [2]						
Placebo	143 (6.1)	22.0	--	--	--	--
Empa 10 mg	106 (4.5)	15.9	0.73	0.57	0.94	0.0144
Empa 25 mg	98 (4.2)	14.6	0.67	0.52	0.86	0.0021
All empa	204 (4.4)	15.3	0.70	0.56	0.87	0.0010
Serious cardiac failure based on SMQ [2]						
Placebo	136 (5.8)	20.9	--	--	--	--
Empa 10 mg	99 (4.2)	14.9	0.72	0.55	0.93	0.0117
Empa 25 mg	93 (4.0)	13.8	0.67	0.51	0.87	0.0025
All empa	192 (4.1)	14.4	0.69	0.55	0.86	0.0010



For all heart failure endpoints, the separation of the event rates between empagliflozin and placebo started shortly after trial onset and was maintained throughout the trial (Figure 12)

Figure 12. Kaplan-Meier estimates of time to heart failure requiring hospitalisation, all empagliflozin vs. placebo – TS



Composite microvascular endpoints

The composite microvascular outcome was defined as the time to first occurrence of any of the following nephropathy or eye related events:

- New or worsening nephropathy defined as any of the following:
  - New onset of macroalbuminuria (UACR >300 mg/g)
  - Doubling of serum creatinine level accompanied by an eGFR ≤45 mL/min/1.73m^2
  - Initiation of continuous renal replacement therapy
  - Death due to renal disease
- Diabetic eye complications
  - Initiation of retinal photocoagulation
  - Vitreous haemorrhage
  - Diabetes-related blindness (included any blindness reported)

For the two composite microvascular outcome endpoints, the risk was reduced in the "all empagliflozin" group compared with the placebo group (patients with event placebo: 424 (20.5%); all empa: 577 (14.0%); HR 0.62 95% CI: 0.54, 0.70). There was a similar treatment effect for the 2 empagliflozin dose groups. The majority of the events of the microvascular outcome endpoints were new onset of nephropathy (see the section below). For all diabetic eye complication endpoints, the incidence rates were low (<5/1000 patient-year) and no significant difference was observed between empagliflozin and placebo.

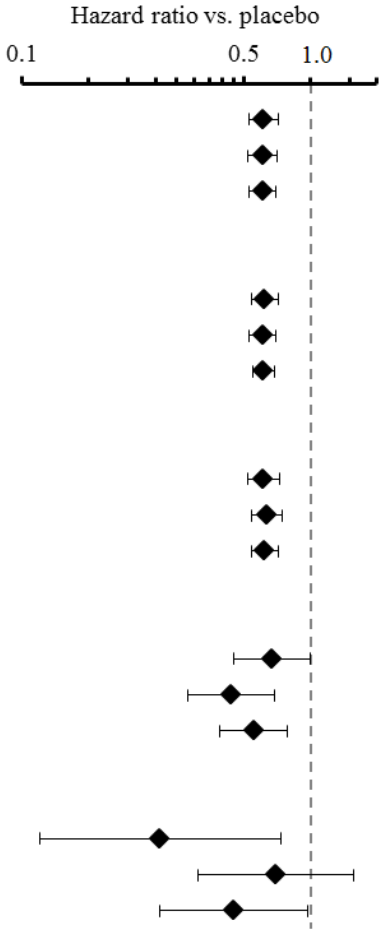
Nephropathy-related endpoints

Nephropathy composite endpoints and components as independent endpoints

For the composite nephropathy endpoints ("new or worsening nephropathy" and "new or worsening nephropathy or CV death"), the risk was reduced in the "all empagliflozin" group and the individual dose groups compared with the placebo group. There were no obvious differences between the 2 empagliflozin dose groups (Table 12). The Kaplan-Meier estimation of cumulative probability of events are shown in Figure 13 and for the composite "new or worsening nephropathy" Figure 14. The analyses of subgroups (including by age, sex, renal function, glucose control and medication use at baseline; *post hoc*) showed consistent beneficial treatment effects across all subgroups.

Table 12. Summary of nephropathy endpoints - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo HR	95% CI		p-value
New or worsening nephropathy (composite)						
Placebo	388 (18.8)	76.0	--	--	--	--
Empa 10 mg	261 (12.7)	47.9	0.61	0.53	0.72	<0.0001
Empa 25 mg	264 (12.8)	47.6	0.61	0.52	0.71	<0.0001
All empa	525 (12.7)	47.8	0.61	0.53	0.70	<0.0001
New or worsening nephropathy or CV death (composite)						
Placebo	497 (23.6)	95.9	--	--	--	--
Empa 10 mg	338 (16.3)	61.4	0.62	0.54	0.72	<0.0001
Empa 25 mg	337 (16.1)	60.1	0.61	0.53	0.70	<0.0001
All empa	675 (16.2)	60.7	0.61	0.55	0.69	<0.0001
New onset of macroalbuminuria (UACR >300 mg/g)						
Placebo	330 (16.2)	64.9	--	--	--	--
Empa 10 mg	222 (10.9)	40.8	0.61	0.52	0.73	<0.0001
Empa 25 mg	237 (11.5)	42.8	0.64	0.54	0.75	<0.0001
All empa	459 (11.2)	41.8	0.62	0.54	0.72	<0.0001
Doubling of s. creatinine with eGFR of ≤45 mL/min/1.73m²						
Placebo	60 (2.6)	9.7	--	--	--	--
Empa 10 mg	42 (1.8)	6.6	0.67	0.45	1.00	0.0481
Empa 25 mg	28 (1.2)	4.4	0.44	0.28	0.69	0.0004
All empa	70 (1.5)	5.5	0.56	0.39	0.79	0.0009
Initiation of continuous renal replacement therapy						
Placebo	14 (0.6)	2.1	--	--	--	--
Empa 10 mg	3 (0.1)	0.4	0.21	0.06	0.74	0.0146
Empa 25 mg	10 (0.4)	1.5	0.70	0.31	1.57	0.3812
All empa	13 (0.3)	1.0	0.45	0.21	0.97	0.0409



[1] No hazard ratios were calculated, since overall number of patients with event was lower than 7x the number of treatment groups.

Figure 13. Kaplan-Meier estimates of time to first new or worsening nephropathy, all empagliflozin vs. placebo – TS

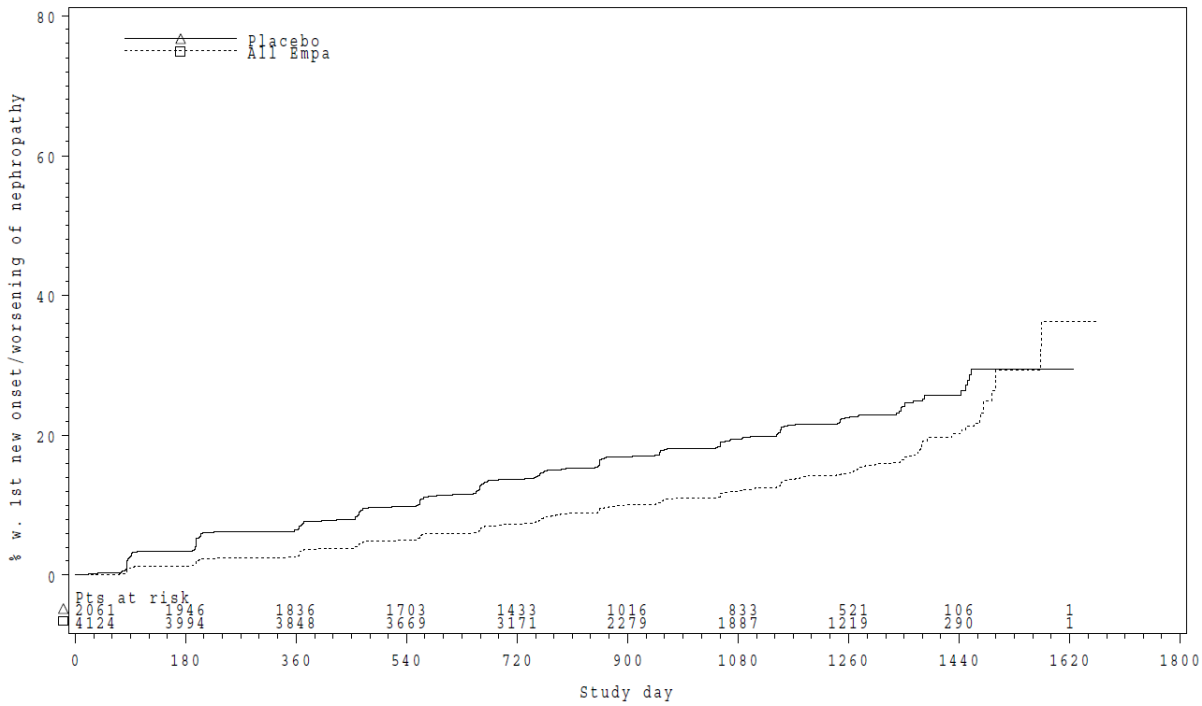
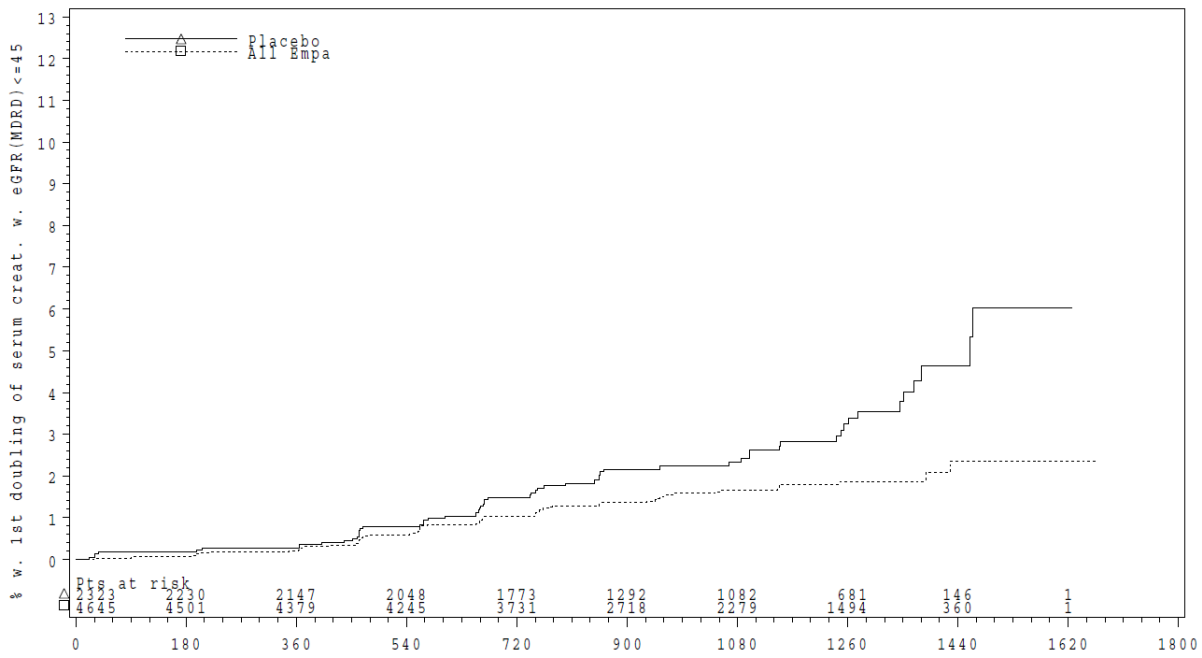


Figure 14. Kaplan-Meier estimates of time to first doubling of s. creatinine with eGFR of ≤45 mL/min/1.73m^2, all empagliflozin vs. placebo – TS



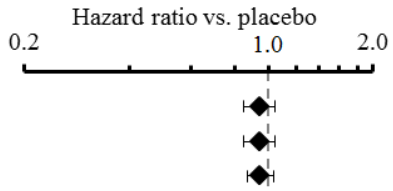
UACR-related endpoints

New onset of albuminuria (UACR ≥30 mg/g) and macroalbuminuria (>300 mg/g)

While the risk of new onset of macroalbuminuria (UACR>300 mg/g) was reduced in the empagliflozin groups compared with the placebo group (Table 12), no significant difference between empagliflozin and placebo was observed for new onset of albuminuria (UACR ≥30 mg/g; Table 13 below).

Table 13. New onset of albuminuria (UACR ≥30 mg/g) - TS

Treatment	Patients with event, n (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
New onset of albuminuria (UACR ≥30 mg/g)						
Placebo	703 (51.2)	266.0	--	--	--	--
Empa 10 mg	722 (51.5)	255.1	0.95	0.85	1.05	0.3207
Empa 25 mg	708 (51.5)	249.8	0.95	0.85	1.05	0.3260
All empa	1430 (51.5)	252.5	0.95	0.87	1.04	0.2547

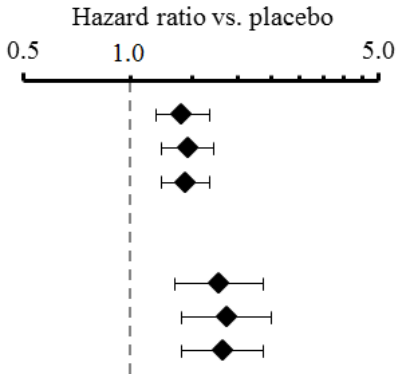


Reversibility of albuminuria

For patients with microalbuminuria (UACR 30 to 300 mg/g) or macro-albuminuria (UACR >300 mg/g) at baseline, more patients showed sustained reversal of their proteinuria after treatment with empagliflozin than with placebo, which started shortly after trial onset and was maintained throughout the trial. There were no obvious differences between the 2 empagliflozin dose groups (Table 14 below)

Table 14. Summary of reversibility of albuminuria - TS

Treatment	Patients with event, n/N[1] (%)	Incidence /1000 p-y	Comparison vs. placebo			
			HR	95% CI		p-value
Sustained reversal of microalbuminuria						
Placebo	219/659 (33.2)	162.0	--	--	--	
Empa 10 mg	275/634 (43.4)	233.9	1.40	1.18	1.68	0.0002
Empa 25 mg	299/678 (44.1)	243.5	1.45	1.22	1.72	<0.0001
All empa	574/1312 (43.8)	238.8	1.43	1.22	1.67	<0.0001
Sustained reversal of macroalbuminuria						
Placebo	74/257 (28.8)	155.2	--	--	--	
Empa 10 mg	126/256 (49.2)	295.6	1.78	1.33	2.37	<0.0001
Empa 25 mg	122/243 (50.2)	313.8	1.87	1.39	2.50	<0.0001
All empa	248/499 (49.7)	304.2	1.82	1.40	2.37	<0.0001

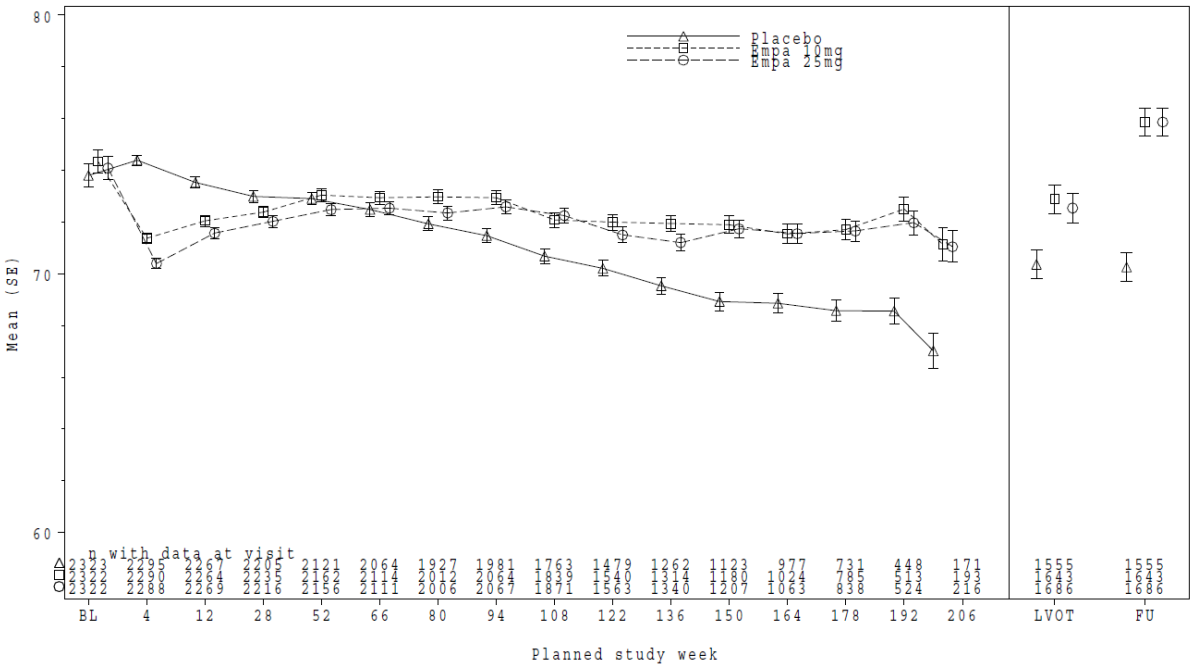


Sustained required 2 consecutive measurements fulfilling the condition and were at least 4 weeks apart.
[1] N = number of analysed patients with microalbuminuria (UACR 30 to 300 mg/g) or macroalbuminuria (UACR >300 mg/g) at baseline

eGFR change over time

When mean eGFR values were analysed over time, there was a steady decrease in eGFR in the placebo group, indicative of natural disease progression. In contrast, the initial decreases in eGFR in the empagliflozin groups were reversible over time, with eGFR values higher in the empagliflozin groups than in the placebo group after about a year (Figure 15). About 30 days after the stop of treatment, eGFR increased from the last value on treatment by about 3.5 ml/min/1.73m^2 in the empagliflozin groups, while no change was seen in the placebo group.

Figure 15. eGFR [mL/min/1.73m^2] MMRM results over time (OC-AD), with unadjusted last value on-treatment and follow-up value (OR, patients with available LVOT and FU values) - TS



Further Efficacy endpoints

This outcome study was designed to investigate the long-term CV safety of empagliflozin. The analyses of HbA_{1c}, FPG, body weight, SBP, and DBP considered all available data including values obtained post-treatment and after the intake of rescue medication (OC-AD), to match the analyses used for the outcome events following the ITT analysis principle.

Of note, in this trial, adjustments to concomitant medications, including those that affect glycaemic control, blood pressure, etc., could be made at the discretion of the investigator to achieve best standard of care.

Reductions in HbA_{1c}, FPG, body weight, SBP, and DBP were seen for empagliflozin compared with placebo at Week 94 (52 for body weight), the time point corresponding to the treatment duration all patients could reach in this trial (Table 15 below). The higher dose showed better efficacy, but the differences were small.

Table 15. Change from baseline in HbA_{1c}, FPG, body weight, SBP, and DBP - MMRM TS[1] (OC-AD)

	N analysed for the time point	Baseline [2], mean (SE)	Change from baseline, adjusted mean (SE)	Comparison to placebo, adjusted mean (95% CI)
HbA_{1c} [%] at Week 94 [1]				
Placebo	1967	8.08 (0.02)	−0.08 (0.02)	--
Empa 10 mg	2058	8.08 (0.02)	−0.50 (0.02)	−0.42 (−0.48, −0.36)
Empa 25 mg	2044	8.07 (0.02)	−0.55 (0.02)	−0.47 (−0.54, −0.41)
FPG [mg/dL] at Week 94				
Placebo	1934	153.45 (0.91)	8.14 (0.98)	--
Empa 10 mg	2030	153.23 (0.91)	−9.11 (0.96)	−17.25 (−19.93, −14.57)
Empa 25 mg	2030	151.81 (0.90)	−12.70 (0.96)	−20.84 (−23.53, −18.16)
Body weight [kg] at Week 52				
Placebo	2138	86.68 (0.40)	−0.34 (0.09)	--
Empa 10 mg	2174	85.97 (0.39)	−2.07 (0.09)	−1.72 (−1.97, −1.48)
Empa 25 mg	2178	86.53 (0.40)	−2.51 (0.09)	−2.17 (−2.41, −1.93)
SBP [mmHg] at Week 94				
Placebo	1974	135.79 (0.36)	−0.52 (0.32)	--
Empa 10 mg	2072	134.91 (0.35)	−3.51 (0.32)	−2.99 (−3.87, −2.11)
Empa 25 mg	2066	135.65 (0.35)	−3.64 (0.32)	−3.12 (−4.00, −2.24)
DBP [mmHg] at Week 94				
Placebo	1974	76.83 (0.21)	−1.12 (0.18)	--
Empa 10 mg	2072	76.60 (0.20)	−2.00 (0.18)	−0.89 (−1.39, −0.39)
Empa 25 mg	2066	76.68 (0.20)	−2.13 (0.18)	−1.01 (−1.51, −0.51)

[1] FAS instead of TS was used for analysis of HbA_{1c}
[2] Baseline value for all patients analysed for the specific parameter

Ancillary analyses

Ancillary analyses

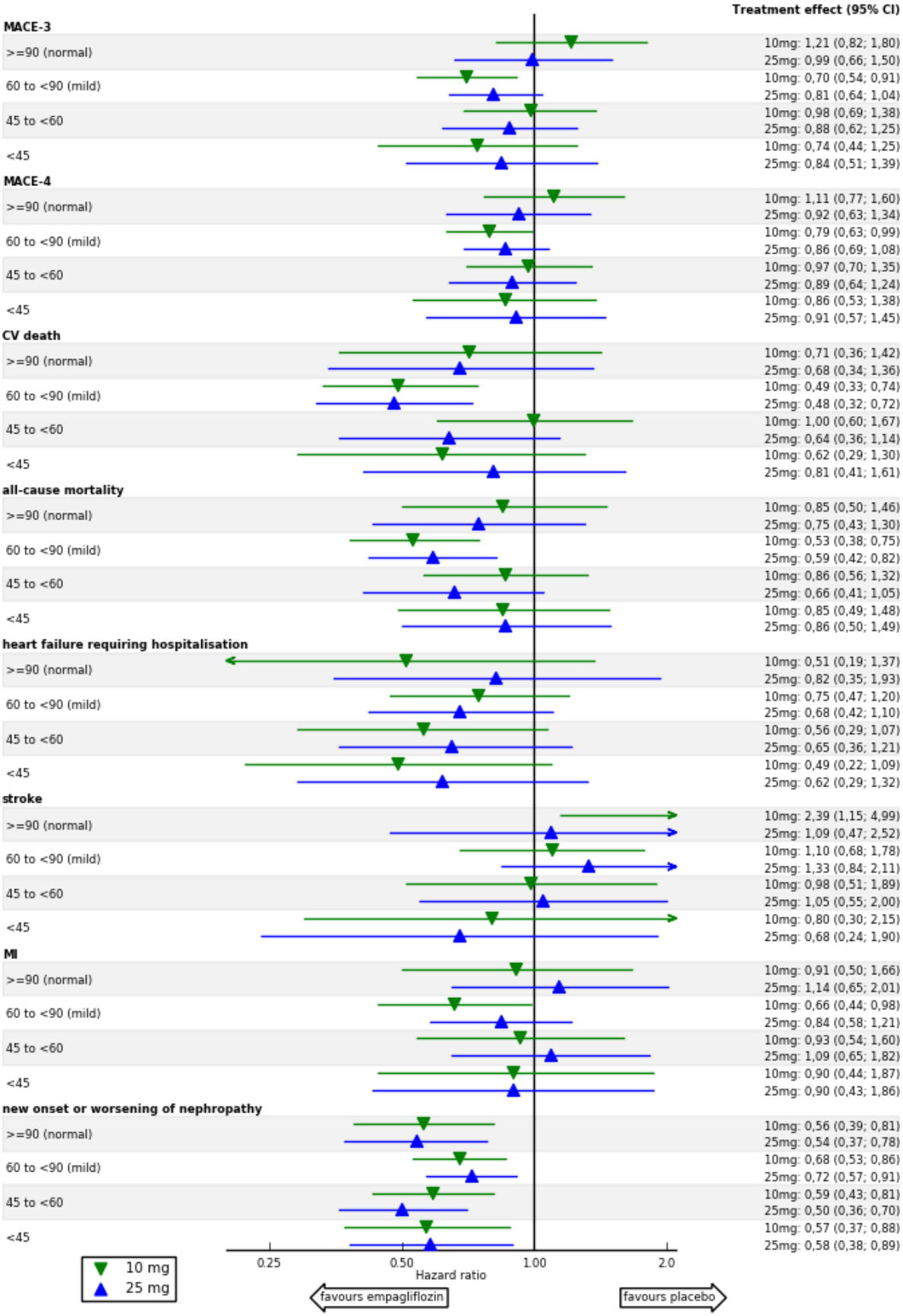
The subgroups of patients with chronic kidney disease (CKD) stage 3A (defined as eGFR 45 to <60 ml/min/1.73 m^2) and CKD stage 3B (30 to <45 ml/min/1.73 m^2) are described in detail because currently, empagliflozin is not recommended for use in patients with persistent eGFR <45 ml/min/1.73 m^2 and the MAH seeks authorisation for use in these patients.

The CV and nephropathy endpoints were analysed according to the eGFR categories ≥90, 60 to <90, 45 to <60, <45 mL/min/1.73 m^2. In total 1249 patients had a baseline eGFR in the category of CKD 3A (45 to <60 ml/min/1.73 m^2). In total 570 patients had a baseline eGFR of <45 mL/min/1.73 m^2, of whom 543 had 30 to <45 ml/min/1.73 m^2. Although eGFR <30 mL/min/1.73m^2 at screening was an exclusion criterion, 27 patients had an eGFR value of <30 mL/min/1.73m^2 at baseline, which was measured about 3 weeks after screening. These 27 patients were pooled with patients with eGFR of 30 to <45 mL/min/1.73 m^2 at baseline which can be considered conservative.

For the CV endpoints analysed, the treatment differences between the eGFR subgroups were small and treatment-by-subgroup interaction p-values were >0.05. The hazard ratio point estimates for patients with CKD 3A or 3B were in line with subjects with better renal function.

Also for new or worsening nephropathy, no relevant treatment differences were observed between the eGFR subgroups and treatment-by-subgroup interaction p-values were >0.05. The hazard ratio point estimates for patients with CKD 3A and 3B were similar to those of the overall study population

Figure 16. Subgroups by baseline eGFR.



Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16. Summary of Efficacy for trial EMPA-REG

Title:	A Phase III, multicentre, international, randomised, parallel group, double blind cardiovascular safety study of BI 10773 (10 mg and 25 mg administered orally once daily) compared to usual care in type 2 diabetes mellitus patients with increased cardiovascular risk. The EMPA-REG OUTCOME Trial		
Study identifier	EudraCT 2009-016178-33 BI Trial Number: 1245.25		
Design	This was a randomised, double-blind, multinational, parallel group, event driven study with 3 treatment groups. Patients were randomised 1:1:1 to empagliflozin 10 mg once daily, empagliflozin 25 mg once daily, or placebo, as add-on to standard of care treatment, including for diabetes, hypertension, and high cholesterol. After screening, all eligible patients underwent a 2-week, open-label, placebo run-in period before randomisation. The end of study visit was to take place within ±7 days of a scheduled visit date after the last dose of study medication for patients who prematurely discontinued or at study closure for patients ongoing when the required number of outcome events was anticipated to have been reached for the trial. A final follow-up visit was planned 30 days after the end of treatment visit. Patients who discontinued or withdrew from trial medication after randomisation (Visit 3 and beyond) were to be followed up until the end of the study using the same visit schedule until the end of the trial. The observational period for a patient was from randomisation until the last visit after study closure announcement (including 30 days after the last ontreatment visit). The planned treatment duration was anticipated to be approximately 6 and 8 years (approximately 300 to 420 weeks), depending on the expected accrual period of 2 years and the assumed 3-point MACE event rate and the different times at which patients were randomised. The actual study duration depended on the first occurrence of primary outcome events; a minimum of 691 patients with adjudicated primary outcome events were required for the primary analysis. 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, myocardial ischaemia (incl. myocardial infarction), cardiac failure, and coronary revascularization procedures, as detailed in the CEC charter. Additionally, specified events of cancer and hepatic events were adjudicated by external independent committees. A project based data monitoring committee (DMC), independent of the sponsor was established to monitor patient safety across several phase IIb/III empagliflozin trials, and to advise the sponsor whether to continue, modify, or stop one or all trials involved. A Steering Committee was established to provide scientific leadership for the design and conduct of this study and interpretation of data.		
	Duration	Main :	Not predefined (event-driven design)
		Run-in :	2 weeks placebo
		Follow up:	30 days after treatment
Hypothesis	Non-inferiority, if reached superiority		
Treatments	Placebo	Matching placebo	
	Empa 10	Empagliflozin 10 mg OD	
	Empa 25	Empagliflozin 25 mg OD	
	All empa	(pooled data of empagliflozin 10 and 25 mg OD groups)	

Endpoints	Primary endpoint	MACE-3	time to first occurrence of cardiovascular (CV) death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), non-fatal stroke.
	Key secondary endpoint	MACE-4	MACE-3 OR hospitalisation for unstable angina pectoris.
	Secondary endpoint*	Silent-MI	any new onset of a silent MI as determined by an ECG measurement in patients with no symptoms suggestive of MI. Analysed in patients without silent MI or relevant cardiac conductions effects at baseline and with available post-baseline ECG measurements. It was also required that there had been no adjudicated and confirmed event of either acute MI, hospitalisation for unstable angina, coronary revascularisation procedures or stent thrombosis following randomisation up to and including the date of the specified ECG measurement.
		Hosp-HF	Heart failure requiring hospitalisation (adjudicated)
	Exploratory endpoints*	Nephropathy	new or worsening nephropathy, composite of new onset of macroalbuminuria; or doubling of serum creatinine level accompanied by eGFR (MDRD formula) ≤45 mL/min/1.73m2; or initiation of continuous renal replacement therapy, death due to renal disease
		all-cause mortality	all-cause mortality
		non-CV mortality	non-CV mortality.
Trial dates	From 26 August 2010 to 21 April 2015 Interim database lock on 31 Aug 2012 Final database lock on 22 Jun 2015		

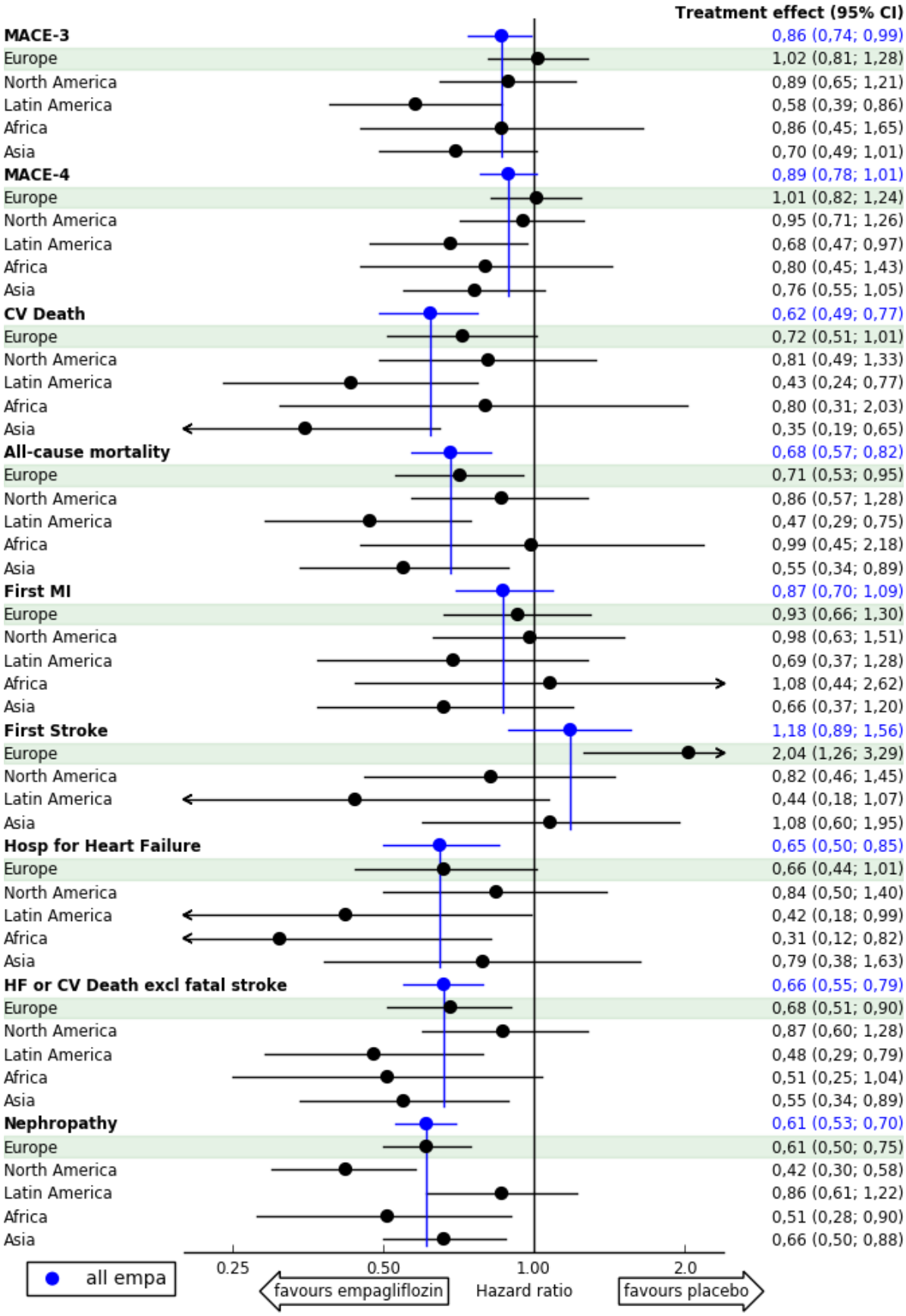
* Around 40 secondary or exploratory endpoints not included in the table.

Primary Analysis

Population		Intention to treat			
Time points		Treated set (until 30 days after treatment discontinuation			
Descriptive statistics	Treatment group		Placebo	Empa 10 mg	Empa 25 mg
		Number of subjects	2333	2345	2342
	MACE-3	N (%)	282 (12.1)	243 (10.4)	247 (10.5)
		Incidence/1000py	43.9	37.1	37.7
	MACE-4	N (%)	333 (14.3)	300 (12.8)	299 (12.8)
		Incidence/1000py	52.5	46.6	46.3
	Hosp-HF	N (%)	95 (4.1)	60 (2.6)	66 (2.8)
		Incidence/1000py	14.5	8.9	9.8
	Nephropathy	N (%)	388 (18.8)	261 (12.7)	264 (12.8)
		Incidence/1000py	76.0	47.9	47.6
	All-cause mortality	N (%)	194 (8.3)	137 (5.8)	132 (5.6)
		Incidence/1000py	28.6	19.8	19.0
	CV mortality	N (%)	137 (5.9)	90 (3.8)	82 (3.5)
		Incidence/1000py	20.2	13.0	11.8
	Non-CV mortality	N (%)	57 (2.4)	47 (2.0)	50 (2.1)
		Incidence/1000py	8.4	6.8	7.2

Effect estimate per comparison	Comparison			all empa v placebo
	Primary endpoint	MACE-3	HR	0.86
			95% CI	0.74; 0.99
			p-value	0.0382 for superiority
	Key secondary endpoint	MACE-4	HR	0.89
			95% CI	0.78; 1.01
			P value	<0.0001 for non-inferiority
			p-value	0.0795 for superiority
	Secondary endpoint	Hosp-HF	HR	0.65
			95% CI	0.50; 0.85
	Exploratory endpoint	Nephropathy	HR	0.61
			95% CI	0.53; 0.70
		All-cause mortality	HR	0.68
			95% CI	0.57; 0.82
		CV mortality	HR	0.62
			95% CI	0.49; 0.77
		Non-CV mortality	HR	0.84
			95% CI	0.60; 1.16

Figure 17. Subgroups by geographic region for selected endpoints.



2.4.2. Discussion on clinical efficacy

Design and conduct of the clinical study

EMPA-REG was a cardiovascular outcome trial in type 2 diabetes patients. The primary objective of such trial is to exclude a harmful effect on cardiovascular events and mortality. MACE-3 was the primary endpoint for the trial, which is the preferred endpoint for safety studies according to EMA guidance(Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)). MACE-4 was assessed as key secondary endpoint which can be accepted. The primary and key secondary endpoints were assessed for both non-inferiority and superiority.

The inclusion criteria specify a population with T2DM at especially high risk for CV events, specified by a history of at least one CV event such as myocardial infarction, stroke, peripheral artery disease or significant coronary artery disease. Contrary to the current SmPC of Jardiance, subjects with moderate renal insufficiency (eGFR between 30 and 60 ml/min 1.73m^2) were fully eligible for treatment both with 10 mg and 25 mg empagliflozin OD. Patients could only be included if glycaemic control was insufficient.

The population that was actually investigated, included 41.1% subjects from Europe and 44.6% of subjects were above 65 years of age. This is considered representative for the European T2DM population with documented atherosclerotic disease. The previously excluded population with eGFR < 45 ml/min/1.73 m^2 was represented by 570 (8.1%) of subjects.

The sample size estimations are considered adequate. The event rates were around 4 %/year and higher than anticipated (2%/year). This emphasizes that the patients were at very high risk indeed. Compared to the original planning, the trial was shorter and retention was higher than expected as the trial was ended (according to plan) when a sufficient number of events was observed.

Patients were randomly assigned to 1 of the 3 treatment groups (empagliflozin 10 mg; empagliflozin 25 mg; placebo) in a 1:1:1 ratio. Randomisation was stratified in a balanced ratio for HbA1c (<8.5 or ≥8.5% at screening), BMI (<30 or ≥30 kg/m2 at randomisation), geographical regions (North America, Latin America, Europe, Africa, and Asia), and renal function at screening (normal: eGFR ≥ 90 mL/min/1.73m^2; mild impairment: eGFR 60 to ≤89 mL/min/1.73m^2; moderate impairment: eGFR 30 to ≤59 mL/min/1.73m^2). As these factors are prognostically important, this stratification helped to ensure baseline comparability of the treatment groups. There are no concerns related to randomisation or blinding or group differences in baseline characteristics.

The type-I error was adequately preserved for the primary and key secondary endpoints (MACE-3 and MACE-4) by a hierarchical approach including both non-inferiority and superiority testing. However, the results of all other endpoints were exploratory and should be considered hypothesis-generating. According to the Points to consider on application with 1. meta-analyses; 2. one pivotal study (CPMP/EWP/2330/99), the minimum requirement for authorisation is generally one controlled study with statistically compelling and clinically relevant results and it is regulatory practice that evidence from a single pivotal trial is generally required to be stronger than the nominal level used in an application with multiple pivotal trials. In addition, internal and external validity, clinical relevance, data quality and internal consistency should be supportive. The phase-3 results submitted with the original MAA are primarily supportive for safety. While the primary endpoint and the mortality data are considered highly reliable, all endpoints besides MACE-3 and MACE-4 in EMPA-REG were exploratory and for these exploratory results the effect of chance findings is an important concern.

Efficacy data and additional analyses

The primary endpoint (**3-point MACE**) showed superiority of "all empagliflozin" treatment to placebo. The results were similar in exploratory analyses for both empagliflozin doses. Due to the wider confidence intervals, these results were not statistically significant. The exploratory breakdown of the first event for 3-point MACE indicated that the lower frequency of 3-point MACE for empagliflozin was primarily due to the lower frequency of CV death. The results of the per protocol analysis (PPA) and sensitivity analyses were generally consistent, but in the PPA statistical significance was not reached.

Some subgroups of the primary endpoint deserve further attention:

- The results for the subgroups age: 50-<65 years and weight: 70-80 kg were inconsistent with both lower and higher subgroups. There was, however, no trend in the results across age and weight classes (Figure 5, 6).
- The results in users of thiazolidinediones and DPP4-inhibitors showed trends in the wrong direction (HR 1.13 and 1.27 respectively for all empa, see also Figure 7). This is especially surprising as these products have been linked to cardiac failure in the past. For thiazolidinediones the mortality results were in line with the overall trial result, but for DPP-4 inhibitors the estimate of the HR for CV mortality was > 1.
- The results in Black or African American patients (n = 357; HR: 1.48) showed trends in the wrong direction. This was driven by strokes and MI, while the effects on CV mortality and HF were apparently maintained. However, as also the trend for all-cause mortality was unfavourable, the uncertainties regarding this subgroup have been mentioned in 4.4 (SmPC).
- The results in subjects with normal renal function (eGFR > 90 ml/min/1.73 m^2) were less favourable than the results with impaired renal function, especially on the component 'stroke' (see below).
- The benefits in Europe and North America were smaller than in Latin America and Asia (see below).

In the end, the results in these subgroups were considered consistent with the overall trial results based on statistical considerations.

For the key secondary endpoint (**4-point MACE**) empagliflozin (doses pooled) was non-inferior, but not superior, to placebo. The results for 10 and 25 mg were similar.

The risk of CV death and all-cause **mortality** was significantly reduced in the "all empagliflozin" group and the individual dose groups compared with the placebo group. Again, there were no obvious differences between the 2 empagliflozin dose groups. The majority of all deaths were CV deaths, and non-CV death was numerically reduced in the empagliflozin groups compared with the placebo group.

Although mortality (all-cause and non-CV) was only tested in an exploratory way, the results are considered robust. Both CV-mortality and non-CV mortality favoured empagliflozin. Vital status information was available for all but 53 patients. The benefit for empagliflozin was confirmed in a sensitivity analysis assuming all empagliflozin treated-patients lost to follow up had died.

The mortality results were obtained in addition to standard of care which included blood pressure-lowering medications (used by 95% of patients at baseline), lipid-lowering medications (81%), and anticoagulants (89%, in the vast majority anti-platelets), most of which have been proven to decrease CV death. The reduction in the risk of death can be translated into a number needed to treat (NNT) of 39 to prevent 1 death in 3.1 years. There was a rapid response to empagliflozin treatment, with a lower probability of death for empagliflozin with the curves separating from placebo as early as the first month based on the Kaplan-Meier estimates. The probability of death continued to separate throughout the observation period. The magnitude of the effect is in line with that seen in the outcome trials that established the use of statins or ACEi /ARBs. (angiotensin converting enzyme inhibitor/angiotensin receptor blockers).

The positive effect of antidiabetics on macrovascular complications has until now only been demonstrated for metformin (UKPDS 34 study). This is the first time since 1998 that the efficacy of an antidiabetic medicinal product in decreasing cardiovascular events has been shown in a large clinical trial. In the case of EMPA-REG the effect on MACE-3 was largely driven by the effect on cardiovascular death. Cardiovascular mortality is the most important mortality in type 2 diabetes.

For all **myocardial infarction**-related endpoints, no significant difference was observed between empagliflozin and placebo, but the point estimate slightly favoured empagliflozin (non-fatal MI, HR: 0.87; 95% CI 0.70, 1.09). Silent MI, defined as single flagged ECG and not confirmed by the adjudication committee, was not part of the primary endpoint. All of these flagged ECG cases were sent to the central adjudication committee for assessing any outcome events. The outcome of unconfirmed single flagged ECG favoured placebo (HR 1.28; 95% CI 0.70, 2.33). The unconfirmed single flagged ECG defined as 'silent MI' was only assessable in a limited number of patients, as it required an ECG at baseline without major abnormalities and excluded patients with prior MI-related adjudicated outcome events. The fact that the primary endpoint was reworded regarding silent MIs raised questions as to whether this could have been a modification potentially based on unblinded data, and not a clarification as described in the study report. The MAH clarified that silent MI had never been a part of the primary endpoint and justified the reasons for this.

Although not statistically significant in the primary analysis, the hazard ratio point estimate for **stroke** was clearly above 1 (non-fatal stroke; HR 1.24; 95% CI 0.92, 1.67). The MAH has compared the On-treatment set (+30 days) with the Treated set and concludes that this result is driven by events during observation after treatment (23 empa, 3 placebo). In the subgroup of patients in Europe, the adverse effect was larger, is already evident in the Kaplan-Meijer curve at 180 days and even reached statistical significance (HR 2.04, 95% CI 1.26-3.29). In light of this finding, the results for other selected endpoints (as reported in the study report) in Europe were summarized (Figure 17). This shows that the results for MACE-3 and all its components, and also, MACE-4 in Europe (and North America) are less favourable than the overall trial results. No plausible explanation for the findings in Europe was found, which may be attributable to chance. In general, the excess of strokes during treatment with empagliflozin (if not chance) may be partly related to the decrease of circulating blood volume, which can be seen as an increased haematocrit in the empagliflozin treated groups. This latter finding has been described in 4.8 (SmPC).

Apparently, the mortality benefits are not explained by a risk reduction for atherosclerotic events. Instead, the MAH suggests that a reduction of **heart failure** related events may be one of the factors driving the benefit. The most prevalent categorisation of the CV deaths were "other CV death", including fatal events deemed not assessable by the CEC (129 of 309 patients with CV death), followed by sudden deaths (91) and worsening of heart failure (30). This pattern could indeed be compatible with mortality from heart failure.

Heart failure is highly prevalent in patients with diabetes (e.g. 22% of those aged ≥65 years) and associated with increased mortality (in the referenced study a 5-year survival rate of only 12.5%) [Bertoni AG, Diabetes Care 2004]. Heart failure related endpoints were predefined (but exploratory) in the EMPA-REG study. For all heart failure endpoints, the risk was reduced in the "all empagliflozin" group and the individual dose groups compared with the placebo group (Hospitalisation for heart failure: HR: 0.65).

The exploratory composite **nephropathy** endpoint "new or worsening nephropathy" was reduced for both empa doses (HR all empa: 0.61). This was primarily driven by "New onset of macroalbuminuria (UACR >300 mg/g)". No obvious difference between empagliflozin and placebo was observed for new onset of albuminuria (HR 0.95).

For patients with microalbuminuria (UACR 30 to 300 mg/g) or macro-albuminuria (UACR >300 mg/g) at baseline, more patients showed sustained reversal of their proteinuria after treatment with empagliflozin than with placebo (patients with improvement, HR > 1 favours empa: microalbuminuria HR 1.43 ; macroalbuminuria: HR 1.82). There were no obvious differences between the 2 empagliflozin dose groups. These results are maintained in subjects with moderate renal insufficiency.

All patients had cardiovascular disorders, and it seems obvious that this patient population had also nefrangioscleroses. Moreover, most patients in this trail were already diagnosed with a renal insufficiency. Although the incidence rates for decreased renal function were lower in the empagliflozin group, the microvascular endpoint 'nephropathy' should be taken with special consideration, since:

- 19,5% of the included patients were diagnosed with a 'diabetic nephropathy', and were equally divided in different groups. Since however the diagnosis of nephropathy was based on the measurement of eGFR and not based on a pathological diagnosis due to a renal biopsy, the distinction between a diabetic nephropathy and an ischemic nephropathy due to cardiovascular diseases could not be made. Moreover, in practice only a subset of patients with diabetes type II have typical diabetes glomerulopathy in biopsies. Therefore it is not sure how many patients indeed had a diabetic nephropathy in this study population
- Microalbuminuria is a common feature of aging and can be associated with a large number of acute and chronic inflammatory as well as vascular pathologies. Furthermore, microalbuminuria is often transient and reversible. Therefore, the adverse event of albuminuria should be taken with some reservation, albuminuria is not a specific parameter for renal insufficiency.

When mean eGFR values were analysed over time, there was a steady decrease in eGFR in the placebo group, indicative of natural disease progression. In contrast, the initial decreases in eGFR in the empagliflozin groups were reversible over time, with eGFR values higher in the empagliflozin groups than in the placebo group after about a year. About 30 days after the stop of treatment, eGFR increased from the last value on treatment by about 3.5 ml/min/1.73m^2 in the empagliflozin groups, while no change was seen in the placebo group. These data suggest that the initial decrease seen with empagliflozin treatment is haemodynamic in nature.

Taken together, prevention of new albuminuria, reversal of existing albuminuria and prevention of the usual decline of eGFR in type 2 diabetes patients all suggest that empagliflozin may be important in the prevention and treatment of diabetic nephropathy. This result was an exploratory finding in EMPA-REG and requires further confirmation. Many questions are still open, e.g. the development of eGFR in subjects with impaired renal function and how these potential benefits interact with other medicinal products, either usually beneficial (ACE-inhibitors) or detrimental (NSAIDs).

The underlying nephro-protective mechanism of empagliflozin is not clear but may at least partly be due to the attenuation of renal hyperfiltration via tubulo-glomerular feedback mechanisms [Skrtic M, Diabetologia, 2014; Cherney DZI, Circulation, 2013]. Renal hyperfiltration results in increased glomerular pressure and can lead to albuminuria, renal function decline, and renal impairment. Altered hemodynamics may also explain the improvement seen in the occurrence of heart failure and either directly or indirectly contribute to the improvement of cardiovascular mortality.

In EMPA-REG, patients could be included with any **eGFR** > 30 ml/min/1.73m^2 and they were eligible for both dose levels of empagliflozin. The MAH proposes to lift the restriction for use in patients with moderate renal insufficiency based on these results.

Based on the analysis of MACE-3, all-cause and CV mortality, it can be agreed that the results for moderate renal insufficiency are in line with the overall trial results. Exploratory results for heart failure requiring hospitalisation and new or worsening nephropathy suggest that the efficacy is at least maintained with worsening renal function.

Efficacy for glycaemic control in subjects with moderate renal insufficiency was similar to previous results. In these patients, no clinically relevant effect on glycaemic control has been shown. Although empagliflozin has shown beneficial CV effects in these patients, the inclusion in SmPC section 4.2 (as proposed by the applicant) of patients with eGFR below 45 ml/min/1.73m^2 was not supported by the CHMP, as glycaemic

efficacy is considered essential for any diabetes product. Therefore, the posology in patients with renal impairment should remain unchanged.

The efficacy data for both **dose** levels tested were highly comparable for the primary and secondary endpoints. There were slight advantages for the higher dose in parameters like, HbA1c, FPG, blood pressure and weight; only in subjects with eGFR >60 ml/min/1.73m^2. For the proposed CV prevention indication, the higher dose has no advantages.

2.4.3. Conclusions on the clinical efficacy

EMPA-REG was a well-designed and well-conducted trial. The trial showed superiority of empagliflozin to placebo on the primary outcome MACE-3, which was driven by benefits on CV mortality; effect shown on all-cause mortality was consistent. Exploratory results suggest that prevention of heart failure and less worsening nephropathy may explain the findings. However, for an application based on a single pivotal trial, the inconsistent additional endpoints (stroke, silent MI) and inconsistent subgroups (especially Europe) raise concerns. The included population was at especially high cardiovascular risk. Therefore, the results cannot be directly extrapolated to the entire diabetic population.

In the population with eGFR between 30 and 60 ml/min/1.73m^2, in which empagliflozin is currently not recommended, the benefits seem maintained.

2.5. Clinical safety

Introduction

In phase 3, the overall incidence of adverse events in patients treated with empagliflozin was similar to placebo. The most frequently reported adverse reaction was hypoglycaemia when used with sulphonylurea or insulin. Increased urination and volume depletion are directly related to the mode of action. Genital and urinary tract infections are common.

Although CV and microvascular outcome events are defined as safety endpoints in the trial protocol, their analyses are described in the efficacy section in this document

Patient exposure

The median observation period was about 3.1 years for each treatment group. The total observation time per treatment group was at least 6794 years (Table 17). The total exposure to treatment per group was at least 5747 years (Table 18).

Table 17. Observational period - TS

	Placebo	Empa 10 mg	Empa 25 mg	All empa
Treated patients, N (%)	2333 (100.0)	2345 (100.0)	2342 (100.0)	4687 (100.0)
Observation time categories, N (%)				
≥52 weeks	2279 (97.7)	2304 (98.3)	2303 (98.3)	4607 (98.3)
≥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]				
Median	3.07	3.15	3.16	3.15
Mean (SD)	2.91 (0.82)	2.96 (0.98)	2.96 (0.79)	2.96 (0.89)
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.

Table 18. Exposure to randomised trial medication - TS

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

Exposure was calculated as date of last intake of trial medication minus date of first intake, plus one day. Interruptions of trial medication were ignored, i.e. considered as if patients had taken trial medication.

Adverse events

The incidence rates for any AE and for SAEs (and fatal SAEs) were lower for patients treated with empagliflozin than placebo. The incidence rates for drug-related AEs as defined by the investigator were higher for patients treated with empagliflozin than placebo. For other categories of AEs, including those leading to discontinuation of study medication, there was no marked imbalance between the 3 treatment groups (Table 19 below).

Table 19. Adverse event overall summary - TS

	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)	
Patients with any AE	2139	(91.7)	178.67	2112	(90.1)	150.34	2118	(90.4)	148.36
Patients with severe AEs [1]	592	(25.4)	NA	536	(22.9)	NA	564	(24.1)	NA
Patients with investigator-defined drug-related AEs	549	(23.5)	11.33	666	(28.4)	14.15	643	(27.5)	13.38
Patients with AEs leading to discontinuation of study med. [2]	453	(19.4)	8.26	416	(17.7)	7.28	397	(17.0)	6.89
Patients with 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 abnormality	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

NA = not analysed; exposure-adjusted incidences are presented where calculated, with rate per 100 patient years.
[1] Worst intensity recorded [2] Non-serious and serious AEs [3] A patient could be counted in more than 1 seriousness category.
Highest percentage in row marked.

Most frequently reported Adverse Events

Of the most frequently reported AEs at PT level, similar rates across the 3 treatment arms were reported for urinary tract infection and hypoglycaemia. Lower incidence rates for hyperglycaemia were reported for patients treated with empagliflozin (10 mg: 3.86/100 patient-years; 25 mg: 3.55/100 pt-yrs) compared with placebo (8.51/100 pt-yrs). Of the less frequently reported AEs, imbalances in incidence rates between empagliflozin and placebo groups were observed for PTs associated with genital infections, or with other AEs known to occur with empagliflozin (such as dysuria, pollakisuria, and polyuria). The rate for PT thirst was higher in the empagliflozin groups (10 mg: 0.12/100 pt-yrs; 25 mg: 0.32/100 pt-yrs) than placebo (0.09/100 pt-yrs). Urinary tract infections were reported slightly more frequently in the placebo group, but lead to discontinuation more among empagliflozin users (Table 20).

The most frequently reported AEs leading to treatment discontinuation at the PT level were myocardial infarction and acute myocardial infarction, with similar rates in all treatment groups.

The overall incidence rates of AEs assessed as drug-related by the investigators were higher for both empagliflozin groups than the placebo group. This was largely due to higher incidence rates for AEs in the SOCs reproductive system and breast disorders, renal and urinary disorders, and investigations. At the PT level, slight imbalances in incidence rates between the empagliflozin and placebo groups followed the differences in the SOCs, with higher incidence rates for the empagliflozin groups compared with placebo observed, for example, for balanoposthitis, vulvovaginal pruritus, genital pruritus, decreased weight, pollakisuria, and polyuria.

The most frequently reported AEs with severe intensity were in the SOCs cardiac disorders and infections and infestations. The frequency of severe cardiac disorders was slightly lower for patients treated with empagliflozin (10 mg: 6.9%; 25 mg: 7.3%) than placebo (9.4%). The frequencies of severe events at the PT level within the SOC cardiac disorders were generally slightly lower for the empagliflozin groups than for placebo. For infections and infestations, the most frequently reported PT, pneumonia, was reported at a slightly lower frequency for patients in the empagliflozin groups than placebo. With regard to severe nervous system disorders, the frequency of ischaemic stroke was slightly lower for the empagliflozin groups (10 mg: 0.4%; 25 mg: 0.2%) than placebo (0.6%) while the frequency of cerebrovascular accident was slightly higher for the empagliflozin groups (10 mg: 0.8%; 25 mg: 0.9%) than placebo (0.5%).

Serious adverse event/deaths/other significant events

The overall incidence rates for fatal AEs were lower for patients treated with empagliflozin than for patients treated with placebo (Table 19). At the PT level, the most frequently reported fatal AEs were myocardial infarction and cardiac arrest. Cardiac arrest, acute myocardial infarction, and cardiac failure were less frequently reported for patients treated with empagliflozin than placebo. Incidence rates for the other most frequently reported PTs (≥0.2% in any group) were generally similar between the empagliflozin and placebo treatment groups or slightly lower for empagliflozin than placebo. As for most of the AE analyses in this trial, the fatal AE analyses were based on a follow-up period of 7 days after treatment stop, and therefore the numbers of patients with fatal AEs differ from the numbers for all-cause mortality (for which the follow-up was until individual trial end). Nonetheless, the reduction in deaths in the empagliflozin groups is seen in both analyses.

The incidence rates of SAEs (which included fatal and non-fatal SAEs) were slightly lower for patients treated with empagliflozin than for patients treated with placebo (Table 19), largely due to lower incidence rates of serious cardiac disorders in the empagliflozin groups than in the placebo group. At the PT level, a number of SAEs had slightly lower incidence rates for patients on empagliflozin than on placebo (angina unstable, cardiac failure, coronary artery disease, cardiac failure congestive, myocardial ischaemia, bradycardia, cardiac arrest, pneumonia). Other PTs had slightly higher incidence rates for patients on empagliflozin than for patients on placebo (urosepsis, cerebrovascular accident).

The overall incidence rates for SAEs that were immediately life-threatening were slightly higher in the empagliflozin groups than in the placebo group, largely due to the higher incidence rates of cardiac disorders that were immediately life-threatening (empagliflozin 10 mg: 0.47/100 pt-yrs; empagliflozin 25 mg: 0.57/100 pt-yrs; placebo: 0.40/100 pt-yrs). However, the incidence rates for combined fatal or immediately-life-threatening SAEs, overall and for the SOC cardiac disorders, were lower for both empagliflozin groups (overall 10 mg: 2.35/100 pt-yrs; 25 mg: 2.21/100 pt-yrs) than for the placebo group (2.68/100 pt-yrs).

Adverse Events of special interest

An adverse event of special interest (serious or non-serious) was an AE of scientific, medical, or regulatory concern. A total of 11 categories of adverse events of special interest were analysed in this trial (Table 20).

The incidence rates of genital infections were higher in the empagliflozin 10 mg and 25 mg groups than in the placebo group. Although non-serious urinary tract infections were similar among all groups, serious or complicated UTIs occurred more with the 25 mg dose, but not with the 10 mg dose.

Although the incidence rate of hepatic injury was slightly lower in both empagliflozin groups than the placebo group, there were slightly more serious cases.

Five patients in total were reported with diabetic **ketoacidosis** (placebo: 1, empa 10mg: 3, empa 25mg: 1). The frequencies of confirmed hypoglycaemic adverse events were comparable in all groups, including frequencies for events where the patient required assistance.

Bone fractures occurred more frequently in the placebo group compared to the empagliflozin groups.

The overall frequencies and incidence rates for malignancy up to trial termination were somewhat higher for the empagliflozin-treated groups; the same was true for patients with malignancy with an onset after 6 months of exposure to study medication (Table 20).

Laboratory findings

There were increases in total cholesterol, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol in all treatment groups from baseline to Week 28. 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. There were also increases in Haemotocrit in the Empa groups versus placebo.

Safety in special populations

AEs in patients with CKD 3A/B were similar between treatment groups although higher than in 'all patients'. For most SOCs, events for placebo were numerically higher (Table 21).

The incidence of AEs and SAEs increases with age, but similarly in placebo and empagliflozin-treated groups. No new risks are identified for elderly patients who use empagliflozin (Table 22).

Table 20. Overall summary of patients with AESIs - TS

AESI Category of event	Placebo N (%)	Rate/100 pt-yrs	Empa 10 mg N (%)	Rate/100 pt-yrs	Empa 25 mg 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
Leading to discontinuation	24 (1.0)	0.42	19 (0.8)	0.32	22 (0.9)	0.36
Serious	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
Leading to discontinuation	8 (0.3)	0.14	7 (0.3)	0.12	6 (0.3)	0.10
Serious	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
Leading to discontinuation	10 (0.4)	0.17	22 (0.9)	0.37	19 (0.8)	0.31
Serious [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
Leading to discontinuation	2 (0.1)	0.03	19 (0.8)	0.32	14 (0.6)	0.23
Serious	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
Leading to discontinuation	14 (0.6)	0.24	4 (0.2)	0.07	8 (0.3)	0.13
Serious	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
Leading to discontinuation	7 (0.3)	0.12	1 (<0.1)	0.02	4 (0.2)	0.07
Serious	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
Leading to discontinuation	29 (1.2)	0.50	46 (2.0)	0.77	36 (1.5)	0.60
Up to trial termination[4]	103 (4.4)	1.57	117 (5.0)	1.76	110 (4.7)	1.65
After 6 months exposure[5]	65 (3.0)	1.41	91 (4.1)	1.90	70 (3.2)	1.44
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
Leading to discontinuation	10 (0.4)	0.17	7 (0.3)	0.12	11 (0.5)	0.18
Serious	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
Leading to discontinuation	2 (0.1)	0.03	0	0	2 (0.1)	0.03
Serious	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
Leading to discontinuation	0	0	2 (0.1)	0.03	0	0
Serious	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.

[1] Required or prolonged hospitalisation

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

[3] All events with a plasma glucose value of ≤70 mg/dL or where assistance was required

[4] All events observed until trial termination were included.

[5] Onset after 6 months of cumulative exposure to study medication; N = 2187 for placebo; N = 2216 for empagliflozin 10 mg; N = 2190 for empagliflozin 25 mg

Table 21. Summary of AEs for patients with CKD 3 at baseline - TS

	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)[2], N	601 (100.0)		598 (100.0)		593 (100.0)	
Patients with any AE	571 (95.0)	262.31	544 (91.0)	178.37	544 (91.7)	184.94
Leading to discount.	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
CKD 3A (eGFR 45 to <60)[2], N	418 (100.0)		420 (100.0)		411 (100.0)	
Patients with any AE	395 (94.5)	275.46	383 (91.2)	168.46	375 (91.2)	157.57
Leading to discount.	106 (25.4)	11.51	84 (20.0)	8.31	78 (19.0)	7.81
Serious adverse events	219 (52.4)	30.86	185 (44.0)	22.71	185 (45.0)	24.03
Decreased renal function (SMQ)	53 (12.7)	5.65	39 (9.3)	3.82	40 (9.7)	4.00
Hepatic injury (SMQ)	15 (3.6)	1.54	16 (3.8)	1.51	14 (3.4)	1.36
Urinary tract infection (BIcMQ)	83 (19.9)	9.47	101 (24.0)	11.22	85 (20.7)	9.26
Genital infection (BIcMQ)	8 (1.9)	0.82	17 (4.0)	1.62	31 (7.5)	3.12
Confirmed hypoglycaemic AEs[1]	163 (39.0)	NA	131 (31.2)	NA	122 (29.7)	NA
Bone fracture (BIcMQ)	25 (6.0)	2.60	20 (4.8)	1.92	19 (4.6)	1.85
Volume depletion (BIcMQ)	33 (7.9)	3.48	34 (8.1)	3.31	25 (6.1)	2.47
Malignancy (BIcMQ)	25 (6.0)	2.55	25 (6.0)	2.38	19 (4.6)	1.84
Hypersensitivity (SMQ)	47 (11.2)	5.07	28 (6.7)	2.70	23 (5.6)	2.28
Venous embolic and thrombotic AEs (SMQ)	4 (1.0)	0.41	2 (0.5)	0.19	8 (1.9)	0.77
CKD 3B (eGFR 30 to <45)[2], N	183 (100.0)		178 (100.0)		182 (100.0)	
Patients with any AE	176 (96.2)	236.94	161 (90.4)	207.41	169 (92.9)	300.89
Leading to discount.	57 (31.1)	14.46	61 (34.3)	17.03	50 (27.5)	13.09
Serious adverse events	99 (54.1)	33.90	86 (48.3)	29.03	84 (46.2)	27.26
Decreased renal function (SMQ)	31 (16.9)	7.92	23 (12.9)	6.22	31 (17.0)	8.47
Hepatic injury (SMQ)	12 (6.6)	2.90	5 (2.8)	1.26	10 (5.5)	2.51
Urinary tract infection (BIcMQ)	49 (26.8)	13.06	44 (24.7)	13.31	43 (23.6)	12.51
Genital infection (BIcMQ)	2 (1.1)	0.47	6 (3.4)	1.54	9 (4.9)	2.26
Confirmed hypoglycaemic AEs[1]	66 (36.1)	NA	63 (35.4)	NA	69 (37.9)	NA
Bone fracture (BIcMQ)	6 (3.3)	1.42	11 (6.2)	2.82	7 (3.8)	1.76
Volume depletion (BIcMQ)	15 (8.2)	3.70	10 (5.6)	2.59	10 (5.5)	2.54
Malignancy (BIcMQ)	8 (4.4)	1.90	14 (7.9)	3.60	9 (4.9)	2.25
Hypersensitivity (SMQ)	24 (13.1)	6.25	10 (5.6)	2.60	18 (9.9)	4.71
Venous embolic and thrombotic AEs (SMQ)	2 (1.1)	0.47	1 (0.6)	0.25	2 (1.1)	0.49

SMQ = Standardised MedDRA query; BIcMQ = BI-customised MedDRA query; NA = not analysed
[1] All events with a plasma glucose value of ≤70 mg/dL or where assistance was required
[2] Unit for eGFR: mL/min/1.73m^2

Table 22. Safety in older patients

Age	<50 years		50 to <65 years		65 to <75 years		≥75 years	
	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs	N (%)	Rate/100 pt-yrs
Number of patients								
Placebo	142 (100.0)		1155 (100.0)		808 (100.0)		228 (100.0)	
Empa 10 mg	154 (100.0)		1146 (100.0)		834 (100.0)		211 (100.0)	
Empa 25 mg	143 (100.0)		1153 (100.0)		833 (100.0)		213 (100.0)	
Patients with any AE								
Placebo	125 (88.0)	157.60	1049 (90.8)	160.26	750 (92.8)	204.99	215 (94.3)	220.68
Empa 10 mg	130 (84.4)	106.25	1022 (89.2)	140.98	766 (91.8)	165.39	194 (91.9)	205.51
Empa 25 mg	131 (91.6)	158.42	1031 (89.4)	133.61	765 (91.8)	166.03	191 (89.7)	169.72
Patients with AEs leading to discontinuation of study medication								
Placebo	19 (13.4)	5.70	181 (15.7)	6.36	188 (23.3)	10.36	65 (28.5)	13.33
Empa 10 mg	15 (9.7)	3.84	184 (16.1)	6.42	159 (19.1)	7.96	58 (27.5)	12.68
Empa 25 mg	12 (8.4)	3.16	163 (14.1)	5.63	177 (21.2)	8.81	45 (21.1)	9.43
Patients with SAEs								
Placebo	51 (35.9)	18.88	413 (35.8)	17.41	391 (48.4)	27.54	133 (58.3)	36.95
Empa 10 mg	45 (29.2)	13.18	403 (35.2)	16.51	321 (38.5)	19.12	107 (50.7)	30.39
Empa 25 mg	52 (36.4)	16.55	399 (34.6)	16.28	373 (44.8)	23.94	89 (41.8)	23.12
Patients with decreased renal function (SMQ)								
Placebo	6 (4.2)	1.81	69 (6.9)	2.41	61 (7.5)	3.23	19 (8.3)	3.71
Empa 10 mg	1 (0.6)	0.25	54 (4.7)	1.84	51 (6.1)	2.50	15 (7.1)	3.14
Empa 25 mg	4 (2.8)	1.03	60 (5.2)	2.04	52 (6.2)	2.50	9 (4.2)	1.86
Patients with hepatic injury (SMQ)								
Placebo	12 (8.5)	3.66	58 (5.0)	2.01	29 (3.6)	1.51	9 (3.9)	1.74
Empa 10 mg	2 (1.3)	0.50	39 (3.4)	1.32	33 (4.0)	1.59	6 (2.8)	1.23
Empa 25 mg	5 (3.5)	1.28	54 (4.7)	1.84	25 (3.0)	1.19	4 (1.9)	0.81
Patients with urinary tract infection (BIcMQ)								
Placebo	26 (18.3)	8.78	177 (15.3)	6.60	165 (20.4)	9.61	55 (24.1)	12.01
Empa 10 mg	20 (13.0)	5.39	189 (16.5)	7.04	156 (18.7)	8.43	61 (28.9)	15.05
Empa 25 mg	24 (16.8)	6.93	167 (14.5)	6.10	175 (21.0)	9.40	50 (23.5)	11.82
Patients with genital infection (BIcMQ)								
Placebo	3 (2.1)	0.89	20 (1.7)	0.68	17 (2.1)	0.88	2 (0.9)	0.38
Empa 10 mg	12 (7.8)	3.19	86 (7.5)	3.01	45 (5.4)	2.21	10 (4.7)	2.10
Empa 25 mg	11 (7.7)	2.93	72 (6.2)	2.50	52 (6.2)	2.52	13 (6.1)	2.71
Patients with confirmed hypoglycaemic AEs[1]								
Placebo	33 (23.2)	NA	309 (26.8)	NA	246 (30.4)	NA	62 (27.2)	NA
Empa 10 mg	38 (24.7)	NA	316 (27.6)	NA	239 (28.7)	NA	63 (29.9)	NA
Empa 25 mg	37 (25.9)	NA	315 (27.3)	NA	241 (28.9)	NA	54 (25.4)	NA
Patients with bone fracture (BIcMQ)								
Placebo	5 (3.5)	1.50	40 (3.5)	1.38	35 (4.3)	1.83	11 (4.8)	2.16
Empa 10 mg	4 (2.6)	1.01	39 (3.4)	1.32	39 (4.7)	1.90	10 (4.7)	2.09
Empa 25 mg	5 (3.5)	1.29	33 (2.9)	1.11	37 (4.4)	1.77	12 (5.6)	2.49
Patients with volume depletion (BIcMQ)								
Placebo	4 (2.8)	1.19	41 (3.5)	1.41	57 (7.1)	3.03	13 (5.7)	2.57
Empa 10 mg	3 (1.9)	0.76	38 (3.3)	1.29	59 (7.1)	2.92	15 (7.1)	3.19
Empa 25 mg	8 (5.6)	2.09	46 (4.0)	1.56	56 (6.7)	2.73	14 (6.6)	2.93
Patients with malignancy (BIcMQ)								
Placebo	1 (0.7)	0.29	16 (1.4)	0.54	39 (4.8)	2.03	22 (9.6)	4.34
Empa 10 mg	0	0	32 (2.8)	1.07	56 (6.7)	2.72	18 (8.5)	3.78
Empa 25 mg	0	0	38 (3.3)	1.27	44 (5.3)	2.10	14 (6.6)	2.89
Patients with hypersensitivity (SMQ)								
Placebo	4 (2.8)	1.18	92 (8.0)	3.27	77 (9.5)	4.20	24 (10.5)	4.87
Empa 10 mg	9 (5.8)	2.34	71 (6.2)	2.46	65 (7.8)	3.25	13 (6.2)	2.73
Empa 25 mg	9 (6.3)	2.34	90 (7.8)	3.14	67 (8.0)	3.28	15 (7.0)	3.15
Patients with venous embolic and thrombotic AEs (SMQ)								
Placebo	1 (0.7)	0.29	5 (0.4)	0.17	13 (1.6)	0.67	1 (0.4)	0.19
Empa 10 mg	1 (0.6)	0.25	5 (0.4)	0.17	3 (0.4)	0.14	0	0
Empa 25 mg	0	0	8 (0.7)	0.27	12 (1.4)	0.56	1 (0.5)	0.20

NA = not analysed
Note: exposure-adjusted incidence rates are presented, with rate per 100 patient years.

2.5.1. Discussion on clinical safety

The safety profile of empagliflozin in trial 1245.25 is consistent with the known safety profile of empagliflozin. Only thirst is proposed by the MAH as a new side effect after their assessment of all available clinical data and in light of the new data from trial 1245.25. Thirst was not included in the definition of volume depletion as used by the MAH and therefore evaluated separately. In the pooling of all placebo-controlled trials with a treatment duration of 18 to 24 weeks (not including 1245.25), which was designated for side-effects labelling, the PT thirst was reported for 1.3% of the patients in either empagliflozin group (10 mg or 25 mg), while not reported in the placebo group. These data are consistent with the results from the largest safety pooling supporting the initial marketing application and from trial 1245.25 (empagliflozin 10 mg: 0.3%; 25 mg: 0.8%; placebo: 0.2%). The addition of thirst is therefore agreed. Besides, elderly patients, who are often exposed to multi drug treatments, including diuretics and ACE-inhibitors are vulnerable for volume depletion. Therefore, a special warning should be added in section 4.4 of the SmPC

The new data about AEs that were collected are in line with previous knowledge about empagliflozin as documented in the SmPC. This also applies to the AEs of special interest. Although this was a large trial, the numbers of rare events are still too low to draw definite conclusions. Of note:

- Hepatic events were carefully assessed by a blinded committee. Although infrequent, serious hepatic injury and/or patients with ALT/AST ≥5x ULN were higher for patients in the empagliflozin groups (increased AST/ALT: 10 mg: 0.7%; 25 mg: 0.6%) than placebo (0.3%). No definite cases of DILI were identified as according to the committee confounding factors were present.
- In total, 7 patients (0.3%) in the empagliflozin 10 mg group and 12 patients (0.5%) in the empagliflozin 25 mg group had PT urosepsis or sepsis possibly originated from the urinary tract, compared with 5 patients (0.2%) in the placebo group. However, the overall incidence rate of (complicated) UTIs was similar in the empagliflozin groups and the placebo group. The text regarding UTI in Section 4.4 of the SmPC is still acceptable.
- The frequency of confirmed hypoglycaemic adverse events was similar in all treatment groups within each subgroup (e.g. by age, renal impairment, use of insulin at baseline), except for the subgroup with SU at baseline. It is somewhat surprising that concomitant use of SUs is associated with less hypoglycaemias (with SU: 24.5% for empagliflozin 10 mg, 25.0% for empagliflozin 25 mg, 23.4% for placebo; without SU: 30.5 % for empagliflozin 10 mg, 29.7 % for empagliflozin 25 mg, 31.2 % for placebo).
- Use of loop diuretics was associated with a higher risk of volume depletion in the empagliflozin groups (10 mg: 4.92/100 pt-yrs; 25 mg: 4.45/100 pt-yrs) than in the placebo group (3.69/100 pt-yrs). This association is already mentioned in section 4.5 of the SmPC.
- There was no clear increase in the incidence of keto-acidosis.
- Malignancies occurred more frequently with empagliflozin treatment (4.3%) compared to placebo treatment (3.3%), also when taking into account only cases after at least 6 months of exposure. However, no specific group of malignancies seems to explain this and after detailed classification the groups become very small.

The MAH summarised AE data for subjects with moderate renal insufficiency and for older patients. Although in these groups the overall rate of AEs is higher than in the overall population, the AE profile is comparable to the total population.

The following additional laboratory value changes should be added to the Jardiance SmPC because these safety issues are now confirmed in empa-reg and other trials with FDC:

- Increase in haematocrit should be added to sections 4.4 and 4.8 of the SmPC.
- Increase in serum lipids should be added to section 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

The established safety profile, as described in the SmPC is confirmed. Thirst can be added as a common adverse reaction. The SmPC should be extended with information on the increase in haematocrit (section 4.4 and section 4.8) and serum lipids (section 4.8).

The safety profile in subjects with moderate renal insufficiency who use empagliflozin is comparable to placebo, although the AE rates are higher than in subjects with normal renal function.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the **Risk Management Plan version 10.3** is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the **Risk Management Plan version 10.3** with the following content:

Safety concerns

Important identified risks	Urinary tract infection
	Genital infection
	Volume depletion
	Hypoglycaemia (with insulin and/or SU)
	Diabetic ketoacidosis with atypical presentation
Important potential risks	Urinary tract carcinogenicity
	Liver injury
	Off-label use (e.g. for weight loss in non-T2DM patients)
	Bone fracture
Missing information	Paediatric patients
	Elderly patients (≥85 years)
	Pregnancy/breast-feeding
	Use in patients with severe hepatic impairment

Pharmacovigilance plan

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports
PASS (1245.96) to assess the risk of renal and liver injury, urinary tract and genital infection, and diabetic ketoacidosis; category 3	To evaluate the risk of urinary tract and genital infection, acute renal and hepatic injury, and diabetic ketoacidosis resulting in hospitalisations, in empagliflozin-treated patients, compared to users of other antidiabetic treatment.	Urinary tract infection, genital infection, renal impairment, liver injury, diabetic ketoacidosis with atypical presentation	Started	Final report, July 2020
PASS (1245.97) to assess the risk of urinary tract malignancies; category 3	To evaluate the risk of renal and bladder cancer in empagliflozin-treated patients, compared to users of other antidiabetic treatment.	Urinary tract carcinogenicity	Started	Final report, June 2021
DUS (1245.122) to assess characteristics of patients initiating empagliflozin, including potential off-label use; category 3	To evaluate the characteristics of patients initiating empagliflozin treatment, including potential off-label use	Off-label use	Started	Q4 2016
Enhanced pharmacovigilance study (1245.146) of ketoacidosis; category 3	To evaluate the risk of diabetic ketoacidosis in patients treated with empagliflozin	Diabetic ketoacidosis with atypical presentation	Started	Q4 2021
Non-clinical experiments; category 3	To investigate the proketogenic mechanism of SGLT-2 inhibition	Diabetic ketoacidosis with atypical presentation	Started	Q4 2016

[1] Type, title and category (1-3).
[2] Planned or started.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Urinary tract infection	Labelling in SmPC sections 4.4 and 4.8. Prescription-only medicine.	None

Genital infection	Labelling in SmPC section 4.8. Prescription-only medicine.	None
Volume depletion	Labelling in SmPC sections 4.4 and 4.8. Prescription-only medicine.	None
Hypoglycaemia (with insulin and/or SU)	Labelling in SmPC sections 4.2 and 4.8. Prescription-only medicine.	None
Diabetic ketoacidosis with atypical presentation	Labelling in SmPC sections 4.4 and 4.8. Prescription only medicine.	None
Important potential risks		
Urinary tract carcinogenicity	Prescription-only medicine.	None
Liver injury	Labelling in SmPC sections 4.2 and 4.4. Prescription-only medicine.	None
Off-label use (e.g. for weight loss in non-T2DM patients)	Prescription-only medicine.	None
Bone fracture	Prescription-only medicine.	None
Missing information		
Paediatric patients	Labelling in SmPC section 4.2. Prescription-only medicine	None
Elderly patients (≥85 years)	Labelling in SmPC sections 4.2 and 4.4. Prescription-only medicine	None
Pregnancy/breast-feeding	Labelling in SmPC section 4.6. Prescription-only medicine	None
Use in patients with severe hepatic impairment	Labelling in SmPC sections 4.2 and 4.4. Prescription-only medicine	None

2.7. Update of the Product information

As a consequence of this application for modification of the indication, sections 4.1 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, sections 4.2, 4.4, 4.5, 4.8 of the SmPC have been updated with additional safety information pertaining to elevated haematocrit, volume depletion, thirst, serum lipids increased.

For detailed information on the changes to the PI, please refer to attachment 1.

3. Benefit-Risk Balance

Jardiance is currently indicated to improve glycaemic control in type 2 diabetes. In this type 2 variation, and based on the results of the EMPA-REG cardiovascular outcome trial, the MAH initially sought an additional indication for prevention of cardiovascular events in patients with type 2 diabetes and established cardiovascular disease to reduce the risk of

- all-cause mortality by reducing cardiovascular death and
- cardiovascular death or hospitalisation for heart failure (see section 5.1).

Also, the MAH sought to expand recommended use in subjects with moderate renal insufficiency (eGFR 30-60 ml/min/1.73m^2).

During the CHMP assessment, the MAH limited the claim for additional indication to patients with type 2 diabetes and established cardiovascular disease to reduce the risk of cardiovascular death.

Also during the assessment, use in subjects with moderate renal insufficiency was sought for the claim with regard to reduction of cardiovascular death only, but not for the glycaemic control part of the proposed indication.

Benefits

Beneficial effects

The EMPA-REG cardiovascular outcome trial included 7028 diabetic patients with established cardiovascular disease (high cardiovascular risk defined as at least one of the following risk factors: myocardial infarction or CVA within 2 months before inclusion, coronary heart disease, instable angina pectoris, peripheral arterial disease) who were randomised between placebo, empagliflozin 10 mg OD and empagliflozin 25 mg OD. Patients were followed up for a median of 3.1 years. The trial was stopped according to plan after 691 events had been observed.

The primary endpoint (**3-point MACE**) was the time to first occurrence of CV death (including fatal stroke and fatal MI), non-fatal MI (excluding silent MI), or non-fatal stroke. The primary analysis [based on the treated set population] showed superiority of "all empagliflozin" treatment to placebo. Patients with events were 282/2333 (12.1%) for placebo and 490/4687 (10.5%) for all empagliflozin treated patients. The HR was 0.86 (95.02% CI: 0.74, 0.99; p (2-sided) = 0.0382). The results were similar (although not statistically significant) in exploratory analyses for both empagliflozin doses (patients with events 10 mg: 243/2345 (10.4%), 25mg: 247/2342 (10.5%)).

The exploratory breakdown of the first event for 3-point MACE indicated that the lower frequency of 3-point MACE for empagliflozin was primarily driven by a lower frequency of CV death (placebo: 107 (4.6%), all empa: 143 (3.1%); HR 0.62; 95% CI 0.49, 0.77). The most prevalent categorisation of the CV deaths was "other CV death", including fatal events deemed not assessable by the CEC (129 of 309 patients with CV death), followed by sudden deaths (91) and worsening of heart failure (30). For all **myocardial infarction**-related endpoints, no significant difference was observed between empagliflozin and placebo, although the point estimate favoured empagliflozin (non-fatal MI, HR: 0.87; 95% CI 0.70, 1.09). Silent MI was not part of the primary endpoint, but the outcome favoured placebo (HR 1.28; 95% CI 0.70, 2.33). However, the hazard ratio point estimate for **stroke** was above 1 (non-fatal stroke; HR 1.24; 95% CI 0.92, 1.67; not statistically significant). In Europe, the HR for stroke was statistically significant (HR 2.04, CI: 1.26, 3.29).

The key secondary endpoint (**4-point MACE**) was the time to first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalisation for unstable angina pectoris. Empagliflozin (doses pooled) was non-inferior, but not superior, to placebo based on this endpoint (HR 0.89 (95.02% CI 0.78, 1.01); p = 0.0795). The results for 10 and 25 mg were similar.

The risk of CV death and all-cause **mortality** was significantly reduced in the "all empagliflozin" group and the individual dose groups compared with the placebo group (all-cause mortality: placebo: 194 (8.3%), empa: 269 (5.7%)). There were no obvious differences between the two empagliflozin dose groups. The majority of all deaths were CV deaths, and non-CV death was numerically reduced in the empagliflozin

groups compared with the placebo group. The result was confirmed in a sensitivity analysis assuming all empagliflozin-treated-patients lost to follow up had died.

The efficacy data for both **dose** levels tested were highly comparable for the primary and secondary endpoints. There were slight advantages for the higher dose in parameters like HbA1c, FPG, blood pressure and weight.

Results in this trial confirmed previous data for glycaemic control in subjects with moderate renal impairment.

Additional data were obtained with regard to pharmacokinetic through levels reflecting on exposure. These data confirm the PK information in the current SmPC.

Uncertainty in the knowledge about the beneficial effects

Heart failure related endpoints were exploratory by design in this trial. For all heart failure endpoints, the risk was reduced in the "all empagliflozin" group and the individual dose groups compared with the placebo group (Patients with events of hospitalisation for heart failure: Placebo 4.1%, All empa 2.7%; HR: 0.65, 95% CI: 0.50, 0.85).

The exploratory composite **nephropathy** endpoint "new or worsening nephropathy" was reduced for both empa doses (HR 0.61, 95% CI: 0.53, 0.70). This was primarily driven by "new onset of macro-albuminuria". However, no obvious difference between empagliflozin and placebo was observed for new onset of albuminuria.

For patients with microalbuminuria (UACR 30 to 300 mg/g) or macro-albuminuria (UACR >300 mg/g) at baseline, more patients showed sustained reversal of their proteinuria after treatment with empagliflozin than with placebo. There were no obvious differences between the 2 empagliflozin dose groups. These results were maintained in subjects with moderate renal insufficiency.

When mean eGFR values were analysed over time, there was a steady decrease in eGFR in the placebo group, indicative of natural disease progression. In contrast, the initial decreases in eGFR in the empagliflozin groups were reversible over time, with eGFR values higher in the empagliflozin groups than in the placebo group after about a year. About 30 days after the stop of treatment, eGFR increased from the last value on treatment by about 3.5 ml/min/1.73m^2 in the empagliflozin groups, while no change was seen in the placebo group.

Although most subgroups with regard to the primary endpoint were consistent with the main analysis, there were some exceptions. In the analysis of Black or African American patients, the HR for MACE-3 favoured placebo (HR: 1.48). The results in users of thiazolidinediones and also DPP4-inhibitors showed trends in the wrong direction (HR 1.13 and 1.27). In these same subgroups, the HRs for CV mortality were 0.77, 0.60 and 1.23 respectively. In Black or African American patients, the HR for all-cause mortality was 1.25.

The benefits in Europe and also North America were smaller than in Latin America and Asia. The HR for MACE-3 in Europe (41.1% of the patients) was 0.97 for the 10 mg dose and 1.07 for the 25 mg dose, for North America (19.9% of the patients) this was 0.78 and 1.01 respectively.

The results for MACE-3 in subjects with normal renal function (eGFR > 90 ml/min/1.73 m^2) were also slightly less favourable than the results in subjects with impaired renal function.

Risks

Unfavourable effects

The safety profile of empagliflozin in the EMPA-REG trial was consistent with the known safety profile of empagliflozin. The overall incidence of adverse events in patients treated with empagliflozin was similar to placebo. The most frequently reported adverse reaction was hypoglycaemia when empagliflozin was used

with sulphonylurea or insulin. Increased urination and volume depletion are directly related to the mode of action. There was no clear increase in the occurrence of keto-acidosis (placebo: 1, empa 10 mg: 3, empa 25mg: 1). In EMPA-REG, **thirst** occurred more frequently with empagliflozin than with placebo (empagliflozin 10 mg: 0.3%; 25 mg: 0.8%; placebo: 0.2%). This ADR is not completely covered by the potentially related entity of 'volume depletion', and has thus been added to SmPC section 4.8.

The MAH summarised AE data for subjects with moderate renal insufficiency and for older patients. Although in these groups the overall rate of AEs is higher than in the overall population, the AE profile is comparable to the total population. EMPA-REG confirmed increases in haematocrit and serum lipids.

Uncertainty in the knowledge about the unfavourable effects

For some rare AEs of special interest, the numbers of events were low despite the size of the trial. Of note:

- Serious hepatic injury and/or patients with ALT/AST ≥5x ULN were higher for patients in the empagliflozin groups (increased AST/ALT: 10 mg: 0.7%; 25 mg: 0.6%) than placebo (0.3%). No definite cases of DILI were identified as according to the hepatic events committee confounding factors were present.
- In total, 7 patients (0.3%) in the empagliflozin 10 mg group and 12 patients (0.5%) in the empagliflozin 25 mg group had PT urosepsis or sepsis possibly originated from the urinary tract, compared with 5 patients (0.2%) in the placebo group. The overall incidence rate of (complicated) UTIs was similar in the empagliflozin groups and the placebo group.
- Malignancies occurred more frequently with empagliflozin treatment (4.3%) compared to placebo treatment (3.3%), also when taking into account only cases after at least 6 months of exposure. However, no specific group of malignancies seems to explain this and after detailed classification the groups become very small.

Effects Table

Table 23. Effects Table for cardiovascular risk prevention by empagliflozin

Effect	Short Description	Unit	Empa	Plc	Uncertainties/ Strength of evidence
Favourable Effects					
MACE-3	time to the first of • cardiovascular (CV) death (including fatal stroke and fatal MI) • non-fatal MI (excluding silent MI) • non-fatal stroke.	% of patients with event	10.5 10 mg: 10.4 25 mg: 10.5	12.1	Primary endpoint HR* 0.86 (0.74, 0.99) P (2-sided) = 0.0382 Confirmed in sensitivity analyses Uncertainties: Non-fatal MI: HR* 0.87 (0.70, 1.09) Non-fatal stroke: HR* 1.24 (0.92, 1.67). Fatal/non-fatal stroke in European subgroup: HR 2.04, (1.26, 3.29).
CV Death	Mortality Adjudicated to CV cause	% of patients with event	3.7 ***	5.9	Exploratory analysis of component of primary endpoint. HR* 0.62 (0.49, 0.77) Confirmed by all-cause mortality: HR* 0.68 (0.57, 0.82)
Hospitalisation for heart failure	Adjudicated events of hospitalisation for heart failure	% of patients with event	2.7	4.1	Exploratory analysis HR* 0.65 (0.50, 0.85)
New or worsening nephropathy	any of • New onset of macro-albuminuria (UACR>300 mg/g), • doubling of serum creatinine level accompanied by an eGFR $\leqslant$45**, • initiation of continuous renal replacement therapy or • death due to renal disease	% of patients with event	12.7	18.8	Exploratory analysis HR* 0.61 (0.53, 0.70)
Unfavourable Effects					
Any AE	Rate of patients reporting any AE.	Incidence per 100 patient years	10 mg: 150.34 25 mg: 148.36	178.67	As assessed in EMPA-REG, result consistent with phase 3 program
Hypoglycaemia	Rate of patients reporting the AE (company query).	Incidence per 100 patient years	10 mg: 15.39 25 mg: 14.75	15.31	As assessed in EMPA-REG, result consistent with phase 3 program
Urinary tract Infection	Rate of patients reporting the AE (company query).	Incidence per 100 patient years	10 mg: 8.02 25 mg: 7.75	8.21	As assessed in EMPA-REG, result consistent with phase 3 program
Genital Infection	Rate of patients reporting the AE (company query).	Incidence per 100 patient years	10 mg: 2.66 25 mg: 2.55	0.73	As assessed in EMPA-REG, result consistent with phase 3 program
Ketoacidosis	Number of patients reporting the AE.		10 mg: 3 25 mg: 1	1	As assessed in EMPA-REG

* HR: Hazard ratio presented as empagliflozin/placebo (<1 favours empagliflozin) and 95% confidence interval.
** Unit for eGFR: mL/min/1.73m *** Numbers for total CV death are slightly higher than as a component of MACE-3, because MI or stroke could have come earlier.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The EMPA-REG trial is a large, well-designed and well-conducted cardiovascular outcome trial. There are no major concerns related to group differences in baseline characteristics. The trial demonstrated superiority (p=0.04) of empagliflozin over placebo on the primary endpoint of MACE-3. When analysed by the individual components, this result is driven primarily by a benefit in CV death, starting to be significant as early as day 59. The components non-fatal myocardial infarction and non-fatal stroke showed statistically non-significant, heterogeneous differences, with a positive trend for non-fatal MI and a negative trend for stroke. The reduction in CV mortality appears largely independent of HbA1c and change from baseline in HbA1c, being even observed in subjects with baseline HbA1c < 7, and with similar results obtained for subjects with a reduction in HbA1c <0.3% or even an increase as compared to subjects with a decrease >0.3%. This separation of glucose lowering effect and reduction in CV mortality was confirmed by additional analyses and may suggest a different mode of action.

All-cause mortality in these patients is mainly attributable to CV causes, but also non-CV causes favoured empagliflozin (although not statistically significant). This positive effect of antidiabetics on macrovascular complications had previously only been demonstrated for metformin (UKPDS 34 study). This was the first time since 1998 that efficacy of an antidiabetic drug was demonstrated in decreasing cardiovascular events in a large clinical trial. The effect size for the reduction in the risk of death expressed as the number needed to treat (NNT) was 39 to prevent 1 death in 3.1 years and is considered clinically relevant. Results are considered reliable as follow-up information for vital status was almost complete (>99%, only 53 patients missing) and the parameter is free from bias.

This type 2 variation is based on the results of a single, but large pivotal clinical trial. The primary and key secondary endpoints were assessed for non-inferiority and superiority. These tests were defined in a hierarchical testing procedure. All other outcomes of the trial are considered exploratory, but show supportive results. This applies in particular to the heart failure and nephropathy related outcomes where significant and potentially clinically relevant results were observed.

The results for stroke remain unexplained. This result was significant in the European population, leading to a neutral HR for the primary endpoint of MACE-3 in Europe (see Figure 17). However, trends were different for North and South America, and overall the HR was non-significant. With regards to the overall trial population, the MAH has provided data to show that part of the effect on stroke can be attributed to off-treatment events occurring late in the trial. There was no evidence of an association between stroke and volume depletion adverse events that occurred prior to a stroke nor with haemo-concentration. A similar trend is not seen for transient cerebral ischaemia (TIA). Also, no relevant difference in baseline characteristics was identified that could be related to such regional differences.

Many subjects were included in the study with an eGFR between 30 and 60 ml/min/1.73m^2. The results are largely in line with the overall trial population. The established mode of action, related to glycaemic control, does seem not to confer the mortality benefits. In this group of patients, the CV prevention effect has been shown, but the effect on glycaemic control is limited.

The safety profile confirms prior knowledge, no unexpected adverse effects occurred. As usual for this class of products, genital infections were more frequent among empagliflozin users. Urinary tract infections were balanced between groups. Bone fractures were not more frequent in empagliflozin treated patients. Ketoacidosis occurred in only 5 cases with only a numerical increase in the 10 mg group (3 vs. 1 in the other groups). Malignancies occurred slightly more frequently in the empagliflozin-treated groups, but no specific malignancy was noticeable after classification, the numbers were too small.

Benefit-risk balance

The overall benefit in terms of reduction in cardiovascular deaths by treating DM patients with a history of a cardiovascular event with empagliflozin is considered clinically relevant and outweighs the risks. The small increase in non-ischemic stroke remains an uncertainty, but could be due to chance. The question is whether the over-all improved CV outcome justifies a new indication. This will be discussed further below.

Discussion on the Benefit-Risk Balance

Results of EMPA-REG indicate that the subgroup of T2DM patients with established CV disease may benefit in terms of cardiovascular outcome. The issue discussed as part of this CHMP assessment was whether these patients and their goals of treatment should be mentioned in section 4.1.

The indication proposed by the MAH was defining two T2DM populations, one large (T2DM) and one more restricted (patients with T2DM and established cardiovascular disease), aiming at two different goals of treatment (glycaemic control and reduction of cardiovascular death). Important in this regard is the view that the cardiovascular benefit appears to be not only explained by the glucose lowering effect of empagliflozin. The MAH supported this by arguments such as the time course of the effect observed with an early benefit, the independence of the size of the glucose lowering effects and the beneficial effects in patients with an eGFR between 30 and 45 ml/min/1.73 m2 where the glucose lowering effects are marginal. It is therefore unlikely that the effect is only based on an effect on atherosclerosis, glycaemia control or blood pressure. However, the exact mechanism of action remains speculative. Renal effects may play a role but further studies are needed to unravel the underlying mechanism(s) and to confirm these beneficial effects.

Apart from the mechanism of action, the MAH gave other arguments to separate glycaemic control and the reduction in cardiovascular mortality in the indication. Mentioning results only in section 5.1 would not be clear for the prescriber for whom sections 4.1 and 4.2 are more important. The posology proposed is different, as the 25 mg dose has no additional advantages (compared to the 10 mg dose) for CV prevention. In modern CV outcome trials investigating three different DPP-4 inhibitors and two GLP-1 analogues, modest differences in glucose control did not translate to improved CV outcomes, with the exception of the LEADER trial with liraglutide that was recently published (N Engl J Med 2016; 375:311-322). Finally, there are also precedents with other risk reducing therapies, such as the statins and ACE-inhibitors where a distinction in goals of treatment has been made in the indication between the metabolic/haemodynamic endpoint and the clinical outcome.

An oral explanation was held by the applicant presenting the rationale for their proposed indication (discussed above). The CHMP concluded that while EMPA REG is a positive cardiovascular outcome trial, treatment of T2DM may cover treatment and/or prevention of many co-morbidities. CHMP is of the view that in the indication section of the SmPC the patient population eligible for treatment with empagliflozin should be mentioned, i.e. patients with T2DM, without mentioning any goal of treatment, i.e. neither improvement of glycaemic control, nor reduction of the risk of cardiovascular death. This means that the wording of the indication will refer to the patient population for whom treatment with empagliflozin is intended, i.e. patients with T2DM, and the information on the EMPA-REG study including the heterogeneity of the MACE-3 endpoint, will be included in section 5.1. The rationale for CHMPs decision is that the improvement in glucose control and reduction of cardiovascular events are the main goals of treatment for T2DM and should not be separated. These have now been demonstrated in the EMPA-REG trial for patients with established CV disease and may also apply to other T2DM patients.

In line with the Guideline on Summary of Product Characteristics with regard to wording of *the indication(s),* the CHMP was of the view that the population studied in the EMPA-REG i.e. T2DM patients with established CV disease, is a sub-population of the already approved T2DM population for Jardiance and that the demonstrated effect of reduction of CV mortality is covered by the general indication "treatment of type 2 diabetes"; similarly, achievement of glycemic control is covered. Thus, the effect on CV mortality does not constitute a separate (prevention) indication. Therefore CHMP did not grant a separate CV prevention indication but deleted the endpoint "glycaemic control" from section 4.1 to clarify that the treatment goal for empagliflozin is not limited to glycaemic control. The results of the EMPA-REG are reflected in section 5.1 of the SmPC.

Furthermore, in the case of the current empagliflozin application based on a single pivotal trial some further considerations were: 1) EMPA-REG was primarily a safety study and the primary endpoint resulted in a p for superiority of only 0.04, 2) patients with established cardiovascular disease are only a subgroup of the total (T2DM) population with overlap between the two indications claimed, 3) the effect on the MACE-3 endpoint was inconsistent with an increase in stroke, and 4) the pharmacological principle is new and the mode of action for the latter effect has not been established.

CHMP also reflected whether to delete the restriction of the indication to patients for whom use of metformin is considered inappropriate and to grant a broad indication of monotherapy and combination therapy in patients with T2DM. The main reason for this restriction has been that only metformin had demonstrated a CV benefit in T2DM, but now this also applies to empagliflozin where 20% of the patients in the EMPA-REG study did not receive metformin and showed an even higher benefit. CHMP finally decided that it is too early for this decision, especially as the safety profile of empagliflozin is not completely mature yet.

A final issue discussed was the inclusion (as proposed by the applicant) of patients with eGFR below 45 ml/min/1.73m^2. In these patients, no clinically relevant effect on glycaemic control has been shown but CV events may be prevented. This extension was not granted, as the CHMP considered glycaemic efficacy is essential for any diabetes product. Therefore, the posology in patients with renal impairment remained unchanged.

The final wording for the modified indication in SmPC section 4.1 as agreed by the CHMP is as follows (new text shown in bold; removed text as strikethrough):

"Jardiance is indicated **for** ~~in~~ the treatment of **adults with insufficiently controlled** type 2 diabetes mellitus ~~to improve glycaemic control in adults~~ as ~~:~~

~~Monotherapy~~

~~When~~ **an adjunct to** diet and exercise

- **as monotherapy when** ~~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~~ **in addition to** other ~~glucose-lowering~~ medicinal products **for the treatment of diabetes** ~~including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control~~

~~(~~For study results with respect to combinations, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1~~ for available data on different combinations~~)."

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of section 4.1, 4.4, 4.8 and 5.1 of the SmPC to reflect new data on cardiovascular outcomes, based on the final study report of the phase III clinical trial EMPA-REG OUTCOME. The Package Leaflet and RMP have been updated accordingly.

The MAH took the opportunity to make some editorial changes and bring the PI in line with the latest QRD template.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.